

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219155Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	219155
Priority or standard	Standard
Submit date(s)	7/23/2024
Received date(s)	7/23/2024
PDUFA goal date	7/23/2025
Division/office	Division of Dermatology and Dentistry (DDD)
Review completion date	7/21/2025
Established/proper name	Delgocitinib
(Proposed) proprietary name	ANZUPGO
Pharmacologic class	JAK inhibitor
Other product name(s)	N/A
Applicant	LEO PHARMA AS
Dosage form(s)/formulation(s)	CREAM
Dosing regimen	Apply twice daily to skin of the affected areas only on the hands and wrists
Applicant-proposed indication(s)/population(s)	Topical treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable.
SNOMED CT code for proposed indication disease term(s)¹	02233005 Chronic hand eczema (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	20 mg/g (2%)
Approved indication(s)/population(s) (if applicable)	Topical treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable
SNOMED CT code for approved indication disease term(s)¹	02233005 Chronic hand eczema (disorder)

¹ For internal tracking purposes only

Abbreviations: CHE, chronic hand eczema; DDD, Division of Dermatology and Dentistry; PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

Table of Contents

Table of Tables	viii
Table of Figures	xv
Table of Equations	xvi
Glossary	1
I. Executive Summary.....	4
1. Overview	4
1.1. Summary of Regulatory Action.....	4
1.2. Conclusions on Substantial Evidence of Effectiveness	5
2. Benefit-Risk Assessment.....	6
2.1. Benefit-Risk Framework	6
2.2. Conclusions Regarding Benefit-Risk	16
II. Interdisciplinary Assessment.....	18
3. Introduction	18
3.1. Review Issue List.....	18
3.1.1. Key Efficacy Review Issues.....	18
3.1.1.1. Impact of the Lack of Run-In Period on the Assessment of Efficacy.....	18
3.1.1.2. Impact of Content Validity, Other Measurement Properties, and Data Interpretability for COA-Based Efficacy Endpoints.....	18
3.1.2. Key Safety Review Issues.....	19
3.1.2.1. Impact of the Formulation Change on the Assessment of Pharmacokinetics and Safety.....	19
3.1.2.2. Impact of the Lack of Run-In Period on the Assessment of Safety	19
3.1.2.3. Evaluation of JAK Inhibitor Class Safety Labeling for Inflammatory Conditions in Context of the Delgocitinib Development Program.....	19
3.2. Approach to the Clinical Review.....	19
3.3. Approach To Establishing Substantial Evidence of Effectiveness	21
4. Patient Experience Data	24
5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology	26
5.1. Nonclinical Assessment of Potential Effectiveness.....	26

5.2. Clinical Pharmacology/Pharmacokinetics	27
6. Efficacy (Evaluation of Benefit)	30
6.1. Assessment of Dose and Potential Effectiveness	30
6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy	30
6.2.1. Trial Design, Trials DELTA 1 and DELTA 2	30
6.2.2. Eligibility Criteria, Trials DELTA 1 and DELTA 2	32
6.2.3. Clinical Endpoints, Trials DELTA 1 and DELTA 2.....	33
6.2.4. Clinical Outcome Assessment Instruments Used To Assess the Primary and Secondary Endpoints, Trials DELTA 1 and DELTA 2.....	34
6.2.4.1. Investigator's Global Assessment for Chronic Hand Eczema	34
6.2.4.2. Hand Eczema Severity Index	35
6.2.4.3. Hand Eczema Symptom Diary	36
6.2.4.4. Hand Eczema Impact Scale	39
6.2.5. Statistical Analysis Plan, DELTA 1 and DELTA 2 Trials.....	42
6.2.6. Results of Analyses, Trials DELTA 1 and DELTA 2.....	46
6.3. Key Efficacy Review Issues	54
6.3.1. Impact of the Lack of Run-In Period on the Assessment of Efficacy.....	54
6.3.2. Impact of Content Validity, Other Measurement Properties, and Data Interpretability for COA-Based Efficacy Endpoints.....	56
6.3.2.1. Fitness for Purpose and Interpretability of the HECSI.....	56
6.3.2.2. Fitness for Purpose and Interpretability of the HEIS PDAL Domain	57
7. Safety (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	62
7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience	67
7.4. FDA Approach to the Safety Review	74
7.5. Adequacy of the Clinical Safety Database	75
7.6. Safety Results	78
7.6.1. Safety Results, Pooled Analyses, Trials DELTA 1 and DELTA 2.....	78

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Pooled Analyses, Trials DELTA 1 and DELTA 2	79
7.6.1.2. Deaths, Pooled Analyses, Trials DELTA 1, DELTA 2 and DELTA 3	80
7.6.1.3. Serious Treatment-Emergent Adverse Events, Pooled Analyses, Trials DELTA 1 and DELTA 2	81
7.6.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Pooled Analyses, Trials DELTA 1 and DELTA 2	84
7.6.1.5. Treatment-Emergent Adverse Events, Pooled Analyses, Trials DELTA 1 and DELTA 2	87
7.6.1.6. Laboratory Findings, Pooled Analyses, Trials DELTA 1 and DELTA 2	107
7.6.1.7. Assessment of Drug-Induced Liver Injury, Pooled Analyses, Trials DELTA 1 and DELTA 2	142
7.6.1.8. Vital Signs, Pooled Analyses, Trials DELTA 1 and DELTA 2	144
7.6.1.9. Subgroups, Pooled Analyses, Trials DELTA 1 and DELTA 2	149
7.6.1.10. Exposure-Adjusted Pooled Analyses, Trials DELTA 1 and DELTA 2	151
7.6.2. Safety Results, Trial 1273	152
7.6.3. Safety Results, Trial DELTA FORCE	154
7.6.3.1. Overview of Treatment-Emergent Adverse Events Summary, Trial DELTA FORCE	154
7.6.3.2. Treatment-Emergent Adverse Events, Trial DELTA FORCE	162
7.7. Key Safety Review Issues	167
7.7.1. Impact of the Formulation Change on the Assessment of Pharmacokinetics and Safety	167
7.7.2. Impact of the Lack of Run-In Period on the Assessment of Safety	168
7.7.3. Evaluation of JAK Inhibitor Class Safety Labeling for Inflammatory Conditions in Context of the Delgocitinib Development Program	171
8. Therapeutic Individualization	179
8.1. Intrinsic Factors	179
8.2. Extrinsic Factors	179
8.3. Plans for Pediatric Drug Development	180
8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential	180
8.4.1. Animal Data	180

9. Product Quality	181
9.1. Device or Combination Product Considerations	182
10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review	182
11. Advisory Committee Summary	184
III. Additional Analyses and Information	185
12. Summary of Regulatory History	185
13. Pharmacology Toxicology	186
13.1. Summary Review of Studies Submitted With the Investigational New Drug Application	186
13.1.1. Pharmacology (Primary and Secondary)	186
13.1.2. Safety Pharmacology	188
13.1.3. Pharmacokinetics	189
13.1.4. Toxicology	195
13.1.4.1. General Toxicology	195
13.1.4.2. Genetic Toxicology	198
13.1.4.3. Special Toxicity Studies	199
13.1.4.4. Reproductive and Developmental Toxicity	199
13.1.5. Excipients/Impurities	212
13.1.6. Extractables/Leachables	213
13.2. Individual Reviews of Studies Submitted With the New Drug Application	216
13.2.1. Carcinogenicity	216
13.3. Labeling	221
14. Clinical Pharmacology	227
14.1. In Vitro Studies	227
14.2. In Vivo Studies	229
14.3. Bioanalytical Method Validation and Performance	258
14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety ...	260
14.5. Pharmacometrics Assessment	260
14.6. Pharmacogenetics	261
15. Study/Trial Design	261

15.1. Phase 3 Protocol Synopsis (DELTA 1)	261
15.2. Phase 3 Protocol Synopsis (DELTA 2)	267
15.3. Phase 3 Protocol Synopsis (DELTA 3)	273
16. Efficacy	276
16.1. Clinical Outcome Assessments.....	276
16.1.1. CHE COA Conceptual Frameworks	276
16.1.2. COA Content Validity.....	278
16.1.2.1. Expert Input	278
16.1.2.2. Patient Input.....	279
16.1.3. COA Scoring Algorithms.....	280
16.1.3.1. Investigator’s Global Assessment for Chronic Hand Eczema	280
16.1.3.2. Hand Eczema Symptom Diary	280
16.1.3.3. Hand Eczema Severity Index	281
16.1.3.4. Hand Eczema Impact Scale	281
16.1.4. IGA-CHE Test-Retest Reliability	281
16.1.5. HESD Itch Score and HESD Pain Score.....	285
16.1.6. HECSI	285
16.1.7. Hand Eczema Impact Scale.....	289
16.2. Different Approaches for Handling Missing Data and Intercurrent Events	290
16.3. Findings in Special/Subgroup Populations	291
17. Clinical Safety	294
17.1. Clinical Safety: Additional Information	294
18. Clinical Virology	304
19. Clinical Microbiology	304
20. Mechanism of Action/Drug Resistance.....	305
21. Other Drug Development Considerations	305
22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)	306
23. Labeling: Key Changes	306
23.1. Approved Labeling Types	309
24. Postmarketing Requirements and Commitments	309

NDA 219155

ANZUPGO (delgocitinib) cream, 2%

25. Financial Disclosure	311
26. References	312
27. Review Team.....	314
27.1. Reviewer Signatures	315

Table of Tables

Table 1. Application Information	i
Table 2. Benefit-Risk Framework.....	10
Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations Delgocitinib	22
Table 4. Patient Experience Data Submitted or Considered.....	25
Table 5. Summary of Clinical Pharmacology and Pharmacokinetics.....	27
Table 6. Investigator’s Global Assessment for Chronic Hand Eczema Scale	35
Table 7. HECSI Severity Score Scale and Area Score Scale	36
Table 8. Calculation of the Total HECSI Score.....	36
Table 9. Subject Disposition, Trials DELTA 1 and DELTA 2.....	47
Table 10. Demographics and Baseline Disease Characteristics, Trials Delta 1and Delta 2 (FAS) ¹	47
Table 11. Rescue Therapy Use, Trials DELTA 1 and DELTA 2 (FAS) ¹	48
Table 12. Results for the Primary Efficacy Endpoint, Trials DELTA 1 and DELTA 2 (FAS) ¹	49
Table 13. Results of the Key Secondary Efficacy Endpoints, Trials DELTA 1 and DELTA 2 (FAS) ¹	49
Table 14. Applicant’s Post Hoc Analysis for the Primary Efficacy Endpoint by the TCS Run-In-Like Periods, Trials DELTA 1 and DELTA 2 (FAS) ¹	55
Table 15. Multiples of Human Exposure for NOAELs Identified in Pivotal Toxicology Studies	59
Table 16. NOAELs, Systemic Exposure, Multiples of Exposures, and Major Findings From Reproductive, Developmental, and Juvenile Animal Toxicology Studies.....	60
Table 17. NOAELs, Systemic Exposure, and Multiples of Exposures From Carcinogenicity Studies in Mice and Rats	61
Table 18. Summary of Treatment Duration of CORECTIM Prior to Adverse Events.....	69
Table 19. Tabulated Summary of CORECTIM Case Reports With Tests Related to CBC.....	71
Table 20. Reports of Adverse Events in the CORECTIM Postmarketing Database Related to Hematological Parameters	72
Table 21. Duration of Exposure, Safety Population, Pooled Trials DELTA 1 and DELTA 2	76
Table 22. Duration of Exposure, Safety Population, Pooled Trials DELTA 1, DELTA 2, and DELTA 3.....	76

Table 23. Overview of Adverse Events, Safety Population, Pooled Trials DELTA 1 and DELTA 2.....	79
Table 24. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Pooled Trials DELTA 1 and DELTA 2.....	82
Table 25. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Pooled Trials DELTA 1 and DELTA 2.....	85
Table 26. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class, FDA Medical Query (Narrow) and Preferred Term, Safety Population, Pooled Trials DELTA 1 and DELTA 2.....	86
Table 27. Subjects With Adverse Events Occurring at $\geq 1\%$ Frequency, Safety Population, Pooled Trials DELTA 1 and DELTA 2.....	89
Table 28. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Broad), Safety Population, Pooled Trials DELTA 1 and DELTA 2	90
Table 29. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Pooled Trials DELTA 1 and DELTA 2.....	94
Table 30. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Broad), Safety Population, Pooled Trials DELTA 1, DELTA 2, and DELTA 3	100
Table 31. Subject With Adverse Events by System Organ Class FDA Medical Query (Narrow) and Preferred Term, Showing Terms Occurring in at Least 1% of Subjects in Any Arm, Safety Population Pooled Trials 1401, DELTA 2, and DELTA 3	103
Table 32. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Pooled Trials DELTA 1 and DELTA 2.....	108
Table 33. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Pooled Trials DELTA 1 and DELTA 2.....	111
Table 34. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Pooled Trials DELTA 1 and DELTA 2.....	111
Table 35. Subjects With One or More Lipids Analyte Values Exceeding Specified Levels, Safety Population, Pooled Trials DELTA 1 and DELTA 2.....	114
Table 36. Shift Summary for LDL From Baseline to Worst (High) Value, Trials DELTA 1 and DELTA 2 Pooled (SAF)	115
Table 37. Shift Summary for LDL From Baseline to Worst (High) Value, Subjects Continuously Treated With Delgocitinib, 2% for 52 Weeks (SAF).....	116
Table 38. Shift Summary for Triglycerides From Baseline to Worst (High) Value, Trials DELTA 1 and DELTA 2, Pooled (SAF)	117

Table 39. Shift Summary for Triglycerides From Baseline to Worst (High) Value, Subjects Continuously Treated With Delgocitinib 20 mg/g for a Year (SAF).....	117
Table 40. Shift Summary for Cholesterol From Baseline to Worst (High) Value, Trials DELTA 1 and DELTA 2, Pooled (SAF)	119
Table 41. Shift Summary for Cholesterol From Baseline to Worst (High) Value, Subjects Continuously Treated With Delgocitinib 20 mg/g for a Year (SAF).....	119
Table 42. Shift Summary for HDL From Baseline to Worst (Low) Value, Trials DELTA 1 and DELTA 2, Pooled (SAF)	120
Table 43. Shift Summary for HDL From Baseline to Worst (Low) Value, Subjects Continuously Treated With Delgocitinib for a Year (SAF).....	121
Table 44. Cytopenia TEAEs in Trials DELTA 1 and DELTA 2, Week 1 to Week 16 Exposure	121
Table 45. Cytopenia TEAEs in Trials DELTA 1, DELTA 2, and DELTA 3, Continuous 52 Weeks Exposure	122
Table 46. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Pooled Trials DELTA 1 and DELTA 2.....	123
Table 47. Shift Summary for Hemoglobin From Baseline to Worst (Low) Value, Week 0 to 16, Vehicle-Controlled Primary Safety Pool (SAF).....	126
Table 48. Shift Summary for Hemoglobin from Baseline to Worst (Low) Value, Subjects Continuously Treated With Delgocitinib Cream 20 mg/g for a Year (SAF).....	127
Table 49. Shift Summary for Thrombocytes From Baseline to Worst (Low) Value, Week 0 to 16 Vehicle, Controlled Primary Safety Pool (SAF)	129
Table 50. Shift Summary for Thrombocytes From Baseline to Worst (Low) Value, Subjects Continuously Treated With Delgocitinib 20 mg/g for a Year (SAF).....	130
Table 51. Shift Summary for Leukocytes From Baseline to Worst (Low) Value, Primary Safety Pool (SAF)	131
Table 52. Shift Summary for Leukocytes From Baseline to Worst (Low) Value, Subjects Continuously Treated With Delgocitinib 20 mg/g for a Year (SAF).....	132
Table 53. Leukopenia: TEAEs (PT: Leukopenia, Neutropenia, Neutrophil Count Decreased, Lymphopenia, Lymphocyte Count Decreased, White Blood Cell Count Decreased) and Worsening Grade Shifts in Leukocyte, Neutrophil, and Lymphocyte Levels, Trials DELTA 1 and DELTA 2	133
Table 54. Leukopenia: TEAE (PT: Leukopenia, Neutropenia, Neutrophil Count Decreased, Lymphopenia, Lymphocyte Count Decreased, White Blood Cell Count Decreased) and Worsening Grade Shifts, Subjects Continuously Treated With Delgocitinib 20 mg/g for a Year	133
Table 55. Shift Summary for Neutrophils From Baseline to Worst (Low) Value, Week 0 to 16 Vehicle-Controlled Primary Safety Pool (SAF).....	134

Table 56. Shift Summary for Neutrophils From Baseline to Worst (Low) Value, Subjects Continuously Treated With Delgocitinib 20 mg/g for a Year (SAF).....	137
Table 57. Shift Summary for Lymphocytes From Baseline to Worst (Low) Value, Week 0 to 16 Vehicle-Controlled Primary Safety Pool (SAF).....	138
Table 58. Shift Summary for Lymphocytes From Baseline to Worst (Low) Value, Subjects Continuously Treated With Delgocitinib 20 mg/g for a Year (SAF).....	140
Table 59. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Pooled Trials DELTA 1 and DELTA 2	143
Table 60. Subjects in Each Quadrant for Cholestatic DILI Screening Plot, Safety Population, Pooled Trials DELTA 1 and DELTA 2	144
Table 61. Shift Summary for Systolic Blood Pressure From Baseline to Worst (High) Value, Pooled Trials DELTA 1 and DELTA 2.....	146
Table 62. Shift Summary for Systolic Blood Pressure From Baseline to Worst (High) Value, Subjects Continuously Treated With Delgocitinib 20 mg/g for a Year	147
Table 63. Shift Summary for Potassium From Baseline to Worst (Low) Value, Pooled Trials DELTA 1 and DELTA 2	148
Table 64. Shift Summary for Potassium From Baseline to Worst (Low) Value, Subjects Continuously Treated With Delgocitinib for 52 Weeks.....	148
Table 65. Sodium and Potassium Electrolytes, Number of Measurements Postbaseline, Primary Pool	149
Table 66. Overview of Adverse Events by Demographic Subgroup, Safety Population, Studies, Trials DELTA 1 and DELTA 2	150
Table 67. Summary of Adverse Events, by Intrinsic Subgroups, Primary Pool.....	151
Table 68. Exposure-Adjusted Analysis, Safety Population, Trials DELTA 1 and DELTA 2	152
Table 69. Most Frequent AEs ($\geq 1\%$) by System Organ Class and Preferred Term, Pooled Trials DELTA 1 and DELTA 2 and Primary Pool (Which Includes Subjects Who Received Delgocitinib Cream, 2% in Trial 1273)	153
Table 70. Summary of Safety Focus Areas, Pooled Trials DELTA 1 and DELTA 2 and Primary Pool Which Includes Trial 1273 (SAF).....	154
Table 71. Clinical Trial DELTA FORCE Submitted in Support of Efficacy and Safety Determinations for Delgocitinib	156
Table 72. Overview of Adverse Events, Safety Population, Trial DELTA FORCE (Weeks 0 to 12).....	157
Table 73. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial DELTA FORCE (Weeks 0 to 12).....	157
Table 74. Subjects With Serious Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term, Safety Population, DELTA FORCE (Weeks 0 to 12).....	158

Table 75. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial DELTA FORCE (Weeks 0 to 12).....	159
Table 76. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class, FDA Medical Query (Narrow) and Preferred Term, Safety Population, Trial DELTA FORCE (Weeks 0 to 12).....	160
Table 77. Subjects With Common Adverse Events Occurring at $\geq 1\%$ Frequency, Safety Population, Trial 1528 (Weeks 0 to 12).....	162
Table 78. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial DELTA FORCE (Weeks 0 to 12).....	163
Table 79. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Broad), Safety Population, Trial DELTA FORCE (Weeks 0 to 12)	165
Table 80. Overview of Adverse Events in Subjects With and Without Run-In Like Period, Pooled Trials DELTA 1 and DELTA 2.....	169
Table 81. Overview of Adverse Events by System Organ Class and Preferred Term in $\geq 1\%$ Subjects With and Without Run-In Like Period, Pooled Trials DELTA 1 and DELTA 2	170
Table 82: Clinical Inspection Sites	183
Table 83. Summary of In Vitro and In Vivo Pharmacology Studies.....	186
Table 84. Summary of Secondary Pharmacology Studies.....	188
Table 85. Summary of Safety Pharmacology Studies	188
Table 86. Summary of Pharmacokinetics Studies	189
Table 87. Study Information, Study JTE052-TX-037	195
Table 88. Observations and Results, Study JTE052-TX-037	195
Table 89. Study Information, Study JTE052-TX-033	196
Table 90. Observations and Results, Study JTE052-TX-033	197
Table 91. Genetic Toxicology Studies.....	198
Table 92. Study Information, Study JTE052-TX-038	200
Table 93. Observations and Results, Study JTE052-TX-038	200
Table 94. Study Information, Study JTE052-TX-015	201
Table 95. Observations and Results, Study JTE052-TX-015	201
Table 96. Study Information, Study JTE052-TX-016	202
Table 97. Observations and Results, Study JTE052-TX-016	203
Table 98. Study Information, Study JTE052-TX-017	204
Table 99. Observations and Results, Study JTE052-TX-017	204

NDA 219155	
ANZUPGO (delgocitinib) cream, 2%	
Table 100. Study Information, Study JTE052-TX-047	205
Table 101. Observations and Results, Study JTE052-TX-047	205
Table 102. Study Information, Study JTE052-TX-036	207
Table 103. Observations and Results, Study JTE052-TX-036	208
Table 104. Study Information, Study JTE052-TX-039	216
Table 105. Observations and Results, Study JTE052-TX-039	216
Table 106. Study Information, Study JTE052-TX-040	218
Table 107. Observations and Results, Study JTE052-TX-040	218
Table 108. Summary of Solute Carrier Transporter Inhibition/Substrate in Cell (Study (b) (4) 208059)	229
Table 109. Demographic Parameters of Subjects, Trial LP0133-2285	232
Table 110. Pharmacokinetic Results (AUC ₀₋₁₂) and C _{max} , Trial LP0133-2285	233
Table 111. Summary of Demographic and Baseline Characteristics, Trial LP0133- 1181	236
Table 112. Summary of Baseline EASI Score, vIGA-AD Score, and BSA Involved for Enrolled Subjects	237
Table 113. Pharmacokinetic Parameters of Delgocitinib by Age Group, Trial LP0133- 1181	239
Table 114. Pharmacokinetic Parameters of Delgocitinib by Age Group, Trial LP0133- 1181	241
Table 115. Summary of Subjects Pharmacokinetic Parameters, Trial DELTA 2	244
Table 116. Summary of Demographic and Baseline Characteristics, Trial DELTA 2	245
Table 117. Pharmacokinetic Parameters of Delgocitinib Under Maximal Use Conditions at Week 1, Week 4 and Week 16	246
Table 118. Delgocitinib Ointment Formulation Composition	247
Table 119. Systemic Concentration (ng/mL) of Delgocitinib: Safety Analysis Set	249
Table 120. Summary of the Pharmacokinetic Parameters for Delgocitinib Following Single Oral Doses	252
Table 121. Pharmacokinetic Parameters of Delgocitinib After Single Dose Administration (Fasted State)	254
Table 122. Pharmacokinetic Parameters of Delgocitinib in Urine After Single Dose	255
Table 123. Pharmacokinetic Parameters of Delgocitinib in Plasma After Multiple- Dose Administration	255
Table 124. Summary of Relative Bioavailability of Delgocitinib Cream Compared to Different Oral Doses, Trials NBX1-1 and 1409	256

NDA 219155	
ANZUPGO (delgocitinib) cream, 2%	
Table 125. Summary of Bioanalytical Method Validation Data	258
Table 126. Summary of Bioanalytical Method Within Study Analysis Data.....	259
Table 127. Phase 3 Protocol Synopsis (Version 4.0; August 20, 2021) for LP0133-1401 (NCT04871711).....	261
Table 128. Phase 3 Protocol Synopsis (Version 4.0; August 20, 2021) for LP0133-1402 (NCT04872101).....	267
Table 129. Phase 3 Protocol Synopsis (Version 4.0; April 3, 2023) for LP0133-1403 (NCT04949841).....	273
Table 130. Test-Retest Reliability: IGA-CHE Score Weighted Kappa Coefficient Estimates and 95% Confidence Interval Between Week 2 and Week 4 and Between Week 4 and Week 8, Trial DELTA 1	282
Table 131. Test-Retest Reliability: IGA-CHE Score Weighted Kappa Coefficient Estimates and 95% Confidence Interval Between Screening and Baseline (FAS) and Between Baseline and Week 2 (Vehicle Only), Trials DELTA 1 and DELTA 2	283
Table 132. Summary of Median HESD Item Scores (Weekly Average) at Baseline and Week 16, Trials DELTA 1 and DELTA 2	284
Table 133. Correlations Between Change From Baseline to Week 16 in PaGA Score and Percent Change From Baseline at Week 16 in HECSI Score, Trials DELTA 1 and DELTA 2 (FAS).....	285
Table 134. Cross-Tabulation of PaGA at Baseline and Week 16, Trial DELTA 1 (FAS).....	286
Table 135. Cross-Tabulation of PaGA at Baseline and Week 16, Trial DELTA 2 (FAS).....	286
Table 136. Percentiles for Percent Change From Baseline in HECSI Score at Week 16 by PaGA at Baseline for Subjects With a 1-Category Improvement in PaGA From Baseline to Week 16, Trial DELTA 1 (FAS)	289
Table 137. Percentiles for Percent Change From Baseline in HECSI Score at Week 16 by PaGA at Baseline for Subjects With a 1-Category Improvement in PaGA From Baseline to Week 16, Trial DELTA 2 (FAS)	289
Table 138. Results of Sensitivity Analysis and Supplementary Analyses for the Primary Efficacy Endpoint, Trial DELTA 1 (FAS) ¹	290
Table 139. Results of Sensitivity Analysis and Supplementary Analyses for the Primary Efficacy Endpoint, Trial DELTA 2 (FAS) ¹	291
Table 140. Results for IGA-CHE Treatment Success ¹ at Week 16 by Age, Sex, Race, Ethnicity, Region, and Baseline IGA-CHE Score, Trial DELTA 1 (FAS) ²	291
Table 141. Results for IGA-CHE Treatment Success ¹ at Week 16 by Age, Sex, Race, Ethnicity, Region, and Baseline IGA-CHE Score, Trial DELTA 2 (FAS) ²	292
Table 142. Subject Specific Information for Hemoglobin Shifts	294

Table 143. Subject Specific Information for Neutrophil Shifts	296
Table 144. Subject Specific Information for Lymphocyte Shifts	298
Table 145. Subject Specific Information for Platelet Shifts	299
Table 146. Subject Specific Information for Leukocyte Shifts	300
Table 147. Primary Response in Subjects With Available Microbiological Data.....	305
Table 148. Key Labeling Changes and Considerations	306
Table 149. Covered Clinical Studies, Trial DELTA 1.....	311
Table 150. Covered Clinical Studies, Trial DELTA 2.....	311
Table 151. Reviewers of Integrated Assessment	314
Table 152. Additional Reviewers of Application	315
Table 27-1 Signatures of Reviewers	315

Table of Figures

Figure 1. Trial Design Schematic for Trial DELTA 1	31
Figure 2. Trial Design Schematic for Trial DELTA 2.....	32
Figure 3. Patient-Reported Outcome Assessment, Hand Eczema Symptom Diary	37
Figure 4. Patient-Reported Outcome Assessment, Hand Eczema Impact Scale	40
Figure 5. Graphical Display of the Closed Testing Procedure for Primary and Key Secondary Efficacy Endpoints.....	44
Figure 6. Results for IGA-CHE Treatment Success ¹ by Visit (FAS) ²	53
Figure 7. Results for HESD Itch ≥ 4 -point Improvement ¹ by Week (FAS) ²	53
Figure 8. Results for HESD Pain ≥ 4 -point Improvement ¹ by Week (FAS) ²	54
Figure 9. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Trials DELTA 1 and DELTA 2.....	143
Figure 10. Spaghetti Plot of Systolic Blood Pressure Levels in Subjects With an Adverse Event of Hypertension, Trials DELTA 1, DELTA 2, DELTA 3	145
Figure 11. Spaghetti Plot of Diastolic Blood Pressure Levels in Subjects With an Adverse Event of Hypertension, Trials DELTA 1, DELTA 2, DELTA 3	145
Figure 12. Schematic of Trial DELTA FORCE	155
Figure 13. Postulated Metabolic Pathways of Delgocitinib.....	192
Figure 14. Design for Phase 1 Pharmacokinetic Trial LP0133-2285	231
Figure 15. Mean Concentration Profile for Delgocitinib With Time in Pharmacokinetic Trial LP0133-2285.....	233

Figure 16. Trial Design for Maximal Use Conditions in Subjects With AD, Trial LP0133-1181.....	235
Figure 17. Geometric Mean Concentrations of Delgocitinib by Treatment Day and Age Cohort in Subjects With Atopic Dermatitis	238
Figure 18. Exploratory Analysis: C_{max} and AUC of Plasma Concentration Profile by Age Cohorts	239
Figure 19. Exploratory Analysis: Treatment Area Exposure by Age Cohorts	240
Figure 20. Geometric Mean Profiles of Systemic Concentration of Delgocitinib in Children.....	241
Figure 21. Geometric Mean Profiles of Delgocitinib With Geometric Standard Deviation in Children.....	242
Figure 22. Design for Phase 3 Trial (DELTA 2)	243
Figure 23. Plasma Concentrations of Delgocitinib in Subjects With Chronic Hand Eczema, Trial LP0133-1180	248
Figure 24. Delgocitinib Plasma Concentration at Week 1 by Treatment Group, Safety Analysis Set	250
Figure 25. Design for Phase 1 QT Prolongation and Proarrhythmic, Trial LP0133-1409.....	251
Figure 26. Geometric Mean ($\pm$ Standard Error) Plasma Concentration Profiles of Delgocitinib.....	252
Figure 27. Plasma Concentrations Profile of Delgocitinib After Single Dose Administration Under the Fasted Condition	254
Figure 28. Daily Dose Distribution, Trial DELTA 2.....	257
Figure 29. Daily Dose Distribution, Trial DELTA 1.....	258
Figure 30. 6-Item HESD Conceptual Framework	276
Figure 31. Final HESD Conceptual Model, Developed Based on Literature Review and Qualitative Concept-Elicitation Research	277
Figure 32. Conceptual Model for the HEIS	277
Figure 33. eCDF of Percent Change From Baseline in HECSI at Week 16 by PaGA Change From Baseline to Week 16, Trial DELTA 1 (FAS).....	287
Figure 34. eCDF of Percent Change From Baseline in HECSI at Week 16 by PaGA Change From Baseline to Week 16, Trial DELTA 2 (FAS).....	288
Figure 35. Fold Change of <i>Staphylococcus Aureus</i> Compared to Baseline	305

Table of Equations

Equation 1. Unknown #1 MDE	214
Equation 2. Unknown #2 MDE	214

NDA 219155

ANZUPGO (delgocitinib) cream, 2%

Equation 3. (b) (4) MDE	214
Equation 4. (b) (4) MDE	215
Equation 5. (b) (4) MDE	215

Glossary

AD	atopic dermatitis
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AI	acceptable intake
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCOP	bovine corneal opacity and permeability
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
BSA	body surface area
CBC	complete blood count
CHE	chronic hand eczema
ClinRO	clinician-reported outcome
C _{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CYP	cytochrome P-450
DCIS	ductal carcinoma in situ
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLQI	Dermatology Life Quality Index
EAIR	exposure-adjusted incidence rate
ECAC	Executive Carcinogenicity Assessment Committee
ECG	electrocardiogram
EH	eczema herpeticum
FAS	full analysis set
FDA	Food and Drug Administration
FEED	fertility and early embryonic development
GCP	good clinical practice
GD	gestation day
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
HDL	high-density lipoprotein
HECSI	Hand Eczema Severity Index
HEIS	Hand Eczema Impact Scale
hERG	human ether-à-go-go-related gene

HESD	Hand Eczema Symptom Diary
HZ	herpes zoster
IC ₅₀	half-maximal inhibitory concentration
IC ₂₀	20% inhibitory concentration
ICE	intercurrent event
ICH	International Council for Harmonisation
IFN	interferon
IGA	Investigator's Global Assessment
IGA-CHE	Investigator's Global Assessment for chronic hand eczema
IL	interleukin
IMP	investigational medicinal product
IND	investigational new drug
IR	incidence rate
JAK	Janus kinase
JAKi	Janus kinase inhibitor
K _i	inhibitor constant
LDL	low-density lipoprotein
LLOQ	lower limit of quantification
MACE	major adverse cardiovascular event
MAR	missing at random
MATE	multidrug and toxin extrusion
MDD	maximum daily dose
MDE	maximum daily exposure
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRHD	maximum recommended human dose
MuST	maximal use conditions
NDA	new drug application
NK	natural killer
NOAEL	no-observed-adverse-effect level
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCMQ	Office of New Drugs custom medical query
OCT	organic cation transporter
OPQ	Office of Pharmaceutical Quality
PaGA	Patient Global Assessment
PC	potency category
PD	pharmacodynamic
PDAL	proximal daily activity limitations
PFDD	patient-focused drug development
P-gp	P-glycoprotein
PI	Prescribing Information
PK	pharmacokinetic
PMR	postmarketing requirement
PRO	patient-reported outcome
PT	preferred term

NDA 219155

ANZUPGO (delgocitinib) cream, 2%

qPCR	quantitative polymerase chain reaction
QT	QT interval
QTc	corrected QT interval
QTcF	QT interval using Fridericia's correction
SAE	serious adverse event
SAP	statistical analysis plan
SCT	safety control threshold
SEE	substantial evidence of effectiveness
SMQ	standardized MedDRA query
SOC	system organ class
STAT	signal transducer and activator of transcription
TB	tuberculosis
TCS	topical corticosteroids
TEAE	treatment-emergent adverse event
T _{max}	time to maximum concentration
TNF	tumor necrosis factor
TS	treatment success
TYK2	tyrosine kinase 2
ULN	upper limit of normal
WOCF	worst observation carried forward

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

On July 23, 2024, the Applicant (LEO Pharma A/S) submitted NDA 219155 for ANZUPGO (delgocitinib) cream, 2% for the topical treatment of moderate-to-severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable. The Applicant is seeking approval for ANZUPGO (delgocitinib) cream, 2% under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act.

Delgocitinib belongs to the pharmacological class of Janus kinase inhibitors (JAKi). Delgocitinib is a new molecular entity that inhibits the activity of all four Janus kinases (JAKs): JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). To date, the only FDA approved product for the treatment of CHE are corticosteroids. However, given the potential for serious adverse reactions with long-term use of corticosteroids, there remains an unmet medical need for safe and effective therapy for CHE.

The efficacy and safety of delgocitinib cream, 2% was evaluated in two 16-week vehicle-controlled trials (DELTA 1 and DELTA 2) and a 36-week open-label extension trial (DELTA 3). These trials enrolled subjects 18 years and older with moderate to severe CHE who had had an inadequate response to, or for whom topical corticosteroids (TCS) are not advisable. Both trials assessed the response on the primary endpoint of proportion of subjects with an Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) with at least a 2-point improvement from baseline at Week 16, an endpoint considered to be clinically meaningful. In both trials, delgocitinib was statistically superior to vehicle. The Applicant has demonstrated that delgocitinib is effective for its intended use in the proposed target population and has met the evidentiary standard required by 21 CFR 314.126(a)(b) to support approval of this NDA.

The safety database included a total of 638 subjects who received treatment with delgocitinib twice daily for 16 weeks and 198 subjects who received delgocitinib twice daily for 52 weeks. The most common adverse reactions that were reported in the delgocitinib group were application site pain, paresthesia, pruritus, erythema, bacterial skin infections including finger cellulitis, paronychia, other skin infections, leukopenia, and neutropenia.

Treatment of inflammatory conditions with products from the JAKi class is associated with the risk of serious and life-threatening adverse reactions. Given the systemic exposure to delgocitinib after topical application, observed adverse reactions, the size of safety database, and the duration of treatment with delgocitinib during clinical trials, the potential risks related to JAK inhibition cannot be excluded. However, the review team concluded that these uncertainties do not preclude approval, as long as they are appropriately described in the Warnings and Precautions section of the product labeling. Approval of this product will also include a postmarketing requirement to further characterize the long-term safety with data from a

randomized, active-controlled clinical trial in subjects with moderate to severe CHE. This trial should be of sufficient size and duration to evaluate safety events of interest.

Furthermore, additional postmarketing requirements will focus on the collection of safety data in populations that have not yet been studied, such as lactating women and pediatric patients. There are no data in breastfeeding women receiving delgocitinib on the presence of delgocitinib in human milk. Postmarketing requirements will include a study in lactating women who have received treatment with delgocitinib to assess concentrations of delgocitinib in breastmilk.

Under the Pediatric Research Equity Act (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for ages 0 to less than 12 years of age because necessary studies are impossible or highly impracticable. We are deferring submission of pediatric studies for ages 12 to 17 years of age for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

The overall benefit-risk of delgocitinib cream, 2% is favorable for the proposed indication as described in Section [2.1](#) Benefit-Risk Framework below. The review team recommends approval of this new drug application with the above-described labeling and postmarketing requirements. The signatories agree with the assessment and recommendations from the team.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with two or more adequate and well-controlled clinical investigations.

The Applicant provided substantial evidence of effectiveness with data from two adequate and well-controlled trials, DELTA 1 and DELTA 2, that evaluated delgocitinib cream, 2% twice daily (BID) compared with vehicle for 16 weeks. The trials enrolled subjects ages 18 years and older with a clinical diagnosis of CHE with disease severity graded as moderate to severe according to Investigator's Global Assessment (IGA-CHE) (i.e., an IGA-CHE score of 3 or 4) who have a documented recent history of inadequate response to treatment with TCS (within 1 year prior to the screening visit) or for whom TCS are documented to be otherwise medically inadvisable (e.g., due to important side effects or safety risks).

The IGA-CHE scale was used to define the study population and conduct the primary efficacy evaluation at the prespecified timepoint. The IGA-CHE scale is a single-item, clinician-reported outcome (ClinRO) designed to evaluate overall CHE severity using a 5-level response scale ranging from 0 (clear) to 4 (severe). The IGA-CHE was determined to be fit-for-purpose for assessing CHE severity to support regulatory decision-making. The primary efficacy endpoint is IGA-CHE treatment success (TS), which is defined as a score of 0 (clear) or 1 (almost clear) with at least a 2-point improvement from baseline at Week 16. Delgocitinib cream, 2% was

superior to vehicle (≤ 0.025) in both trials on the primary efficacy endpoint. The results on the primary efficacy endpoint were:

- DELTA 1- placebo: 9.9% versus delgocitinib, 2%: 19.7%
- DELTA 2- placebo: 6.9% versus delgocitinib, 2%: 29.1%

Trials DELTA 1 and DELTA 2 included many secondary endpoints adjusted for multiplicity, including IGA-CHE response at multiple timepoints, Hand Eczema Severity Index (HECSI) scores, and patient-reported outcome responses based on the Hand Eczema Symptom Diary (HESD), Dermatology Life Quality Index (DLQI) score, and Hand Eczema Impact Scale (HEIS) score.

The secondary endpoints included the subject assessment of the key symptoms of CHE, itch and pain, using HESD subscores. The HESD Itch score is a weekly average of daily itch severity on an 11-point scale from 0 to 10 that assesses the maximal intensity of pruritus in the last 24 hours, with 0 being no pruritus and 10 being the worst pruritus. The HESD Pain score is a weekly average of daily pain severity on an 11-point scale from 0 to 10 that assesses the maximal intensity of pain in the last 24 hours, with 0 being no pain and 10 being the worst pain. For both Trials DELTA 1 and DELTA 2, delgocitinib was statistically superior to vehicle on the percent of responders with HESD Itch ≥ 4 -point improvement and HESD Pain ≥ 4 -point improvement. The HESD Itch and HESD Pain scores were determined to be fit-for-purpose for assessing CHE-associated itch and pain symptoms, respectively, to support regulatory decision-making.

The results of the primary and above secondary endpoints will be included in product labeling (Section [14](#)).

(b) (4)

The review team concluded, and the signatories agree, that the Applicant has provided substantial evidence of effectiveness to support the indication of the treatment of moderate-to-severe chronic hand eczema. For additional discussion of the efficacy results, refer to Section [6](#).

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

The Applicant submitted an NDA for delgocitinib cream, 2%, for the proposed indication of moderate-to-severe CHE in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable.

Delgocitinib is a JAK inhibitor, which inhibits the activity of JAK1, JAK2, JAK3, and TYK2. Janus kinases are intracellular enzymes that transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function.

Chronic hand eczema is a persistent inflammatory skin condition affecting the hands and wrists with a high prevalence of 9 to 10% annually and 15% lifetime in the general population. The

condition involves skin barrier dysfunction and multiple inflammatory pathways (Th1, Th2, Th17, and JAK pathways), with etiology predominantly related to allergic contact dermatitis, irritant contact dermatitis, or atopic hand dermatitis. CHE significantly impairs quality of life, causing work-related disabilities, psychological burden including anxiety and depression, and social isolation. Current CHE management begins with nonpharmacologic approaches including allergen/irritant identification and avoidance, emollients, and behavioral modifications. Topical corticosteroids, indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, have been the standard of care for CHE treatment for all age groups ([Eichenfield et al. 2014](#)). Other topical agents approved for atopic dermatitis (topical calcineurin inhibitors, phosphodiesterase-4 inhibitors) are used off-label for CHE. For moderate-to-severe CHE with inadequate topical response, systemic therapies include dupilumab (used off-label) and immunosuppressive agents (cyclosporin, methotrexate, mycophenolate mofetil, azathioprine), but these carry significant safety concerns, including potential for rebound, hypersensitivity reactions, and systemic toxicities, that limit long-term use. Therefore, there is an unmet need for treatment options.

To establish the safety and effectiveness of delgocitinib cream, 2% for the treatment of moderate-to-severe CHE, the Applicant submitted data from two adequate and well-controlled clinical trials of similar design. Trials 1401 (DELTA 1, enrolled 487 adult subjects) and 1402 (DELTA 2, enrolled 472 adult subjects) were randomized, double-blind, placebo-controlled trials that evaluated delgocitinib cream, 2% applied BID compared to vehicle for 16 weeks. Trials DELTA 1 and DELTA 2 were followed by an open-label extension period up to Week 52 in Trial DELTA 3.

Enrolled subjects were 18 years of age and older with moderate-to-severe CHE (defined as an IGA-CHE score of 3 or 4) with a history of inadequate response to, or for whom topical corticosteroids are not advisable. The primary efficacy endpoint was the proportion of subjects who achieved IGA-CHE TS at Week 16, defined as a score of 0 (clear) or 1 (almost clear) with at least a 2-point improvement from baseline. In Trials DELTA 1 and DELTA 2, delgocitinib was statistically superior to vehicle (19.7% versus 9.9% and 29.1% versus 6.9%, respectively).

Other key endpoints that supported the efficacy of the delgocitinib cream, 2% included the proportion of subjects with:

- HESD itch ≥ 4 -point improvement from Baseline to Week 16 (47% active versus 23% vehicle for Trial DELTA 1; 47% active versus 20% vehicle for Trial DELTA 2),
- HESD Pain ≥ 4 -point improvement from Baseline to Week 16 (49% active versus 28% vehicle for Trial DELTA 1; 49% active versus 23% vehicle for Trial DELTA 2).

The primary safety database consisted of pooled data from subjects from the 16-week vehicle-controlled period of Trials DELTA 1 and DELTA 2, and up to 36 additional weeks of open-label treatment in Trial DELTA 3. The primary safety database included 638 subjects exposed to delgocitinib BID. For subjects who rolled over into open-label Trial DELTA 3, a total of 198 subjects were continuously exposed to delgocitinib BID for 52 weeks.

Higher rates of the following treatment-emergent adverse events were reported in subjects who received delgocitinib in the pooled Trials DELTA 1 and DELTA 2 compared to vehicle: COVID-19 (11.1% versus 10.6%), upper respiratory tract infection (1.4% versus 0.3%), hypertension (1.1% versus 0%), back pain (1.1% versus 0.3%), and influenza (1.1% versus

0.6%). Review by the clinical team of narrative summaries, timing of onset, vital signs and ECGs, subject comorbidities, and evaluation of potential alternative causes did not support a causal relationship between delgocitinib and these adverse events. Accordingly, none of these events are considered adverse reactions, and the review team determined no adverse reactions occurred in $\geq 1\%$ subjects on delgocitinib cream and greater than vehicle. Adverse reactions that occurred in $< 1\%$ of subjects who received delgocitinib and proposed for labeling include eczema herpeticum, herpes zoster, basal cell carcinoma, application site pain, paresthesia, pruritus, erythema, bacterial skin infections including finger cellulitis, paronychia, other skin infections, leukopenia, and neutropenia.

Analysis of hematologic parameters showed a numerical imbalance in worsening grade shifts for leukocytes in subjects who received delgocitinib (13.6%, Exposure-Adjusted Incidence Rate (EAIR) 44.2) compared to subjects who received vehicle (6.2%, EAIR 21.3) during the 16-week vehicle-controlled period. Smaller imbalances were observed for neutrophils (4.4%, EAIR 14.2 for delgocitinib versus 3.7%, EAIR 12.8 for vehicle) and lymphocytes (2.5%, EAIR 8.1 for delgocitinib versus 1.9%, EAIR 6.4 for vehicle). The leukocyte imbalance was primarily driven by shifts from Grade 0 at baseline to Grade 1 postbaseline. There were select cases where a causal relationship with delgocitinib to leukopenia and neutropenia treatment-emergent adverse events (TEAEs) could not be ruled out and cases in which subjects never returned to their pretreatment hematologic values. Products from the class of JAKi are associated with cytopenia in patients treated for inflammatory conditions. Therefore, the review team recommends including leukopenia and neutropenia as adverse reactions occurring in $< 1\%$ of subjects in Section 6 of labeling.

Labeling for JAK inhibitor products approved for the treatment of inflammatory conditions carry Boxed Warnings for serious and life-threatening adverse reactions including: serious infections (tuberculosis, bacterial, invasive fungal, viral, and opportunistic infections) leading to hospitalization or death; malignancies including lymphoma and nonmelanoma skin cancers; increased all-cause mortality including sudden cardiovascular death; major cardiovascular events (cardiovascular death, myocardial infarction, stroke); and thrombosis (deep venous thrombosis, pulmonary embolism, arterial thrombosis).

The review team considered the following factors to inform the recommendation for delgocitinib labeling that will adequately address the adverse reactions observed during the clinical trials as well as the uncertainties of the rare and latent safety risks associated with products of the JAK inhibitor class.

1. Measurable systemic exposure: in the maximal use trial in subjects with CHE (body surface area [BSA] range 0.25 to 3%), delgocitinib demonstrated systemic absorption (range 0.01 to 7.30 ng/mL [0.03 to 23.52nM]) with median maximum plasma concentration (C_{max}) of 0.61 ng/mL (1.96nM). One subject reached a concentration of 29.2 ng/mL (94.09nM). This does not represent negligible systemic exposure defined as subnanomolar.
2. Absence of established safety threshold: no scientifically established systemic exposure threshold exists below which JAK inhibitor-related adverse events do not occur. Therefore, the potential for adverse reactions observed with products from JAKi class cannot be excluded.
3. Adverse events observed during clinical trials: neutropenia and leukopenia were observed during the controlled period of the clinical trials. Also, during the clinical trials, cases of herpes zoster and a case of eczema herpeticum were reported. Given the mechanism of action

of JAKi, a role for delgocitinib cannot be excluded. In addition, postmarketing data for the product approved in Japan (not approved in the United States) with the same active moiety (delgocitinib ointment, 0.5%) revealed 86 cases of eczema herpeticum and 21 cases of herpes zoster, including in pediatric patients. Although the causality cannot be established from postmarketing reports, a role for delgocitinib cannot be excluded.

4. Extent of safety database: treatment of inflammatory conditions with products from JAKi class is associated with serious and life-threatening adverse reactions. Given the size of safety database and duration of treatment with delgocitinib during clinical trials, potential risks related to JAK inhibition cannot be excluded.
5. Delgocitinib will be used on a limited BSA

The proposed indication is for the treatment of patients with moderate-to-severe CHE in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable. Labeling for delgocitinib cream should include a Warning and Precaution section describing potential risks related to JAK inhibition. A Boxed Warning is not warranted at this time because delgocitinib labeling will specify application to the hands and wrists only (<5% BSA) and include a restriction on the amount of product used in 2 weeks and 1 month which may mitigate the risk of off-label use on a larger body surface area.

Given the residual uncertainties about JAK-inhibitor-related risks for adverse reaction (AR), the FDA will require a postmarketing study (PMR) to evaluate the long-term safety to further characterize the risk profile and ensure appropriate risk mitigation for this drug product. A PMR will be issued to the Applicant to conduct a randomized, active-controlled trial of sufficient size and duration to characterize safety events of interest including cytopenia and viral reactivation.

Furthermore, additional postmarketing requirements will focus on the collection of safety data in populations that have not yet been studied such as lactating women and pediatric patients.

In conclusion, based on the available safety and efficacy data, the benefit-risk of delgocitinib cream, 2% used twice daily is favorable in the population of adult patients with moderate to severe chronic hand eczema who have had an inadequate response to, or for whom topical corticosteroids are not advisable. The review team recommends approval of NDA 219155 with the agreed upon labeling and PMRs, as detailed above. The signatories agree with these recommendations. This approval will address an unmet need for patients who suffer from moderate to severe chronic hand eczema who have had an inadequate response to or for whom topical corticosteroids are not advisable.

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	- Chronic hand eczema (CHE) is a heterogenous, fluctuating, pruritic and painful inflammatory skin disease of the hands and wrists that persists for more than 3 months or recurs at least twice per year (Cheng et al. 2022; Ho and Molin 2023; Borg et al. 2024; Sheehan 2025). The clinical manifestations may include dry, scaly, erythematous and pruritic hand macules or papules that may be accompanied by vesicles, pustules, edema, linear fissures or erosions, and hyperkeratosis (Cheng et al. 2022; Ho and Molin 2023; Tancredi et al. 2023; Zalewski and Szepietowski 2023). Lesions are usually bilateral and may involve the palmar or dorsal surface or both. In long-standing disease, nail changes may be seen (Zalewski and Szepietowski 2023; Sheehan 2025). CHE has an estimated 1-year prevalence of 9 to 10% and a lifetime prevalence of 15% in the general population, with a similar prevalence among adolescents and adults (Cheng et al. 2022; Ho and Molin 2023; Tancredi et al. 2023; Borg et al. 2024; Sheehan 2025). Risk factors for CHE include concurrent atopic dermatitis (especially in children), frequent hand washing or exposure to wet conditions, and exposures to irritants or allergens in occupational (especially wet work) or domestic settings (including various substances found in cosmetics, jewelry, clothing, and medications) (Tancredi et al. 2023; Zalewski and Szepietowski 2023; Borg et al. 2024). High-risk occupations include health care workers, food handlers, hairdressers, and cleaners (Cheng et al. 2022; Sheehan 2025). - An etiology-based approach categorizes CHE as predominately related to allergic contact dermatitis (ACD), irritant contact hand dermatitis (ICD), or atopic hand dermatitis (Silverberg et al. 2021; Cheng et al. 2022; Ho and Molin 2023; Tancredi et al. 2023; Zalewski and Szepietowski 2023) though these categories may overlap. (Zalewski and Szepietowski 2023) ACD is a hypersensitivity reaction to a chemical substance such as nickel, chromate, rubber, or preservatives (Ho and Molin 2023). ICD arises from prolonged exposure to irritants, including detergents, solvents, sweat, and water, that compromise the skin barrier (Ho and Molin 2023), while atopic hand eczema is the most common	CHE represents a condition with significant unmet medical need, particularly for patients with moderate to severe disease who have inadequate response to or cannot use topical corticosteroids. The chronic nature of the condition and its substantial impact on patients' quality of life, work capacity, and psychological well-being support the need for effective treatment options beyond current therapies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	form of CHE (Ho and Molin 2023). The pathogenesis of CHE is multifactorial with a complex interplay of genetics, environment, and exposures (Cheng et al. 2022; Ho and Molin 2023; Zalewski and Szepietowski 2023). Skin barrier dysfunction results in altered moisture retention, with reduction in ceramides in the stratum corneum, downregulation of structural barrier proteins such as filaggrin (i.e., FLG, FLG-2) and hornerin (HRNR), and decreased expression of enzymes involved in lipid metabolism (Ho and Molin 2023; Zalewski and Szepietowski 2023) leading to increased susceptibility to irritant and contact dermatitis. Hyperkeratosis occurs when contact allergens and/or irritants trigger the release of keratinocyte-derived cytokines such as tumor necrosis factor (TNF)-alpha that promote inflammation and epidermal hyperproliferation, resulting in thickened skin and scale formation (Ho and Molin 2023). CHE involves several cytokine pathways, including Th1, Th2 and Th17, that vary according to the main triggers (Ho and Molin 2023). Exposure to irritants (cytotoxic or chemical) that cause direct skin damage results in innate immune system responses with a Th1/Th17 immune profile in ICD (Cheng et al. 2022; Ho and Molin 2023; Tancredi et al. 2023). In contrast, ACD is characterized by a delayed type IV adaptive immune response induced by contact with allergens such as nickel or fragrance, leading to the selection of both CD4+ and CD8+ T lymphocytes, with specific Th1 differentiation (Tancredi et al. 2023). Meanwhile, atopic hand eczema has a predominant Th2-type response with increased expression of type 2 immune cytokines (e.g., IL-4 and IL-13) (Tancredi et al. 2023; Zalewski and Szepietowski 2023). In patients with an atopic predisposition, there is also activation of Janus kinase (JAK) pathways (Ho and Molin 2023). • CHE significantly impacts quality of life, with negative effects that range from work-related disabilities, productivity loss, impaired work functioning, missed school, and impaired sleep. CHE can contribute to a considerable psychological burden with poor self-esteem, anxiety and/or depression, and social isolation (Cheng et al. 2022; Ho and Molin 2023; Tancredi et al. 2023; Borg et al. 2024).	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	- The initial approach to CHE management is nonpharmacologic, including confirmation of the diagnosis by exclusion of dermatologic mimickers such as tinea and scabies, identification of relevant allergens and irritants, and the regular use of emollients for hand moisturization and skin hydration (Ho and Molin 2023). In addition, behavioral modification is important when irritant or allergic triggers are present, including avoidance of allergens, irritants, and exacerbating activities and exposures (such as excessive hand washing) and use of personal protective equipment, such as vinyl or other nonlatex gloves and barrier creams (Sheehan 2025). - Topical corticosteroids (TCSs), indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, have been the mainstay of initial CHE treatment for all age groups (Eichenfield et al. 2014) and are usually part of the initial treatment plan. However, the long-term use of TCS is associated with adverse events such as epidermal atrophy with further epidermal barrier dysfunction. Healthcare providers frequently use other topical products approved for the treatment of atopic dermatitis (AD) as steroid-sparing agents in CHE treatment, including topical calcineurin inhibitors (TCIs) such as tacrolimus or pimecrolimus, with anti-inflammatory effects, and phosphodiesterase-4 (PDE4) inhibitors such as crisaborole and roflumilast, which regulate the production of inflammatory cytokines through the degradation of cyclic adenosine monophosphate (Cheng et al. 2022; Ho and Molin 2023). - Management of patients with moderate to severe CHE with inadequate response to topical therapies includes the use of systemic products indicated for atopic dermatitis (though none are specifically approved for this indication in the United States). Alitretinoin is approved only in Europe and a few other countries worldwide, indicated for treatment severe CHE unresponsive to treatment with potent TCS; it is not approved in the United States for this indication. Although the use of systemic corticosteroids may provide rapid improvement, discontinuation of the drug may result in recurrence of the disease with greater severity (rebound). Due to the potential for adverse effects and	While topical corticosteroids are FDA-approved for the relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses and have been the standard of care for treatment of CHE, long-term TCS use is associated with adverse events such as HPA axis suppression, epidermal atrophy and further barrier dysfunction. Other topical agents approved for atopic dermatitis (topical calcineurin inhibitors, PDE4 inhibitors) are used off-label for CHE. For moderate to severe CHE with inadequate topical response, systemic therapies include dupilumab (used off-label) and immunosuppressive agents (cyclosporin, methotrexate, mycophenolate mofetil, azathioprine), but these carry significant safety concerns, including potential for rebound, hypersensitivity reactions, and systemic toxicities, that limit long-term use. Systemic corticosteroids may provide rapid improvement, but discontinuation may result in disease recurrence with greater severity. While topical corticosteroids are approved and effective for many patients, there remains an unmet need for patients with moderate to severe CHE who have inadequate response to TCS or for whom TCS are not advisable. Available systemic alternatives are used off-label and carry safety risks that may limit their long-term use, creating a treatment gap for this patient population. Approval of delgocitinib would provide another option for the topical treatment of moderate to severe CHE in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	rebound, the American Academy of Dermatology recommends that systemic corticosteroids generally be avoided in the treatment of AD because potential risks generally outweigh the benefits (Sidbury et al. 2014). Potential adverse effects include reversible hypothalamic-pituitary-adrenal axis suppression with the potential for glucocorticoid insufficiency, hyperglycemia, and other endocrine effects. A particular concern in children and adolescents is the risk of decreased linear growth during treatment (Sidbury et al. 2014). Other systemic agents such as dupilumab, an IL-4 receptor and IL-13 receptor-alpha receptor antagonist, is used off-label. Current labeling includes warnings for potential adverse reactions including hypersensitivity, conjunctivitis, and keratitis and an association with eosinophilic disease in subjects treated for asthma. Other immunosuppressive agents such as cyclosporin, methotrexate, mycophenolate mofetil, and azathioprine can provide temporary remission in some patients, but their adverse reaction profiles may limit their long-term use (Cheng et al. 2022; Ho and Molin 2023; Tancredi et al. 2023). • Second-line, nonpharmacologic therapies include ultraviolet light (UV) phototherapy, specifically local psoralen plus UVA therapy (PUVA), which has been reported to improve investigator-rated control of hand eczema compared to narrow-band UVB therapy. However, the need for frequent clinic visits that are required to achieve treatment success makes this treatment a challenge for patients (Ho and Molin 2023).	
Benefit	• Efficacy was evaluated using the Investigator's Global Assessment for chronic hand eczema (IGA-CHE) score, which is the investigator's overall assessment of chronic hand eczema severity at a given time point on a scale ranging from 0 (clear) to 4 (severe). Delgocitinib 20 mg/g was superior to in both trials for the primary endpoint of IGA-CHE Treatment Success (defined as a score of 0 (clear) or 1 (almost clear) with at least a 2-point improvement from baseline). – DELTA 1 IGA response: 20% active versus 10% vehicle (difference from vehicle [95% CI] 10% [4%, 16%]) – DELTA 2 IGA response: 29% active versus 7% vehicle (difference from vehicle [95% CI] 22% [16%, 29%])	The submitted data has met the evidentiary standard for providing substantial evidence of effectiveness in subjects with moderate to severe CHE in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Other key endpoints that supported the efficacy of the 20 mg/g BID dosage of delgocitinib included the proportion of subjects with HESD itch ≥ 4-point improvement from baseline to Week 16 (47% active and 23% vehicle for Trial DELTA 1; 47% active and 20% vehicle for Trial DELTA 2) and HESD pain ≥ 4-point improvement from baseline to Week 16 (49% active and 28% vehicle for Trial DELTA 1; 49% active and 23% vehicle for Trial DELTA 2).	
Risk and risk management	- The safety profile of delgocitinib was characterized in 638 subjects exposed for 16 weeks in vehicle-controlled trials and 198 subjects with continuous exposure for 52 weeks. - Delgocitinib achieves measurable systemic exposure with plasma concentrations that, though low, are not considered negligible. - No adverse reactions occurred in $\geq 1\%$ subjects on delgocitinib cream compared to vehicle. Adverse reactions $< 1\%$ that will be communicated in labeling include: eczema herpeticum, herpes zoster, basal cell carcinoma, application site pain, paresthesia, pruritus, erythema, bacterial skin infections including finger cellulitis, paronychia, other skin infections, leukopenia, and neutropenia. - In the vehicle-controlled 16-week period, 638 subjects received delgocitinib [PYO =197] and 321 subjects received vehicle [PYO =94], reflecting both a 2:1 randomization scheme and greater exposure time in the delgocitinib group. During this period a numerical imbalance was observed in subjects experiencing any worsening grade shifts in leukocytes (13.6% delgocitinib versus 6.2% vehicle). While it is acknowledged that the unequal exposure would be expected to result in more events in the delgocitinib group, an imbalance in hematologic parameters persists even when accounting for exposure differences through rate calculations: EAIR 44.2 versus 21.3. - Cases of herpes zoster in subjects < 50 years of age and a case of eczema herpeticum were reported in the open-label period. Postmarketing data from the same moiety (CORECTIM) revealed additional possible immune-related events including 86 cases of eczema herpeticum and 21 cases of herpes zoster. Although the observed events may be consistent with	While the clinical safety database supports approval, the totality of evidence demonstrates that delgocitinib achieves measurable systemic exposure (with plasma concentrations, though low, not considered negligible) and may increase the risk of systemic adverse reactions. Given the known serious risks associated with JAK inhibitors for inflammatory conditions and the evidence of potential systemic immunosuppressive effects in the development program, prescribers and patients should be informed of potential risks. The identified and potential risks can be adequately managed through comprehensive labeling that includes potential risks of JAK inhibition. Given the residual uncertainties about potential risks associated with JAK inhibition due to the limited safety database, a long-term safety postmarketing requirement (PMR) is necessary to further characterize the risk profile and ensure appropriate risk mitigation for this drug product. A PMR will be issued for an active-controlled trial. The trial should be of sufficient size and duration to characterize safety events of interest (e.g., cytopenias and viral reactivation).

NDA 219155

ANZUPGO (delgocitinib) cream, 2%

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	background incidence rates for herpes zoster and eczema herpeticum, the mechanistic plausibility for a causal relationship cannot be dismissed. The review identified no additional serious safety concerns that warrant consideration of a risk evaluation and mitigation strategy (REMS). • The safety database size and duration may not fully capture rare or delayed adverse events associated with JAK inhibition (e.g., cytopenias, viral reactivation).	

Abbreviations: BID, twice daily; CHE, chronic hand eczema; FLG, filaggrin; HRNR, hornerin; ICD, irritant contact hand dermatitis; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; IL, interleukin; JAK, Janus kinase; PMR, postmarketing requirement; PUVA, psoralen plus ultraviolet A; PYO, patient years of observation; REMS, risk evaluation and mitigation strategy; TCIs, topical calcineurin inhibitors; TCSs, topical corticosteroids; Th, T-helper cell; TNF, Tumor necrosis factor; UV, ultraviolet

2.2. Conclusions Regarding Benefit-Risk

The benefit-risk assessment for delgocitinib cream supports approval for the treatment of moderate to severe chronic hand eczema in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable.

Benefits

Delgocitinib provides substantial evidence of effectiveness based on two adequate and well-controlled trials enrolling 960 subjects. The primary efficacy endpoint demonstrated statistically significant improvements with treatment differences of 10% (DELTA 1) and 22% (DELTA 2) compared to vehicle. Secondary endpoints showed clinically meaningful improvements in itch (47% versus 20 to 23% vehicle) and pain (49% versus 23 to 28% vehicle), with 4-point or greater improvements on 11-point scales. These results represent meaningful therapeutic benefit for a condition that significantly impacts quality of life, with patients experiencing work-related disabilities and psychological burden.

Risks

The safety of delgocitinib was evaluated in two randomized, double-blind, multicenter, vehicle-controlled clinical trials in which 959 adults with moderate to severe CHE received delgocitinib or vehicle cream topically twice daily for 16 weeks. A total of 638 subjects were treated with delgocitinib. In both trials, adverse reactions that were reported in $\leq 1\%$ of subjects in the delgocitinib group were application site pain, paresthesia, pruritus, erythema, bacterial skin infections including finger cellulitis, paronychia, other skin infections, leukopenia, and neutropenia. In an open label extension Trial 3, 801 subjects were treated for up to an additional 36 weeks after completing Trials 1 or 2. A total of 198 subjects received continuous treatment with delgocitinib for 52 weeks. Eczema herpeticum was observed in one subject and herpes zoster was observed in two subjects treated with delgocitinib.

There was measurable systemic exposure to delgocitinib in maximal use trial (range 0.01 - 7.30 ng/mL [0.03 – 23.52 nM] with median C_{max} of 0.61 ng/mL (1.96nM). One subject reached a concentration of 29.2 ng/mL (94.09nM). This does not represent negligible systemic exposure defined as subnanomolar. Data from clinical trials during the first 16 weeks (controlled period) demonstrated imbalances in hematologic parameters (13.6% versus 6.2% vehicle experiencing worsening leukocyte shifts, EAIR 44.2 versus 21.3). Cytopenias are a well-recognized adverse reaction associated with treatment with products of JAKi class.

In addition, adverse events, including herpes zoster in healthy subjects under 50 years of age and eczema herpeticum were observed. JAK inhibitors can impair natural killer (NK) cell function because JAK-signal transducer and activator of transcription (STAT) signaling is crucial for NK cell development, activation, and function. JAKi can increase the risk of viral reactivation, particularly herpes zoster due to immunosuppressive effects. As NK cells in patients with eczema herpeticum (EH) exhibit reduced activity and altered functionality. Also, because delgocitinib is systemically absorbed, the role of delgocitinib in the development of EH and herpes zoster (HZ) cannot be excluded.

The Applicant provided postmarketing data from the same active moiety (delgocitinib ointment, 0.5%: CORECTIM). There were 86 cases of EH and 21 cases of HZ, including pediatric

NDA 219155

ANZUPGO (delgocitinib) cream, 2%

patients. Although, it is not possible to establish causality due to limited information for these postmarketing reports, a role of delgocitinib cannot be excluded.

The safety database for delgocitinib of fewer than 700 subjects for 16 weeks and fewer than 200 subjects for 52 weeks is not sufficiently large to exclude adverse reactions seen with JAKi products.

Risk Management

Physician labeling and a Medication Guide are sufficient for risk management. Under 21 CFR 208.1, the Medication Guide is required to help prevent serious adverse events. Risk evaluation and mitigation strategies is not required.

Overall Assessment

The Applicant has demonstrated that delgocitinib cream, 2% is safe and effective for its intended use in the proposed target population. Given the residual uncertainties about JAK inhibitor-related risks for AR, post-marketing requirements will include an evaluation of the long-term safety, and collection of safety data in populations that have not been studied, such as lactating women and pediatric patients.

II. Interdisciplinary Assessment

3. Introduction

Key efficacy and safety review issues are identified below.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Impact of the Lack of Run-In Period on the Assessment of Efficacy

At the End-of-Phase 2 meeting, the Agency advised that an inadequate response to TCS therapy may not be reliably determined based on medical history alone and recommended incorporating a run-in period with standard care measures (e.g., moisturizers, irritant avoidance) and TCS therapy to prospectively confirm inadequate response. The Applicant did not incorporate a run-in period in their phase 3 trials and expressed concern that such a run-in period would unnecessarily re-expose subjects to therapies previously deemed ineffective and delay access to an investigational product in a setting with limited treatment options.

In response to Agency concerns regarding appropriate definition of the study population, the Applicant analyzed data under TCS run-in-like conditions within the phase 3 trials (comparing subjects who discontinued daily TCS no earlier than 2, 4, or 8 weeks prior to screening, and subjects who used daily TCS on the hands after screening, up to 2 weeks before baseline). See Section [6.3.1](#).

3.1.1.2. Impact of Content Validity, Other Measurement Properties, and Data Interpretability for COA-Based Efficacy Endpoints

There was uncertainty regarding whether the HECSI was fit-for-purpose and interpretable (b) (4). There was limited validity evidence and the scoring algorithm was not clearly interpretable. Refer to Section [16.1.3.3](#) for details.

There was uncertainty regarding whether the HEIS proximal daily activity limitations (PDAL) was fit-for-purpose and interpretable (b) (4). Validity evidence provided for the items and score for the HEIS PDAL did not demonstrate that the content was relevant and interpretable given CHE type and physician-rated CHE severity. Refer to Section [16.1.2](#) for details.

3.1.2. Key Safety Review Issues

3.1.2.1. Impact of the Formulation Change on the Assessment of Pharmacokinetics and Safety

The Applicant used the final to-be-marketed formulation, containing (b) (4) mg/g (b) (4), in the majority of clinical trials, including maximal use studies. However, an earlier formulation containing (b) (4) mg/g (b) (4) was also used during development. The change was adequately supported by the submitted data, and it was determined to have no impact on product performance or clinical safety. Refer to Section [7.7.1](#) for details.

3.1.2.2. Impact of the Lack of Run-In Period on the Assessment of Safety

The Applicant did not include a run-in period in the phase 3 trials as recommended by the Agency to identify the study population with an inadequate response to topical corticosteroids (TCS). However, per inclusion criteria, enrollment included subjects who had a documented recent history of inadequate response to treatment with TCS (at any time within 1 year before the screening visit) or for whom TCS are documented to be otherwise medically inadvisable (e.g. due to important side effects or safety risks). In addition, inclusion criteria specified enrollment of subjects who were adherent to standard non-medicated skin care including avoidance of known and relevant irritants and allergens. Also, enrollment included subjects who discontinued daily TCS no earlier than 2, 4, or 8 weeks prior to screening, compared with subjects who used daily TCS on the hands after screening, up to 2 weeks before baseline (“run-in-like” exposure). There was no difference in adverse events between subjects with or without TCS “run-in-like” periods (Refer to Section [7.7.2](#) for details).

3.1.2.3. Evaluation of JAK Inhibitor Class Safety Labeling for Inflammatory Conditions in Context of the Delgocitinib Development Program

JAK inhibitors for the treatment of inflammatory conditions include a Box Warning for serious infections, increased all-cause mortality, malignancy and lymphoproliferative disorders, MACE, and thrombosis. The size of the safety database for delgocitinib was not sufficiently large and long to exclude all the above adverse events. However, during the development program adverse events of neutropenia and lymphopenia as well as serious infections (EH and HZ) were observed. The labeling will include potential risks associated with JAKi class in Warnings and Precautions section. In addition, the Applicant will be required to conduct a well-controlled clinical trial to further evaluate adverse events of special interest (as PMR.) A discussion of labeling is included in Sections [7.2](#) and [7.7.3](#) of this review.

3.2. Approach to the Clinical Review

The Applicant submitted data from 15 clinical trials to support approval of delgocitinib cream for the topical treatment of moderate to severe CHE in adults who have had an inadequate response

to, or for whom topical corticosteroids are not advisable. These trials included seven completed clinical trials in subjects with CHE, including:

- Two 16-week vehicle-controlled phase 3 trials (LP0133-1401/DELTA 1 [n =487] and LP0133-1402/DELTA 2 [n =473]) in adult subjects with moderate to severe CHE
- A 36-week open-label single-arm extension phase 3 trial (LP0133-1403/DELTA 3 [n =801]) in subjects with moderate to severe CHE continuing from Trials DELTA 1 and DELTA 2
- A 24-week phase 3, randomized, assessor-blinded active comparator, parallel-group, 2-arm trial (LP0133-1528 DELTA FORCE) to compare the efficacy and safety of delgocitinib cream, 20 mg/g twice daily with alitretinoin capsules once daily in 513 adult subjects with severe CHE
- A phase 1 pharmacokinetic (PK) trial (LP0133-2285) in 16 adult subjects with moderate to severe CHE
- A phase 2 dose-ranging trial (LP0133-1273) in 258 subjects with mild to severe CHE
- A phase 2 proof of concept trial (LP0133-1180) in 91 subjects with at least mild CHE

In addition, the Applicant submitted data from trials that evaluated the effects of delgocitinib cream on dermal safety (LP0133-1408 and -1411), the potential for QT interval (QT) prolongation (LP0133-1409), and in different populations/indications. The Applicant provided supportive data from two trials in subjects with atopic dermatitis (AD) (LP0133-1181 and -1275). Trial LP0133-1181 was an 8-week, phase 1, open-label, multicenter, single-arm trial to evaluate the safety and pharmacokinetics of twice daily topical delgocitinib under maximal use conditions (MuST) in 46 adults, adolescents, and children with moderate to severe AD. Trial LP0133-1275 was an 8-week, phase 2b, double-blind, randomized, 5-arm, vehicle-controlled dose-ranging trial to evaluate delgocitinib cream 1, 3, 8, and 20 mg/g compared to vehicle in 250 adult subjects with mild to severe AD.

The review team focused the evaluation of the safety and efficacy of delgocitinib cream on data from the two vehicle-controlled phase 3 trials (DELTA 1 and DELTA 2) and the open-label extension trial (DELTA 3) that evaluated subjects with moderate to severe CHE. Data from the phase 2 dose-ranging trial (LP0133-1273) was not pooled with the data from the phase 3 trials DELTA 1 and DELTA 2 because of differences in study design and study population. The study population was defined using a different scale and had different disease severity (mild to severe CHE) than phase 3 trials. In addition, Trial LP0133-1273 (and trials LP0133-1181, 1273, 1275, and 1408) evaluated a formulation of delgocitinib cream that included a different concentration of (b) (4).

Assessment of the data for subjects with moderate to severe CHE enrolled in Trial LP0133-1273 and DELTA FORCE and subjects with AD identified no unique safety signals (refer to Section [7.6.2](#) of this review).

3.3. Approach To Establishing Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication:

For the topical treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable.

SEE was established with:

- a. Adequate and well-controlled clinical investigation(s):
 - i. ☒ Two or more adequate and well-controlled clinical investigations, OR
 - ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

- b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence ([May 1998](#); [December 2019](#); [September 2023](#))

OR

- c. ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)([May 1998](#))

2. Complete response, if applicable

- a. ☐ SEE was established
- b. ☐ SEE was not established (if checked, omit item 2)

Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations Delgocitinib

Trial Identifier	Trial Population	Trial Design	Regimen, Duration	Primary and Key Secondary Endpoints	No. of Patients Planned; Actual Randomized	No. of Centers and Countries
LP0133-1401 (DELTA 1)	Adults with moderate to severe CHE.	Control Type: Placebo concurrent	Drug: Delgocitinib	Primary: IGA-CHE TS at Week 16	Planned: 470	Centers: 51
		Randomization: Standard	Dose: 20 mg/g	Secondary:	Actual: 487	Countries: 6
		Randomization Ratio: 2:1	Number treated:	• HECSI-75 at Week 16 • HECSI-75 at Week 8 • HECSI-90 at Week 16. • IGA-CHE TS at Week 8 • IGA-CHE TS at Week 4		
		Blinding: Double-blind	• Delgocitinib: 325			
			• Vehicle-control: 162			
		Biomarkers: No biomarkers	Duration: 16 weeks			
		Innovative design features: None				
LP0133-1402 (DELTA 2)	Adults with moderate to severe CHE.	Control Type: Placebo concurrent	Drug: Delgocitinib	Primary: IGA-CHE TS at Week 16.	Planned: 450	Centers: 49
		Randomization: Standard	Dose: 20 mg/g	Secondary:	Actual: 473	Countries: 7
		Randomization Ratio: 2:1	Number treated:	• HECSI-75 at Week 16 • HECSI-75 at Week 8 • HECSI-90 at Week 16 • IGA-CHE TS at Week 8 • IGA-CHE TS at Week 4		
		Blinding: Double-blind	• Delgocitinib: 313			
			• Vehicle-control: 159			
		Biomarkers: No biomarkers	Duration: 16 weeks			
		Innovative design features: None				

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Trial Identifier	Trial Population	Trial Design	Regimen, Duration	Primary and Key Secondary Endpoints	No. of Patients Planned; Actual Randomized	No. of Centers and Countries
LP0133-1403 (DELTA 3)	Subjects continuing from Trials DELTA 1 and DELTA 2.	Open-label extension Biomarkers: No biomarkers Innovative design features: None	Drug: Delgocitinib Dose: 20 mg/g Number treated: • Delgocitinib: 801 Duration: 36 weeks	Primary: Number of TEAEs from baseline up to Week 38. Secondary: • IGA-CHE at each week visit from baseline up to Week 36. • IGA-CHE score of 0 (clear) or 1 (almost clear) at each week visit from baseline up to Week 36. • HECSI score at each scheduled visit from baseline up to Week 36. • HECSI-75 at each scheduled visit from baseline up to Week 36. • HECSI-90 at each scheduled visit from baseline up to Week 36.	Planned: 600 Actual: 801	Centers: 99 Countries: 10

Source: Clinical Study Report and adsl.xpt

Investigator's Global Assessment for CHE is based on a 5-point scale ranging from 0 (clear) to 4 (severe).

IGA-CHE TS: IGA-CHE treatment success, for e.g., an IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥2-step improvement from baseline.

Abbreviations: CHE, chronic hand eczema; HECSI, Hand Eczema Severity Index; HECSI-75, at least 75% improvement in HECSI score from baseline; HECSI-90, at least 90% improvement in HECSI score from baseline; IGA-CHE, Investigator's Global Assessment for CHE; IGA-CHE TS, IGA-CHE treatment success; No., number; TEAE, treatment-emergent adverse event

4. Patient Experience Data

There were no patient-focused drug development (PFDD) meetings exploring the impact of CHE on patients. However, CHE is frequently associated with an atopic diathesis. Therefore, there are relevant comments from the PFDD meeting exploring the social and economic burdens of AD that was held on September 23, 2019. In collaboration with the U.S. FDA, five groups that are serving the AD community (Allergy & Asthma Network, Asthma and Allergy Foundation of America, Global Parents for Eczema Research, International Topical Steroid Awareness Network, and National Eczema Association) organized the meeting to address the burdens associated with AD and the challenges of managing the disease. Because AD is primarily a pediatric disorder, this meeting did not focus on the effects of this skin disease on the ability to work and other challenges experienced by adults with hand eczema related to their activities of daily living.

Patients shared concerns regarding the appearance of their skin, symptoms of pruritus and pain, recurrent infections, loss of sleep, social isolation, depression/anxiety and financial burdens. Per the respondents to the *More Than Skin Deep* survey conducted at the PFDD meeting, 79% of patients identified itch as the most problematic symptom of AD. Patients described itch as contributing to skin damage and physical harm, shame, difficulty with mood and attention, negative effects on social and intimate relationships, poor school and work performance, negative self-image, depression, and anxiety. An adult attendee stated, “I still wake up unconsciously clawing at my skin. When I itch during the day, I can find a distraction or I can try and control it, but there’s no control over scratching in my sleep.”

In addition, patients reported that the appearance of the skin is the second most burdensome aspect of AD that led to numerous negative impacts on daily life, including low mood, poor self-image, lack of confidence, discomfort, and pain. One patient stated, “At age 26, I had the worst flare of my life. I became unrecognizable, being covered from my scalp to my legs, with all my hair falling out as well. During this time, I would wake up in the morning with instant anxiety.”

Patients with AD who attended the meeting described serious impacts on mental health, including anxiety and depression, and social interactions. A recurring theme was the oppressive, omnipresent influence of AD on all aspects of their lives. One patient shared, “I got depressed. I was suicidal. I couldn’t look at myself in the mirror because I didn’t control who I was. [Eczema] was controlling me.” The meeting also highlighted the challenges with interacting and maintaining relationships with friends, family, and strangers. One AD patient at the meeting shared, “My social life is nonexistent. Something as simple as going to my best friend’s house had to be cut because she had a cat. Every relationship has been completely transformed. Even going to the beach or the pool creates fear or simply avoidance because of the unknown effects on this disease.”

The meeting also described the economic burden of AD, including medical costs and costs from lost work or school. One meeting participant shared, “My skin was so bad that I ended up in the hospital for weeks at a time with severe staph infections. That obviously caused me to miss endless days of school, and then even work further on in life.”

The meeting showed that the burden of treating AD was almost as great as the burden associated with the disease itself. Overall, a vast majority, 89% of meeting participants and survey respondents, reported limited treatment effectiveness and/or harms from current therapies.

This PFDD meeting underscored the large number of unmet medical needs among people affected by AD. When patients were asked about the ideal treatment benefit, “immediate and sustained relief from itch” received the greatest number of responses by polling and was selected by 51% of survey respondents. The second most widely endorsed treatment benefit was “increased ability to go about daily life,” with 15% of survey respondents selecting it. One AD patient shared, “I want to have a medication that lets us eczema warriors live our lives fully and not just exist through the next flare.” Many people expressed a desire for more targeted approaches to therapy based on biomarkers, clinical features, and/or treatment goals and a need for more evidence to inform treatment decisions, especially for children. One AD patient stated, “We need different types of treatments because not everyone is the same.”

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 outcomes - Hand Eczema Symptom Diary (HESD; key secondary endpoint) - Hand Eczema Impact Scale (HEIS; secondary endpoint)	The HESD is discussed in Section 6.2.4.3 . The HEIS is discussed in Section 6.2.4.4 .
☐	Observer-reported outcome	
☒	Clinician-reported outcome - Investigator's Global Assessment for chronic hand eczema (IGA-CHE; primary endpoint) - Hand Eczema Severity Index (HECSI; key secondary endpoint)	The IGA-CHE is discussed in Section 6.2.4.1 . The HECSI is discussed in Section 6.2.4.2 .
☐	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: Literature review	
☐	If no patient experience data were submitted by Applicant, indicate here.	
☒	Perspectives shared at patient stakeholder meeting	
☒	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

Abbreviations: HECSI, Hand Eczema Severity Index; HEIS, Hand Eczema Impact Scale; HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for chronic hand eczema

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

The nonclinical data support the potential effectiveness of delgocitinib based on the following findings:

- Delgocitinib exhibited inhibitory activity against human JAK1, JAK2, JAK3, and TYK2 in a kinase assay.
- Delgocitinib inhibited the phosphorylation of STATs stimulated by cytokines interleukin (IL)-2, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-23 in human peripheral-blood-derived mononuclear cells.
- Delgocitinib inhibited human T cell and B cell proliferation.
- Delgocitinib inhibited IL-13 secretion by mast cells stimulated with IL-4 in an IgE-crosslinking setting in human cord-blood-derived mononuclear cells.
- Delgocitinib inhibited tumor necrosis factor (TNF)- α production in monocytes isolated from human peripheral blood in response to GM-CSF stimulation.
- Delgocitinib reversed the IL-4 and IL-13-mediated reduced expression of skin-barrier-related genes in primary human keratinocytes.
- Oral delgocitinib suppressed skin inflammation in mice with 2,4-dinitrofluorobenzene-induced dermatitis.
- Topical delgocitinib suppressed skin inflammation in rats with 2,4-dinitrochlorobenzene-induced dermatitis.
- Topical delgocitinib improved skin barrier function in a dry skin mouse model.
- Oral and topical delgocitinib suppressed IL-31-induced scratching behavior in mice.

5.2. Clinical Pharmacology/Pharmacokinetics

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information								
	Pharmacologic Activity								
Established pharmacologic class (EPC)	Janus kinase (JAK) inhibitor								
Mechanism of action	Delgocitinib, a JAK inhibitor, inhibits the activity of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). JAK signaling involves recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, and activation and subsequent localization of STATs to the nucleus, leading to the expression of cytokine-responsive genes to induce specific biological responses in target cells. The exact mechanism of action of delgocitinib in the treatment of moderate to severe CHE is currently not known.								
Active moieties	Delgocitinib								
QT prolongation	No QTc interval prolongation based on concentration-QTc analysis.								
	General Information								
Bioanalysis	An HPLC-MS/MS method for quantification of delgocitinib was developed and validated over a range of 5 to 5000 pg/mL with an LLOQ of 5 pg/mL. The method was successfully used to determine delgocitinib in the in vivo studies.								
Healthy subjects versus patients	Pharmacokinetics were determined in subjects with moderate to severe chronic hand eczema. No PK assessment in healthy subjects was conducted.								
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	<table> <tr> <td>Parameter</td><td>Mean ± SD</td></tr> <tr> <td>AUC</td><td>4.2±1.88 h*ng/mL</td></tr> <tr> <td>C_{max}</td><td>0.53±0.28 ng/mL</td></tr> <tr> <td>C₂₄</td><td>N/A</td></tr> </table>	Parameter	Mean ± SD	AUC	4.2±1.88 h*ng/mL	C _{max}	0.53±0.28 ng/mL	C ₂₄	N/A
Parameter	Mean ± SD								
AUC	4.2±1.88 h*ng/mL								
C _{max}	0.53±0.28 ng/mL								
C ₂₄	N/A								
Range of effective dose(s) or exposure	2% cream applied twice daily								
Maximally tolerated dose or exposure	Not applicable								
Dose proportionality	Not applicable								
Accumulation	There was no accumulation of delgocitinib following twice-daily administration for 14 days in the maximal use trial.								
Time to achieve steady-state									
Bridge between to-be-marketed and clinical trial/study formulations	The final formulation was used in the maximal use trial and phase 3 trials.								

Characteristic	Drug Information
	Absorption
Bioavailability	Absolute bioavailability of delgocitinib cream, 2% was not determined; however, the systemic exposure of delgocitinib cream under maximal use conditions in subjects with CHE was found to be lower than the oral dose used in the TQT study.
T _{max}	6.4±4.36 hours on Day 8 following twice a day application for 8 days
Food effect (fed/fasted)	Not applicable
Geometric least square mean and 90% CI	Not applicable
	Distribution
Volume of distribution	Not applicable
Plasma protein binding	Not applicable
Drug as substrate of transporters	In vitro studies showed that delgocitinib is a substrate of P-glycoprotein (P-gp).
	Elimination
Mass balance results	Mass balance study was not conducted.
Clearance	Not applicable
Half-life	Approximately 21 hours following twice-daily dosing for 8 days based on data from a limited number of subjects
Metabolic pathway(s)	Limited metabolism of delgocitinib was observed in vitro and in vivo, with no major human-specific metabolites. Metabolism occurred by oxidation and through glucuronide conjugation. Delgocitinib was mainly metabolized by Cytochrome P450 (CYP) A4/5, with minor contribution from CYP2C9, CYP2C19 and CYP2D6.
Primary excretion pathways (% dose)	Approximately 75% of the total delgocitinib was excreted unchanged in urine.
	Intrinsic Factors and Specific Populations
Body weight	No studies were conducted to determine the therapeutic individualization based on body weight.
Age	No studies were conducted to establish safety and efficacy in pediatric patients. Based on the clinical trials, no overall differences in safety or effectiveness were observed between subjects 65 years of age and older and younger adult subjects.
Renal impairment	Studies in subjects with renal impairment were not conducted due to low systemic exposures and the lack of a relationship between plasma concentration and adverse events, including adverse events of special interest (AESIs).
Hepatic impairment	Studies in subjects with hepatic impairment were not conducted due to low systemic exposures and the lack of a relationship between plasma concentration and adverse events, including AESIs.
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	Based on in vitro studies, delgocitinib is not an inhibitor of CYP enzymes including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, or CYP3A5, and it is not an inducer of CYP1A2, CYP2B6, or CYP3A4.
Inhibition/induction of transporter systems	Based on in vitro studies, delgocitinib is a substrate of P-gp but not a substrate of BCRP and not an inhibitor of P-gp or BCRP. It is a weak substrate of OCT2 and OAT3, but not a substrate of OAT1 and showed no inhibition of OCT2, OATP1B1, or OATP1B3.

NDA 219155

ANZUPGO (delgocitinib) cream, 2%

Characteristic	Drug Information
	<i>Immunogenicity (if Applicable)</i>
Bioanalysis	Not applicable
Incidence	Not applicable
Clinical impact	Not applicable

Source: Clinical Pharmacology Reviewer

Abbreviations: BCRP, breast cancer resistance protein; CI, confidence interval; EPC, established pharmacologic class; P-gp, P-glycoprotein, OAT, organic anion transporter; OCT, organic cation transporter; OATP, organic anion transporting polypeptide; CYP, cytochrome P450; TQT, thorough QT; CHE, chronic hand eczema; AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; C₂₄, observed plasma concentration after 24 hours; SD, standard deviation; PK, pharmacokinetic; HPLC-MS/MS, high-performance liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantitation; STATs, signal transducers and activators of transcription; JAK, Janus kinase; TYK, tyrosine kinase; QT_c, corrected QT interval

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The Applicant conducted two phase 3 trials (DELTA 1 [LP0133-1401] and DELTA 2 [LP0133-1402]). The proposed dosing regimen was determined to be acceptable for approval.

The dosing regimen of twice-daily delgocitinib cream 20 mg/g, administered in Trials DELTA 1 and DELTA 2, was selected based on the results from a dose-ranging trial (LP0133-1273). Trial LP0133-1273 was a phase 2b double-blind, multicenter, randomized, 5-arm, vehicle-controlled, parallel-group trial, designed to establish dose response and to investigate the efficacy and safety of twice-daily topical application of delgocitinib cream for 16 weeks in adult subjects with mild to severe CHE. A total of 258 subjects were randomized in a 1:1:1:1:1 ratio to 4 different strengths of delgocitinib cream (1, 3, 8, or 20 mg/g) or vehicle cream.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Trial Design, Trials DELTA 1 and DELTA 2

Trials DELTA 1 and DELTA 2 were randomized, double-blind, vehicle-controlled, parallel-group, multicenter, phase 3 trials to evaluate the safety and efficacy of twice-daily delgocitinib cream 20 mg/g compared with vehicle cream in adult subjects with moderate to severe chronic hand eczema.

[Figure 1](#) and [Figure 2](#) present the trial design schematics for Trials DELTA 1 and DELTA 2, respectively. Trial DELTA 1 was designed to enroll and randomize approximately 470 subjects. Trial DELTA 2 was designed to enroll and randomize approximately 450 subjects. The protocols for both trials specified enrolling subjects from approximately 55 sites in Europe and Canada. Subjects were specified to be randomized in a 2:1 ratio to receive either delgocitinib cream 20 mg/g or vehicle cream. The protocols specified stratifying the randomization by region and baseline IGA-CHE score.

The first application of investigational medicinal product (IMP) was specified to be administered at the trial site at baseline (Day 1). The subsequent IMP administrations were performed by the subjects at home twice daily for 16 weeks. For both trials, subjects were scheduled to have the following trial site visits: screening (Day -28 to -7), baseline (Day 1), and Weeks 1, 2, 4, 8, 12, and 16. The protocols specified that all eligible subjects who did not permanently discontinue IMP prior to Week 16 would be invited to participate in the long-term extension trial (LP0133-1403; DELTA 3).

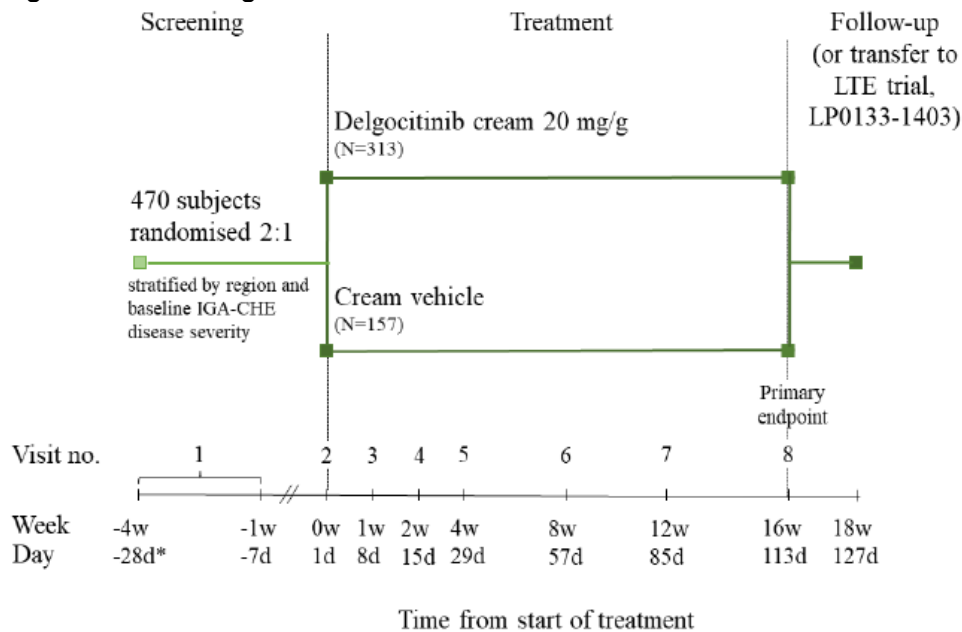
The protocols specified that, if deemed to be medically necessary by the investigator (i.e., to control intolerable CHE symptoms), rescue treatment for CHE could be prescribed to trial subjects at the discretion of the investigator. The investigators were instructed to make every

attempt to conduct efficacy and safety assessments (e.g., disease severity scores, safety laboratory assessments) immediately before administering any rescue treatment. The protocols specified that if rescue treatment was initiated, the subject was to stop treatment with IMP immediately and would not be allowed to restart treatment with IMP. Subjects who discontinued IMP were specified to be asked to attend an early termination visit, a follow-up visit (performed via phone, but can be a site visit if needed) 2 weeks after the last application of IMP, and also the primary endpoint visit at Week 16.

The protocols stated:

“Rescue treatment is defined as treatment initiated to treat intolerable CHE symptoms during the treatment and follow-up periods. It will be recorded in the eCRF if a medication is given as rescue treatment.”

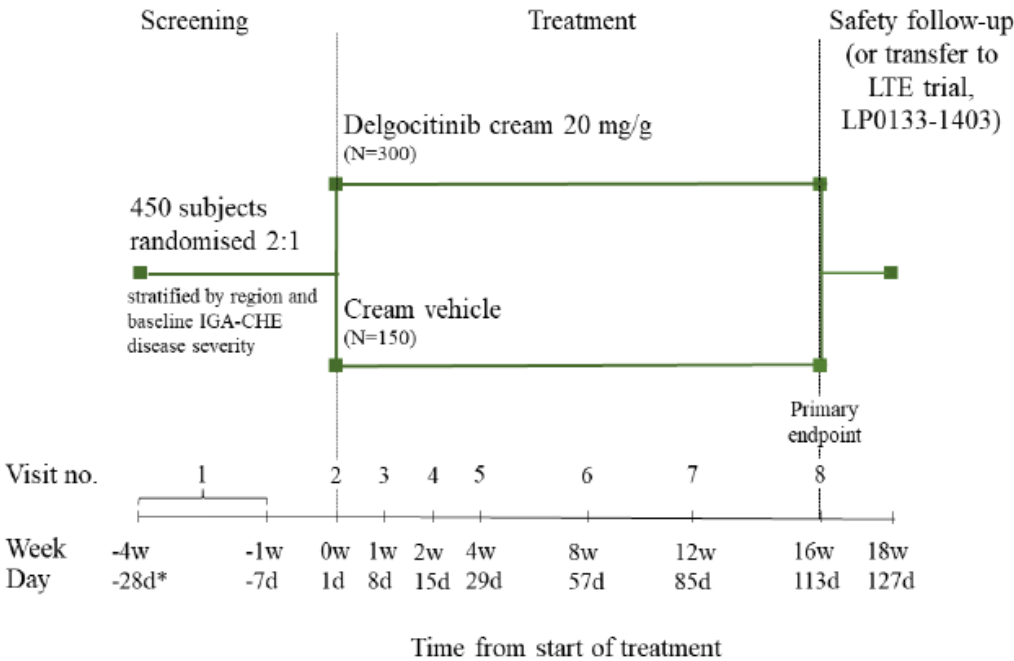
Figure 1. Trial Design Schematic for Trial DELTA 1



Source: page 24 of the protocol (Version 4.0) for Trial LP0133-1401

Abbreviations: d, day; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; LTE, long-term extension; N, number of subjects; w, week

Figure 2. Trial Design Schematic for Trial DELTA 2



Source: page 24 of the protocol (Version 4.0) for Trial LP0133-1402
Abbreviations: d, day; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; N, number of subjects; LTE, long-term extension; w, week

6.2.2. Eligibility Criteria, Trials DELTA 1 and DELTA 2

Key eligibility criteria for both trials are summarized in this section and the full criteria are available in [Table 127](#) and [Table 128](#) in Section 15.

Inclusion Criteria

- Age 18 years or older at screening.
- Clinical diagnosis of CHE, defined as hand eczema that has persisted for more than 3 months or returned twice or more within the last 12 months.
- Disease severity graded as moderate to severe at screening and baseline according to IGA-CHE (i.e., an IGA-CHE score of 3 or 4).
- Hand eczema symptom diary itch score (weekly average) of ≥ 4 points at baseline. The baseline weekly average was to be calculated from daily assessments of itch severity during the 7 days immediately preceding the baseline visit (Day -7 to Day -1). A minimum of 4 itch scores out of the 7 days was required to calculate the baseline average score.
- Subjects who had a documented recent history of inadequate response to treatment with TCS (at any time within 1 year before the screening visit) or for whom TCS were documented to be otherwise medically inadvisable (e.g., due to important side effects or safety risks).
 - Inadequate response was defined as a history of failure to achieve and maintain a low disease activity state (comparable to an IGA-CHE score of ≤ 2) despite treatment with a daily regimen of TCS of class III-IV (potent to very potent) for Europe and class IV-I

(medium potency to very/ultra-high potency) for Canada, applied for at least 28 days or for the maximum duration recommended by the product prescribing information, whichever was shorter.

- Important side effects or safety risks were those that outweighed the potential treatment benefits and included intolerance to treatment, hypersensitivity reactions, and significant skin atrophy as assessed by the physician.

Exclusion Criteria

- Concurrent skin diseases on the hands, e.g., tinea manuum.
- Active AD requiring medical treatment in regions other than the hands and feet.
- Active psoriasis on any part of the body.
- Hyperkeratotic hand eczema in combination with a history of psoriasis on any part of the body.
- Clinically significant infection (e.g., impetiginized hand eczema) on the hands.

6.2.3. Clinical Endpoints, Trials DELTA 1 and DELTA 2

The protocols specified the following primary efficacy endpoint:

- Proportion of subjects with IGA-CHE treatment success, defined as score of 0 or 1 at Week 16 with at least a 2-step improvement from baseline

The protocols specified the following secondary efficacy endpoints (controlled for multiplicity):

- Proportion of subjects with at least a 4-grade reduction in HESD itch score (weekly average) from baseline to Week 16
- Proportion of subjects with at least a 4-grade reduction in HESD pain score (weekly average) from baseline to Week 16
- Proportion of subjects with at least a 4-grade reduction in HESD score (weekly average) from baseline to Week 16
- Proportion of subjects with IGA-CHE treatment success at Week 8
- Proportion of subjects with IGA-CHE treatment success at Week 4
- Proportion of subjects with reduction of HESD itch score (weekly average) of ≥ 4 points at Week 8
- Proportion of subjects with reduction of HESD itch score (weekly average) of ≥ 4 points at Week 4
- Proportion of subjects with reduction of HESD itch score (weekly average) of ≥ 4 points at Week 2
- Proportion of subjects with reduction of HESD score (weekly average) of ≥ 4 points at Week 8

- Proportion of subjects with reduction of HESD score (weekly average) of ≥ 4 points at Week 4
- Proportion of subjects with reduction of HESD pain score (weekly average) of ≥ 4 points at Week 8
- Proportion of subjects with reduction of HESD pain score (weekly average) of ≥ 4 points at Week 4
- Proportion of subjects with HECSI-90 at Week 16
- Proportion of subjects with HECSI-75 at Week 16
- Proportion of subjects with HECSI-75 at Week 8
- Percentage change in HECSI score from baseline to Week 16
- Change in DLQI score from baseline to Week 16
- Change in HESD score (weekly average) from baseline to Week 16
- Change in HESD itch score (weekly average) from baseline to Week 16
- Change in HESD pain score (weekly average) from baseline to Week 16
- Change in HEIS score from baseline to Week 16
- Change in HEIS PDAL score from baseline to Week 16
- Proportion of subjects with reduction of DLQI score of ≥ 4 points at Week 16

6.2.4. Clinical Outcome Assessment Instruments Used To Assess the Primary and Secondary Endpoints, Trials DELTA 1 and DELTA 2

The primary and secondary COA-based efficacy endpoints in Trials DELTA 1 and DELTA 2 included scores from the IGA-CHE. Key COA-based secondary efficacy endpoints included scores from the HESD, HECSI, and the HEIS. COAs used in these endpoints are described below. The IGA-CHE and HESD itch and pain scores were determined to be valid (i.e., fit-for-purpose) and interpretable to evaluate the effects of delgocitinib on subjects' symptoms.

6.2.4.1. Investigator's Global Assessment for Chronic Hand Eczema

The IGA-CHE ([Table 6](#)) is a single-item ClinRO designed to assess CHE severity using a 5-level response scale ranging from 0 (clear) to 4 (severe), with higher scores representing greater CHE severity. The recall period is the subject's current state. In Trials DELTA 1 and DELTA 2, the IGA-CHE was administered at Screening (Day -28 to -7), Baseline (Day 1), and Weeks 1, 2, 4, 8, 12, and 16.

Table 6. Investigator's Global Assessment for Chronic Hand Eczema Scale

IGA-CHE severity	IGA-CHE score	Sign and intensity
Clear	0	No signs of erythema, scaling, hyperkeratosis/lichenification, vesiculation, oedema or fissures
Almost clear	1	Barely perceptible erythema No signs of scaling, hyperkeratosis/ lichenification, vesiculation, oedema or fissures
Mild	2	At least one: - Slight but definite erythema (pink) - Slight but definite scaling (mostly fine scales) - Slight but definite hyperkeratosis/lichenification and at least one: - Scattered vesicles, without erosion - Barely palpable oedema - Superficial fissures
Moderate	3	At least one: - Clearly perceptible erythema (dull red) - Clearly perceptible scaling (coarse scales) - Clearly perceptible hyperkeratosis/lichenification and at least one: - Clustered vesicles, without visible erosion - Definite oedema - Definite fissures
Severe	4	At least one: - Marked erythema (deep or bright red) - Marked and thick scaling - Marked hyperkeratosis/lichenification and at least one: - High density of vesicles with erosions - Marked oedema - One or more deep fissures

Source: page 73 of the protocols (Version 4.0) for Trials LP0133-1401 and LP0133-1402
Abbreviation: IGA-CHE, Investigator's Global Assessment for chronic hand eczema

6.2.4.2. Hand Eczema Severity Index

The HECSI is a ClinRO designed to assess the extent of hand eczema on each of five hand regions (fingertips, fingers [except fingertips], palms of hands, backs of hands, and wrists) and the severity of six clinical signs (erythema, infiltration/papulation, vesicles, fissures, scaling, oedema) for each of five hand regions.

First, the investigator assesses the relative percentage of hand eczema involvement for the given hand region (total of both hands, e.g., 10 fingers). Each region is assessed separately and scored from 0 to 100%. The percentage of involvement of the given hand region is converted to a 5-level response scale representing the area score for both hands together ([Table 7](#)) (skin lesions on the hands not representing eczema are not to be included in the assessment). Second, the investigator rates the average severity of each of the 6 clinical signs of hand eczema for the given hand region using a 4-level response scale ranging from 0 ("none/absent") to 3 ("severe") ([Table 7](#)). These two steps are repeated for all 5 hand regions. New CHE lesions that occur on previously untreated areas are specified to be included in the assessment.

For each of the hand regions, the region score is calculated by adding up the severity scores for the 6 clinical signs of hand eczema and multiplying that value with the area score ([Table 8](#)). The HECSI score equals the sum of the region scores and ranges from 0 (lowest possible score) to

360 (highest possible score); the severity score is based on both hands, with higher scores indicating more severe and/or more extensive disease. A scoring calculator is available online ([HECSI 2025](#)). The recall period is the subject's current state.

In Trials DELTA 1 and DELTA 2, the HECSI was administered at Baseline (Day 1) and Weeks 1, 2, 4, 8, 12, and 16.

Table 7. HECSI Severity Score Scale and Area Score Scale

Severity score (SS) scale (based on both hands)		Area score (AS) scale (based on the affected area of both hands)	
0	None/absent	0	0% affected area
1	Mild	1	1% to 25% affected area
2	Moderate	2	26% to 50% affected area
3	Severe	3	51% to 75% affected area
		4	76% to 100% affected area

Note: half-scores (0.5, 1.5, 2.5) are not allowed.

Note: half-scores (0.5, 1.5, 2.5, 3.5) are not allowed.

Source: page 74 of the protocol (Version 4.0) for Trial LP0133-1401 and page 73 of the protocol (Version 4.0) for Trial LP0133-1402
Abbreviations: AS, area score; SS, severity score

Table 8. Calculation of the Total HECSI Score

Hand region	Erythema	Infiltration/ papulation	Vesicles	Fissures	Scaling	Oedema	Area score	Score
Fingertips	(SS +	SS +	SS +	SS +	SS +	SS)	× AS	
Fingers (except fingertips)	(SS +	SS +	SS +	SS +	SS +	SS)	× AS	
Palm of hands	(SS +	SS +	SS +	SS +	SS +	SS)	× AS	
Back of hands	(SS +	SS +	SS +	SS +	SS +	SS)	× AS	
Wrists	(SS +	SS +	SS +	SS +	SS +	SS)	× AS	
The total HECSI score equals the sum of the 5 above region scores:								(range 0-360)

Source: page 74 of the protocol (Version 4.0) for Trial LP0133-1401 and page 73 of the protocol (Version 4.0) for Trial LP0133-1402
Abbreviations: AS, area score; HECSI, Hand Eczema Severity Index; SS, severity score

6.2.4.3. Hand Eczema Symptom Diary

The HESD is a 6-item patient-reported outcome (PRO) collected daily with an electronic diary (eDiary) assessing the severity of CHE signs and symptoms (i.e., itch, pain, cracking, redness, dryness, flaking). Subjects rate the sign or symptom at its “worst” on an 11-level response scale,

with higher scores indicating greater severity (0 = “No [sign or symptom]”, 10 = “Severe [sign or symptom]”). At least 4 of 7 days of weekly eDiary data are required to calculate the baseline score and weekly scores. The HESD score is derived as weekly average of the 6 item scores. The recall period is the past 24 hours. See [Figure 3](#) below for a copy of the HESD.

In Trials DELTA 1 and DELTA 2, the HESD was administered electronically daily from Screening (Visit 1; Day –28 to –7) to Week 16. The baseline score is determined based on the average during the 7 days immediately preceding the baseline visit (Day –7 to Day –1).

Figure 3. Patient-Reported Outcome Assessment, Hand Eczema Symptom Diary

Hand Eczema Symptom 4:20 PM

Hand Eczema Symptom Diary

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Back Next

Hand Eczema Symptom 4:20 PM

Rate the severity of any **itch** on your hands, at its worst, over the past 24 hours:

0 1 2 3 4 5 6 7 8 9 10

↑ No itch Severe itch ↑

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Back Next

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Hand Eczema Symptom4:20 PM

Rate the severity of any **pain** on your hands, at its worst, over the past 24 hours:

012345678910

↑↑

No painSevere pain

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Back

Next

Hand Eczema Symptom4:20 PM

Rate the severity of any **cracking of the skin** on your hands, at its worst, over the past 24 hours:

012345678910

↑↑

No crackingSevere cracking

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Back

Next

Hand Eczema Symptom4:20 PM

Rate the severity of any **redness** of the skin on your hands, at its worst, over the past 24 hours:

012345678910

↑↑

No rednessSevere redness

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Back

Next

Hand Eczema Symptom4:20 PM

Rate the severity of any **dryness** of the skin on your hands, at its worst, over the past 24 hours:

012345678910

↑↑

No drynessSevere dryness

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Back

Next

38

Integrated Review Template, version 4.0 (11/1/23)

Reference ID: 5629504

Hand Eczema Symptom 4:20 PM

Rate the severity of any **flaking of the skin** on your hands, at its worst, over the past 24 hours:

0 1 2 3 4 5 6 7 8 9 10

↑ No flaking ↑ Severe flaking

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Back Next

Hand Eczema Symptom 4:20 PM

Thank You

You have now completed this questionnaire.

If you would like to review or change any of your answers, tap **Back**.

When you are satisfied with your answers, tap **Save**.

Saving your answers means you will not be able to change them again.

Back Save

Source: Pages 5-8 of the Subject Facing Screens Report (LP0133-1401_1402_1403) of the COA dossier

6.2.4.4. Hand Eczema Impact Scale

The HEIS is a 9-item PRO assessing impacts of CHE over the past 7 days on domains of functioning and health-related quality of life. The HEIS generates a total score and a 3-item PDAL domain score assessing the ability to use soaps/cleaning products, complete housework involving hands getting wet, and wash oneself. Each item is rated on a 5-level response scale ranging from 0 (not at all) to 4 (extremely). A higher score indicates greater impact. The total HEIS score is calculated by taking the average of all 9 items. The HEIS PDAL score is the average of the 3 items in that domain.

See [Figure 4](#) below for a copy of the HEIS PDAL. In Trials DELTA 1 and DELTA 2, the HEIS was administered at Baseline (Day 1) and Weeks 1, 2, 4, 8, 12, 16.

Figure 4. Patient-Reported Outcome Assessment, Hand Eczema Impact Scale

The figure displays four screenshots of the Hand Eczema Impact Scale (HEIS) app interface, arranged in a 2x2 grid. Each screenshot shows a question about the impact of hand eczema over the past 7 days, with five response options: 'Extremely', 'A lot', 'Moderately', 'A little', and 'Not at all'. The app interface includes a progress bar at the top, a clock showing 08:32 AM, and 'Back' and 'Next' buttons at the bottom.

Top Left Screenshot: The question is 'Over the past 7 days, how much has your hand eczema impacted on the **quality of your sleep**?'. The progress bar is at 10%.

Top Right Screenshot: The question is 'Over the past 7 days, how has your hand eczema impacted on your ability to use **soaps/cleaning products**?'. The progress bar is at 25%.

Bottom Left Screenshot: The title 'Hand Eczema Impact Scale (HEIS)' is displayed. The progress bar is at 30%.

Bottom Right Screenshot: The question is 'Over the past 7 days, how **embarrassed** have you felt about how your hands look due to your hand eczema?'. The progress bar is at 30%.

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Hand Eczema Impact Scale

08:32 AM

Over the past 7 days, how much has your hand eczema made it hard to **hold or grip objects** (e.g. a cell phone, a pen or pencil)?

Extremely

A lot

Moderately

A little

Not at all

Back

Next

Hand Eczema Impact Scale

08:32 AM

Over the past 7 days, how much has your hand eczema made it hard to do **housework** that involved your **hands getting wet** (e.g. washing dishes)?

Extremely

A lot

Moderately

A little

Not at all

Back

Next

Hand Eczema Impact Scale

08:32 AM

Over the past 7 days, how much have you disliked the **appearance of your hands**?

Extremely

A lot

Moderately

A little

Not at all

Back

Next

Hand Eczema Impact Scale

08:32 AM

Over the past 7 days, how much has your hand eczema made it hard to **work** (e.g. paid work or voluntary)?

Extremely

A lot

Moderately

A little

Not at all

Back

Next

Hand Eczema Impact Scale 08:32 AM

Over the past 7 days, how much has your hand eczema made you feel **frustrated**?

Extremely

A lot

Moderately

A little

Not at all

Back Next

Hand Eczema Impact Scale 08:32 AM

Thank You

You have now completed this questionnaire.

If you would like to review or change any of your answers, tap **Back**.

When you are satisfied with your answers, tap **Save**.

Saving your answers means you will not be able to change them again.

Back Save

Source: Pages 41-52 (for the entire instrument) of the Subject Facing Screens Report (LP0133-1401_1402_1403) of the COA dossier

6.2.5. Statistical Analysis Plan, DELTA 1 and DELTA 2 Trials

Analysis Populations

The protocols and the statistical analysis plans (SAPs) specified the following analysis populations:

- Full analysis set (FAS): all subjects randomized and exposed to IMP. Subjects were included in the analyses according to the planned treatment.
- Safety analysis set: all subjects exposed to IMP. Subjects were to be included in the analyses according to the treatment they actually received.

The FAS was specified to be the analysis population for efficacy and the safety analysis set was specified to be the analysis population for safety.

Estimands

The protocols and SAPs specified the following as the main estimand for the primary and binary multiplicity-controlled secondary efficacy endpoints:

- Treatment: delgocitinib 20 mg/g and cream vehicle
- Population: FAS
- Endpoint: a binary response at a specified timepoint
- Intercurrent events (ICEs) and strategy for handling:
 - Initiation of rescue treatment: subjects who received rescue treatment prior to the specified timepoint for the endpoint were considered as nonresponders [composite variable strategy]
 - Permanent discontinuation of IMP: subjects who permanently discontinue IMP prior to the specified timepoint for the endpoint were considered as nonresponders [composite variable strategy]
- Summary measure: difference in proportions between delgocitinib and vehicle.

The protocols and SAPs specified the following as the main estimand for the continuous multiplicity-controlled secondary efficacy endpoints:

- Treatment: delgocitinib 20 mg/g and cream vehicle
- Population: FAS
- Endpoint: absolute change or percent change from baseline to Week 16
- ICEs and strategy for handling:
 - Initiation of rescue treatment: subjects who received rescue treatment prior to Week 16 were to have data after initiation imputed using the worst observation carried forward (WOCF) prior to initiation (including baseline value) [composite variable strategy]
 - Permanent discontinuation of IMP: subjects who permanently discontinue IMP prior to Week 16 were to have data after discontinuation imputed using WOCF prior to discontinuation (including baseline value) [composite variable strategy]
- Summary measure: difference in mean change or percentage change from baseline to the endpoint of interest between delgocitinib and vehicle.

Analysis Methods

The protocols and SAPs specified analyzing the primary and binary secondary efficacy endpoints using the Cochran-Mantel-Haenszel (CMH) test stratified by region and baseline IGA-CHE score. The difference in proportions and its 95% CI were specified to be calculated by the Mantel-Haenszel method. Missing data were specified to be imputed using the nonresponder imputation approach.

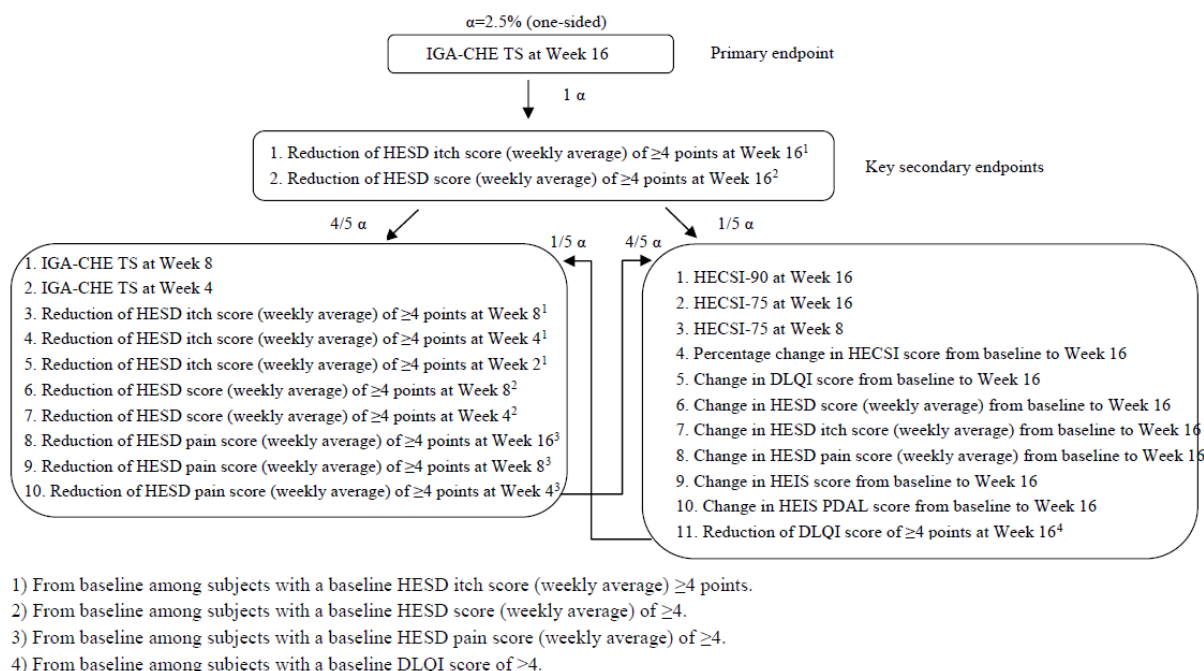
The protocols and SAPs specified analyzing the continuous secondary efficacy endpoints using an analysis of covariance model with effects of treatment group, region, baseline IGA-CHE score, and baseline value (endpoint of interest). The least square means for each treatment group were specified to be estimated based on the model. In addition, the difference in least square

means between the treatment groups was specified to be estimated along with its corresponding 95% CI. Missing data were specified to be imputed using the WOCF (including baseline value) imputation approach.

Multiplicity Adjustment Plan

The protocols and SAPs specified using a closed testing procedure with hierarchical tests, alpha splitting, and alpha recycling to control the overall Type I error at a nominal one-sided 2.5% level (equivalent to a two-sided 5% level). Superiority of delgocitinib cream 20 mg/g in terms of IGA-CHE TS at Week 16 (i.e., the primary efficacy endpoint) was the first hypothesis tested at the overall one-sided significance level of 2.5%. In the procedure, if a test was significant, the significance level could be reallocated according to the weight and the direction of the arrows as specified in [Figure 5](#). Each hypothesis was tested at its local significance level (α -local). This process was repeated until no further tests were significant.

Figure 5. Graphical Display of the Closed Testing Procedure for Primary and Key Secondary Efficacy Endpoints



Source: page 108 of the protocol (Version 4.0) for Trial LP0133-1401 and page 104 of the protocol (Version 4.0) for Trial LP0133-1402

Abbreviations: DLQI, Dermatology Life Quality Index; HECSI, Hand Eczema Severity Index; HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; PDAL, proximal daily activity limitations

Sensitivity and Supplementary Analyses

The protocols specified the following sensitivity analyses for the primary efficacy endpoint:

Multiple Imputation

Missing data were imputed from a Bernoulli distribution with parameter p-values 0.1 and 0.2. The same parameter p was used for both treatment groups. The parameter values 0.1 and 0.2 were based on the response rates of IGA-CHE TS and HESD itch score (weekly average)

≥ 4 points, respectively, at Week 16 in the cream vehicle group in LP0133-1273 and were to introduce uncertainty due to missing data. A multiple imputation procedure (100 iterations) was used for each value of p . For each of the 100 complete datasets, the difference in response rates were analyzed by the Mantel-Haenszel method stratified by region and baseline IGA-CHE score. The results of the analyses were combined using Rubin's rule to provide the estimated treatment difference and associated standard error, and the 95% CI for the treatment difference was calculated.

Tipping Point Analysis

For subjects who did not experience ICEs prior to the endpoint of interest, missing data were handled as follows:

- For subjects in the delgocitinib cream 20 mg/g group, missing data were imputed as nonresponse.
- For subjects in the cream vehicle group, missing data were imputed from a Bernoulli distribution with parameter p (ranging from 0 to 1). By varying the parameter p , different percentages of subjects in the cream vehicle group were assumed to be responders, deviating from the default zero percent used in the primary analysis. A multiple imputation procedure (100 iterations) was used for each value of p .

For each of the 100 complete datasets, the difference in response rates was analyzed by the Mantel-Haenszel method stratified by region and baseline IGA-CHE score. The results of the analyses were combined using Rubin's rule to provide the estimated treatment difference and associated standard error, and the 95% CI for the treatment difference was calculated. The tipping point was found as the value of p which changed the conclusion from statistically significant to nonsignificant and was judged from a clinical perspective.

The protocols specified the following supplementary analyses for the primary efficacy endpoint.

Supplementary Estimand: "Pandemic-Modified Composite" Strategy

This strategy evaluated the treatment effect in adult subjects with moderate to severe CHE, without initiation of rescue treatment or permanent discontinuation of IMP, in a world without the COVID-19 pandemic, where interest lies in the treatment effect as it would have been observed had the COVID-19 pandemic not happened.

- For subjects who experienced ICEs independent of the pandemic prior to the endpoint of interest, observed data after the ICEs were to be considered nonresponse.
- For subjects who experienced an ICE related to the pandemic prior to the endpoint of interest, observed data after the ICE were to be "treated as missing" and imputed assuming missing at random (MAR).

Missing data for subjects who did not attend the visit for the endpoint of interest and did not experience ICEs prior to this visit were to be imputed as nonresponse, unless data were missing due to the pandemic, in which case they were to be imputed assuming MAR. The procedure for imputing values was to be implemented in a 2-step procedure, where all missing or "treated as missing" data were to be imputed using multiple imputation (100 iterations) assuming MAR within treatment groups. Once the 100 complete data sets had been generated by multiple

imputation, nonresponder imputation of relevant data points not affected by the pandemic was to be applied according to the rules described above. For each of the 100 complete datasets, the difference in response rates was to be analyzed using the CMH test stratified by region and baseline IGA-CHE score. The results of the analyses were to be combined using Rubin's rule to provide the estimated treatment difference and associated standard error, and the 95% CI for the treatment difference was to be calculated.

Supplementary Estimand: “Treatment Policy” Strategy

This strategy evaluated the treatment effect in adult subjects with moderate to severe CHE, regardless of initiation of rescue treatment or permanent discontinuation of IMP, in a world without the COVID-19 pandemic. Observed data were to be used in the analysis, including the data observed after the occurrence of ICEs independent of the pandemic. To support the “treatment policy” strategy, subjects who experienced ICEs prior to Week 16 were to be asked to attend the primary endpoint visit at Week 16 for collection of data. For subjects who experienced an ICE related to the pandemic prior to Week 16, observed data at Week 16 were to be “treated as missing” and imputed assuming MAR.

Missing data at Week 16 independent of the pandemic were to be imputed using multiple imputation (100 iterations) assuming MAR within 4 groups defined according to treatment group and whether the subject had experienced an ICE (independent of the pandemic). Missing data or “treated as missing” data at Week 16 due to the pandemic were to be imputed using multiple imputation assuming MAR within treatment group using data from subjects who had not experienced an ICE. For each of the 100 imputed datasets, the difference in response rates were to be analyzed using the CMH test stratified by region and baseline IGA-CHE score. The results of the analyses were to be combined using Rubin's rule to provide the estimated treatment difference and associated standard error, and the 95% CI for the treatment difference was to be calculated.

6.2.6. Results of Analyses, Trials DELTA 1 and DELTA 2

Subject Disposition, Demographics and Baseline Disease Characteristics

Trial DELTA 1 enrolled and randomized a total of 487 subjects (325 to delgocitinib, 162 to vehicle) from 55 sites. Trial DELTA 2 enrolled and randomized a total of 473 subjects (314 to delgocitinib, 159 to vehicle) from 55 sites. [Table 9](#) presents the subject disposition for the vehicle-controlled phase of the trials. In both trials, the treatment and discontinuation rates were higher in the vehicle group compared to the delgocitinib group. In addition, the treatment and trial discontinuation rates were higher in Trial DELTA 2 compared to Trial DELTA 1. The demographics and baseline disease characteristics were generally balanced across the two treatment groups and are presented in [Table 10](#).

Table 9. Subject Disposition, Trials DELTA 1 and DELTA 2

Subject Disposition	Trial DELTA 1		Trial DELTA 2	
	Delgocitinib	Vehicle	Delgocitinib	Vehicle
Randomized subjects	325	162	314	159
Full analysis set ¹ , n (%) ²	325 (100.0)	162 (100.0)	313 (99.7)	159 (100.0)
Discontinued from IMP, n (%) ²	20 (6.2)	21 (13.0)	22 (7.0)	37 (23.3)
Adverse event	2 (0.6)	6 (3.7)	1 (0.3)	6 (3.8)
Lack of efficacy	5 (1.5)	7 (4.3)	6 (1.9)	14 (8.8)
Lost to follow-up	0	2 (1.2)	2 (0.6)	1 (0.6)
Pregnancy	0	0	2 (0.6)	0
Withdrawal by subject	11 (3.4)	5 (3.1)	10 (3.2)	16 (10.1)
Other	2 (0.6)	1 (0.6)	1 (0.3)	0
Discontinued from Trial, n (%) ²	14 (4.3)	14 (8.6)	21 (6.7)	32 (20.1)
Adverse events	0	2 (1.2)	0	3 (1.9)
Lack of efficacy	1 (0.3)	3 (1.9)	4 (1.3)	6 (3.8)
Lost to follow-up	1 (0.3)	2 (1.2)	4 (1.3)	2 (1.3)
Withdrawal by subject	10 (3.1)	7 (4.3)	12 (3.8)	21 (13.2)
Other	2 (0.6)	0	1 (0.3)	0

Source: page 35 of clinical study report for Trial LP0133-1401 and page 35 of clinical study report for Trial LP0133-1402. Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt

¹ FAS: all subjects randomized and dosed.

² The percentages were calculated based on the number of subjects who were randomized.

Abbreviations: FAS, full analysis set; IMP, investigational medicinal product; n, number of subjects with disposition

Table 10. Demographics and Baseline Disease Characteristics, Trials Delta 1 and Delta 2 (FAS)¹

Characteristics	Trial DELTA 1		Trial DELTA 2	
	Delgocitinib (N=325)	Vehicle (N=162)	Delgocitinib (N=313)	Vehicle (N=159)
Age (years)				
Mean (SD)	44.3 (14.3)	42.9 (14.1)	45.3 (14.6)	42.6 (14.3)
Median	45.0	42.5	46.0	42.0
Min, max	19, 87	20, 73	18, 83	18, 86
Categories, n (%)				
18 to <65 years	297 (91.4)	154 (95.1)	285 (91.1)	150 (94.3)
65 to <85 years	27 (8.3)	8 (4.9)	28 (8.9)	8 (5.0)
≥85 years	1 (0.3)	0	0	1 (0.6)
Sex, n (%)				
Female	202 (62.2)	104 (64.2)	203 (64.9)	108 (67.9)
Male	123 (37.8)	58 (35.8)	110 (35.1)	51 (32.1)
Race, n (%)				
White	283 (87.1)	144 (88.9)	294 (93.9)	146 (91.8)
American Indian or Alaska Native	1 (0.3)	0	0	0
Asian	14 (4.3)	5 (3.1)	8 (2.6)	7 (4.4)
Black or African American	3 (0.9)	1 (0.6)	2 (0.6)	1 (0.6)
Multiple ²	2 (0.6)	1 (0.6)	1 (0.3)	3 (1.9)
Native Hawaiian or Other Pacific Islander			1 (0.3)	0
Not reported	20 (6.2)	11 (6.8)	2 (0.6)	1 (0.6)
Other	2 (0.6)	0	5 (1.6)	1 (0.6)
Ethnicity, n (%)				
Hispanic or Latino	14 (4.3)	4 (2.5)	2 (0.6)	5 (3.1)
Not Hispanic or Latino	292 (89.8)	147 (90.7)	309 (98.7)	152 (95.6)
Not reported	19 (5.8)	11 (6.8)	2 (0.6)	2 (1.3)
Region, n (%)				
Europe	260 (80.0)	130 (80.2)	249 (79.6)	126 (79.2)
North America	65 (20.0)	32 (19.8)	64 (20.4)	33 (20.8)

Characteristics	Trial DELTA 1		Trial DELTA 2	
	Delgocitinib (N=325)	Vehicle (N=162)	Delgocitinib (N=313)	Vehicle (N=159)
IGA-CHE, n (%)				
Moderate	218 (67.1)	109 (67.3)	238 (76.0)	121 (76.1)
Severe	107 (32.9)	53 (32.7)	75 (24.0)	38 (23.9)
HESD itch				
N	324	162	312	157
Mean (SD)	7.1 (1.6)	7.2 (1.7)	7.0 (1.5)	7.0 (1.5)
Median	7.2	7.6	7.1	7.1
Min, max	1.9, 10	3.3, 10	2.3, 10	2.6, 10
HESD pain				
N	324	162	312	157
Mean (SD)	6.8 (2)	6.8 (2)	6.6 (1.8)	6.5 (2)
Median	7.1	7.2	6.7	6.7
Min, max	0.8, 10	0.9, 10	0, 10	1, 10
HESD total score				
N	324	162	312	157
Mean (SD)	7.2 (1.7)	7.2 (1.7)	7 (1.5)	6.9 (1.5)
Median	7.2	7.3	7.0	7.1
Min, max	1.4, 10	2.6, 10	2.8, 10	2.1, 10

Source: page 38 of clinical study report for Trial LP0133-1401 and page 38 of clinical study report for Trial LP0133-1402. Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt, adiga.xpt and adhesd.xpt

¹ FAS: all subjects randomized and dosed.

² Subjects who reported more than one race are categorized as Mixed race.

Abbreviations: FAS, full analysis set; HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; min, minimum, max, maximum; N, number of subjects in the trial arm; n, number of subjects with characteristic; SD, standard deviation

Rescue Therapy Use

The use of rescue therapy is summarized in [Table 11](#). A greater proportion of subjects in the vehicle group (4.3% in Trial DELTA 1 and 7.5% in Trial DELTA 2) used rescue therapy than in the delgocitinib group (2.2% in Trial DELTA 1 and 1.0% in Trial DELTA 2). In both trials, a higher proportion of subjects used topical rescue medications than systemic rescue medications.

Table 11. Rescue Therapy Use, Trials DELTA 1 and DELTA 2 (FAS)¹

Rescue Therapy	Trial DELTA 1		Trial DELTA 2	
	Delgocitinib (N=325)	Vehicle (N=162)	Delgocitinib (N=313)	Vehicle (N=159)
Any rescue therapy, n (%)	7 (2.2)	7 (4.3)	3 (1.0)	12 (7.5)
Dermatologicals	5 (1.5)	7 (4.3)	3 (1.0)	11 (6.9)
Antineoplastic and immunomodulating agents	3 (0.9)	1 (0.6)	0	0
Systemic medication	0	1 (0.6)	0	3 (1.9)

Source: page 264 of clinical study report for Trial LP0133-1401 and page 262 of clinical study report for Trial LP0133-1402.

Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt

¹ FAS: all subjects randomized and dosed

Abbreviations: FAS, full analysis set; N, number of subjects in the trial arm; n, number of subjects receiving rescue therapy

Results for the Primary Efficacy Endpoint

[Table 12](#) presents the results of the primary efficacy endpoint (i.e., proportion of subjects with IGA-CHE treatment success at Week 16) in the FAS population for Trials DELTA 1 and DELTA 2. In both trials, delgocitinib was statistically superior to vehicle on the primary efficacy endpoint (p-values ≤ 0.025). The treatment effect was larger in Trial DELTA 2.

Table 12. Results for the Primary Efficacy Endpoint, Trials DELTA 1 and DELTA 2 (FAS)¹

Endpoint	Trial DELTA 1		Trial DELTA 2	
	Delgocitinib (N=325)	Vehicle (N=162)	Delgocitinib (N=313)	Vehicle (N=159)
Proportion of subjects with IGA-CHE treatment success ² at Week 16	19.7% (64/325)	9.9% (16/162)	29.1% (91/313)	6.9% (11/159)
Difference (95% CI) ³	9.8% (3.6%, 16.1%)		22.2% (15.8%, 28.5%)	
p-Value ⁴	0.006		<0.001	

Source: page 55 of clinical study report for Trial LP0133-1401 and page 55 of clinical study report for Trial LP0133-1402. Statistical Reviewer's Analysis (same as Applicant's Analysis); adiga.xpt

¹ FAS: all subjects randomized and dosed. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered nonresponse.

² IGA-CHE treatment success is defined as IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥ 2 -step improvement from baseline.

³ Mantel-Haenszel risk difference, stratified by region and baseline IGA-CHE score.

⁴ Cochran-Mantel-Haenszel test, stratified by region and baseline IGA-CHE score.

Abbreviations: CI, confidence interval; FAS, full analysis set; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; N, number of subjects in trial arm

[Table 138](#) and [Table 139](#) in Section 16.2 present the numbers and percentages of subjects who had missing data after handling the ICEs (i.e., initiation of rescue treatment and permanent discontinuation) for Trials DELTA 1 and DELTA 2, respectively. The tables also present the results for the sensitivity analyses for the handling of missing data as well as the supplementary analyses. There was only one subject in the delgocitinib group for Trial DELTA 1 and one subject in the vehicle group for Trial DELTA 2 that had missing data to be imputed. Consequently, in both trials, the results were similar across the primary analysis and the sensitivity analyses for handling missing data. The Applicant's tipping point analysis did not tip (i.e., $p\text{-value} \geq 0.05$) for any of the iterations evaluated by the Applicant for both trials. Under the extreme case (i.e., subjects with missing data in the delgocitinib group imputed as nonresponders and subjects with missing data in the vehicle group imputed as responders), delgocitinib remained significantly superior to vehicle ($p\text{-values} < 0.05$) in both trials. The sensitivity analyses for the primary estimand, including the tipping point analysis, supported the conclusion of the primary analysis. In addition, the analyses of the first supplementary estimand (i.e., pandemic-modified composite) and the second supplementary estimand (i.e., treatment policy) also led to the same conclusion as the primary analysis of the primary estimand (i.e., composite) in both trials.

Results for the Key Secondary Efficacy Endpoints

[Table 13](#) present the results for the key secondary efficacy endpoints in the FAS population. For both trials, delgocitinib was statistically superior to vehicle on all the secondary efficacy endpoints ($p\text{-values} < 0.043$).

Table 13. Results of the Key Secondary Efficacy Endpoints, Trials DELTA 1 and DELTA 2 (FAS)¹

Endpoint	Trial DELTA 1		Trial DELTA 2	
	Delgocitinib (N=325)	Vehicle (N=162)	Delgocitinib (N=313)	Vehicle (N=159)
Proportion of subjects with HESD itch ≥ 4 -point improvement from baseline to Week 16 ²	47.1% (152/323)	23.0% (37/161)	47.2% (146/309)	19.9% (31/156)
Difference (95% CI) ⁵	24.1% (15.5%, 32.6%)		27.4% (19.0%, 35.8%)	
p-Value ⁵	<0.001		<0.001	

Endpoint	Trial DELTA 1		Trial DELTA 2	
	Delgocitinib (N=325)	Vehicle (N=162)	Delgocitinib (N=313)	Vehicle (N=159)
Proportion of subjects with HESD ≥4-point improvement from baseline to Week 16 ⁴	47.2% (146/309)	24.4% (38/156)	44.5% (137/308)	20.9% (32/153)
Difference (95% CI) ⁵	22.8% (14.0%, 31.7%)		23.7 (15.1%, 32.2%)	
p-Value ⁵	<0.001		<0.001	
Proportion of subjects with IGA-CHE treatment success ² at Week 8	22.8% (74/325)	10.5% (17/162)	32.3% (101/313)	9.4% (15/159)
Difference (95% CI) ⁵	12.3% (5.7%, 18.9%)		22.9% (16.0%, 29.8%)	
p-Value ⁵	0.001		<0.001	
Proportion of subjects with IGA-CHE treatment success ² at Week 4	15.4% (50/325)	4.9% (8/162)	14.7% (46/313)	8.2% (13/159)
Difference (95% CI) ⁵	10.4% (5.3%, 15.6%)		6.5% (0.8%, 12.3%)	
p-Value ⁵	<0.001		0.043	
Proportion of subjects with HESD itch ≥4-point improvement from baseline to Week 8 ²	42.7% (138/323)	21.7% (35/161)	42.4% (131/309)	13.5% (21/156)
Difference (95% CI) ⁵	21.0% (12.6%, 29.4%)		29.0% (21.3%, 36.7%)	
p-Value ⁵	<0.001		<0.001	
Proportion of subjects with HESD itch ≥4-point improvement from baseline to Week 4 ²	30.7% (99/323)	11.2% (18/161)	30.4% (94/309)	12.2% (19/156)
Difference (95% CI) ⁵	19.5% (12.5%, 26.5%)		18.3% (11.0%, 25.6%)	
p-Value ⁵	<0.001		<0.001	
Proportion of subjects with HESD itch ≥4-point improvement from baseline to Week 2 ²	15.5% (50/323)	6.2% (10/161)	12.9% (40/309)	6.4% (10/156)
Difference (95% CI) ⁵	9.3% (3.8%, 14.7%)		6.6% (1.1%, 12.0%)	
p-Value ⁵	0.004		0.031	
Proportion of subjects with HESD ≥4-point improvement from baseline to Week 8 ⁴	39.8% (123/309)	17.3% (27/156)	37.3% (115/308)	12.4% (19/153)
Difference (95% CI) ⁵	22.5% (14.4%, 30.6%)		25.0% (17.5%, 32.5%)	
p-Value ⁵	<0.001		<0.001	
Proportion of subjects with HESD ≥4-point improvement from baseline to Week 4 ⁴	29.8% (92/309)	10.3% (16/156)	26.0% (80/308)	9.2% (14/153)
Difference (95% CI) ⁵	19.5% (12.5%, 26.5%)		16.9% (10.2%, 23.7%)	
p-Value	<0.001		<0.001	
Proportion of subjects with HESD pain ≥4-point improvement from baseline to Week 16 ³	49.1% (143/291)	27.5% (41/149)	48.6% (143/294)	22.7% (32/141)
Difference (95% CI) ⁵	21.7% (12.4%, 30.9%)		26.0% (17.0%, 35.1%)	
p-Value ⁵	<0.001		<0.001	
Proportion of subjects with HESD pain ≥4-point improvement from baseline to Week 8 ³	46.0% (134/291)	22.1% (33/149)	42.2% (124/294)	12.8% (18/141)
Difference (95% CI) ⁵	23.9% (15.2%, 32.7%)		29.6% (21.7%, 37.4%)	
p-Value ⁵	<0.001		<0.001	

Endpoint	Trial DELTA 1		Trial DELTA 2	
	Delgocitinib (N=325)	Vehicle (N=162)	Delgocitinib (N=313)	Vehicle (N=159)
Proportion of subjects with HESD pain $\geq$ 4-point improvement from baseline to Week 4 ³	34.4% (100/291)	14.8% (22/149)	31.0% (91/294)	10.6% (15/141)
Difference (95% CI) ⁵	19.6% (11.8%, 27.5%)		20.5% (13.1%, 27.8%)	
p-Value ⁵	<0.001		<0.001	
Proportion of subjects with HECSI-90 at Week 16	29.5% (96/325)	12.3% (20/162)	31.0% (97/313)	8.8% (14/159)
Difference (95% CI) ⁵	17.2% (10.1%, 24.3%)		22.2% (15.4%, 29.0%)	
p-Value ⁵	<0.001		<0.001	
Proportion of subjects with HECSI-75 at Week 16	49.2% (160/325)	23.5% (38/162)	49.5% (155/313)	18.2% (29/159)
Difference (95% CI) ⁵	25.7% (17.2%, 34.3%)		31.3% (23.1%, 39.5%)	
p-Value ⁵	<0.001		<0.001	
Proportion of subjects with HECSI-75 at Week 8	50.2% (163/325)	25.9% (42/162)	50.5% (158/313)	19.5% (31/159)
Difference (95% CI) ⁵	24.2% (15.5%, 33.0%)		31.0% (22.7%, 39.3%)	
p-Value ⁵	<0.001		<0.001	
Percentage change in HECSI score from baseline to Week 16				
LS mean	-56.5%	-21.2%	-58.9%	-13.4%
Difference (95% CI) ⁶	-35.2% (-46.7%, -23.8%)		-45.5% (-56.4%, -34.6%)	
p-Value ⁶	<0.001		<0.001	
Change in DLQI score from baseline to Week 16				
LS mean	-7.6	-3.9	-7.0	-3.1
Difference (95% CI) ⁶	-3.6 (-4.7, -2.6)		-3.9 (-5.0, -2.8)	
p-Value ⁶	<0.001		<0.001	
Change in HESD score (weekly average) from baseline to Week 16				
LS mean	-3.4	-1.7	-3.2	-1.4
Difference (95% CI) ⁶	-1.7 (-2.2, -1.2)		-1.9 (-2.4, -1.4)	
p-Value ⁶	<0.001		<0.001	
Change in HESD itch score (weekly average) from baseline to Week 16				
LS mean	-3.6	-1.9	-3.4	-1.4
Difference (95% CI) ⁶	-1.7 (-2.3, -1.2)		-2.0 (-2.5, -1.4)	
p-Value ⁶	<0.001		<0.001	
Change in HESD pain score (weekly average) from baseline to Week 16				
LS mean	-3.4	-1.8	-3.3	-1.3
Difference (95% CI) ⁶	-1.6 (-2.1, -1.0)		-2.0 (-2.6, -1.5)	
p-Value ⁶	<0.001		<0.001	
Change in HEIS from baseline to Week 16				
LS mean ⁶	-1.5	-0.8	-1.4	-0.6
Difference (95% CI) ⁶	-0.6 (-0.8, -0.5)		-0.8 (-1.0, -0.6)	
p-Value ⁶	<0.001		<0.001	
Change in HEIS PDAL score from baseline to Week 16				
LS mean	-1.5	-0.9	-1.5	-0.7
Difference (95% CI) ⁶	-0.6 (-0.8, -0.4)		-0.8 (-1.0, -0.6)	
p-Value ⁶	<0.001		<0.001	

Endpoint	Trial DELTA 1		Trial DELTA 2	
	Delgocitinib (N=325)	Vehicle (N=162)	Delgocitinib (N=313)	Vehicle (N=159)
Proportion of subjects with reduction of DLQI score of ≥ 4 points at Week 16 ⁷	74.4% (227/305)	50.0% (74/148)	72.2% (216/299)	45.8% (70/153)
Difference (95% CI) ⁵	24.5% (15.0%, 33.9%)		26.4% (17.0%, 35.9%)	
p-Value ⁵	<0.001		<0.001	

Source: page 55-91 of clinical study report for Trial LP0133-1401 and page 55-91 of clinical study report for Trial LP0133-1402.

Statistical Reviewer's Analysis (same as Applicant's Analysis); adiga.xpt, adhesd.xpt, adhecsi.xpt, and addlqi.xpt

¹ FAS: all subjects randomized and dosed.

² Among subjects with a baseline HESD itch score (weekly average) ≥ 4 points.

³ Among subjects with a baseline HESD pain score (weekly average) ≥ 4 points.

⁴ Among subjects with a baseline HESD score (weekly average) ≥ 4 points.

⁵ Mantel-Haenszel risk difference and p-value are calculated by Cochran-Mantel-Haenszel test, stratified by region and baseline IGA-CHE score. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered nonresponse.

⁶ ANCOVA model with treatment and region as fixed factors, baseline IGA-CHE score and baseline score as covariates. Data considered nonresponse by using WOCF (including the baseline value) after initiation of rescue treatment or after permanent discontinuation of IMP.

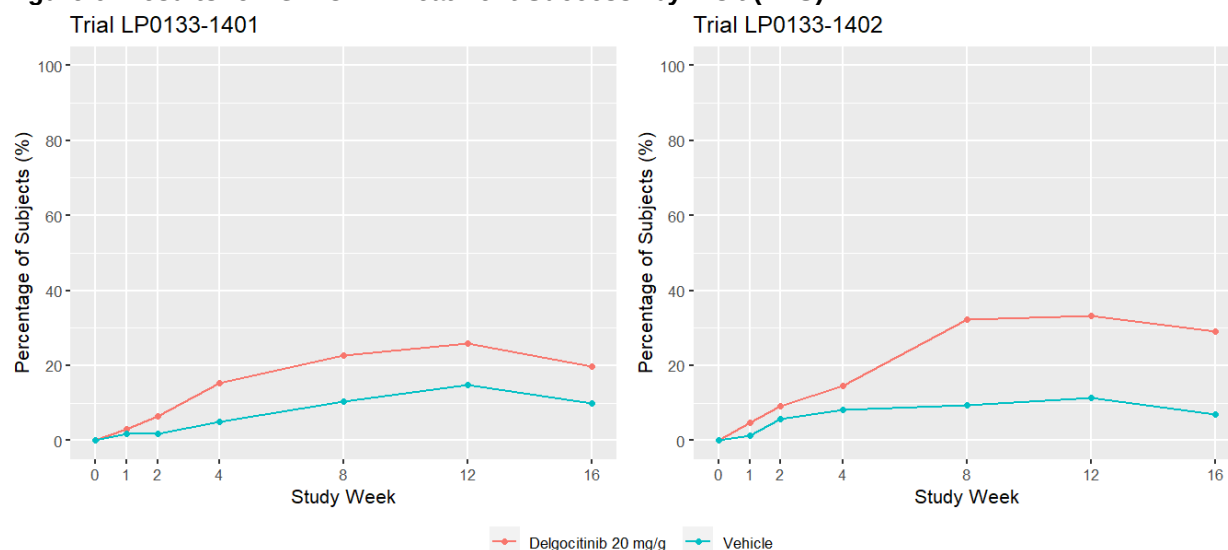
⁷ Among subjects with a baseline DLQI score ≥ 4 points.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; DLQI, Dermatology Life Quality Index; FAS, full analysis set; HEIS, Hand Eczema Impact Scale; HESCI, Hand Eczema Severity Index; HESCI-75, improvement of HESCI by 75%; HESCI-90, improvement of HESCI by 90%; HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; LS, least squares; N, number of subjects in trial arm; PDAL, proximal daily activity limitations; WOCF, worst observation carried forward

Efficacy Over Time

[Figure 6](#), [Figure 7](#), and [Figure 8](#) present the proportion of subjects with IGA-CHE treatment success, the proportion of subjects with HESD itch ≥ 4 -point improvement, and the proportion of subjects with HESD pain ≥ 4 -point improvement by visit/week for each treatment group. In both trials, the proportion of responders was generally higher in the delgocitinib group compared to the vehicle group.

Figure 6. Results for IGA-CHE Treatment Success¹ by Visit (FAS)²



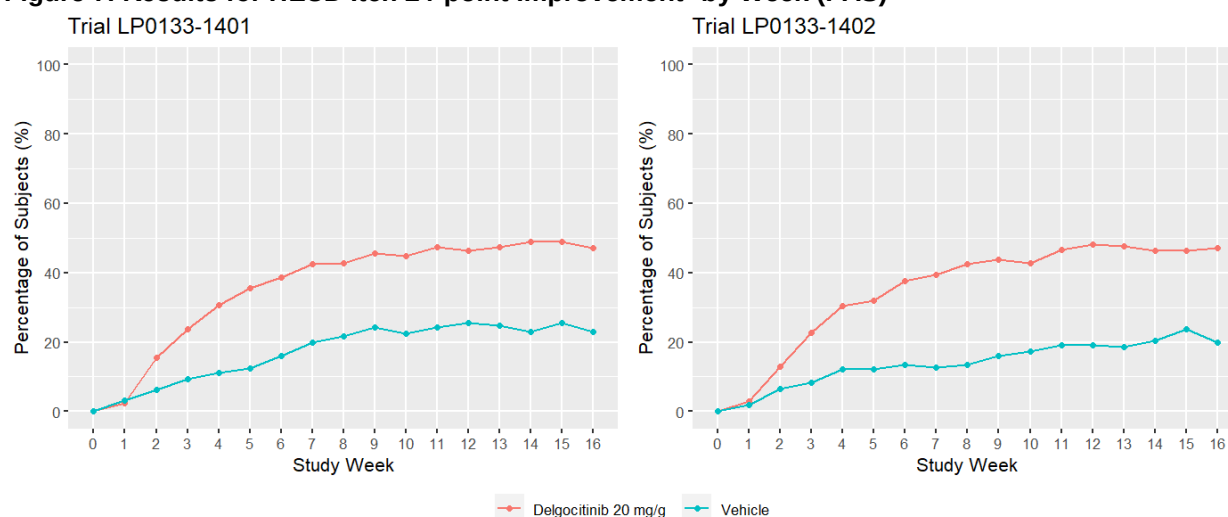
Source: page 54 of clinical study report for Trial LP0133-1401 and page 54 of clinical study report for Trial LP0133-1402. Statistical Reviewer's Analysis (same as Applicant's Analysis); adiga.xpt

¹ IGA-CHE treatment success is defined as IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥ 2 -step improvement from baseline.

² FAS: all subjects randomized and dosed. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered nonresponse.

Abbreviations: FAS, full analysis set; IGA-CHE, Investigator's Global Assessment for chronic hand eczema

Figure 7. Results for HESD Itch ≥ 4 -point Improvement¹ by Week (FAS)²



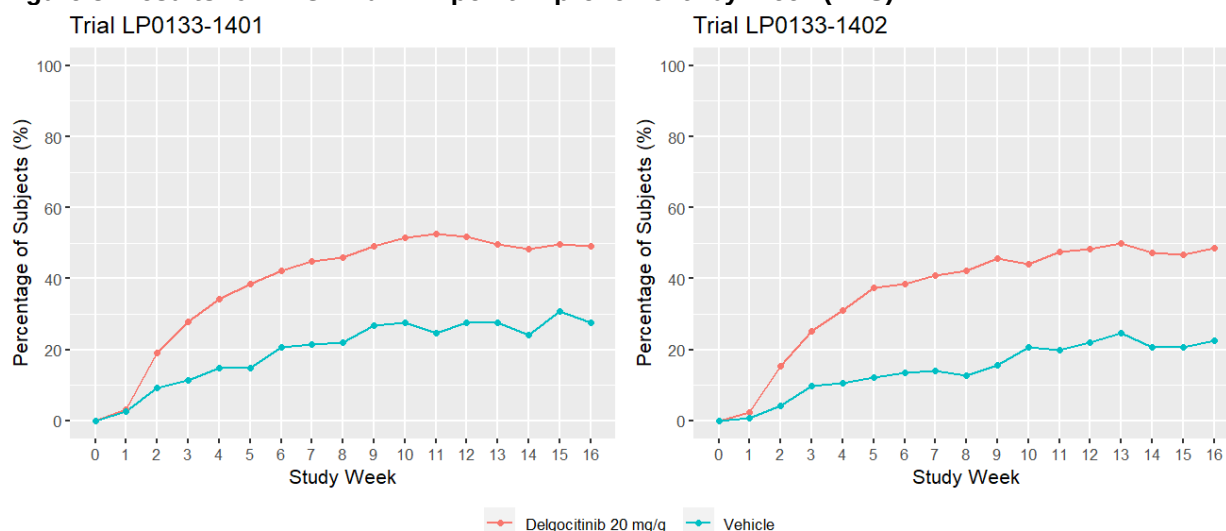
Source: page 63 of clinical study report for Trial LP0133-1401 and page 63 of clinical study report for Trial LP0133-1402. Statistical Reviewer's Analysis (same as Applicant's Analysis); adiga.xpt

¹ Responders were defined as subject who achieved reduction in HESD itch score (weekly average) of ≥ 4 points.

² FAS: all subjects randomized and dosed. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered nonresponse.

Abbreviations: FAS, full analysis set; HESD, Hand Eczema Symptom Diary

Figure 8. Results for HESD Pain ≥ 4 -point Improvement¹ by Week (FAS)²



Source: Page 75 of clinical study report for Trial LP0133-1401 and page 75 of clinical study report for Trial LP0133-1402. Statistical Reviewer's Analysis (same as Applicant's Analysis); adiga.xpt

¹ Responders were defined as subject who achieved reduction in HESD pain score (weekly average) of ≥ 4 points.

² FAS: all subjects randomized and dosed. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered nonresponse.

Abbreviations: FAS, full analysis set; HESD, Hand Eczema Symptom Diary

Subgroup Analyses

Results for subgroup analyses by age (<65 and ≥ 65 years), sex, race, ethnicity, region, and baseline IGA score are presented in [Table 140](#) to [Table 141](#) in Section [16.3](#). For Trial DELTA 1, the treatment effect was higher in males and in the North America subgroup for region. However, for Trial DELTA 2, the treatment effect was generally consistent across the subgroups for sex and region. For race and ethnicity, the sample sizes for some of the subgroups were relatively small; therefore, it would be difficult to detect any differences in efficacy between these subgroups and their complements.

6.3. Key Efficacy Review Issues

6.3.1. Impact of the Lack of Run-In Period on the Assessment of Efficacy

Issue

The phase 3 trials (DELTA 1 and DELTA 2) did not include a TCS run-in period to identify and randomize subjects with inadequate response to treatment with TCS.

Background

At the End-of-Phase 2 meeting, the Agency advised that an inadequate response to TCS therapy may not be reliably determined based on medical history alone. To address this, the Agency recommended incorporating a run-in period with standard care measures (e.g., moisturizers, irritant avoidance) and TCS therapy to prospectively confirm inadequate response.

The Applicant, however, did not incorporate a run-in-period and expressed concern that such a run-in period would unnecessarily re-expose subjects to therapies previously deemed ineffective and delay access to an investigational product in a setting with limited treatment options. In their NDA submission, the Applicant further argued that defining inadequate response based on a single short course of TCS with limited follow-up does not appropriately reflect the chronic, relapsing nature of CHE. The Applicant noted that while patients may experience temporary improvement with a short course of potent TCS, the durability of response, timing of relapse, need for retreatment, and cumulative treatment burden remain uncertain. Therefore, the Applicant concluded that selection based on documented medical history was more reflective of the target patient population.

Assessment

Although the Applicant did not incorporate a run-in-period into trial design as recommended by the Agency, in response to Agency concerns regarding appropriate definition of the study population, the Applicant analyzed data under TCS run-in-like conditions within the phase 3 trials (comparing subjects who discontinued daily TCS no earlier than 2, 4, or 8 weeks prior to screening, and subjects who used daily TCS on the hands after screening, up to 2 weeks before baseline). The Applicant conducted post hoc subgroup analyses of the primary and key secondary endpoints at Week 16 by these TCS run-in-like periods.

[Table 14](#) presents the results for the Applicant's post hoc analysis for the primary efficacy endpoint (i.e., proportion of subjects with IGA-CHE treatment success at Week 16) by the TCS run-in-like periods. In Trial DELTA 1, the treatment effect was similar for TCS run-in-like subgroups. In Trial DELTA 2, the treatment effect was slightly smaller for subjects in the TCS run-in-like subgroup than those not in the TCS run-in-like subgroup; however, there was considerable overlap in the 95% CIs.

Table 14. Applicant's Post Hoc Analysis for the Primary Efficacy Endpoint by the TCS Run-In-Like Periods, Trials DELTA 1 and DELTA 2 (FAS)¹

Trials/Run-In-Like Subgroups	Delgocitinib	Placebo	Difference (95% CI)²
Trial DELTA 1			
TCS ≤2 weeks before screening			
Yes	27/142 (19.0%)	6/67 (9.0%)	9.8% (0.4%, 19.3%)
No	37/183 (20.2%)	10/95 (10.5%)	9.8% (1.3%, 18.4%)
TCS ≤4 weeks before screening			
Yes	34/175 (19.4%)	9/84 (10.7%)	8.6% (-0.3%, 17.5%)
No	30/150 (20.0%)	7/78 (9.0%)	11.3% (2.2%, 20.4%)
TCS ≤8 weeks before screening			
Yes	40/210 (19.0%)	10/99 (10.1%)	8.9% (0.9%, 16.9%)
No	24/115 (20.9%)	6/63 (9.5%)	11.3% (0.9%, 21.8%)
Trial DELTA 2			
TCS ≤2 weeks before screening			
Yes	28/111 (25.2%)	5/54 (9.3%)	15.3% (4.2%, 26.5%)
No	63/202 (31.2%)	6/105 (5.7%)	25.4% (17.6%, 33.2%)
TCS ≤4 weeks before screening			
Yes	36/150 (24.0%)	5/77 (6.5%)	17.6% (8.8%, 26.3%)
No	55/163 (33.7%)	6/82 (7.3%)	26.5% (17.3%, 35.7%)
TCS ≤8 weeks before screening			
Yes	49/189 (25.9%)	6/104 (5.8%)	20.2% (12.6%, 27.9%)
No	42/124 (33.9%)	5/55 (9.1%)	25.0% (13.9%, 36.1%)

Trials/Run-In-Like Subgroups	Delgocitinib	Placebo	Difference (95% CI)²
Pooled Trials			
TCS ≤2 weeks before screening			
Yes	55/253 (21.7%)	11/121 (9.1%)	11.8% (4.6%, 19.0%)
No	100/385 (26.0%)	16/200 (8.0%)	18.4% (12.7%, 24.2%)
TCS ≤4 weeks before screening			
Yes	70/325 (21.5%)	14/161 (8.7%)	12.1% (5.8%, 18.3%)
No	85/313 (27.2%)	13/160 (8.1%)	20.1% (13.6%, 26.6%)
TCS ≤8 weeks before screening			
Yes	89/399 (22.3%)	16/203 (7.9%)	14.3% (8.8%, 19.8%)
No	66/239 (27.6%)	11/118 (9.3%)	19.0% (11.3%, 26.6%)

Source: Statistical Reviewer's Analysis; adsl.xpt, adiga.xpt

¹ FAS: all subjects randomized and dosed. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered nonresponse.

² Mantel-Haenszel risk difference, stratified by region and baseline IGA-CHE score.

Abbreviations: CI, confidence interval; FAS, full analysis set; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; TCS, topical corticosteroids

Conclusion

The treatment effect in subjects with and without TCS run-in-like period was generally similar to the overall population. Therefore, the impact of the lack of a formal run-in period on the assessment of efficacy appears low.

6.3.2. Impact of Content Validity, Other Measurement Properties, and Data Interpretability for COA-Based Efficacy Endpoints

6.3.2.1. Fitness for Purpose and Interpretability of the HECSI

Issue

There was uncertainty regarding whether the HECSI was fit-for-purpose and interpretable (b) (4).

Background

The HECSI is a ClinRO that is a widely used assessment in clinical practice and clinical trials (Rönsch et al. 2019) to evaluate the severity and extent of patients' CHE symptoms on the hands and wrists. The Applicant included the HECSI as it is intended to measure both the extent and the intensity of the disease based on multiple clinical signs. Published evidence indicates the HECSI demonstrates adequate internal consistency (Janstrup et al. 2023) and inter-rater and intra-rater reliability in the assessment of hand eczema (Held et al. 2005).

Assessment

The Applicant did not provide justification for the inclusion of each of the six CHE signs (erythema, infiltration/papulation, vesicles, fissures, scaling, edema) in the HECSI. Evidence was not provided to address whether each of the six CHE signs were clinically equivalent to warrant equal weighting in the total HECSI score. Although the HECSI measures clinical signs that are broadly relevant to CHE, the overall score may not validly represent the severity of the hand

eczema. The clinical signs may not be relevant for all patients within or between CHE subtypes leading to over- or underestimation of clinical severity. For this reason, the overall score is not considered a valid representation of CHE severity and cannot be clearly interpreted.

The Applicant's psychometric analysis report indicated weaker internal reliability (<0.70) for both the total HECSI score (incorporating the area calculation) (0.62) and for the score with the area calculation removed (0.54). There was an indication that this scale was not unidimensional, and thus, that the score could not be meaningfully interpreted to reliably characterize the concept of interest (i.e., severity and extent of hand eczema). Combined with the instrument's complex scoring algorithm, which could result in imprecise or inaccurate scores, there remains a concern that scores did not clinically characterize CHE signs such that they were clearly interpretable. Differences in the proportion of subjects achieving $>75\%$ (HECSI-75) and $>90\%$ (HECSI-90) improvement at Week 16 from baseline cannot be interpreted because the metric is an insufficient indicator of responsiveness, and scores may not adequately reflect CHE severity due to the reasons above.

Despite the limitations discussed above, for completeness, the Agency requested the Applicant conduct quantitative anchor-based analyses using data from Trial DELTA 1 and Trial DELTA 2 to aid in the interpretation of the HECSI-based endpoint scores. Based on these analyses, the Applicant proposed a range of meaningful change thresholds of 50 to 90% improvement in HECSI-based endpoint scores. The Agency reviewed the Applicant's anchor-based analyses and concluded a plausible range of meaningful change values would be a 69 to 82% improvement in HECSI-based endpoint scores. Given the issues with the interpretability of the HECSI score itself (i.e., did not clinically characterize the severity and extent of hand eczema), these meaningful change analyses based on the endpoint scores have limited interpretability. Refer to Section 16.1.6 for details of the FDA's evaluation of meaningful within-subject percent change in the HECSI scores.

Conclusion

The factors above render the HECSI not fit-for-purpose for the context of use and the HECSI-based endpoint scores uninterpretable (b) (4).

6.3.2.2. Fitness for Purpose and Interpretability of the HEIS PDAL Domain

Issue

There was uncertainty regarding whether the HEIS PDAL domain was fit-for-purpose to support labeling claims.

Background

The HEIS is a PRO that assesses the impact of CHE on key aspects of functioning and health-related quality of life. The domain score (b) (4) (PDAL) consists of three items evaluating the impact of hand eczema on subjects' ability to 1) use soaps/cleaning products; 2) complete housework that involves getting their hands wet; and 3) wash themselves. The Applicant completed concept elicitation and cognitive debriefing research to evaluate the content validity of the HEIS. Most subjects understood items within the HEIS, although a few had

difficulty understanding questions related to impacts to work, the use of soaps/cleaning products, and disliking the appearance of the hands. Most subjects found the questions to be relevant (e.g., dislike of appearance, embarrassment, self-consciousness, soap/cleaning products). However, touching objects, wearing gloves, and work were reportedly less relevant, based on CHE type and physician-rated CHE severity.

Items comprising the HEIS PDAL domain were evaluated with subjects (“ability to use products,” “hard to do housework,” and “hard to wash yourself”), and modified to integrate subject feedback. It was concluded that patients would likely understand and use the recall period of the “past 7 days” appropriately within the context of a clinical trial.

Assessment

While the development of the HEIS broadly aligned with good COA development guidelines, multiple functional impacts measured by the HEIS co-occur with other dermatologic disease and are therefore not specific to CHE. In the score, equal weighting may not reflect daily life impacts of CHE, and such functional effects may vary by occupational contexts (e.g., washing soap may be more relevant for healthcare workers, household cleaning may be more relevant for caregivers or parents, etc.).

The HEIS PDAL domain comprised items that may be influenced by factors external to the clinical trial. For example, items comprising the scale assess the use of soaps/cleaning products, housework that involves the hands getting wet, and washing oneself. As irritants can exacerbate CHE symptoms, it is not possible to disentangle or control for material (i.e., product-related), environmental (e.g., hard water, water temperature, exposure to other chemicals), or behavioral (e.g., length of exposure, avoidance behavior as noted in the qualitative research stated above) factors that could influence scores on the HEIS.

Conclusion

The HEIS PDAL domain was not considered fit-for-purpose (b) (4).

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical safety profile of delgocitinib was evaluated in safety pharmacology studies in rats and dogs (oral); repeat-dose toxicity studies in mice (dermal; 3 months), rats (oral; up to 6 months), dogs (oral; up to 9 months), and minipigs (dermal; up to 9 months); genotoxicity studies; reproductive and developmental toxicity studies in rats and rabbits; juvenile animal toxicity studies in rats and minipigs; and carcinogenicity studies in mice (dermal) and rats (oral). Additional studies included a phototoxicity study in mice, primary skin irritation studies in rabbits and minipigs, a skin sensitization study, a skin photosensitization study and a dermal phototoxicity study in guinea pigs, and a bovine corneal opacity and permeability (BCOP) test. The results from these studies are summarized below.

Safety Pharmacology

Delgocitinib had no effects on cardiovascular, respiratory, or neurological parameters at clinically relevant doses. Delgocitinib had no remarkable inhibitory effect on the human ether-à-go-go-related gene (hERG) current at clinically relevant concentrations. Delgocitinib had an inhibitory effect on gastrointestinal transport (↓27%) in rats at an oral dose of 30 mg/kg.

General Toxicology

No treatment-related changes were observed in a 9-month dermal toxicity study in minipigs treated with delgocitinib ointment. The no-observed-adverse-effect level (NOAEL) was 5% (20 mg/kg/day) delgocitinib ointment, the maximum feasible dose. Skin lesions were observed in a 9-month oral toxicity study in dogs at 3.0 mg/kg/day and the dose was lowered to 1.5 mg/kg/day from Week 24. The NOAEL was 0.6 mg/kg/day.

Table 15. Multiples of Human Exposure for NOAELs Identified in Pivotal Toxicology Studies

Study	Route	NOAEL	Systemic Exposure (AUC_{0-24h}, ng.hr/mL)	Multiples of Exposures* (Based on AUC Comparison)
9-month toxicity study in minipigs	Dermal	5% (20 mg/kg/day)	114.38	15
9-month toxicity study in dogs	Oral	0.6 mg/kg/day	1521.9	206

Source: Nonclinical reviewer's analysis

*Multiples of exposures are ratios of systemic exposure between animals and humans (recommended human dose, 2% (20 mg/g) BID (2.1 g/day) with AUC_{0-12h} = 3.7 ng.h/mL) (AUC_{0-24h} = 7.4 ng.h/mL).

Abbreviations: AUC, area under the concentration-time curve; AUC0-12h, area under the concentration-time curve from 0 to 12 hours; AUC0-24h, area under the concentration-time curve from 0 to 24 hours; BID, twice daily; NOAEL, no observed adverse effect level

Reproductive and Developmental Toxicology and Juvenile Animal Toxicology

Reproductive and developmental toxicology studies included fertility and early embryonic development studies in male and female rats, embryo-fetal development studies in rats and rabbits, and a pre- and postnatal development study in rats. Adverse effects were seen at higher doses in each of the reproductive and developmental toxicology studies, but a NOAEL was established in each study with acceptable margins of exposures.

Juvenile animal studies were conducted in rats (oral) and minipigs (dermal). There were no changes suggestive of systemic or target organ toxicity at up to the highest dose level, 30 mg/kg/day, in juvenile rats. In juvenile minipigs, there were no treatment-related findings following 28-day repeated dermal application of delgocitinib ointment 5% (20 mg/kg/day).

The results of these studies are shown in the table below, including NOAEL, systemic exposure, multiples of exposures, and major findings.

Table 16. NOAELs, Systemic Exposure, Multiples of Exposures, and Major Findings From Reproductive, Developmental, and Juvenile Animal Toxicology Studies

Study	NOAEL (mg/kg/day)	Systemic Exposure (AUC _{0-24h} , µg.hr/mL)	Multiples of Exposures*	Major Findings
Rat female FEED Early embryonic development toxicity	3	0.817	110	Postimplantation losses and a decrease in the number of live embryos were observed at 10 mg/kg/day and 30 mg/kg/day (oral gavage), respectively.
Rat female FEED Maternal fertility and general toxicity	30	8.05	1087	Decreases in body weight gain, food consumption, number of corpora lutea, implantations, and fertility index were observed in female rats at 100 mg/kg/day (oral gavage).
Rat male FEED	30	9.685	1308	There were no effects on male fertility or early embryonic development at doses up to 30 mg/kg/day.
Rat EFD Maternal toxicity	30	10.655	1446	No significant maternal toxicity was noted at doses up to 30 mg/kg/day.
Rat EFD Embryofetal Toxicity	3	0.888	120	Decreases in fetal weight and skeletal variations were observed at doses ≥10 mg/kg/day. An increase in postimplantation loss was observed at 30 mg/kg/day.
Rabbit EFD Maternal toxicity	10	7.3375	992	No significant maternal toxicity was noted at doses up to 10 mg/kg/day.
Rabbit EFD Embryofetal toxicity	3	1.4336	193	An increase in postimplantation loss index, reduced number of live fetuses, and decrease in fetal weights were observed at 10 mg/kg/day.
Rat PPND Maternal toxicity	30	11.51	1555	No significant maternal toxicity was noted at doses up to 30 mg/kg/day.
Rat PPND Developmental toxicity	10	2.801	378	Extended gestation period, a decrease in the birth index, an increase in the number of dead newborns, decreased fetal viability, and reduced pup weights were noted during the early postnatal period at 30 mg/kg/day.
Rat juvenile	30	11.075	1496	No changes suggestive of systemic or target organ toxicity at doses up to 30 mg/kg/day (oral gavage).
Minipig juvenile	5%/20 mg/g	<LLOQ	N/A	No treatment-related findings up to 5% (20 mg/kg/day) delgocitinib ointment (dermal).

Source: Nonclinical reviewer's analysis

*Multiples of exposures are ratios of systemic exposure between animals and humans (recommended human dose, 2% (20 mg/g) BID (2.1 g/day) with AUC_{0-12h}=3.7 ng.h/mL) (AUC_{0-24h}=7.4 ng.h/mL).

Abbreviations: AUC_{0-12h}, area under the concentration-time curve from 0 to 12 hours; AUC_{0-24h}, area under the concentration-time curve from 0 to 24 hours; BID, twice daily; EED, early embryonic development; EFD, embryo-fetal development; FEED, fertility and early embryonic development; LLOQ, lower limit of quantitation; NOAEL, no observed adverse effect level; PPND, pre- and postnatal development

Genetic Toxicity

Delgocitinib was not mutagenic in the Ames assay. Delgocitinib had the potential to induce polyploidy in human peripheral blood lymphocytes, but not chromosomal structural aberrations in vitro. Delgocitinib did not induce chromosomal aberrations (structural or numerical aberrations) in rat bone marrow cells in vivo. Delgocitinib ointment (5%) did not induce micronuclei in the epidermal cells of hairless mice.

Carcinogenicity

In the dermal carcinogenicity study in mice, delgocitinib ointment (1%, 3% and 5%) was administered once daily for 104 weeks. No drug-related neoplastic findings were noted at topical doses up to 5% delgocitinib ointment. In the 2-year oral carcinogenicity study in rats, increased incidence of benign thymoma was noted in females at 30 mg/kg/day (see Section 13.2 for detailed information).

Table 17. NOAELs, Systemic Exposure, and Multiples of Exposures From Carcinogenicity Studies in Mice and Rats

Study	Route	NOAEL*	Systemic Exposure (AUC _{0-24h} , µg.hr/mL) (M/F)	Multiples of Exposures** (Based on AUC Comparison) (M/F)
104-week carcinogenicity study in mice	Dermal	5% 30 mg/kg/day	4.79/4.37	647/591
104-week carcinogenicity study in rats	Oral	10 mg/kg/day	4.48/4.29	605/580

Source: Nonclinical reviewer's analysis

*The dose at which no neoplastic findings were observed.

**Multiples of exposures are ratios of systemic exposure between animals and humans (recommended human dose, 2% (20 mg/g) BID (2.1 g/day) with AUC_{0-12h}=3.7 ng.h/mL) (AUC_{0-24h}=7.4 ng.h/mL).

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-12h}, area under the concentration-time curve from 0 to 12 hours; AUC_{0-24h}, area under the concentration-time curve from 0 to 24 hours; BID, twice daily; F, female; M, male; NOAEL, no observed adverse effect level

Special Toxicology

In minipigs, delgocitinib ointment was determined to be nonirritating after 24-hour exposure. The skin sensitization potential of vehicle and 3% delgocitinib ointment was evaluated in guinea pigs and no sensitization was observed. Phototoxicity was evaluated for delgocitinib ointment in guinea pigs, and no effects were observed. Delgocitinib ointment was evaluated in a BCOP test and was found to have no ocular irritant properties. Delgocitinib was immunotoxic in a 4-week oral dose study in rats; however, this is an expected effect because of the pharmacological/immunosuppressive nature of delgocitinib.

Overall, the nonclinical safety assessment supports the approval of this product. ANZUPGO is approvable from a pharmacology/toxicology perspective.

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

Janus kinase inhibitors have been associated with a range of serious adverse events, reflected in class labeling including Boxed Warnings and Warnings and Precautions. For JAKi approved to treat inflammatory conditions, Boxed Warnings include serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral (including herpes zoster reactivation), and opportunistic infections; malignancies, including lymphoma and nonmelanoma skin cancers; increased all-cause mortality including sudden cardiovascular death; MACE, including cardiovascular death, myocardial infarction, and stroke; and thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis. Such class-wide labeling was informed by a well-controlled long-term safety trial for tofacitinib and is included in labeling for systemic JAKi to treat inflammatory conditions (e.g., baricitinib, upadacitinib tablets) and is included in labeling for the only currently approved topical JAKi (ruxolitinib cream).

Considerations for Including a Box Warning and Warnings and Precautions in Labeling as Per Class Labeling for JAKi

Measurable Systemic Exposure

Delgocitinib cream, 2% demonstrated measurable systemic absorption in clinical trials (refer to Section 14 of this review). In the maximal use trial LP0133-2285 in 15 subjects with CHE (median BSA 1%, range 0.25 to 3%), mean C_{max} reached nonsubnanomolar levels of 1.53 ng/mL (4.93nM, range 0.03 to 23.52nM) on Day 1 and 0.53 ng/mL (1.71nM, range 0.55 to 3.47nM) on Day 8, with individual subjects reaching concentrations as high as 7.30 ng/mL (23.52nM). In phase 3 trial DELTA 2 (estimated BSA range 0.2 to 4.4%), one subject reached 29.2 ng/mL (94.09nM), and even excluding this outlier, maximum concentrations of 5.65 ng/mL (18.21nM) were observed (refer to Section 14 of this review). The Agency waives certain pharmacology-toxicology and cardiac safety assessments only when systemic exposure under maximal use conditions is subnanomolar (negligible). Systemic exposure to delgocitinib exceeds this threshold for AEs, we cannot exclude the potential of delgocitinib to cause AEs observed with the JAK inhibitors.

Unknown Exposure Threshold for Adverse Events

There is no scientifically established systemic exposure threshold below which JAK inhibitor-related adverse events do not occur. The Applicant acknowledges this limitation, stating that "establishing a threshold for systemic ADRs [adverse drug reactions] is not feasible." Given that JAK inhibitors to treat inflammatory conditions as a class have demonstrated serious risks including increased mortality, MACE, thrombosis, and considering that delgocitinib is a pan-JAK inhibitor affecting all four members of the JAK family (JAK1, JAK2, JAK3, and TYK2), the potential for class-wide effects cannot be dismissed based solely on low exposure levels when the threshold for safety is unknown.

Observed Systemic Adverse Reactions and Laboratory Abnormalities

Cytopenias are established adverse reactions associated with JAK inhibitors approved for inflammatory conditions, including neutropenia, lymphopenia, and anemia with baricitinib and upadacitinib, and thrombocytopenia and lymphopenia with abrocitinib.

In vehicle-controlled trials with delgocitinib, 638 subjects received delgocitinib (person-years of observation = 197) and 321 subjects received vehicle (person-years of observation = 94). While it is acknowledged that the unequal exposure would be expected to result in more events in the delgocitinib group, an imbalance in hematologic parameters persists even when accounting for exposure differences through rate calculations: 13.6% of delgocitinib-treated subjects experienced any grade worsening leukocyte shifts compared to 6.2% in the vehicle group (EAIR 44.2 versus 21.3). Neutrophil shifts occurred in 4.4% versus 3.7% and lymphocyte shifts in 2.5% versus 1.9%, respectively. The current exposure-adjusted data reveals a meaningful imbalance that cannot be dismissed given the established mechanistic possibility for hematologic effects with JAK inhibitors. For some subjects, a causal association of hematologic shifts to delgocitinib could not be excluded, and some subjects did not return to pretreatment hematologic values. Refer to Section [7.6.1.6](#) of this review for individual subject narratives, and Section [17](#) of this review for comprehensive individual subject analyses of hematologic changes.

Additionally, during the open-label period of the phase 3 trials, two cases of herpes zoster occurred in otherwise healthy subjects less than 50 years of age, and one case of eczema herpeticum was reported in delgocitinib-treated subjects (refer to Section [7.7.3](#) of this review). While these cases occurred during the open-label period without a concurrent vehicle control for comparison, and the observed rates may be consistent with background incidence rates for herpes zoster and eczema herpeticum, the mechanistic plausibility for a causal relationship cannot be dismissed. JAK inhibitors are known to impair antiviral immune responses by disrupting cytokine signaling pathways critical for NK cell function. NK cells play a central role in early host defense against viral infections, providing biological plausibility that delgocitinib may have contributed to these viral reactivation events.

Postmarketing data from CORECTIM (delgocitinib ointment, 0.5%), which contains the same active moiety, revealed additional immune-related events, including 86 cases of eczema herpeticum and 21 cases of herpes zoster. Notably, events were observed even in pediatric patients as young as 4 and 10 years of age. Important limitations of this postmarketing data include differences in the patient population (atopic dermatitis), product application over larger body surface area, dosage forms and strengths, and lack of a control group for rate comparison. In addition, there is a lack of information regarding the number of patients who used the product and the duration of exposure. Nonetheless, the moiety is the same (delgocitinib), and given the established mechanistic plausibility for JAK-inhibitor-associated immune suppression there is residual uncertainty regarding delgocitinib's potential association with these systemic immune-related adverse events. Refer to Section [7.3](#) of this review for details.

Extent of Safety Database

In the phase 3 clinical trials, less than 700 subjects exposed to delgocitinib in vehicle-controlled trials for 16 weeks and less than 200 subjects with continuous exposure to Week 52. The safety database is not robust enough to exclude that adverse event observed with JAKi products for the treatment of inflammatory conditions.

Applicant Arguments Against a Boxed Warning

Effective Pan-JAK Inhibition Is Confined to The Skin by the Topical Cream Formulation

The Applicant stated that ANZUPGO was specifically developed as a topical formulation that allows effective diffusion within the skin compartment to target inflammation locally; the cream is not formulated with “penetration enhancers,” which minimizes transdermal absorption and subsequent systemic circulation exposure. This results in systemic exposure levels that remain lower than levels where meaningful systemic pharmacological effects would occur, contrasted with (b) (4) which “includes skin penetration enhancers;” the bioavailability of topical delgocitinib cream is 0.6%, approximately an order of magnitude less than (b) (4) (b) (4) bioavailability.

Review Team Assessment

Contrary to the Applicant’s assertion that their formulation lacks penetration enhancers, delgocitinib cream (b) (4). The Applicant’s comparison to (b) (4) is misleading, as multiple types of penetration enhancers exist, and the presence of (b) (4) can facilitate dermal penetration and systemic absorption. In addition, the theoretical absence of penetration enhancers would not guarantee safety, particularly given that chronic hand eczema patients may have compromised skin barrier function that could increase absorption unpredictably.

Regarding the Applicant’s argument that the bioavailability of topical delgocitinib cream is 0.6%, approximately an order of magnitude less than (b) (4) bioavailability, even with 0.6% bioavailability, measurable delgocitinib plasma concentrations were detected in clinical trials, demonstrating that the drug does reach systemic circulation (refer to Section 14 of this review). Comparing bioavailability percentages to another moiety that has different potency and different JAK inhibition (JAK 1 and JAK2) does not eliminate the fundamental concern about JAK inhibition-related adverse events.

Negligible Level of Systemic Exposure Is Well Characterized by a Highly Sensitive PK Assay

The Applicant stated: a state-of-the-art “LC-MS/MS” assay was developed with a lower limit of quantification (LLOQ) of 0.005 ng/mL in human plasma; this assay is 200-fold more sensitive than the delgocitinib assay developed by Japan Tobacco (LLOQ of 1 ng/mL) and 60-fold more sensitive than the (b) (4) assay; the high sensitivity allowed for measurable concentrations in most clinical samples despite negligible systemic exposure.

Review Team Assessment

There is observed systemic exposure to delgocitinib that is not in subnanomolar range and therefore not considered negligible.

Establishing a Threshold for Systemic ADRs Is Not Feasible, as the Exposure Levels Required for These Effects Cannot Be Reached With the Topical Formulation of Delgocitinib in CHE

The Applicant acknowledged that an exposure threshold for JAK-inhibitor-related adverse events cannot be established with available data; however, safety margins from nonclinical studies and clinical exposure levels significantly under half-maximal inhibitory concentration (IC₅₀) values in whole blood indicate delgocitinib cream is not expected to have systemic JAK-inhibitor-related effects. Systemic exposure levels with delgocitinib cream are approximately 14-fold lower than the lowest tested oral dose and more than 100-fold lower than IC₅₀ values assessed using a whole blood-based assay for ex vivo IL-4 inhibition, and lower than 20% inhibitory concentration (IC₂₀) values for ex vivo interferon (IFN)-α inhibition. No drug-related cases of serious infection, MACE, malignancies, or venous thromboembolic events were observed in clinical trials.

Review Team Assessment

The Applicant acknowledged that an exposure threshold cannot be established. Without a defined safe exposure threshold level, any systemic exposure represents an unknown risk.

The Applicant's calculations based on IC₅₀ and IC₂₀ ex vitro values are undermined by actual *clinical* observations. The documented imbalance in hematologic laboratory shifts in the vehicle-controlled trials suggests evidence of systemic pharmacological activity. Furthermore, the company's reliance on ex vitro assays for only 2 cytokines (IL-4 and IFN-α) out of >50 JAK-mediated pathways is insufficient to predict clinical safety. The Applicant's assertion that "systemic exposure levels with delgocitinib cream are approximately 14-fold lower than the lowest tested oral dose" lacks clinical relevance since no oral formulation of delgocitinib is approved for any indication. The referenced "lowest tested oral dose" was administered as a single dose to healthy volunteers in a cardiac safety study (Trial LP0133-1409). This comparison provides no meaningful safety margin assessment for the proposed indication and patient population.

Finally, though no drug-related cases of serious infection, MACE, malignancies, or venous thromboembolic events were observed in clinical trials, the absence of events in clinical trials does not rule out rare but serious adverse events that could occur in larger populations or with longer exposure periods. The safety database is not of sufficient size and duration to reliably exclude adverse events seen with JAK inhibition.

Systemic Exposure to Delgocitinib Sustained at Levels That Do Not Support the Development of Systemic Toxicity

The Applicant stated: no subjects had continuous delgocitinib exposure levels approaching concentrations sufficient for meaningful systemic JAK inhibition effects. The majority of subjects had plasma concentrations below 1 ng/mL, with no subjects presenting exposure levels above 2 ng/mL continuously throughout trials. Nonclinical studies showed that continuous exposure for at least 3 months at systemic levels around 40 ng/mL is needed before JAK inhibition-related adverse effects are observed. Human exposure of approximately 0.5 ng/mL provides a safety margin in excess of 80-fold.

Review Team Assessment

The Applicant's argument that no subjects had elevated "continuous" delgocitinib exposure levels fails to account for potential JAK-inhibition-related risks associated with intermittent peak concentrations and cumulative effects over time. In addition, individual patients could experience higher peak concentrations due to factors such as compromised skin barrier function, extensive application areas, or individual pharmacokinetic variability that were not fully captured in the controlled clinical trial setting. Furthermore, the Applicant's extrapolation from nonclinical data showing that 3 months of exposure at 40 ng/mL is needed for adverse effects may not accurately predict human sensitivity to JAK inhibition.

Delgocitinib competitively inhibited JAK1, JAK2, JAK3, and TYK2 with respect to adenosine triphosphate. The inhibitor constant (K_i) values for delgocitinib on JAK1, JAK2, JAK3, and TYK2 were 2.08, 1.71, 5.45, and 13.9 nmol/L, respectively. Furthermore, delgocitinib inhibited the JAK activity of JAK1, JAK2, JAK3, and TYK2 with IC_{50} mean values of 2.8 nmol/L, 2.6 nmol/L, 12.5 nmol/L, and 57.8 nmol/L, respectively. The C_{max} in the maximal use study in subjects with CHE (LP0133-2285) was 1.53 ng/mL (4.93 nmol/L) and 0.53 ng/mL (1.71 nmol/L) on Day 1 and 8, respectively. Overall, the C_{max} is on par with the IC_{50} of JAK1 and JAK2. While the systemic concentration/ IC_{50} ratio is much lower than oral JAK inhibitors, the systemic safety concern cannot be ruled out based on the systemic exposure/ IC_{50} comparison.

Extensive Postmarketing Safety Data for Exposure to the Same Drug Substance in Japan (CORECTIM) Provide No Evidence of Systemic Adverse Drug Reactions

The Applicant stated: delgocitinib ointment (CORECTIM) has been approved in Japan for atopic dermatitis since 2020 with an "estimated cumulative exposure of 4,252,624 patients through July 2024." Systemic exposure levels with delgocitinib cream 20 mg/g are similar to those observed with approved CORECTIM in Japan. Postmarketing surveillance has resulted in 15 serious infections from 13 patients among over 4 million exposed patients, with no all-cause mortality, MACE, or thromboembolic events, and one serious malignancy reported. The current CORECTIM package insert does not include risks related to systemic JAK inhibition, indicating that delgocitinib cream does not carry the typical risks associated with the JAK inhibitor boxed warning.

Review Team Assessment

Given the limitations of the postmarketing data including number of patients exposed, duration of exposure, patient history and laboratory assessment, causality for the reported cases of EH and HZ cannot be established. However, the role of delgocitinib based on its mechanism of action and known adverse reactions (e.g., virus reactivation, serious infection) cannot be excluded.

Combination With Systemic Immunosuppressants

The use of delgocitinib cream has not been studied in combination with biologic products acting on the immune system within the clinical development program (e.g., therapeutic biologics, other JAK inhibitors, or potent immunosuppressants such as azathioprine or cyclosporine). Such products were specified as prohibited in the trial protocols given the potential to interfere with the clinical efficacy and safety evaluations performed. All JAK inhibitors to treat inflammatory conditions carry a limitation of use for such medications; [REDACTED] (b) (4)

“Based on common mechanisms of action shared between systemic immunosuppressants and immunomodulators and topical delgocitinib, additive immunological effects could be expected. However, given the targeted local mechanism of delgocitinib cream with negligible amounts of the drug substance reaching the systemic circulation, any such additive effects would be of primary theoretical concern for the area of application. In terms of efficacy, this could result in an amplification of anti-inflammatory effects and represent an important therapeutic intention of the prescribing clinician. From the safety perspective, while local skin infections have been observed with use of delgocitinib cream, none of them have been severe or treatment-limiting. At most, a caution for the additional use of delgocitinib cream on top of a chosen systemic immunosuppressant or immunomodulator, considering the prescribing information of the individual medication, would be sufficient and empower clinicians to make informed decisions with the maximum ability to treat their patients.”

Because delgocitinib was not evaluated for safety in combination with other immunosuppressants, limitation of use section of labeling should include a recommendation that delgocitinib should not be used in combination with other JAKi or potent immunosuppressants.

Conclusion

In conclusion, based on the measurable systemic exposure to delgocitinib, absence of established safety threshold of systemic exposure, adverse events observed during clinical trials, and limited safety database, the review team recommends that labeling for delgocitinib cream include the potential risk of adverse reaction related to JAK inhibition in the Warnings and Precautions section of labeling. Labeling with a Boxed Warning is not recommended at this time because of the following reasons: 1) the product will be applied to less than 5% BSA in CHE patients, 2) data from the maximum use study showed low systemic exposure (for approximately 33% of the subjects the systemic exposure was sub-nanomolar on Day 1 and for 20% of the subjects it was sub-nanomolar on Day 8); 3) adverse reactions such as thrombosis, malignancy, and MACE were not observed during the development program; and 4) the risk of these major toxicities are dose-dependent. Based on the above, the risk for major toxicities is considered low for the proposed indication.

However, because there were exposures in the nano-molar range and the safety database is of size and duration that cannot reliably exclude potential adverse reactions associated with other JAK inhibitors for the treatment of inflammatory conditions, the labeling will include in the Warnings and Precaution section information regarding the potential risks of JAK inhibition. In addition, to further characterize the long-term safety, the Applicant will be required to conduct a post-marketing active-controlled clinical trial of sufficient size and duration to further characterize safety events of interest.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Delgocitinib cream, 2% and ointment, 0.5% are approved for marketing in other jurisdictions.

Delgocitinib Cream (ANZUPGO)

Delgocitinib cream, 2%, under the brand name ANZUPGO is currently approved for use in adults for the treatment of moderate to severe CHE in the European Union (marketing authorization September 19, 2024), United Kingdom, Switzerland, and the United Arab Emirates. Delgocitinib cream is also being evaluated for use in other markets. To date, no patients in the postmarketing database have been treated for more than one year (response to information request dated May 23, 2025). Since the launch of the product to the cutoff date (April 30, 2025), the Applicant received a total of 28 postmarketing safety reports. The duration of exposure from the reports where the information was provided varied from 1 day to 3 months.

The key findings from the available postmarketing data (October 2024 through April 2025) are:

- 28 adverse events (AEs) spontaneously reported (50% of unknown duration)
- 21 AEs of local cutaneous reactions: 8 AEs of hand dermatitis.
- No AEs of thrombosis, neutropenia, leukopenia, or abnormal lipids

Delgocitinib Ointment (CORECTIM)

Delgocitinib ointment, 0.5%, was initially approved in Japan in January 2020 for the treatment of AD in adults and marketed under the brand name CORECTIM. The population was extended to include patients aged 2 to 16 years (March 2021) and then 6 months to <2 years (January 2023) with approval of delgocitinib ointment, 0.25%.

Exposure

The Applicant stated that the CORECTIM postmarketing database (January 2020 until April 30, 2025) contains 3,571 case reports “representing use by an estimated 4 million patients between 2020 and January 2025.” Most of these (3,549 of 3,571) case reports described nonserious AEs (response to information request dated May 23, 2025). The Applicant determined the duration of exposure prior to the AE directly from the report or by using the treatment start date and date of the AE. However, in approximately two-thirds of the case reports, the treatment duration is unknown. The Applicant notes that “[t]here are 24 case reports where the duration of exposure prior to onset of the AE is known to exceed 1 year, all of which are nonserious. None of these cases raised any safety concern.” The Applicant further stated, “[e]ven though treatment duration is not available in many cases, it does not undermine the substantiveness of the finding that 4 years of postmarketing safety data from CORECTIM do not reveal any safety concerns.”

The table below provides a summary of the known treatment durations prior to AEs.

Table 18. Summary of Treatment Duration of CORECTIM Prior to Adverse Events

Treatment duration prior to onset of AE	Number of case reports (patients)
0-6 months	867
6-12 months	86
≥12months	24
Unknown (treatment duration, start date, end date or AE date not reported)	2389

Source: From Applicant's Response to 5/23/2025 FDA Information Request for Post-marketing data for Corectim and Anzupgo (Panel 1, pg 7; received 5/29/2025)
Abbreviation: AE, adverse event

Adverse Events and Adverse Events of Special Interest

The Applicant submitted an integrated analysis of the cumulative postmarketing safety data for CORECTIM from June 2020 through January 2024. Among 3,446 AEs, the most frequently reported AEs (≥1% of all events) in this analysis by preferred terms (PTs) were: application site erythema (9.6%), application site irritation (5.8%), application site acne (5.6%), application site pruritus (3.4%), application site folliculitis (2.2%), eczema herpeticum (2.2%), and skin irritation (1.7%). Application site acne, folliculitis, herpes simplex, and eczema herpeticum are listed adverse events in the Japanese labeling for CORECTIM.

Regarding infection, there were 86 reports of EH and 21 reports of herpes zoster infection among patients on delgocitinib ointment in the postmarketing setting.

EH is a potentially life-threatening systemic infection caused by the herpes simplex virus (HSV). In the United States, the annual incidence of pediatric hospitalization for EH between 2002 and 2012 ranged from 4 to 7.3 per million children, with risk highest for infants, toddlers, and preschool children ([Lee 2025](#)). Risk factors for EH include compromised skin barrier, as seen in conditions such as AD, and immunosuppression due to medications or certain conditions (such as malignancy). About 3% of patients with AD are estimated to develop EH during their lifetime, although EH is a rare occurrence in AD ([Damour et al. 2020](#)).

Herpes zoster infection (shingles) is due to reactivation of the varicella-zoster virus. The incidence of HZ varies by age and is approximately two to nine cases per 1,000 people in the U.S. population annually ([CDC 2024](#)). Risk factors for HZ include immunosuppression through medications or conditions (such as HIV/AIDS or malignancy), older age (especially age greater than 50), family history of zoster, and physical trauma ([Marra et al. 2020](#)). In the postmarketing data for delgocitinib ointment, 0.5%, more than half of the patients with HZ were less than 50 years of age (including a 4-year-old patient and a 10-year-old patient), while two patients had HZ multiple times (twice in the 4-year-old patient and three times in a 19-year-old patient). There was no information on whether HZ was multidermatomal nor any other patient risk factors were provided.

In both EH and HZ, a defect in NK cell function is thought to be involved in the development of both conditions ([Goodyear et al. 1996](#); [Kawakami et al. 2017](#); [Della Chiesa et al. 2019](#)), while JAK inhibitors have been associated with NK cell dysfunction ([Vian et al. 2019](#); [Meudec et al.](#)

[2023](#)). Therefore, there is biologic plausibility and, in the absence of other risk factors, causality of delgocitinib for these AEs cannot be excluded.

The Applicant searched the postmarketing safety database for adverse events of special interest (AESIs) which included malignancy, thromboembolic events, gastrointestinal (GI) perforation, and MACE. The Applicant identified one malignancy in a female of unknown age who used CORECTIM for AD and developed metastases from breast carcinoma to lymph nodes. The report did not include the temporal relationship of the serious adverse event (SAE) with administration of CORECTIM or the outcome of the event, which led to discontinuation of treatment with CORECTIM. In a search for events of “nonmelanoma skin cancer”, the Applicant identified one report of “skin tumor.” The report specified no other details regarding the event, including the location of the tumor, temporal relationship to the administration of CORECTIM, or action taken with drug. The case was not medically confirmed and was considered as nonserious based on limited available information. To date, the Applicant identified no postmarketing cases of embolic, thrombotic, gastrointestinal perforation, or cardiovascular adverse events in patients treated with CORECTIM.

Laboratory Data and Clinically Significant Shifts

The Applicant analyzed results from laboratory assessments of complete blood count (CBC) and lipid profiles for patients who underwent testing in the postmarketing surveillance database for ANZUPGO and CORECTIM and related clinically significant shifts. The Applicant stated:

“Postmarketing reports include the clinical data that was volunteered by the reporter and do not necessarily include laboratory assessments, which are not routinely performed or recorded. Postmarketing reports rarely contain pretreatment or post-treatment values, or follow-up values, and some of the assessment dates are missing. Therefore, the postmarketing database is generally a less reliable source than randomized controlled clinical trials for observation of presence or absence of clinically significant shifts. Nevertheless, the reported laboratory assessment results do not raise any safety concerns.”

Hematology

The postmarketing safety database for CORECTIM identified 14 cases that included test results. Review of these cases by the Applicant showed 6 reports in the CORECTIM database that included tests related to CBC (below) and none related to lipid profiles. Given the limited information overall and the lack of baseline test results, the review team was not able to assess whether any clinically significant laboratory shifts occurred in the postmarketing database.

A tabulated summary of CORECTIM case reports with tests related to CBC is shown in [Table 19](#) below.

Table 19. Tabulated Summary of CORECTIM Case Reports With Tests Related to CBC

Case no	Event PT/ Event date	Test Name (PT)	Test value	Test unit	Test date	CORECTIM treatment dates	Co-suspect drugs
(b) (6)	Application site cellulitis	White blood cell count	8,300	cells/ μ L	(b) (6)	(b) (6)	Myser (Difluprednate)
	(b) (6)		7,100	cells/ μ L	Unknown		
(b) (6)	Drug effect incomplete Eczema Erythema Lichen	Eosinophilia	16	%	Unknown	Treatment dates unknown	
		Monocyte count	5.2	%	Unknown		
		Haemoglobi n	12,600	g/dL	Unknown		
		Lymphocyte count	32.6	%	Unknown		
		Basophil count	0.4	%	Unknown		
		White blood cell count	7,200	cells/ μ L	Unknown		

Case no	Event PT/ Event date	Test Name (PT)	Test value	Test unit	Test date	CORECTIM treatment dates	Co-suspect drugs
		Neutrophil count	45.8	%	Unknown		
		Platelet count	313,000	cells/ μ L	Unknown		
(b) (6)	Cellulitis	White blood cell count	29,700	cells/ μ L	(b) (6)	(b) (6)	Voilla (Dexamethason e valerate) (b) (6)
	(b) (6)	White blood cell count	7,800	cells/ μ L			(b) (6) (withdrawn) (b) (6) (re-started)
(b) (6)	Anaphylactic reaction ¹	White blood cell count	5,300	cells/ μ L		(b) (6)	
		Red blood cell count	4.62	10 ⁶ cells/ μ L			
		Platelet count	360,000	cells/ μ L			
		Eosinophil count	0				
(b) (6)	Dermatitis exfoliative generalized	White blood cell count	10,000	cells/ μ L		(b) (6)	
	(b) (6)	Neutrophil count	.59	%			
	(b) (6)	Lymphocyte count	22.2	%			
	Otitis externa	Monocyte count	5.6	%			
	(b) (6)	Eosinophil count	12.8	%			
	Skin infection	Basophil count	0.4	%			
	(b) (6)	White blood cell count	14,200	cells/ μ L			
	Therapeutic product effect incomplete	Platelet count	469,000	cells/ μ L			
		Lymphocyte count	1.43				
		Basophil count	0.7	%			
		Lymphocyte count	10.1	%			
		Monocyte count	0.94				
		Monocyte count	6.6	%			
		Neutrophil count	11.19				

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Case no	Event PT/ Event date	Test Name (PT)	Test value	Test unit	Test date	CORECTIM treatment dates	Co-suspect drugs
		Neutrophil count	78.8	%	(b) (6)		
		Eosinophil count	0.54				
		Eosinophil count	3.8	%			
		Basophil count	0.1				
		White blood cell count	16,900	cells/ μ L			
		Platelet count	367,000	cells/ μ L			
		White blood cell count	15,000	cells/ μ L			
		Platelet count	420,000	cells/ μ L			
(b) (6)	Red blood cell count increased	Red blood cell count	5.91	10^6 cells/ μ L		(b) (6)	
		Red blood cell count	5.91	10^6 cells/ μ L			
		Red blood cell count	6.04	10^6 cells/ μ L			
		Red blood cell count	5.60	10^6 cells/ μ L			

Note: ¹Serious. The patient experienced two episodes of anaphylactic reactions after applying CORECTIM after taking a bath. After discontinuing CORECTIM, the patient had new episodes and later was diagnosed with food-dependent exercise-induced anaphylaxis due to wheat, and was instructed to avoid exercise, bathing, or other activities that would raise her body temperature for 2-4 hours after eating.

Source: Applicant Response to IR May 23, 2025
Abbreviations: PT, preferred term; CBC, complete blood count

Reports of Adverse Events in the CORECTIM and ANZUPGO Postmarketing Database Related to Hematological Parameters

Search of the postmarketing database by the Applicant for increased and decreased hematologic parameters (Medical Dictionary for Regulatory Activities [MedDRA] terms “Red blood cell analyses, White blood cell analyses, Platelet analyses, Neutropenias, Anaemias, Leukopenias, Thrombocytopenias, Thrombocytoses”) identified two cases in patients (“red blood cell count increased” and “immune thrombocytopenia”) who received CORECTIM and none in patients who received ANZUPGO. There was limited information in these reports as presented below.

Table 20. Reports of Adverse Events in the CORECTIM Postmarketing Database Related to Hematological Parameters

Case no.	AE	Seriousness	Comment
(b) (6)	Red blood cell count increased	non-serious	CORECTIM treatment started (b) (6) erythrocytes increased in (b) (6) normalized in (b) (6) (4 lab values available), CORECTIM dose was not changed. See also Panel 2
	Immune thrombocytopenia	serious	AE and treatment dates not available, no test or lab results reported.

Source: Applicant Response to IR May 23, 2025

Reports of Adverse Events in the CORECTIM and ANZUPGO Postmarketing Database Related to Abnormal Lipid Parameters

Search of the postmarketing safety databases by the Applicant for both CORECTIM and ANZUPGO for lipid abnormalities (MedDRA terms “Cholesterol analyses, Triglyceride analyses, Elevated triglycerides, Elevated cholesterol, Elevated cholesterol with elevated triglycerides, Hyperlipidemia, Lipoprotein and lipid tests”) did not identify any AEs related to the lipid profile for either CORECTIM or ANZUPGO.

Tuberculosis

Search of the postmarketing safety databases by the Applicant for both CORECTIM and ANZUPGO using the MedDRA high level term “Tuberculous infections” identified no AEs of tuberculosis in either database.

Hypoglycemia

Preclinical evidence in literature reports suggest that JAK and TYK2 inhibitors may cause hypoglycemia in diabetics by protecting pancreatic β -cells from immune-mediated destruction and improving insulin sensitivity, thereby enhancing endogenous insulin production and action ([Gurzov et al. 2016](#); [Bako et al. 2019](#)). European Medicines Agency labeling for oral JAK inhibitors (e.g., tofacitinib, baricitinib and upadacitinib) states that there have been reports of hypoglycemia following initiation of JAK inhibitors, and dose adjustment of antidiabetic medicinal products may be necessary in the event that hypoglycemia occurs.

In order to further characterize any potential impact of delgocitinib on hypoglycemia in subjects with diabetes, the Applicant provided a cumulative review of all United States and foreign cases of hypoglycemia or blood glucose decrease associated with the use of delgocitinib cream, 2%. The postmarketing data sources for CORECTIM (ointment) and ANZUPGO (cream) included both the safety database and the medical literature (MedDRA search terms: Hypoglycemia standardized MedDRA query [SMQ] Narrow search, Blood glucose abnormal [PT] and Blood glucose fluctuation [PT]) (cutoff date of April 30, 2025). The search identified no relevant cases from the literature. However, in their safety database, the Applicant identified one case of hypoglycemia from Trial DELTA 2 in a subject who received vehicle and none in subjects treated with delgocitinib.

A 19-year-old female subject with no known history of diabetes developed hypoglycemia on Day 57 of administration of vehicle. The blood glucose level was 2.3 mmol/L (41 mg/dL). No concomitant medication was administered. The subject recovered without discontinuation of vehicle. The event was reported as moderate in severity and assessed by the investigator as not related to investigational drug. On reassessment, the blood glucose level was 4.4 mmol/L (79 mg/dL).

Search of the safety database for long-term safety Trial DELTA 3 (not pooled with the controlled trials) using the same MedDRA terms, confirmed that there were no events of hypoglycemia.

In conclusion, the relevance of the postmarketing safety data for delgocitinib ointment, 0.5% and cream, 2% is limited due insufficient information regarding the number of patients who received treatment with delgocitinib and duration of treatment. The causality of delgocitinib in the onset of EH and HZ cannot be established. However, a role for delgocitinib cannot be excluded. The

effect of delgocitinib on bone marrow cannot be assessed because routine blood work was not obtained.

7.4. FDA Approach to the Safety Review

The Applicant submitted safety data from seven completed clinical trials in the development program for delgocitinib cream in subjects with CHE.

- Two 16-week vehicle-controlled phase 3 trials (LP0133-1401/DELTA 1 and LP0133-1402/DELTA 2) in subjects with moderate to severe CHE
- A 36-week open-label single-arm extension trial (LP0133-1403/DELTA 3) in subjects with moderate to severe CHE continuing from Trials DELTA 1 and DELTA 2
- A 24-week active comparator, open-label trial comparing delgocitinib with alitretinoin capsules (LP0133-1528 DELTA FORCE) in subjects with severe CHE
- A phase 1 PK trial (LP0133-2285)
- A phase 2 dose-ranging trial (LP0133-1273) in subjects with mild to severe CHE
- A phase 2 proof of concept trial (LP0133-1180) in subjects with at least mild CHE

The Applicant submitted additional safety data from two completed clinical trials that evaluated delgocitinib cream in subjects with atopic dermatitis (phase 1 PK/MUST trial LP0133-1181 and phase 2 dose-ranging trial LP0133-1275) and three completed clinical trials that evaluated delgocitinib cream in healthy subjects (phototoxicity trial LP0133-1408, photoallergenicity trial LP0133-1411, and QT prolongation trial LP0133-1408).

The review team focused the evaluation of the safety and efficacy of delgocitinib cream on data from the two vehicle-controlled, phase 3 trials (DELTA 1 and DELTA 2) and open-label extension trial DELTA 3. Analysis of the safety data related to the additional trials did not reveal any unique safety signals from those observed in trials DELTA 1, DELTA 2, and DELTA 3, and was, therefore, considered supportive (refer to Section [7.6.2](#) for analysis of phase 2b trials 1273 and Section [7.6.3.1](#) for analysis for active comparator trial DELTA FORCE).

The review team identified no major data quality or integrity issues that would preclude performing a safety review for this marketing application. There were no major issues identified with respect to recording, coding, and categorizing AEs. Review of the Applicant's translations of verbatim terms to MedDRA PTs for the adverse events reported in the trials were found to be acceptable.

The protocol defined treatment-emergent adverse events (TEAEs) as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product." AEs reported in trials DELTA 1, DELTA 2, and DELTA 3 were coded according to the MedDRA (v. 24.0).

Adverse event severity was described as mild, moderate, or severe according to the investigator's clinical judgement. Mild was defined as "[a]n AE that is usually transient and may require only

minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living,” moderate was defined as “[a]n AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the subject,” and severe was defined as “[a]n AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.” Causality was assessed by the investigator as probably related, possibly related, or not related. Regardless of how causality was assessed by the investigator, the review team also reviewed case report forms and narrative summaries of subjects with adverse events that may have represented safety signals.

A SAE was defined as “any untoward medical occurrence that: results in death, is life-threatening – at risk of death at the time of the SAE (not an event that hypothetically might have caused death if more severe), requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is a medically important condition.”

An AESI was defined as a “(serious or non-serious) event type of scientific and medical concern specific to the product or development program, for which additional monitoring may be appropriate.” The following were predefined as AESIs in trials DELTA 1, DELTA 2, and DELTA 3: eczema herpeticum, deep vein thrombosis, and pulmonary embolism. Other safety areas of interest for delgocitinib included known JAK inhibitor drug class adverse drug reactions and safety issues, the adverse drug reactions from the delgocitinib ointment CORECTIM program, and rare events.

Laboratory samples in trials DELTA 1 and DELTA 2, were collected according to visit schedules during the trials at Weeks 0, 2, 4, 8, 12, and 16. In trial DELTA 3, laboratory samples were collected every 8 weeks. Clinically relevant laboratory findings were identified by the Applicant based on common terminology criteria for adverse events (CTCAE), Council for International Organizations of Medical Sciences, and National Cholesterol Education Program Adult Treatment Panel III guideline thresholds, and by the review team based on the FDA’s [Standard Safety Tables and Figures Integrated Guide](#).

7.5. Adequacy of the Clinical Safety Database

The primary analysis dataset for the review of safety for delgocitinib cream, 2% for the treatment of moderate to severe CHE included pooled data from the vehicle-controlled phase 3 trials DELTA 1 and DELTA 2 from Weeks 0 to 16. The safety population includes all randomized subjects who received at least one dose of the study medication during the double-blind, 16-week treatment period in these two trials. Safety data from this population were analyzed according to the treatment that subjects actually received. In the pooled phase 3 trials, 638 subjects received delgocitinib. The safety population by trial and duration of treatment is presented below.

Table 21. Duration of Exposure, Safety Population, Pooled Trials DELTA 1 and DELTA 2

Parameter	Trial DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2	
	Delgocitinib N=325	Vehicle Control N=162	Delgocitinib N=313	Vehicle Control N=159	Delgocitinib N=638	Vehicle Control N=321
Duration of treatment, weeks						
Mean (SD)	15.6 (2.7)	14.8 (3.8)	15.6 (2.8)	13.9 (4.8)	15.6 (2.8)	14.4 (4.3)
Median (Q1, Q3)	16.1 (16, 16.3)	16.1 (15.8, 16.1)	16.1 (16, 16.3)	16.1 (15.7, 16.3)	16.1 (16, 16.3)	16.1 (15.7, 16.3)
Min, max	0.4, 19.7	1, 19	0.3, 24.1	0.4, 20.3	0.3, 24.1	0.4, 20.3
Total exposure (person years)	97	46	93	42	191	88
Subjects treated, by duration, n (%)						
<8 weeks	10 (3.1)	15 (9.3)	15 (4.8)	25 (15.7)	25 (3.9)	40 (12.5)
≥8 to <16 weeks	54 (16.6)	36 (22.2)	54 (17.3)	31 (19.5)	108 (16.9)	67 (20.9)
≥16 to <24 weeks	261 (80.3)	111 (68.5)	243 (77.6)	103 (64.8)	504 (79.0)	214 (66.7)
≥24 to <28 weeks	0	0	1 (0.3)	0	1 (0.2)	0

Source: adex.xpt and adsl.xpt; Software: R

Duration is 16 weeks.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

The long-term safety analysis dataset for the review of safety for delgocitinib cream for the treatment of moderate to severe CHE included pooled data for subjects who received 52 weeks of continuous treatment with delgocitinib from the vehicle-controlled phase 3 trials DELTA 1 and DELTA 2 and open-label single-arm extension trial DELTA 3, and intermittent treatment over 52 weeks in these trials. A total of 736 subjects with CHE were exposed to delgocitinib cream, 2% for at least 6 months (Intermittent-use pool):

- 533 subjects received 16 weeks of delgocitinib cream twice daily in Trials DELTA 1 and DELTA 2 followed by 10 weeks of as-needed treatment in Trial DELTA 3;
- 203 subjects received 16 weeks of vehicle twice daily in Trials DELTA 1 or DELTA 2 followed by 26 weeks of delgocitinib cream as needed in Trial DELTA 3.

The long-term safety population is summarized below by trial and duration of treatment. Of 736 subjects with CHE exposed to delgocitinib cream, 2%, twice daily, a total of 466 subjects were exposed for 52 weeks: 16 weeks with twice-daily treatment and 36 weeks with as-needed treatment. Among these 466 subjects, a total of 198 subjects were continuously exposed to delgocitinib cream twice daily for 52 weeks (Long-term safety pool) with no treatment breaks.

Table 22. Duration of Exposure, Safety Population, Pooled Trials DELTA 1, DELTA 2, and DELTA 3

Parameter	Delgocitinib Continuous Treatment Over 52 Weeks N=198	Delgocitinib Intermittent Treatment Over 52 Weeks N=362	Vehicle Control 16 Weeks N=241
Duration of treatment, weeks			
Mean (SD)	52.5 (0.7)	37.4 (10.1)	16.2 (0.5)
Median (Q1, Q3)	52.1 (52.1, 52.9)	38.8 (29.9, 46.8)	16.1 (16, 16.3)
Min, max	51.1, 55.3	15.9, 52.7	14.9, 19
Total exposure (person years)	199	259	75

Parameter	Delgocitinib Continuous Treatment Over 52 Weeks N=198	Delgocitinib Intermittent Treatment Over 52 Weeks N=362	Vehicle Control 16 Weeks N=241
Subjects treated, by duration, n (%)			
<16 weeks	0	5 (1.4)	85 (35.3)
≥16 to <34 weeks	0	128 (35.4)	156 (64.7)
≥34 to <52 weeks	46 (23.2)	226 (62.4)	0
≥52 to <55 weeks	150 (75.8)	3 (0.8)	0
≥55 weeks	2 (1.0)	0	0

Source: adex.xpt and adsl.xpt; Software: R

Delgocitinib 20 mg/g (Continuous Treatment Over 52 weeks) refers to subjects who received Delgocitinib in trials DELTA 1 and DELTA 2 and continuously received Delgocitinib in trial DELTA 3 over the 52 weeks.

Delgocitinib 20 mg/g (Intermittent Treatment Over 52 weeks) refers to subjects who received Delgocitinib in DELTA 1 and DELTA 2 and did not receive Delgocitinib continuously in trial DELTA 3 over the 52 weeks.

The two columns contain nonoverlapping subjects.

Vehicle control 16 weeks: subjects who received vehicle control in Trials DELTA 1 and DELTA 2 and continuously stay off treatment in Trial DELTA 3 over the 52 weeks.

Duration is 52 weeks.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

The total subject exposure to delgocitinib cream for the treatment of moderate to severe CHE provides adequate data for the evaluation of safety. The total exposures for 16 weeks and 52 weeks are sufficient to characterize the safety of the product over short and longer treatment periods. Because of the size of the safety database, rare adverse events associated with JAKi may not have been identified. However, the potential for these adverse reactions will be communicated in labeling to inform prescribers and patients of the risks.

Relevant Characteristics of the Safety Population

The demographic characteristics were well balanced across treatment groups in the safety population. There were no clinically relevant differences in the demographics or baseline characteristics of subjects who received delgocitinib cream, 2% compared with vehicle. Across treatment groups in Trials DELTA 1 and DELTA 2, the mean age of enrolled subjects was 44.1 years. Approximately 8% of subjects were 65 years of age or older, 64% were female, 90% were White, 4% were Asian, and 1% were Black. Approximately 94% of subjects identified as not Hispanic or Latino and 3% of subjects identified as Hispanic or Latino.

Subtypes of CHE according to the primary etiology were atopic hand eczema (35.9%), hyperkeratotic eczema (21.5%), irritant contact dermatitis (19.6%), allergic contact dermatitis (13.9%), vesicular hand eczema (9.1%), and contact urticaria/protein contact dermatitis (0.1%). Across all trial arms, 28% of subjects were diagnosed with two or more overlapping CHE subtypes.

Of all subjects, 46% were diagnosed with AD, and 1.14% were treated for AD within 28 days prior to baseline (1% with topical treatment, and 0.2% with systemic). In addition, 38.7% of subjects had an atopic diathesis (allergic rhinitis, asthma, etc.). Occupation (e.g., food handler, veterinarian, farmer, hairdresser, healthcare worker, etc.) was contributory to the development and/or chronicity of CHE in 36.6% of subjects (specific occupation was not recorded); CHE impacted employment in 60.8% of subjects. Of the 78.6% of subjects who were patch tested, 36% had positive results, and 18% of these results were considered related to CHE. A total of 29.8% of subjects were diagnosed with irritant dermatitis, and 20.2% of these were diagnosed

with contact allergic dermatitis. All subjects had received prior systemic therapy, which included oral corticosteroids. A total of 12% of subjects previously received alitretinoin, 7.4% of subjects received traditional immunosuppressive agents, 0.6% of subjects received dupilumab, 0.2% of subjects received other biologics, and 4.7% other therapies.

The demographics and baseline characteristics of the long-term safety pool (52 weeks) were consistent with the short-term safety pool (16 weeks), as expected, since the same subjects continued from Trials DELTA 1 and DELTA 2 into Trial DELTA 3.

7.6. Safety Results

7.6.1. Safety Results, Pooled Analyses, Trials DELTA 1 and DELTA 2

The overall incidence, severity, and actions taken in response to the TEAEs were generally well balanced between the delgocitinib and vehicle groups. However, there were more AEs leading to permanent discontinuation of the study drug for subjects in the vehicle group. All AEs leading to permanent discontinuation of the study product in the delgocitinib cream group were single events with no clustering of events at the PT level. [Table 23](#) below provides an overview of the TEAEs reported during the 16-week, vehicle-controlled phase 3 Trials DELTA 1 and DELTA 2.

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Pooled Analyses, Trials DELTA 1 and DELTA 2

Table 23. Overview of Adverse Events, Safety Population, Pooled Trials DELTA 1 and DELTA 2

Event Category	Trial DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n (%)	Vehicle Control N=162 n (%)	Delgocitinib N=313 n (%)	Vehicle Control N=159 n (%)	Delgocitinib N=638 n (%)	Vehicle Control N=321 n (%)	Risk Difference % (95% CI)
SAE	6 (1.8)	3 (1.9)	5 (1.6)	3 (1.9)	11 (1.7)	6 (1.9)	-0.1 (-2.4, 1.5)
SAEs with fatal outcome	0	0	0	0	0	0	0.0 (-1.2, 0.6)
Life-threatening SAEs	0	0	0	0	0	0	0.0 (-1.2, 0.6)
SAEs requiring hospitalization	6 (1.8)	3 (1.9)	5 (1.6)	3 (1.9)	11 (1.7)	6 (1.9)	-0.1 (-2.4, 1.5)
AE leading to permanent discontinuation of study drug	2 (0.6)	6 (3.7)	1 (0.3)	5 (3.1)	3 (0.5)	11 (3.4)	-3.0 (-5.6, -1.3)*
AE leading to dose modification of study drug	0	0	0	0	0	0	0.0 (-1.2, 0.6)
AE leading to interruption of study drug	0	0	0	0	0	0	0.0 (-1.2, 0.6)
AE leading to reduction of study drug	0	0	0	0	0	0	0.0 (-1.2, 0.6)
AE leading to dose delay of study drug	0	0	0	0	0	0	0.0 (-1.2, 0.6)
Any AE	148 (45.5)	82 (50.6)	143 (45.7)	71 (44.7)	291 (45.6)	153 (47.7)	-2.1 (-8.7, 4.6)
Severe and worse	12 (3.7)	5 (3.1)	3 (1.0)	4 (2.5)	15 (2.4)	9 (2.8)	-0.5 (-3.1, 1.6)
Moderate	60 (18.5)	35 (21.6)	48 (15.3)	21 (13.2)	108 (16.9)	56 (17.4)	-0.5 (-5.8, 4.4)
Mild	76 (23.4)	42 (25.9)	92 (29.4)	46 (28.9)	168 (26.3)	88 (27.4)	-1.1 (-7.2, 4.7)

Source: adae.xpt; Software: R

* Indicates that 95% confidence interval excludes zero.

Treatment-emergent adverse events defined as an event that started after the first application of IMP or that started before the first application of IMP and worsened in severity after first dose of IMP.

Duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medical product; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

7.6.1.2. Deaths, Pooled Analyses, Trials DELTA 1, DELTA 2 and DELTA 3

There were three deaths in the development program:

- A 63-year-old male subject ((b) (6)) with a medical history of CHE, obesity, hypertension, hyperlipidemia, and prior tobacco use, died due to metastatic esophageal cancer. The subject received vehicle cream for 16 weeks during Trial DELTA 2 and subsequently received a single application of delgocitinib cream, 2% in extension Trial DELTA 3 before discontinuing treatment.

The trial investigator assessed the death as unrelated to the study product and this reviewer agrees. The subject had multiple risk factors for esophageal cancer, including obesity, history of smoking, older age, and male sex, with minimal exposure to delgocitinib (a single application). The nature and timeline of disease progression are more consistent with a preexisting malignancy than with any plausible drug-induced effect.

- A 72-year-old male subject ((b) (6)) with a complex medical history, including CHE, hypertension, epilepsy, renal cell carcinoma, chronic alcohol use, hepatitis B virus infection, and liver cirrhosis, died of unknown causes on Day 362. At the time of death, he had been on study drug continuously for approximately 4 months and intermittently for approximately 8 months

The subject initially presented to the emergency department with a left-sided peripheral facial nerve palsy. Evaluation included normal head computed tomography (CT) and ECG. Laboratory testing revealed elevated inflammatory markers (C-reactive protein, gamma-glutamyl transferase, aspartate aminotransferase [AST]), thrombocytopenia (platelet count $50 \times 10^3/\mu\text{L}$), and negative COVID-19 status. He was discharged the same day with prednisolone and pantoprazole. Subsequent diagnostic imaging and biopsy results were not available. The subject fell within 2 weeks of discharge, was rehospitalized, and died approximately 1 week later.

The trial investigator assessed the death as unrelated to the study product and provided no alternative etiology. This reviewer agrees; given the subject's advanced age, multiple comorbidities (including cirrhosis and a history of malignancy), and recent fall, the death is unlikely to be attributable to delgocitinib. However, due to the limited clinical information a contributory role for delgocitinib cannot be definitively ruled out.

- A 72-year-old male subject ((b) (6)) with a medical history of CHE and hypertension experienced a fatal myocardial infarction (MI) approximately 218 days (about 7 months) after his last dose of delgocitinib cream, 2%. The subject had completed 16 weeks of treatment in Trial DELTA 2 and an additional 4 weeks of treatment in Trial DELTA 3.

The subject had been receiving antihypertensive therapy for 3 months prior to the event. He died 10 days after the MI. The trial investigator assessed the death as unrelated to the study drug and attributed it to the myocardial infarction. This reviewer concurs with that

assessment, given the extended time interval (>31 weeks) between the last exposure to delgocitinib and the onset of the SAE.

However, due to the limited information available regarding the subject's other potential cardiovascular risk factors, as well as the known association between JAKi and MACE, a contributory role of delgocitinib cannot be definitively ruled out.

7.6.1.3. Serious Treatment-Emergent Adverse Events, Pooled Analyses, Trials DELTA 1 and DELTA 2

During the initial treatment period for trials DELTA 1 and DELTA 2, SAEs were reported at a comparable rate in the delgocitinib group and the vehicle group ([Table 24](#) below). SAEs occurred at a rate of <1% for all system organ classes (SOCs) in the delgocitinib and vehicle groups. The highest risk difference in the pooled trials occurred with the SOC of infections and infestations (0.3%). For this SOC, four subjects reported four events in the delgocitinib cream group (COVID-19 pneumonia, keratitis bacterial, peritonsillar abscess, and tonsillitis) and no subjects reported events in the vehicle group. None of the events were considered related to treatment by the investigator nor clinical reviewer, and there was no clustering of events over time. For all other SOC, the risk difference was 0.2%. Within all SOC, SAEs were reported as single events within each treatment group, with no clustering at the PT level.

One subject in the delgocitinib group experienced the SAE hand dermatitis which required hospitalization. The narrative summary is below:

- A 31-year-old female subject ((b) (6)) enrolled in Trial DELTA 2, with history of hospitalization related to CHE and AD (inactive at baseline), was hospitalized for an exacerbation of CHE on Day 115. The subject received delgocitinib twice daily until Day 85 when she discontinued treatment due to lack of efficacy. She noted an increase in the severity of CHE on Day 70 and was hospitalized on Day 115 for 11 days “due to worsening of hand eczema.” Her treatment included “bath-PUVA, clobetasol ointment, triclosan cream with betamethasone, liquor carbonis detergens 5% ointment, and oral antihistamines.” The reason for the prolonged hospitalization was not stated. The investigator and Applicant both assessed the SAE as unrelated to the IMP. However, given limited information, the clinical reviewer cannot rule out a causal association with delgocitinib.

Table 24. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Pooled Trials DELTA 1 and DELTA 2

System Organ Class Preferred Term	Trial DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n (%)	Vehicle Control N=162 n (%)	Delgocitinib N=313 n (%)	Vehicle Control N=159 n (%)	Delgocitinib N=638 n (%)	Vehicle Control N=321 n (%)	Risk Difference % (95% CI)
Any SAE	6 (1.8)	3 (1.9)	5 (1.6)	3 (1.9)	11 (1.7)	6 (1.9)	-0.1 (-2.4, 1.5)
Cardiac disorders (SOC)	0	0	0	1 (0.6)	0	1 (0.3)	-0.3 (-1.7, 0.3)
Cardiac tamponade	0	0	0	1 (0.6)	0	1 (0.3)	-0.3 (-1.7, 0.3)
Gastrointestinal disorders (SOC)	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Inguinal hernia	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Infections and infestations (SOC)	2 (0.6)	0	2 (0.6)	0	4 (0.6)	0	0.6 (-0.6, 1.6)
COVID-19 pneumonia	0	0	1 (0.3)	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Keratitis bacterial	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Peritonsillar abscess	0	0	1 (0.3)	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Tonsillitis	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Injury, poisoning and procedural complications (SOC)	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Post procedural haemorrhage	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Musculoskeletal and connective tissue disorders (SOC)	1 (0.3)	1 (0.6)	0	0	1 (0.2)	1 (0.3)	-0.2 (-1.6, 0.6)
Intervertebral disc protrusion	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Osteoarthritis	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Gallbladder adenocarcinoma	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Nervous system disorders (SOC)	1 (0.3)	0	2 (0.6)	1 (0.6)	3 (0.5)	1 (0.3)	0.2 (-1.3, 1.1)
Epilepsy	0	0	1 (0.3)	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Generalized tonic-clonic seizure	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Migraine	0	0	1 (0.3)	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Notalgia paraesthetica	0	0	0	1 (0.6)	0	1 (0.3)	-0.3 (-1.7, 0.3)
Respiratory, thoracic and mediastinal disorders (SOC)	0	0	0	1 (0.6)	0	1 (0.3)	-0.3 (-1.7, 0.3)
Pulmonary oedema	0	0	0	1 (0.6)	0	1 (0.3)	-0.3 (-1.7, 0.3)

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

System Organ Class Preferred Term	Trial DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n (%)	Vehicle Control N=162 n (%)	Delgocitinib N=313 n (%)	Vehicle Control N=159 n (%)	Delgocitinib N=638 n (%)	Vehicle Control N=321 n (%)	Risk Difference % (95% CI)
Skin and subcutaneous tissue disorders (SOC)	0	1 (0.6)	1 (0.3)	1 (0.6)	1 (0.2)	2 (0.6)	-0.5 (-2.1, 0.3)
Hand dermatitis	0	0	1 (0.3)	1 (0.6)	1 (0.2)	1 (0.3)	-0.2 (-1.6, 0.6)
Dermatitis atopic	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)
Vascular disorders (SOC)	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)
Venous thrombosis	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as an event that started after the first application of IMP or that started before the first application of IMP and worsened in severity after first dose of IMP.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; IMP, investigational medical product; incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

7.6.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Pooled Analyses, Trials DELTA 1 and DELTA 2

During the 16-week vehicle-controlled period, AEs leading to permanent discontinuation of study drug were few and more frequent in the vehicle group than in the delgocitinib group (refer to [Table 25](#) and [Table 26](#) below). In subjects who received delgocitinib, no PTs were reported in >1 subject. The following AEs leading to discontinuation were reported in subjects who received delgocitinib and none in subjects who received vehicle: skin bacterial infection, contact dermatitis, and eczema.

Narrative summaries of the subjects who discontinued delgocitinib due to skin bacterial infection and contact dermatitis are below:

- Skin bacterial infection: A 38-year-old female ((b) (6)) with a history of allergic rhinitis developed a nonserious, moderate severity “skin bacterial infection” of the hand on the first day of treatment with delgocitinib cream. No further details are provided. The AE is reported resolved on Day 13 and the investigator assessed the AE as unrelated to the IMP. Given limited information, this reviewer cannot rule out a causal association.
- Contact dermatitis: A 38-year-old female ((b) (6)) with a history of CHE developed “contact dermatitis” of the hands on Day 9 of treatment with delgocitinib cream. The subject reported erythema, edema, and papules, which resolved 3 days after discontinuation of IMP. An IMP patch test was negative, which suggests that this event was not due to allergy but rather irritant contact dermatitis. The event was considered possibly related to IMP by investigator and clinical reviewer.

Table 25. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Pooled Trials DELTA 1 and DELTA 2

System Organ Class Preferred Term	Trial DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n (%)	Vehicle Control N=162 n (%)	Delgocitinib N=313 n (%)	Vehicle Control N=159 n (%)	Delgocitinib N=638 n (%)	Vehicle Control N=321 n (%)	Risk Difference % (95% CI)
Any AE leading to discontinuation	2 (0.6)	6 (3.7)	1 (0.3)	5 (3.1)	3 (0.5)	11 (3.4)	-3.0 (-5.6, -1.3)*
General disorders and administration site conditions (SOC)	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)
Application site eczema	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)
Infections and infestations (SOC)	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Skin bacterial infection	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Musculoskeletal and connective tissue disorders (SOC)	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)
Polyarthritis	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)
Skin and subcutaneous tissue disorders (SOC)	1 (0.3)	4 (2.5)	1 (0.3)	5 (3.1)	2 (0.3)	9 (2.8)	-2.5 (-5.0, -1.0)*
Eczema	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Dermatitis contact	0	1 (0.6)	1 (0.3)	1 (0.6)	1 (0.2)	2 (0.6)	-0.5 (-2.1, 0.3)
Dermatitis atopic	0	1 (0.6)	0	1 (0.6)	0	2 (0.6)	-0.6 (-2.2, -0.0)*
Hand dermatitis	0	2 (1.2)	0	3 (1.9)	0	5 (1.6)	-1.6 (-3.6, -0.7)*

Source: adae.xpt; Software: R

* Indicates that 95% confidence interval excludes zero.

Treatment-emergent adverse events defined as an event that started after the first application of IMP or that started before the first application of IMP and worsened in severity after first dose of IMP.

Duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medical product; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

Table 26. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class, FDA Medical Query (Narrow) and Preferred Term, Safety Population, Pooled Trials DELTA 1 and DELTA 2

System Organ Class OCMQ (Narrow) Preferred Term	Trial DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n (%)	Vehicle Control N=162 n (%)	Delgocitinib N=313 n (%)	Vehicle Control N=159 n (%)	Delgocitinib N=638 n (%)	Vehicle Control N=321 n (%)	Risk Difference % (95% CI)
General disorders and administration site conditions (SOC)							
Local administration reaction (OCMQ)	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)
Application site eczema	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)
Infections and infestations (SOC)							
Bacterial infection (OCMQ)	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Skin bacterial infection	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Musculoskeletal and connective tissue disorders (SOC)							
Arthritis (OCMQ)	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)
Polyarthritis	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)
Skin and subcutaneous tissue disorders (SOC)							
Rash (OCMQ)	0	1 (0.6)	1 (0.3)	1 (0.6)	1 (0.2)	2 (0.6)	-0.5 (-2.1, 0.3)
Dermatitis contact	0	1 (0.6)	1 (0.3)	1 (0.6)	1 (0.2)	2 (0.6)	-0.5 (-2.1, 0.3)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any adverse event that first occurred or worsened in severity after first date/time of IMP administration of each cycle until first administration date/time of the following cycle or date of last contact.

Duration is median 3.1 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

Abbreviations: CI, confidence interval; OCMQ, OND custom medical query; IMP, investigational medical product; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class

7.6.1.5. Treatment-Emergent Adverse Events, Pooled Analyses, Trials DELTA 1 and DELTA 2

During the 16-week, vehicle-controlled period of Trials DELTA 1 and DELTA 2, TEAEs were reported at a comparable rate in the delgocitinib group and the vehicle group. During this period at least one TEAE was reported in 291 subjects (45.6%) who received delgocitinib and in 153 (47.4%) subjects who received vehicle. Severity of TEAEs was similar between the treatment groups, and the majority were considered mild or moderate for both groups.

TEAEs reported in 1% or more of subjects are presented below by MedDRA PT in [Table 27](#), by broad Office of New Drugs custom medical queries (OCMQs) in [Table 28](#) and by narrow OCMQ in [Table 29](#). Higher rates of the following adverse events were reported in subjects who received delgocitinib in the pooled Trials DELTA 1 and DELTA 2 compared to vehicle: COVID-19 (11.1% versus 10.6%), upper respiratory tract infection (1.4% versus 0.3%), hypertension (1.1% versus 0%), back pain (1.1% versus 0.3%), and influenza (1.1% versus 0.6%). The 95% confidence intervals for these risk differences did not exclude zero for any of these preferred terms, suggesting that the observed differences are not statistically significant and may be due to chance. Furthermore, review by the clinical team of narrative summaries, including timing of onset, vital signs and ECGs, subject comorbidities, evaluation of potential alternative causes, and consideration of low biologic plausibility did not support a causal relationship between delgocitinib and these adverse events. Accordingly, none of these events are considered adverse reactions (including those with a $\geq 1\%$ absolute difference in incidence: upper respiratory tract infection and hypertension), and are not proposed for addition to labeling. There were no ADRs that occurred in $\geq 1\%$ in the delgocitinib group and greater than vehicle proposed for labeling.

The review team evaluated narrative summaries for adverse events occurring in $\leq 1\%$ of subjects who received delgocitinib and not observed in subjects who received vehicle. The reviewers determined that the following events may have a possible causal association with delgocitinib, and these are proposed for inclusion in labeling:

- Finger cellulitis: One subject developed “cellulitis of the left middle finger,” on Day 15 of delgocitinib. The AE began as mild (2 days) and progressed to moderate severity (15 days). The AE was considered possibly related to delgocitinib by both the investigator and the review team. The subject recovered with antibiotic treatment but without interruption of the IMP.
- Paronychia: One subject developed “paronychia (application site affected),” on Day 39 of delgocitinib. The AE was assessed as moderate severity and considered not related by the investigator. However, due to limited information, the review team assessed the event as possibly related. The subject recovered after 17 days of antibiotic treatment without interruption of the IMP.
- Bacterial skin infections (two events in two subjects):
 - One subject developed “bacterial infection on hand dermatitis” on Day 1 of delgocitinib. IMP was discontinued after 3 days, and the subject recovered after 13 days with antibiotics and very potent topical corticosteroids. The AE was of moderate severity and

considered not related by the investigator. However, due to insufficient information, it was assessed as possibly related by the review team.

- One subject developed “bacterial skin infection of hands” on Day 16 of delgocitinib. The AE was of moderate severity and considered possibly related by both the investigator and the review team. The subject recovered after 14 days of antibiotic treatment without interruption of the IMP.

Table 27. Subjects With Adverse Events Occurring at ≥1% Frequency, Safety Population, Pooled Trials DELTA 1 and DELTA 2

Preferred Term	Trial DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n (%)	Vehicle Control N=162 n (%)	Delgocitinib N=313 n (%)	Vehicle Control N=159 n (%)	Delgocitinib N=638 n (%)	Vehicle Control N=321 n (%)	Risk Difference % (95% CI)
Any AE	148 (45.5)	82 (50.6)	143 (45.7)	71 (44.7)	291 (45.6)	153 (47.7)	-2.1 (-8.7, 4.6)
Upper respiratory tract infection	4 (1.2)	1 (0.6)	5 (1.6)	0	9 (1.4)	1 (0.3)	1.1 (-0.4, 2.4)
Hypertension	6 (1.8)	0	1 (0.3)	0	7 (1.1)	0	1.1 (-0.1, 2.2)
Back pain	5 (1.5)	1 (0.6)	2 (0.6)	0	7 (1.1)	1 (0.3)	0.8 (-0.7, 2.0)
Gastrointestinal infection	1 (0.3)	0	4 (1.3)	0	5 (0.8)	0	0.8 (-0.4, 1.8)
COVID-19	35 (10.8)	14 (8.6)	36 (11.5)	20 (12.6)	71 (11.1)	34 (10.6)	0.5 (-3.9, 4.5)
Influenza	2 (0.6)	1 (0.6)	5 (1.6)	1 (0.6)	7 (1.1)	2 (0.6)	0.5 (-1.2, 1.7)
Oral herpes	4 (1.2)	1 (0.6)	3 (1.0)	1 (0.6)	7 (1.1)	2 (0.6)	0.5 (-1.2, 1.7)
Headache	9 (2.8)	4 (2.5)	19 (6.1)	9 (5.7)	28 (4.4)	13 (4.0)	0.3 (-2.7, 2.9)
Gastroenteritis	3 (0.9)	0	3 (1.0)	2 (1.3)	6 (0.9)	2 (0.6)	0.3 (-1.4, 1.5)
Rhinitis	5 (1.5)	1 (0.6)	1 (0.3)	1 (0.6)	6 (0.9)	2 (0.6)	0.3 (-1.4, 1.5)
Tonsillitis	4 (1.2)	1 (0.6)	0	0	4 (0.6)	1 (0.3)	0.3 (-1.1, 1.3)
Allergy to metals	7 (2.2)	3 (1.9)	0	0	7 (1.1)	3 (0.9)	0.2 (-1.7, 1.5)
Eczema	3 (0.9)	1 (0.6)	3 (1.0)	2 (1.3)	6 (0.9)	3 (0.9)	0.0 (-1.8, 1.3)
Blood triglycerides increased	3 (0.9)	2 (1.2)	1 (0.3)	0	4 (0.6)	2 (0.6)	0.0 (-1.7, 1.1)
Arthralgia	2 (0.6)	3 (1.9)	5 (1.6)	1 (0.6)	7 (1.1)	4 (1.2)	-0.1 (-2.1, 1.2)
Hypercholesterolaemia	5 (1.5)	3 (1.9)	0	0	5 (0.8)	3 (0.9)	-0.2 (-2.0, 1.1)
Abdominal pain	1 (0.3)	0	2 (0.6)	2 (1.3)	3 (0.5)	2 (0.6)	-0.2 (-1.8, 0.9)
Application site paraesthesia	1 (0.3)	2 (1.2)	2 (0.6)	0	3 (0.5)	2 (0.6)	-0.2 (-1.8, 0.9)
Sinusitis	4 (1.2)	2 (1.2)	0	1 (0.6)	4 (0.6)	3 (0.9)	-0.3 (-2.1, 0.8)
Depression	2 (0.6)	2 (1.2)	0	0	2 (0.3)	2 (0.6)	-0.3 (-2.0, 0.6)
Fatigue	1 (0.3)	0	1 (0.3)	2 (1.3)	2 (0.3)	2 (0.6)	-0.3 (-2.0, 0.6)
Bronchitis	2 (0.6)	2 (1.2)	1 (0.3)	1 (0.6)	3 (0.5)	3 (0.9)	-0.5 (-2.3, 0.6)
Influenza like illness	1 (0.3)	2 (1.2)	2 (0.6)	1 (0.6)	3 (0.5)	3 (0.9)	-0.5 (-2.3, 0.6)
Application site pruritus	0	2 (1.2)	1 (0.3)	0	1 (0.2)	2 (0.6)	-0.5 (-2.1, 0.3)
Hypertriglyceridaemia	0	2 (1.2)	1 (0.3)	0	1 (0.2)	2 (0.6)	-0.5 (-2.1, 0.3)
Thermal burn	1 (0.3)	0	0	2 (1.3)	1 (0.2)	2 (0.6)	-0.5 (-2.1, 0.3)
Nasopharyngitis	23 (7.1)	14 (8.6)	21 (6.7)	10 (6.3)	44 (6.9)	24 (7.5)	-0.6 (-4.4, 2.7)
Urinary tract infection	2 (0.6)	3 (1.9)	4 (1.3)	2 (1.3)	6 (0.9)	5 (1.6)	-0.6 (-2.7, 0.8)
Allergy to chemicals	2 (0.6)	3 (1.9)	0	0	2 (0.3)	3 (0.9)	-0.6 (-2.4, 0.4)
Blood glucose increased	0	1 (0.6)	0	1 (0.6)	0	2 (0.6)	-0.6 (-2.2, -0.0) *
Dry eye	0	1 (0.6)	0	1 (0.6)	0	2 (0.6)	-0.6 (-2.2, -0.0) *
Lymphadenopathy	0	1 (0.6)	0	1 (0.6)	0	2 (0.6)	-0.6 (-2.2, -0.0) *

	Trial DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n (%)	Vehicle Control N=162 n (%)	Delgocitinib N=313 n (%)	Vehicle Control N=159 n (%)	Delgocitinib N=638 n (%)	Vehicle Control N=321 n (%)	Risk Difference % (95% CI)
Preferred Term							
Dermatitis contact	4 (1.2)	4 (2.5)	3 (1.0)	2 (1.3)	7 (1.1)	6 (1.9)	-0.8 (-3.0, 0.7)
Pharyngitis	2 (0.6)	0	3 (1.0)	5 (3.1)	5 (0.8)	5 (1.6)	-0.8 (-2.9, 0.6)
Dermatitis atopic	2 (0.6)	2 (1.2)	0	2 (1.3)	2 (0.3)	4 (1.2)	-0.9 (-2.9, 0.1)
Herpes simplex	0	0	1 (0.3)	4 (2.5)	1 (0.2)	4 (1.2)	-1.1 (-3.0, -0.1) *
Hand dermatitis	1 (0.3)	7 (4.3)	3 (1.0)	6 (3.8)	4 (0.6)	13 (4.0)	-3.4 (-6.2, -1.6) *

Source: adae.xpt; Software: R

*Indicates that 95% confidence interval excludes zero.

Treatment-emergent adverse events defined as an event that started after the first application of IMP or that started before the first application of IMP and worsened in severity after first dose of IMP.

Duration is 16 weeks.

Coded as MedDRA preferred terms.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medical product; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 28. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Broad), Safety Population, Pooled Trials DELTA 1 and DELTA 2

	Trial DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n (%)	Vehicle Control N=162 n (%)	Delgocitinib N=313 n (%)	Vehicle Control N=159 n (%)	Delgocitinib N=638 n (%)	Vehicle Control N=321 n (%)	Risk Difference % (95% CI)
System Organ Class							
OCMQ (Broad)							
Blood and lymphatic system disorders (SOC)							
Leukopenia	3 (0.9)	0	2 (0.6)	1 (0.6)	5 (0.8)	1 (0.3)	0.5 (-1.0, 1.6)
Anemia	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Thrombocytopenia	0	0	0	1 (0.6)	0	1 (0.3)	-0.3 (-1.7, 0.3)
Cardiac disorders (SOC)							
Systemic hypertension	6 (1.8)	0	2 (0.6)	0	8 (1.3)	0	1.3 (0.1, 2.5) *
Palpitations	2 (0.6)	0	0	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Acute coronary syndrome	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Cardiac conduction disturbance	0	1 (0.6)	2 (0.6)	0	2 (0.3)	1 (0.3)	0.0 (-1.4, 0.9)
Myocardial ischemia	0	1 (0.6)	2 (0.6)	0	2 (0.3)	1 (0.3)	0.0 (-1.4, 0.9)
Arrhythmia	3 (0.9)	1 (0.6)	0	1 (0.6)	3 (0.5)	2 (0.6)	-0.2 (-1.8, 0.9)
Heart failure	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.6)	2 (0.3)	2 (0.6)	-0.3 (-2.0, 0.6)
Ear and labyrinth disorders (SOC)							
Vertigo	0	1 (0.6)	1 (0.3)	0	1 (0.2)	1 (0.3)	-0.2 (-1.6, 0.6)

System Organ Class OCMQ (Broad)	Trial DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n (%)	Vehicle Control N=162 n (%)	Delgocitinib N=313 n (%)	Vehicle Control N=159 n (%)	Delgocitinib N=638 n (%)	Vehicle Control N=321 n (%)	Risk Difference % (95% CI)
Endocrine disorders (SOC)							
Hyperglycemia	2 (0.6)	1 (0.6)	0	1 (0.6)	2 (0.3)	2 (0.6)	-0.3 (-2.0, 0.6)
Hypoglycemia	0	0	0	1 (0.6)	0	1 (0.3)	-0.3 (-1.7, 0.3)
Eye disorders (SOC)							
Glaucoma	0	0	0	1 (0.6)	0	1 (0.3)	-0.3 (-1.7, 0.3)
Gastrointestinal disorders (SOC)							
Diarrhea	5 (1.5)	0	10 (3.2)	2 (1.3)	15 (2.4)	2 (0.6)	1.7 (-0.1, 3.3)
Nausea	3 (0.9)	1 (0.6)	0	0	3 (0.5)	1 (0.3)	0.2 (-1.3, 1.1)
Vomiting	3 (0.9)	1 (0.6)	0	0	3 (0.5)	1 (0.3)	0.2 (-1.3, 1.1)
Dyspepsia	1 (0.3)	0	3 (1.0)	2 (1.3)	4 (0.6)	2 (0.6)	0.0 (-1.7, 1.1)
Abdominal pain	1 (0.3)	0	4 (1.3)	3 (1.9)	5 (0.8)	3 (0.9)	-0.2 (-2.0, 1.1)
Constipation	0	0	1 (0.3)	1 (0.6)	1 (0.2)	1 (0.3)	-0.2 (-1.6, 0.6)
General disorders and administration site conditions (SOC)							
Fatigue	4 (1.2)	0	1 (0.3)	2 (1.3)	5 (0.8)	2 (0.6)	0.2 (-1.5, 1.3)
Pyrexia	0	1 (0.6)	1 (0.3)	0	1 (0.2)	1 (0.3)	-0.2 (-1.6, 0.6)
Peripheral edema	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)
Volume depletion	0	0	0	1 (0.6)	0	1 (0.3)	-0.3 (-1.7, 0.3)
Dizziness	0	1 (0.6)	1 (0.3)	1 (0.6)	1 (0.2)	2 (0.6)	-0.5 (-2.1, 0.3)
Fall	0	2 (1.2)	1 (0.3)	1 (0.6)	1 (0.2)	3 (0.9)	-0.8 (-2.6, 0.1)
Local administration reaction	1 (0.3)	3 (1.9)	3 (1.0)	2 (1.3)	4 (0.6)	5 (1.6)	-0.9 (-3.0, 0.4)
Hepatobiliary disorders (SOC)							
Hepatic failure	0	0	2 (0.6)	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Hepatic injury	5 (1.5)	3 (1.9)	7 (2.2)	3 (1.9)	12 (1.9)	6 (1.9)	0.0 (-2.3, 1.7)
Immune system disorders (SOC)							
Anaphylactic reaction	0	1 (0.6)	1 (0.3)	1 (0.6)	1 (0.2)	2 (0.6)	-0.5 (-2.1, 0.3)
Angioedema	0	1 (0.6)	1 (0.3)	2 (1.3)	1 (0.2)	3 (0.9)	-0.8 (-2.6, 0.1)
Hypersensitivity	10 (3.1)	18 (11.1)	9 (2.9)	9 (5.7)	19 (3.0)	27 (8.4)	-5.4 (-9.2, -2.4) *

System Organ Class OCMQ (Broad)	Trial DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n (%)	Vehicle Control N=162 n (%)	Delgocitinib N=313 n (%)	Vehicle Control N=159 n (%)	Delgocitinib N=638 n (%)	Vehicle Control N=321 n (%)	Risk Difference % (95% CI)
Infections and infestations (SOC)							
Viral infection	44 (13.5)	19 (11.7)	53 (16.9)	26 (16.4)	97 (15.2)	45 (14.0)	1.2 (-3.8, 5.7)
Pneumonia	3 (0.9)	2 (1.2)	5 (1.6)	1 (0.6)	8 (1.3)	3 (0.9)	0.3 (-1.5, 1.7)
Bacterial infection	19 (5.8)	10 (6.2)	16 (5.1)	7 (4.4)	35 (5.5)	17 (5.3)	0.2 (-3.2, 3.1)
Nasopharyngitis	33 (10.2)	16 (9.9)	28 (8.9)	15 (9.4)	61 (9.6)	31 (9.7)	-0.1 (-4.3, 3.7)
Purulent material	0	0	1 (0.3)	1 (0.6)	1 (0.2)	1 (0.3)	-0.2 (-1.6, 0.6)
Opportunistic infection	3 (0.9)	1 (0.6)	1 (0.3)	2 (1.3)	4 (0.6)	3 (0.9)	-0.3 (-2.1, 0.8)
Fungal infection	4 (1.2)	3 (1.9)	2 (0.6)	2 (1.3)	6 (0.9)	5 (1.6)	-0.6 (-2.7, 0.8)
Metabolism and nutrition disorders (SOC)							
Lipid disorder	11 (3.4)	5 (3.1)	5 (1.6)	0	16 (2.5)	5 (1.6)	1.0 (-1.3, 2.8)
Musculoskeletal and connective tissue disorders (SOC)							
Back pain	7 (2.2)	2 (1.2)	2 (0.6)	0	9 (1.4)	2 (0.6)	0.8 (-0.9, 2.1)
Fracture	2 (0.6)	0	1 (0.3)	0	3 (0.5)	0	0.5 (-0.7, 1.4)
Arthralgia	4 (1.2)	3 (1.9)	6 (1.9)	1 (0.6)	10 (1.6)	4 (1.2)	0.3 (-1.7, 1.8)
Gout	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Rhabdomyolysis	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Arthritis	5 (1.5)	5 (3.1)	7 (2.2)	1 (0.6)	12 (1.9)	6 (1.9)	0.0 (-2.3, 1.7)
Myalgia	2 (0.6)	1 (0.6)	0	1 (0.6)	2 (0.3)	2 (0.6)	-0.3 (-2.0, 0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)							
Malignancy	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Nervous system disorders (SOC)							
Headache	11 (3.4)	5 (3.1)	20 (6.4)	9 (5.7)	31 (4.9)	14 (4.4)	0.5 (-2.7, 3.1)
Seizure	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Dysgeusia	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Somnolence	1 (0.3)	0	1 (0.3)	2 (1.3)	2 (0.3)	2 (0.6)	-0.3 (-2.0, 0.6)
Syncope	0	0	0	1 (0.6)	0	1 (0.3)	-0.3 (-1.7, 0.3)
Paresthesia	2 (0.6)	4 (2.5)	2 (0.6)	0	4 (0.6)	4 (1.2)	-0.6 (-2.6, 0.6)

System Organ Class OCMQ (Broad)	Trial DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n (%)	Vehicle Control N=162 n (%)	Delgocitinib N=313 n (%)	Vehicle Control N=159 n (%)	Delgocitinib N=638 n (%)	Vehicle Control N=321 n (%)	Risk Difference % (95% CI)
Psychiatric disorders (SOC)							
Insomnia	1 (0.3)	0	2 (0.6)	0	3 (0.5)	0	0.5 (-0.7, 1.4)
Mania	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Study agent abuse potential	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Depression	3 (0.9)	2 (1.2)	1 (0.3)	0	4 (0.6)	2 (0.6)	0.0 (-1.7, 1.1)
Anxiety	1 (0.3)	0	1 (0.3)	1 (0.6)	2 (0.3)	1 (0.3)	0.0 (-1.4, 0.9)
Psychosis	1 (0.3)	1 (0.6)	0	0	1 (0.2)	1 (0.3)	-0.2 (-1.6, 0.6)
Renal and urinary disorders (SOC)							
Urinary retention	0	1 (0.6)	1 (0.3)	0	1 (0.2)	1 (0.3)	-0.2 (-1.6, 0.6)
Renal & urinary tract infection	3 (0.9)	4 (2.5)	6 (1.9)	4 (2.5)	9 (1.4)	8 (2.5)	-1.1 (-3.5, 0.7)
Reproductive system and breast disorders (SOC)							
Excessive menstrual bleeding	0	0	2 (0.6)	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Abnormal uterine bleeding	1 (0.3)	1 (0.6)	2 (0.6)	0	3 (0.5)	1 (0.3)	0.2 (-1.3, 1.1)
Bacterial vaginosis	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)
Respiratory, thoracic and mediastinal disorders (SOC)							
Bronchospasm	2 (0.6)	1 (0.6)	2 (0.6)	0	4 (0.6)	1 (0.3)	0.3 (-1.1, 1.3)
Dyspnea	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Respiratory failure	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Cough	1 (0.3)	1 (0.6)	3 (1.0)	1 (0.6)	4 (0.6)	2 (0.6)	0.0 (-1.7, 1.1)
Skin and subcutaneous tissue disorders (SOC)							
Alopecia	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Erythema	1 (0.3)	0	2 (0.6)	1 (0.6)	3 (0.5)	1 (0.3)	0.2 (-1.3, 1.1)
Rash	6 (1.8)	7 (4.3)	9 (2.9)	3 (1.9)	15 (2.4)	10 (3.1)	-0.8 (-3.5, 1.3)
Urticaria	3 (0.9)	2 (1.2)	2 (0.6)	3 (1.9)	5 (0.8)	5 (1.6)	-0.8 (-2.9, 0.6)
Pruritus	0	3 (1.9)	1 (0.3)	1 (0.6)	1 (0.2)	4 (1.2)	-1.1 (-3.0, -0.1) *
Vascular disorders (SOC)							
Hemorrhage	8 (2.5)	1 (0.6)	2 (0.6)	0	10 (1.6)	1 (0.3)	1.3 (-0.3, 2.6)
Thrombosis	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)
Thrombosis venous	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)

Source: Internal review of Applicant's submitted datasets for DELTA 1 and DELTA 2

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query

Table 29. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Pooled Trials DELTA 1 and DELTA 2

System Organ Class OCMQ (Narrow)	Trial DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n (%)	Vehicle Control N=162 n (%)	Delgocitinib N=313 n (%)	Vehicle Control N=159 n (%)	Delgocitinib N=638 n (%)	Vehicle Control N=321 n (%)	Risk Difference % (95% CI)
Blood and lymphatic system disorders (SOC)							
Anemia	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Leukopenia	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Thrombocytopenia	0	0	0	1 (0.6)	0	1 (0.3)	-0.3 (-1.7, 0.3)
Cardiac disorders (SOC)							
Systemic hypertension	6 (1.8)	0	2 (0.6)	0	8 (1.3)	0	1.3 (0.1, 2.5) *
Palpitations	2 (0.6)	0	0	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Cardiac conduction disturbance	0	1 (0.6)	2 (0.6)	0	2 (0.3)	1 (0.3)	0.0 (-1.4, 0.9)
Arrhythmia	1 (0.3)	1 (0.6)	0	0	1 (0.2)	1 (0.3)	-0.2 (-1.6, 0.6)
Heart failure	0	0	0	1 (0.6)	0	1 (0.3)	-0.3 (-1.7, 0.3)
Ear and labyrinth disorders (SOC)							
Vertigo	0	1 (0.6)	1 (0.3)	0	1 (0.2)	1 (0.3)	-0.2 (-1.6, 0.6)
Endocrine disorders (SOC)							
Hyperglycemia	2 (0.6)	1 (0.6)	0	1 (0.6)	2 (0.3)	2 (0.6)	-0.3 (-2.0, 0.6)
Hypoglycemia	0	0	0	1 (0.6)	0	1 (0.3)	-0.3 (-1.7, 0.3)
Gastrointestinal disorders (SOC)							
Diarrhea	1 (0.3)	0	2 (0.6)	0	3 (0.5)	0	0.5 (-0.7, 1.4)
Nausea	3 (0.9)	1 (0.6)	0	0	3 (0.5)	1 (0.3)	0.2 (-1.3, 1.1)
Vomiting	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Dyspepsia	0	0	2 (0.6)	1 (0.6)	2 (0.3)	1 (0.3)	0.0 (-1.4, 0.9)
Abdominal pain	1 (0.3)	0	4 (1.3)	3 (1.9)	5 (0.8)	3 (0.9)	-0.2 (-2.0, 1.1)
Constipation	0	0	1 (0.3)	1 (0.6)	1 (0.2)	1 (0.3)	-0.2 (-1.6, 0.6)

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

System Organ Class OCMQ (Narrow)	Trial DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA		
	Delgocitinib N=325 n (%)	Vehicle Control N=162 n (%)	Delgocitinib N=313 n (%)	Vehicle Control N=159 n (%)	Delgocitinib N=638 n (%)	Vehicle Control N=321 n (%)	Risk Difference % (95% CI)
General disorders and administration site conditions (SOC)							
Fatigue	4 (1.2)	0	1 (0.3)	2 (1.3)	5 (0.8)	2 (0.6)	0.2 (-1.5, 1.3)
Pyrexia	0	1 (0.6)	1 (0.3)	0	1 (0.2)	1 (0.3)	-0.2 (-1.6, 0.6)
Fall	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)
Peripheral edema	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)
Dizziness	0	1 (0.6)	1 (0.3)	1 (0.6)	1 (0.2)	2 (0.6)	-0.5 (-2.1, 0.3)
Local administration reaction	1 (0.3)	3 (1.9)	3 (1.0)	2 (1.3)	4 (0.6)	5 (1.6)	-0.9 (-3.0, 0.4)
Hepatobiliary disorders (SOC)							
Hepatic injury	3 (0.9)	2 (1.2)	2 (0.6)	1 (0.6)	5 (0.8)	3 (0.9)	-0.2 (-2.0, 1.1)
Immune system disorders (SOC)							
Hypersensitivity	3 (0.9)	4 (2.5)	2 (0.6)	2 (1.3)	5 (0.8)	6 (1.9)	-1.1 (-3.3, 0.3)
Infections and infestations (SOC)							
Viral infection	41 (12.6)	18 (11.1)	46 (14.7)	26 (16.4)	87 (13.6)	44 (13.7)	-0.1 (-4.9, 4.4)
Nasopharyngitis	33 (10.2)	16 (9.9)	28 (8.9)	15 (9.4)	61 (9.6)	31 (9.7)	-0.1 (-4.3, 3.7)
Purulent material	0	0	1 (0.3)	1 (0.6)	1 (0.2)	1 (0.3)	-0.2 (-1.6, 0.6)
Bacterial infection	9 (2.8)	7 (4.3)	13 (4.2)	6 (3.8)	22 (3.4)	13 (4.0)	-0.6 (-3.6, 1.8)
Fungal infection	4 (1.2)	3 (1.9)	2 (0.6)	2 (1.3)	6 (0.9)	5 (1.6)	-0.6 (-2.7, 0.8)
Metabolism and nutrition disorders (SOC)							
Lipid disorder	11 (3.4)	5 (3.1)	5 (1.6)	0	16 (2.5)	5 (1.6)	1.0 (-1.3, 2.8)
Musculoskeletal and connective tissue disorders (SOC)							
Back pain	5 (1.5)	2 (1.2)	2 (0.6)	0	7 (1.1)	2 (0.6)	0.5 (-1.2, 1.7)
Fracture	2 (0.6)	0	1 (0.3)	0	3 (0.5)	0	0.5 (-0.7, 1.4)
Arthralgia	2 (0.6)	3 (1.9)	5 (1.6)	1 (0.6)	7 (1.1)	4 (1.2)	-0.1 (-2.1, 1.2)
Arthritis	1 (0.3)	2 (1.2)	2 (0.6)	0	3 (0.5)	2 (0.6)	-0.2 (-1.8, 0.9)
Myalgia	1 (0.3)	0	0	1 (0.6)	1 (0.2)	1 (0.3)	-0.2 (-1.6, 0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)							
Malignancy	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

System Organ Class OCMQ (Narrow)	Trial DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA		
	Delgocitinib N=325 n (%)	Vehicle Control N=162 n (%)	Delgocitinib N=313 n (%)	Vehicle Control N=159 n (%)	Delgocitinib N=638 n (%)	Vehicle Control N=321 n (%)	Risk Difference % (95% CI)
Nervous system disorders (SOC)							
Headache	11 (3.4)	5 (3.1)	20 (6.4)	9 (5.7)	31 (4.9)	14 (4.4)	0.5 (-2.7, 3.1)
Seizure	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Dysgeusia	1 (0.3)	0	0	0	1 (0.2)	0	0.2 (-1.0, 0.9)
Paresthesia	2 (0.6)	4 (2.5)	2 (0.6)	0	4 (0.6)	4 (1.2)	-0.6 (-2.6, 0.6)
Psychiatric disorders (SOC)							
Insomnia	1 (0.3)	0	2 (0.6)	0	3 (0.5)	0	0.5 (-0.7, 1.4)
Anxiety	1 (0.3)	0	1 (0.3)	1 (0.6)	2 (0.3)	1 (0.3)	0.0 (-1.4, 0.9)
Depression	2 (0.6)	2 (1.2)	0	0	2 (0.3)	2 (0.6)	-0.3 (-2.0, 0.6)
Renal and urinary disorders (SOC)							
Renal & urinary tract infection	3 (0.9)	4 (2.5)	6 (1.9)	4 (2.5)	9 (1.4)	8 (2.5)	-1.1 (-3.5, 0.7)
Reproductive system and breast disorders (SOC)							
Abnormal uterine bleeding	0	0	2 (0.6)	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Excessive menstrual bleeding	0	0	2 (0.6)	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Respiratory, thoracic and mediastinal disorders (SOC)							
Bronchospasm	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Dyspnea	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Cough	1 (0.3)	1 (0.6)	3 (1.0)	1 (0.6)	4 (0.6)	2 (0.6)	0.0 (-1.7, 1.1)
Skin and subcutaneous tissue disorders (SOC)							
Alopecia	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0	0.3 (-0.9, 1.1)
Erythema	1 (0.3)	0	2 (0.6)	1 (0.6)	3 (0.5)	1 (0.3)	0.2 (-1.3, 1.1)
Urticaria	2 (0.6)	1 (0.6)	0	1 (0.6)	2 (0.3)	2 (0.6)	-0.3 (-2.0, 0.6)
Rash	5 (1.5)	7 (4.3)	8 (2.6)	3 (1.9)	13 (2.0)	10 (3.1)	-1.1 (-3.7, 0.9)
Pruritus	0	3 (1.9)	1 (0.3)	1 (0.6)	1 (0.2)	4 (1.2)	-1.1 (-3.0, -0.1)*

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

System Organ Class OCMQ (Narrow)	Trial DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA		
	Delgocitinib N=325 n (%)	Vehicle Control N=162 n (%)	Delgocitinib N=313 n (%)	Vehicle Control N=159 n (%)	Delgocitinib N=638 n (%)	Vehicle Control N=321 n (%)	Risk Difference % (95% CI)
Vascular disorders (SOC)							
Hemorrhage	8 (2.5)	1 (0.6)	2 (0.6)	0	10 (1.6)	1 (0.3)	1.3 (-0.3, 2.6)
Thrombosis	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)
Thrombosis venous	0	1 (0.6)	0	0	0	1 (0.3)	-0.3 (-1.7, 0.3)

Source: adae.xpt; Software: R

* Indicates that 95% confidence interval excludes zero.

Treatment-emergent adverse events defined as an event that started after the first application of IMP or that started before the first application of IMP and worsened in severity after first dose of IMP.

Duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.

Abbreviations: CI, confidence interval; OCMQ, OND custom medical query; IMP, investigational medical product; incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class

Local Tolerability and Dermal Safety

Subjects and investigators evaluated local tolerability by active assessment in Trials DELTA 1, DELTA 2, and DELTA 3.

Subject Assessments

Subjects evaluated local tolerability weekly through the end of treatment. Subjects rated the worst stinging/burning related to IMP applications during the previous week in an eDiary from Day 7 onwards with a 4-point scale (“0 = no stinging or burning, 1 mild = slight warm, tingling sensation, not really bothersome, 2 moderate = definitive warm, tingling sensations, that is somewhat bothersome, 3 severe = hot, tingling/stinging sensation that has caused definite discomfort”). The assessment of local tolerability by the subject was reported as an AE at the discretion of the investigator, regardless of suspected relatedness of the local skin reaction to the IMP.

In the primary pool, subjects who received active and vehicle reported similar rates of no or mild stinging/burning (80.7% and 73.6% respectively) at the end of Week 1, and more subjects on vehicle (11.0%) reported severe stinging/burning compared to active (4.9%). As the trials progressed, local tolerability for subjects in both groups improved, and by Week 16 approximately 90% of subjects in both treatment groups had no stinging or burning. Severe stinging/burning led to early termination in 3.2% of subjects on active and 8.9% of subjects on vehicle. For subjects who enrolled in open-label Trial DELTA 3 for an additional 36 weeks of treatment, tolerability gradually improved over time (subjects on active with no or mild stinging increased from 83.9% at Week 1 to 90.2% at Week 36).

There were no differences in local tolerability reactions in subjects by primary CHE subtype (allergic contact dermatitis, irritant contact dermatitis, contact urticaria/protein contact dermatitis, atopic hand eczema, vesicular hand eczema pompholyx, hyperkeratotic eczema) within or across treatment groups.

Investigator Assessments

In Trials DELTA 1 and DELTA 2, investigators assessed local tolerability weekly and at the end of treatment. In Trial DELTA 3, assessments were performed every 4 weeks and at treatment completion. Active assessments for local tolerability were not performed for each subject using separate scales. Instead, investigators performed targeted evaluations when local skin reactions were suspected to be related to the IMP. In such cases, reactions were scored using the Berger and Bowman scale, which evaluates local skin signs including irritation, erythema, papules, edema, vesicular eruption, glazed appearance, fissures, exudates, and scabs. Investigators were instructed to assess only signs specifically attributable to the IMP, excluding those related to underlying CHE. The suspected etiology of the reaction was recorded in the electronic case report form as one of the following:

- Irritant contact dermatitis caused by IMP
- Allergic contact dermatitis caused by IMP (confirmation required a positive IMP patch test)
- Other (specify)

If a reaction met criteria for an AE, the final diagnosis was captured accordingly.

Patch Test Findings by Trial

Trial DELTA 1

Six subjects experienced suspected local skin reactions and underwent patch testing (2 on active, 4 on vehicle). All scored results were negative, except for one vehicle-treated subject who did not return for the second reading. All AEs originating from patch testing were coded with PTs related to eczema.

Trial DELTA 2

Nine subjects had suspected local skin reactions; five underwent patch testing (1 on active, 4 on vehicle). Four subjects had negative scores at both readings. One vehicle-treated subject had a weak positive reaction at the first reading and a doubtful result at the second. AEs included one event of “application site erythema” in the active arm; all events in the vehicle arm were related to eczema.

Trial DELTA 3

Three active-treated subjects had suspected local reactions; two underwent patch testing. One had a negative score (one reading only), and one had a doubtful result. AEs reported following patch testing included “application site erythema” and “contact dermatitis.”

Given the low number of positive or equivocal patch test results, the predominance of negative findings, and the frequency of reactions in vehicle-treated subjects, the overall assessment of skin irritation and sensitization via patch testing did not indicate allergic contact dermatitis related to delgocitinib.

Adverse Reactions in <1% of Subjects

The review team analyzed application site TEAEs that were reported in <1% of subjects in Trials DELTA 1 and DELTA 2. The following AE preferred terms were reported in <1% of subjects, were considered probably or possibly related to delgocitinib by both investigators and the review team, and are proposed for inclusion in labeling:

- Application site pain (0.6%)
- Application site paresthesia (0.4%)
- Application site pruritus (0.1%)
- Application site erythema (0.1%)

Long-Term Safety

The review team analyzed adverse events for subjects who received continuous and intermittent delgocitinib treatment over 52 weeks in the vehicle-controlled Trials DELTA 1 and DELTA 2 and the single-arm open-label long-term extension Trial DELTA 3.

There were no increases in the rates of SAEs or AEs leading to withdrawal from the trial and/or permanent discontinuation of IMP with long-term intermittent or continuous treatment for 52 weeks. In addition, there were no increases over time in the rates of severe AEs, which were similar between intermittent or continuous treatment groups. The distribution pattern of AEs

across SOC and PTs was generally similar across treatment groups and pools (Primary pool and Long-term safety pool/Intermittent-use pool). The review team identified no clinically relevant differences.

No new safety signals were identified based on FDA broad and narrow medical queries and EAIRs (refer to [Table 30](#) and [Table 31](#)). Analysis of vital signs, ECGs, laboratory findings and shift tables for subjects continuously treated for 52 weeks (refer to Section [7.6.1.6](#)) did not identify any new safety signals with long-term use of delgocitinib for 52 weeks.

While the current long-term safety database is sufficient to support approval, it has limitations in detecting rare or delayed adverse events. The conduct of a long-term, vehicle-controlled trial was not pursued by the Applicant due to ethical concerns related to prolonged use of vehicle in subjects with moderate to severe CHE with inadequate response to topical corticosteroids and the potential for high dropout rates which could bias results. A total of 638 subjects received 16 weeks of treatment, but fewer than 200 were treated continuously for 52 weeks. Trial DELTA 3, the long-term extension trial, employed an open-label, as-needed design to reflect real-world clinical practice. As a result, vehicle-controlled data are limited to the 16-week parent trials (Trials DELTA 1 and DELTA 2). Given the potential for dose-dependent, rare, and long-latency adverse events related to JAKi and the limited long-term safety database, the review team recommends appropriate class labeling to inform prescribers and patients of risks not fully evaluated in the delgocitinib clinical program. Refer to Section [7.2](#) of this review for the review team's rationale for inclusion of a Boxed Warning.

Table 30. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Broad), Safety Population, Pooled Trials DELTA 1, DELTA 2, and DELTA 3

System Organ Class OCMQ (Broad)	Delgocitinib Continuous Treatment Over 52 Weeks PY=199.1 E=458 Event (EAER)	Delgocitinib Intermittent Treatment Over 52 Weeks PY=259.3 E=907 Event (EAER)	Vehicle Control 16 Weeks PY=74.8 E=645 Event (EAER)
Blood and lymphatic system disorders (SOC)			
Thrombocytopenia	0	0	2 (2.7)
Leukopenia	2 (1.0)	8 (3.1)	6 (8.0)
Anemia	0	5 (1.9)	0
Cardiac disorders (SOC)			
Tachycardia	1 (0.5)	2 (0.8)	0
Systemic hypertension	9 (4.5)	9 (3.5)	3 (4.0)
Palpitations	0	2 (0.8)	1 (1.3)
Myocardial ischemia	1 (0.5)	3 (1.2)	1 (1.3)
Myocardial infarction	0	2 (0.8)	0
Heart failure	3 (1.5)	3 (1.2)	4 (5.3)
Cardiac conduction disturbance	0	3 (1.2)	2 (2.7)
Arrhythmia	2 (1.0)	7 (2.7)	10 (13.4)
Acute coronary syndrome	1 (0.5)	2 (0.8)	0
Ear and labyrinth disorders (SOC)			
Vertigo	1 (0.5)	1 (0.4)	2 (2.7)
Endocrine disorders (SOC)			
Hypoglycemia	0	0	1 (1.3)
Hyperglycemia	3 (1.5)	2 (0.8)	4 (5.3)

System Organ Class OCMQ (Broad)	Delgocitinib Continuous Treatment Over 52 Weeks PY=199.1 E=458 Event (EAER)	Delgocitinib Intermittent Treatment Over 52 Weeks PY=259.3 E=907 Event (EAER)	Vehicle Control 16 Weeks PY=74.8 E=645 Event (EAER)
Eye disorders (SOC)			
Glaucoma	0	0	1 (1.3)
Gastrointestinal disorders (SOC)			
Vomiting	2 (1.0)	8 (3.1)	6 (8.0)
Nausea	2 (1.0)	7 (2.7)	2 (2.7)
Dyspepsia	7 (3.5)	10 (3.9)	3 (4.0)
Dry mouth	0	1 (0.4)	0
Diarrhea	12 (6.0)	30 (11.6)	13 (17.4)
Constipation	0	1 (0.4)	0
Abdominal pain	5 (2.5)	7 (2.7)	4 (5.3)
General disorders and administration site conditions (SOC)			
Pyrexia	1 (0.5)	3 (1.2)	2 (2.7)
Peripheral edema	0	2 (0.8)	2 (2.7)
Local administration reaction	2 (1.0)	3 (1.2)	8 (10.7)
Fatigue	1 (0.5)	8 (3.1)	4 (5.3)
Fall	3 (1.5)	3 (1.2)	7 (9.4)
Dizziness	1 (0.5)	1 (0.4)	5 (6.7)
Hepatobiliary disorders (SOC)			
Hepatic injury	7 (3.5)	21 (8.1)	12 (16.0)
Hepatic failure	2 (1.0)	3 (1.2)	2 (2.7)
Cholecystitis	0	2 (0.8)	2 (2.7)
Immune system disorders (SOC)			
Hypersensitivity	26 (13.1)	43 (16.6)	45 (60.2)
Angioedema	1 (0.5)	2 (0.8)	4 (5.3)
Anaphylactic reaction	1 (0.5)	0	2 (2.7)
Infections and infestations (SOC)			
Viral infection	100 (50.2)	188 (72.5)	118 (157.7)
Purulent material	2 (1.0)	4 (1.5)	2 (2.7)
Pneumonia	14 (7.0)	24 (9.3)	13 (17.4)
Opportunistic infection	2 (1.0)	4 (1.5)	5 (6.7)
Nasopharyngitis	75 (37.7)	150 (57.8)	97 (129.7)
Fungal infection	6 (3.0)	6 (2.3)	11 (14.7)
Bacterial infection	31 (15.6)	70 (27.0)	38 (50.8)
Metabolism and nutrition disorders (SOC)			
Lipid disorder	16 (8.0)	18 (6.9)	17 (22.7)
Musculoskeletal and connective tissue disorders (SOC)			
Tendinopathy	2 (1.0)	1 (0.4)	4 (5.3)
Rhabdomyolysis	1 (0.5)	0	0
Osteoporosis	0	1 (0.4)	0
Myalgia	1 (0.5)	5 (1.9)	6 (8.0)
Gout	1 (0.5)	0	0
Fracture	1 (0.5)	6 (2.3)	1 (1.3)
Back pain	8 (4.0)	16 (6.2)	10 (13.4)
Arthritis	13 (6.5)	18 (6.9)	15 (20.1)
Arthralgia	10 (5.0)	13 (5.0)	11 (14.7)

System Organ Class OCMQ (Broad)	Delgocitinib Continuous Treatment Over 52 Weeks PY=199.1 E=458 Event (EAER)	Delgocitinib Intermittent Treatment Over 52 Weeks PY=259.3 E=907 Event (EAER)	Vehicle Control 16 Weeks PY=74.8 E=645 Event (EAER)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)			
Malignancy	0	1 (0.4)	2 (2.7)
Nervous system disorders (SOC)			
Syncope	1 (0.5)	1 (0.4)	5 (6.7)
Somnolence	0	3 (1.2)	4 (5.3)
Seizure	0	1 (0.4)	1 (1.3)
Paresthesia	4 (2.0)	5 (1.9)	5 (6.7)
Headache	12 (6.0)	49 (18.9)	28 (37.4)
Dysgeusia	0	1 (0.4)	0
Psychiatric disorders (SOC)			
Study agent abuse potential	1 (0.5)	0	0
Psychosis	1 (0.5)	2 (0.8)	2 (2.7)
Parasomnia	0	0	1 (1.3)
Mania	1 (0.5)	0	0
Insomnia	1 (0.5)	3 (1.2)	2 (2.7)
Depression	2 (1.0)	4 (1.5)	2 (2.7)
Anxiety	3 (1.5)	6 (2.3)	5 (6.7)
Renal and urinary disorders (SOC)			
Urinary retention	0	2 (0.8)	0
Renal & urinary tract infection	4 (2.0)	20 (7.7)	9 (12.0)
Reproductive system and breast disorders (SOC)			
Excessive menstrual bleeding	0	1 (0.4)	0
Bacterial vaginosis	0	0	1 (1.3)
Abnormal uterine bleeding	0	2 (0.8)	2 (2.7)
Respiratory, thoracic and mediastinal disorders (SOC)			
Respiratory failure	4 (2.0)	1 (0.4)	3 (4.0)
Respiratory depression	1 (0.5)	0	1 (1.3)
Dyspnea	3 (1.5)	1 (0.4)	2 (2.7)
Cough	3 (1.5)	6 (2.3)	5 (6.7)
Bronchospasm	5 (2.5)	4 (1.5)	6 (8.0)
Skin and subcutaneous tissue disorders (SOC)			
Urticaria	1 (0.5)	7 (2.7)	6 (8.0)
Rash	10 (5.0)	16 (6.2)	10 (13.4)
Pruritus	2 (1.0)	2 (0.8)	10 (13.4)
Erythema	1 (0.5)	4 (1.5)	2 (2.7)
Alopecia	1 (0.5)	3 (1.2)	0

	Delgocitinib Continuous Treatment Over 52 Weeks PY=199.1 E=458 Event (EAER)	Delgocitinib Intermittent Treatment Over 52 Weeks PY=259.3 E=907 Event (EAER)	Vehicle Control 16 Weeks PY=74.8 E=645 Event (EAER)
System Organ Class OCMQ (Broad)			
Vascular disorders (SOC)			
Thrombosis venous	0	1 (0.4)	1 (1.3)
Thrombosis arterial	0	2 (0.8)	0
Thrombosis	0	3 (1.2)	1 (1.3)
Hypotension	1 (0.5)	0	0
Hemorrhage	7 (3.5)	11 (4.2)	5 (6.7)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined in Trials DELTA 1 and DELTA 1 as events that started after the first application of IMP or that started before the first application of IMP and worsened in severity after first dose of IMP, and in Trial DELTA 3 as AEs with onset after baseline visit. AEs reported as ongoing at baseline were reported as medical history. Any worsening of an ongoing AE after baseline visit were recorded as a new AE.

Delgocitinib 20 mg/g (Continuous Treatment Over 52 weeks) refers to subjects who received Delgocitinib in Trials DELTA 1 and DELTA 2 and continuously received Delgocitinib in Trial DELTA 3 over the 52 weeks.

Delgocitinib 20 mg/g (Intermittent Treatment Over 52 weeks) refers to subjects who received Delgocitinib in Trials DELTA 1 and DELTA 2 and did not receive Delgocitinib continuously in Trial DELTA 3 over the 52 weeks.

The two columns contain nonoverlapping subjects.

Vehicle control 16 weeks: subjects who received vehicle control in Trials DELTA 1 and DELTA 2 and continuously stay off treatment in Trial DELTA 3 over the 52 weeks.

Duration is 52 weeks.

Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.

Abbreviations: AE, adverse event; E, number of events; EAER, exposure adjusted event rate; OCMQ, OND custom medical query; IMP, investigational medical product; incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; PY, patient years of observation; SOC, system organ class

Table 31. Subject With Adverse Events by System Organ Class FDA Medical Query (Narrow) and Preferred Term, Showing Terms Occurring in at Least 1% of Subjects in Any Arm, Safety Population Pooled Trials 1401, DELTA 2, and DELTA 3

	Delgocitinib Continuous Treatment Over 52 Weeks PY=199.1 E=458 Event (EAER)	Delgocitinib Intermittent Treatment Over 52 Weeks PY=259.3 E=907 Event (EAER)	Vehicle Control 16 weeks PY=74.8 E=645 Event (EAER)
System Organ Class OCMQ (Narrow) Preferred Term			
Blood and lymphatic system disorders (SOC)			
Thrombocytopenia (OCMQ)	0	0	2 (2.7)
Thrombocytopenia	0	0	2 (2.7)
Cardiac disorders (SOC)			
Systemic hypertension (OCMQ)	9 (4.5)	9 (3.5)	3 (4.0)
Hypertension	9 (4.5)	7 (2.7)	3 (4.0)
Arrhythmia (OCMQ)	2 (1.0)	4 (1.5)	4 (5.3)
Sinus bradycardia	0	0	2 (2.7)
Endocrine disorders (SOC)			
Hyperglycemia (OCMQ)	2 (1.0)	2 (0.8)	3 (4.0)
Type 2 diabetes mellitus	0	1 (0.4)	2 (2.7)

System Organ Class	Delgocitinib Continuous Treatment Over 52 Weeks PY=199.1 E=458	Delgocitinib Intermittent Treatment Over 52 Weeks PY=259.3 E=907	Vehicle Control 16 weeks PY=74.8 E=645
OCMQ (Narrow)			
Preferred Term	Event (EAER)	Event (EAER)	Event (EAER)
Gastrointestinal disorders (SOC)			
Nausea (OCMQ)	1 (0.5)	5 (1.9)	1 (1.3)
Nausea	1 (0.5)	5 (1.9)	1 (1.3)
Dyspepsia (OCMQ)	2 (1.0)	3 (1.2)	2 (2.7)
Abdominal pain upper	2 (1.0)	3 (1.2)	2 (2.7)
Diarrhea (OCMQ)	1 (0.5)	11 (4.2)	6 (8.0)
Diarrhoea	1 (0.5)	9 (3.5)	6 (8.0)
Abdominal pain (OCMQ)	5 (2.5)	6 (2.3)	4 (5.3)
Abdominal pain upper	2 (1.0)	3 (1.2)	2 (2.7)
Abdominal pain	3 (1.5)	2 (0.8)	2 (2.7)
General disorders and administration site conditions (SOC)			
Pyrexia (OCMQ)	1 (0.5)	3 (1.2)	2 (2.7)
Pyrexia	1 (0.5)	3 (1.2)	2 (2.7)
Local administration reaction (OCMQ)	2 (1.0)	3 (1.2)	8 (10.7)
Vaccination site pain	1 (0.5)	0	2 (2.7)
Application site pain	1 (0.5)	3 (1.2)	5 (6.7)
Fatigue (OCMQ)	1 (0.5)	8 (3.1)	4 (5.3)
Fatigue	0	2 (0.8)	4 (5.3)
Asthenia	1 (0.5)	4 (1.5)	0
Dizziness (OCMQ)	1 (0.5)	1 (0.4)	5 (6.7)
Presyncope	0	0	3 (4.0)
Hepatobiliary disorders (SOC)			
Hepatic injury (OCMQ)	2 (1.0)	7 (2.7)	5 (6.7)
Aspartate aminotransferase increased	1 (0.5)	3 (1.2)	3 (4.0)
Alanine aminotransferase increased	1 (0.5)	3 (1.2)	2 (2.7)
Immune system disorders (SOC)			
Hypersensitivity (OCMQ)	5 (2.5)	3 (1.2)	6 (8.0)
Drug hypersensitivity	1 (0.5)	0	2 (2.7)
Allergy to chemicals	3 (1.5)	1 (0.4)	3 (4.0)

System Organ Class	Delgocitinib Continuous Treatment Over 52 Weeks PY=199.1 E=458	Delgocitinib Intermittent Treatment Over 52 Weeks PY=259.3 E=907	Vehicle Control 16 weeks PY=74.8 E=645
OCMQ (Narrow)			
Preferred Term	Event (EAER)	Event (EAER)	Event (EAER)
Infections and infestations (SOC)			
Viral infection (OCMQ)	84 (42.2)	149 (57.5)	105 (140.4)
Viral upper respiratory tract infection	4 (2.0)	3 (1.2)	1 (1.3)
Viral rhinitis	0	2 (0.8)	2 (2.7)
Skin papilloma	2 (1.0)	0	3 (4.0)
Oral herpes	1 (0.5)	15 (5.8)	4 (5.3)
Nasal herpes	0	0	2 (2.7)
Influenza	11 (5.5)	16 (6.2)	10 (13.4)
Herpes zoster	1 (0.5)	0	2 (2.7)
Herpes simplex	0	2 (0.8)	2 (2.7)
Hand-foot-and-mouth disease	3 (1.5)	1 (0.4)	0
Gastroenteritis viral	0	1 (0.4)	4 (5.3)
COVID-19	62 (31.1)	98 (37.8)	70 (93.6)
Asymptomatic COVID-19	0	0	2 (2.7)
Pneumonia (OCMQ)	1 (0.5)	3 (1.2)	2 (2.7)
Pneumonia	1 (0.5)	3 (1.2)	2 (2.7)
Nasopharyngitis (OCMQ)	75 (37.7)	150 (57.8)	97 (129.7)
Viral rhinitis	0	2 (0.8)	2 (2.7)
Upper respiratory tract infection	7 (3.5)	29 (11.2)	9 (12.0)
Rhinitis	1 (0.5)	10 (3.9)	8 (10.7)
Pharyngitis bacterial	0	0	2 (2.7)
Pharyngitis	3 (1.5)	7 (2.7)	10 (13.4)
Nasopharyngitis	62 (31.1)	98 (37.8)	64 (85.6)
Fungal infection (OCMQ)	6 (3.0)	6 (2.3)	11 (14.7)
Onychomycosis	2 (1.0)	0	2 (2.7)
Bacterial infection (OCMQ)	15 (7.5)	42 (16.2)	28 (37.4)
Urinary tract infection	3 (1.5)	14 (5.4)	4 (5.3)
Staphylococcal skin infection	0	0	3 (4.0)
Scarlet fever	0	0	2 (2.7)
Pharyngitis bacterial	0	0	2 (2.7)
Hordeolum	0	2 (0.8)	2 (2.7)
Cystitis	0	5 (1.9)	2 (2.7)
Metabolism and nutrition disorders (SOC)			
Lipid disorder (OCMQ)	16 (8.0)	17 (6.6)	15 (20.1)
Low density lipoprotein increased	4 (2.0)	4 (1.5)	2 (2.7)
Hypertriglyceridaemia	0	1 (0.4)	6 (8.0)
Hypercholesterolaemia	5 (2.5)	4 (1.5)	4 (5.3)
Blood triglycerides increased	4 (2.0)	3 (1.2)	2 (2.7)
Musculoskeletal and connective tissue disorders (SOC)			
Myalgia (OCMQ)	0	2 (0.8)	2 (2.7)
Myalgia	0	2 (0.8)	2 (2.7)
Back pain (OCMQ)	6 (3.0)	14 (5.4)	10 (13.4)
Back pain	5 (2.5)	14 (5.4)	9 (12.0)
Arthritis (OCMQ)	3 (1.5)	5 (1.9)	4 (5.3)
Osteoarthritis	2 (1.0)	2 (0.8)	3 (4.0)
Arthralgia (OCMQ)	3 (1.5)	9 (3.5)	9 (12.0)
Arthralgia	3 (1.5)	9 (3.5)	9 (12.0)

System Organ Class	Delgocitinib Continuous Treatment Over 52 Weeks PY=199.1 E=458	Delgocitinib Intermittent Treatment Over 52 Weeks PY=259.3 E=907	Vehicle Control 16 weeks PY=74.8 E=645
OCMQ (Narrow)			
Preferred Term	Event (EAER)	Event (EAER)	Event (EAER)
Nervous system disorders (SOC)			
Paresthesia (OCMQ)	4 (2.0)	5 (1.9)	5 (6.7)
Paraesthesia	1 (0.5)	2 (0.8)	2 (2.7)
Application site paraesthesia	1 (0.5)	2 (0.8)	2 (2.7)
Headache (OCMQ)	12 (6.0)	49 (18.9)	28 (37.4)
Migraine	2 (1.0)	4 (1.5)	2 (2.7)
Headache	10 (5.0)	45 (17.4)	25 (33.4)
Psychiatric disorders (SOC)			
Depression (OCMQ)	1 (0.5)	3 (1.2)	2 (2.7)
Depression	1 (0.5)	3 (1.2)	2 (2.7)
Anxiety (OCMQ)	1 (0.5)	3 (1.2)	5 (6.7)
Stress	0	0	2 (2.7)
Anxiety	1 (0.5)	1 (0.4)	2 (2.7)
Renal and urinary disorders (SOC)			
Renal & urinary tract infection (OCMQ)	3 (1.5)	19 (7.3)	8 (10.7)
Urinary tract infection	3 (1.5)	14 (5.4)	4 (5.3)
Cystitis	0	5 (1.9)	2 (2.7)
Respiratory, thoracic and mediastinal disorders (SOC)			
Dyspnea (OCMQ)	3 (1.5)	1 (0.4)	2 (2.7)
Dyspnoea	3 (1.5)	1 (0.4)	2 (2.7)
Cough (OCMQ)	3 (1.5)	6 (2.3)	5 (6.7)
Cough	3 (1.5)	6 (2.3)	5 (6.7)
Bronchospasm (OCMQ)	2 (1.0)	3 (1.2)	3 (4.0)
Asthma	2 (1.0)	3 (1.2)	2 (2.7)
Skin and subcutaneous tissue disorders (SOC)			
Urticaria (OCMQ)	0	3 (1.2)	2 (2.7)
Urticaria	0	3 (1.2)	2 (2.7)
Rash (OCMQ)	9 (4.5)	13 (5.0)	10 (13.4)
Urticaria	0	3 (1.2)	2 (2.7)
Dermatitis contact	4 (2.0)	3 (1.2)	4 (5.3)
Dermatitis	2 (1.0)	3 (1.2)	2 (2.7)
Pruritus (OCMQ)	2 (1.0)	2 (0.8)	10 (13.4)
Pruritus	1 (0.5)	2 (0.8)	6 (8.0)
Notalgia paraesthetica	0	0	2 (2.7)
Application site pruritus	1 (0.5)	0	2 (2.7)
Erythema (OCMQ)	1 (0.5)	4 (1.5)	2 (2.7)
Application site erythema	0	1 (0.4)	2 (2.7)

System Organ Class	Delgocitinib Continuous Treatment Over 52 Weeks PY=199.1 E=458	Delgocitinib Intermittent Treatment Over 52 Weeks PY=259.3 E=907	Vehicle Control 16 weeks PY=74.8 E=645
OCMQ (Narrow)			
Preferred Term	Event (EAER)	Event (EAER)	Event (EAER)
Vascular disorders (SOC)			
Hemorrhage (OCMQ)	7 (3.5)	9 (3.5)	5 (6.7)
Epistaxis	1 (0.5)	1 (0.4)	2 (2.7)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as Trials DELTA 1 and DELTA 2: An event that started after the first application of IMP or that started before the first application of IMP and worsened in severity after first dose of IMP. Trial DELTA 3: AEs with onset after baseline visit. AEs reported as ongoing at baseline were reported as medical history. Any worsening of an ongoing AE after baseline visit were recorded as a new AE.

Delgocitinib 20 mg/g (Continuous Treatment Over 52 weeks) refers to subjects who received Delgocitinib in Trials DELTA 1 and DELTA 2 and continuously received Delgocitinib in trial DELTA 3 over the 52 weeks.

Delgocitinib 20 mg/g (Intermittent Treatment Over 52 weeks) refers to subjects who received Delgocitinib in trials DELTA 1 and DELTA 2 and did not receive Delgocitinib continuously in Trial DELTA 3 over the 52 weeks.

The two columns contain nonoverlapping subjects.

Vehicle control 16 weeks: subjects who received vehicle control in Trials DELTA 1 and DELTA 2 and continuously stay off treatment in Trial DELTA 3 over the 52 weeks.

Duration is 52 weeks.

Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

Abbreviations: AE, adverse event; E, number of events; EAER, exposure adjusted event rate; OCMQ, OND custom medical query; IMP, investigational medical product; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; PY, patient years of observation; SOC, system organ class

7.6.1.6. Laboratory Findings, Pooled Analyses, Trials DELTA 1 and DELTA 2

Blood sampling for laboratory assessments was performed at Weeks 0, 2, 4, 8, 12, and 16 in Trials DELTA 1 and DELTA 2. There were no significant differences in laboratory findings (chemistry, kidney function, or liver biochemistry) between the delgocitinib and vehicle groups in Trials DELTA 1 and DELTA 2 (refer to [Table 32](#), [Table 33](#), and [Table 34](#) below). The 95% confidence intervals for these risk differences did not exclude zero for any of these preferred terms, suggesting that any observed differences are not statistically significant and may be due to chance.

Table 32. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Pooled Trials DELTA 1 and DELTA 2

Laboratory Parameter	DELTA 1		DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n/N _w (%)	Vehicle Control N=162 n/N _w (%)	Delgocitinib N=313 n/N _w (%)	Vehicle Control N=159 n/N _w (%)	Delgocitinib N=638 n/N _w (%)	Vehicle Control N=321 n/N _w (%)	Risk Difference % (95% CI)
Sodium, low (mEq/L)							
Level 1 (<132)	1/324 (0.3)	0/159 (0)	0/311 (0)	1/155 (0.6)	1/635 (0.2)	1/314 (0.3)	-0.2 (-1.6, 0.6)
Level 2 (<130)	1/324 (0.3)	0/159 (0)	0/311 (0)	1/155 (0.6)	1/635 (0.2)	1/314 (0.3)	-0.2 (-1.6, 0.6)
Level 3 (<125)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Sodium, high (mEq/L)							
Level 1 (>150)	1/324 (0.3)	0/159 (0)	0/311 (0)	0/155 (0)	1/635 (0.2)	0/314 (0)	0.2 (-1.1, 0.9)
Level 2 (>155)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Level 3 (>160)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Potassium, low (mEq/L)							
Level 1 (<3.6)	9/324 (2.8)	8/159 (5.0)	6/311 (1.9)	1/155 (0.6)	15/635 (2.4)	9/314 (2.9)	-0.5 (-3.2, 1.5)
Level 2 (<3.4)	3/324 (0.9)	3/159 (1.9)	1/311 (0.3)	0/155 (0)	4/635 (0.6)	3/314 (1.0)	-0.3 (-2.2, 0.8)
Level 3 (<3)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Potassium, high (mEq/L)							
Level 1 (>5.5)	3/324 (0.9)	1/159 (0.6)	4/311 (1.3)	0/155 (0)	7/635 (1.1)	1/314 (0.3)	0.8 (-0.7, 2.0)
Level 2 (>6)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Level 3 (>6.5)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Chloride, low (mEq/L)							
Missing	NA	NA	NA	NA	NA	NA	NA
Chloride, high (mEq/L)							
Missing	NA	NA	NA	NA	NA	NA	NA
Bicarbonate, low (mEq/L)							
Missing	NA	NA	NA	NA	NA	NA	NA
Bicarbonate, high (mEq/L)							
Missing	NA	NA	NA	NA	NA	NA	NA

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Laboratory Parameter	DELTA 1		DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n/N _w (%)	Vehicle Control N=162 n/N _w (%)	Delgocitinib N=313 n/N _w (%)	Vehicle Control N=159 n/N _w (%)	Delgocitinib N=638 n/N _w (%)	Vehicle Control N=321 n/N _w (%)	Risk Difference % (95% CI)
Glucose, low (mg/dL)							
Level 1 (<70)	39/324 (12.0)	11/159 (6.9)	24/311 (7.7)	13/155 (8.4)	63/635 (9.9)	24/314 (7.6)	2.3 (-1.8, 5.9)
Level 2 (<54)	2/324 (0.6)	1/159 (0.6)	5/311 (1.6)	3/155 (1.9)	7/635 (1.1)	4/314 (1.3)	-0.2 (-2.2, 1.2)
Level 3 (<40)	0/324 (0)	0/159 (0)	1/311 (0.3)	1/155 (0.6)	1/635 (0.2)	1/314 (0.3)	-0.2 (-1.6, 0.6)
Glucose, fasting, high (mg/dL)							
Missing	NA	NA	NA	NA	NA	NA	NA
Glucose, random, high (mg/dL)							
Level 2 (≥200)	5/324 (1.5)	6/159 (3.8)	6/311 (1.9)	5/155 (3.2)	11/635 (1.7)	11/314 (3.5)	-1.8 (-4.6, 0.2)
Level 3 (>250)	1/324 (0.3)	4/159 (2.5)	3/311 (1.0)	1/155 (0.6)	4/635 (0.6)	5/314 (1.6)	-1.0 (-3.1, 0.3)
Calcium, low (mg/dL)							
Level 1 (<8.4)	1/324 (0.3)	1/159 (0.6)	1/311 (0.3)	0/155 (0)	2/635 (0.3)	1/314 (0.3)	-0.0 (-1.5, 0.9)
Level 2 (<8)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Level 3 (<7.5)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Calcium, high (mg/dL)							
Level 1 (>10.5)	5/324 (1.5)	1/159 (0.6)	3/311 (1.0)	1/155 (0.6)	8/635 (1.3)	2/314 (0.6)	0.6 (-1.1, 1.9)
Level 2 (>11)	3/324 (0.9)	1/159 (0.6)	1/311 (0.3)	1/155 (0.6)	4/635 (0.6)	2/314 (0.6)	-0.0 (-1.7, 1.1)
Level 3 (>12)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Magnesium, low (mg/dL)							
Missing	NA	NA	NA	NA	NA	NA	NA
Magnesium, high (mg/dL)							
Missing	NA	NA	NA	NA	NA	NA	NA
Phosphate, low (mg/dL)							
Missing	NA	NA	NA	NA	NA	NA	NA
Protein, total, low (g/dL)							
Level 1 (<6)	0/324 (0)	1/159 (0.6)	1/311 (0.3)	2/155 (1.3)	1/635 (0.2)	3/314 (1.0)	-0.8 (-2.6, 0.1)
Level 2 (<5.4)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Level 3 (<5)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Albumin, low (g/dL)							
Level 1 (<3.1)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Level 2 (<2.5)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Level 3 (<2)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Laboratory Parameter	DELTA 1		DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n/N _w (%)	Vehicle Control N=162 n/N _w (%)	Delgocitinib N=313 n/N _w (%)	Vehicle Control N=159 n/N _w (%)	Delgocitinib N=638 n/N _w (%)	Vehicle Control N=321 n/N _w (%)	Risk Difference % (95% CI)
CPK, high (U/L)							
Missing	NA	NA	NA	NA	NA	NA	NA
Amylase, high (U/L)							
Missing	NA	NA	NA	NA	NA	NA	NA
Lipase, high (U/L)							
Missing	NA	NA	NA	NA	NA	NA	NA
Blood urea nitrogen, high (mg/dL)							
Level 1 (>23)	32/324 (9.9)	20/159 (12.6)	38/311 (12.2)	9/155 (5.8)	70/635 (11.0)	29/314 (9.2)	1.8 (-2.5, 5.6)
Level 2 (>27)	7/324 (2.2)	3/159 (1.9)	6/311 (1.9)	2/155 (1.3)	13/635 (2.0)	5/314 (1.6)	0.5 (-1.8, 2.2)
Level 3 (>31)	0/324 (0)	1/159 (0.6)	1/311 (0.3)	1/155 (0.6)	1/635 (0.2)	2/314 (0.6)	-0.5 (-2.1, 0.3)

Source: adlb.xpt; Software: R

Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; NA, not applicable; N_w, number of subjects with data

Table 33. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Pooled Trials DELTA 1 and DELTA 2

Laboratory Parameter	Trial DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n/N _w (%)	Vehicle Control N=162 n/N _w (%)	Delgocitinib N=313 n/N _w (%)	Vehicle Control N=159 n/N _w (%)	Delgocitinib N=638 n/N _w (%)	Vehicle Control N=321 n/N _w (%)	Risk Difference % (95% CI)
Creatinine, high (mg/dL)							
Level 1 ($\geq 1.5\times$ baseline)	1/324 (0.3)	3/159 (1.9)	6/311 (1.9)	3/155 (1.9)	7/635 (1.1)	6/314 (1.9)	-0.8 (-3.1, 0.7)
Level 2 ($\geq 2\times$ baseline)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Level 3 ($\geq 3\times$ baseline)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
eGFR, low (mL/min/1.73 m ²)							
Level 1 ($\geq 25\%$ decrease)	13/324 (4.0)	6/159 (3.8)	20/311 (6.4)	5/155 (3.2)	33/635 (5.2)	11/314 (3.5)	1.7 (-1.3, 4.3)
Level 2 ($\geq 50\%$ decrease)	1/324 (0.3)	0/159 (0)	1/311 (0.3)	0/155 (0)	2/635 (0.3)	0/314 (0)	0.3 (-0.9, 1.1)
Level 3 ($\geq 75\%$ decrease)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

eGFR values are calculated from serum creatinine using CKD-EPI equation.

Abbreviations: CI, confidence interval; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data**Table 34. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Pooled Trials DELTA 1 and DELTA 2**

Laboratory Parameter	DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n/N _w (%)	Vehicle Control N=162 n/N _w (%)	Delgocitinib N=313 n/N _w (%)	Vehicle Control N=159 n/N _w (%)	Delgocitinib N=638 n/N _w (%)	Vehicle Control N=321 n/N _w (%)	Risk Difference % (95% CI)
Alkaline phosphatase, high (U/L)							
Level 1 ($> 1.5\times$ ULN)	3/324 (0.9)	0/159 (0)	3/311 (1.0)	2/155 (1.3)	6/635 (0.9)	2/314 (0.6)	0.3 (-1.4, 1.5)
Level 2 ($> 2\times$ ULN)	0/324 (0)	0/159 (0)	1/311 (0.3)	2/155 (1.3)	1/635 (0.2)	2/314 (0.6)	-0.5 (-2.1, 0.3)
Level 3 ($> 3\times$ ULN)	0/324 (0)	0/159 (0)	0/311 (0)	1/155 (0.6)	0/635 (0)	1/314 (0.3)	-0.3 (-1.8, 0.3)
Alanine aminotransferase, high (U/L)							
Level 1 ($> 3\times$ ULN)	1/324 (0.3)	0/159 (0)	2/311 (0.6)	0/155 (0)	3/635 (0.5)	0/314 (0)	0.5 (-0.7, 1.4)
Level 2 ($> 5\times$ ULN)	0/324 (0)	0/159 (0)	1/311 (0.3)	0/155 (0)	1/635 (0.2)	0/314 (0)	0.2 (-1.1, 0.9)
Level 3 ($> 10\times$ ULN)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Laboratory Parameter	DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n/N _w (%)	Vehicle Control N=162 n/N _w (%)	Delgocitinib N=313 n/N _w (%)	Vehicle Control N=159 n/N _w (%)	Delgocitinib N=638 n/N _w (%)	Vehicle Control N=321 n/N _w (%)	Risk Difference % (95% CI)
Aspartate aminotransferase, high (U/L)							
Level 1 (>3X ULN)	1/324 (0.3)	1/159 (0.6)	0/311 (0)	0/155 (0)	1/635 (0.2)	1/314 (0.3)	-0.2 (-1.6, 0.6)
Level 2 (>5X ULN)	1/324 (0.3)	0/159 (0)	0/311 (0)	0/155 (0)	1/635 (0.2)	0/314 (0)	0.2 (-1.1, 0.9)
Level 3 (>10X ULN)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Bilirubin, total, high (mg/dL)							
Level 1 (>1.5X ULN)	9/324 (2.8)	2/159 (1.3)	10/311 (3.2)	1/155 (0.6)	19/635 (3.0)	3/314 (1.0)	2.0 (0.0, 3.8)
Level 2 (>2X ULN)	2/324 (0.6)	0/159 (0)	1/311 (0.3)	0/155 (0)	3/635 (0.5)	0/314 (0)	0.5 (-0.7, 1.4)
Level 3 (>3X ULN)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

For specific evaluation of drug-induced liver injury (DILI), see the figures "Hepatocellular Drug-Induced Liver Injury Screening Plot" and "Cholestatic Drug-Induced Liver Injury Screening Plot" and the tables "Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot" and "Subjects in Each Quadrant for Cholestatic DILI Screening Plot."

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

Assessment of Hypoglycemia in Patients With Diabetes

Nonclinical data from the literature suggest that JAK and TYK2 inhibitors may cause hypoglycemia in diabetics. The authors postulate that JAK and TYK2 inhibitors protect pancreatic β -cells from immune-mediated destruction and improve insulin sensitivity, thereby enhancing endogenous insulin production and action ([Gurzov et al. 2016](#); [Bako et al. 2019](#)). Product labeling for oral JAK inhibitors (e.g., tofacitinib, baricitinib, and upadacitinib) in the European Union informs prescribers that there have been reports of hypoglycemia following initiation of JAK inhibitors, and dose adjustment of antidiabetic medicinal products may be necessary in the event that hypoglycemia occurs.

In the clinical trials, incidence rates of TEAEs of hypoglycemia or blood glucose decreased associated with delgocitinib 2% exposure (MedDRA search terms: hypoglycemia (SMQ) narrow search, blood glucose abnormal (PT), and blood glucose fluctuation (PT) were 0% among subjects with known diabetes who received delgocitinib or vehicle and 0.2% among those without diabetes who received vehicle (Applicant response to information request dated May 29, 2025).

Lipids

Lipid parameters were measured in a nonfasted state during the phase 3 trials. The review team analyzed values exceeding specified levels (refer to [Table 35](#) below). There was a numerical difference in the number of subjects who developed high low-density lipoprotein (LDL) [Level 3 (190 mg/dL)] in the delgocitinib group (11.5%) compared with the vehicle group (7.0%) with a 4.5% risk difference. However, analysis of shift tables and subject narratives did not support a safety signal. Additionally, the collection of lipid parameters in a nonfasted state limits the interpretability of these findings and precludes meaningful clinical assessment of lipid changes. Table

Shift tables and discussion of all lipid parameter TEAEs follow [Table 35](#) below.

Table 35. Subjects With One or More Lipids Analyte Values Exceeding Specified Levels, Safety Population, Pooled Trials DELTA 1 and DELTA 2

Laboratory Parameter	DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n/N _w (%)	Vehicle Control N=162 n/N _w (%)	Delgocitinib N=313 n/N _w (%)	Vehicle Control N=159 n/N _w (%)	Delgocitinib N=638 n/N _w (%)	Vehicle Control N=321 n/N _w (%)	Risk Difference % (95% CI)
Cholesterol, total, high (mg/dL)							
Level 1 (>200)	181/324 (55.9)	87/159 (54.7)	168/311 (54.0)	80/155 (51.6)	349/635 (55.0)	167/314 (53.2)	1.8 (-4.9, 8.5)
Level 2 (>210)	141/324 (43.5)	65/159 (40.9)	136/311 (43.7)	61/155 (39.4)	277/635 (43.6)	126/314 (40.1)	3.5 (-3.2, 10.1)
Level 3 (>225)	96/324 (29.6)	38/159 (23.9)	90/311 (28.9)	40/155 (25.8)	186/635 (29.3)	78/314 (24.8)	4.5 (-1.7, 10.2)
HDL, males, low (mg/dL)							
Level 1 (<40)	51/122 (41.8)	22/58 (37.9)	43/110 (39.1)	17/48 (35.4)	94/232 (40.5)	39/106 (36.8)	3.7 (-7.6, 14.5)
Level 2 (<30)	6/122 (4.9)	4/58 (6.9)	5/110 (4.5)	3/48 (6.2)	11/232 (4.7)	7/106 (6.6)	-1.9 (-8.6, 3.1)
Level 3 (<20)	1/122 (0.8)	0/58 (0)	0/110 (0)	0/48 (0)	1/232 (0.4)	0/106 (0)	0.4 (-3.1, 2.4)
HDL, females, low (mg/dL)							
Level 1 (<50)	61/202 (30.2)	37/101 (36.6)	56/201 (27.9)	31/107 (29.0)	117/403 (29.0)	68/208 (32.7)	-3.7 (-11.6, 3.9)
Level 2 (<40)	17/202 (8.4)	15/101 (14.9)	17/201 (8.5)	12/107 (11.2)	34/403 (8.4)	27/208 (13.0)	-4.5 (-10.3, 0.5)
Level 3 (<20)	0/202 (0)	0/101 (0)	0/201 (0)	0/107 (0)	0/403 (0)	0/208 (0)	0.0 (-1.8, 0.9)
LDL, high (mg/dL)							
Level 1 (>130)	214/324 (66.0)	101/159 (63.5)	192/311 (61.7)	98/155 (63.2)	406/635 (63.9)	199/314 (63.4)	0.6 (-5.9, 7.1)
Level 2 (>160)	102/324 (31.5)	48/159 (30.2)	101/311 (32.5)	40/155 (25.8)	203/635 (32.0)	88/314 (28.0)	3.9 (-2.3, 10.0)
Level 3 (>190)	36/324 (11.1)	8/159 (5.0)	37/311 (11.9)	14/155 (9.0)	73/635 (11.5)	22/314 (7.0)	4.5 (0.5, 8.1) *
Triglycerides, high (mg/dL)							
Level 1 (>150)	152/324 (46.9)	83/159 (52.2)	171/311 (55.0)	77/155 (49.7)	323/635 (50.9)	160/314 (51.0)	-0.1 (-6.8, 6.7)
Level 2 (>300)	40/324 (12.3)	23/159 (14.5)	38/311 (12.2)	17/155 (11.0)	78/635 (12.3)	40/314 (12.7)	-0.5 (-5.2, 3.8)
Level 3 (>500)	9/324 (2.8)	6/159 (3.8)	12/311 (3.9)	2/155 (1.3)	21/635 (3.3)	8/314 (2.5)	0.8 (-1.9, 2.9)

Source: adlb.xpt; Software: R

* Indicates that 95% confidence interval excludes zero.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

Shift Tables and TEAEs for Lipid Parameters

LDL

The LDL shift table from baseline to worst (high) value for the pooled Trials DELTA 1 and DELTA 2 (active and vehicle) to Week 16 is shown below in [Table 36](#). One subject (0.7%) who received delgocitinib shifted from normal baseline LDL value to a very high (>4.9 mmol/L) worst postbaseline value. The subject decreased from “high” (4.8 mmol/L) LDL levels at screening to “normal” levels at baseline (2.4 mmol/L) to “very high” (5.1 to 5.6 mmol/L) levels at Weeks 2 to 12. At Week 16, the LDL level returned to “high” (4.8 mmol/L). Shifts for other baseline grades to worst baseline levels were comparable between subjects who received delgocitinib versus vehicle. A total of 6 subjects who received 52 weeks of continuous exposure to delgocitinib shifted from borderline high baseline value to very high worst postbaseline value.

In the primary safety pool to Week 16, AEs of “low-density lipoprotein increased” were reported with delgocitinib (6 subjects, 0.8%, EAIR 2.72) and none with vehicle (0%). In the long-term safety pool, AEs of “low-density lipoprotein increased” were reported in 1% (nine subjects, EAIR 1.49) of subjects who received delgocitinib and in 0.1% (1 subject, EAIR 0.45) of subjects who received vehicle or were off treatment. None of the events were serious, severe, or led to discontinuation or withdrawal from the trials and none were considered related by the reviewer.

Table 36. Shift Summary for LDL From Baseline to Worst (High) Value, Trials DELTA 1 and DELTA 2 Pooled (SAF)

	Baseline		Worst post-baseline value				
	Grade	n (%)	Normal	Borderline high	High	Very high	Missing
Delgocitinib 20 mg/g (N=638)	Normal	141 (22.1)	69 (48.9)	71 (50.4)		1 (0.7)	
	Borderline high	368 (57.7)	6 (1.6)	273 (74.2)	76 (20.7)	10 (2.7)	3 (0.8)
	High	79 (12.4)	2 (2.5)	10 (12.7)	46 (58.2)	21 (26.6)	
	Very high	50 (7.8)		1 (2.0)	8 (16.0)	41 (82.0)	
	Missing						
	Total	638 (100.0)	77 (12.1)	355 (55.6)	130 (20.4)	73 (11.4)	3 (0.5)
Vehicle (N=321)	Normal	88 (27.4)	45 (51.1)	42 (47.7)			1 (1.1)
	Borderline high	174 (54.2)	3 (1.7)	130 (74.7)	32 (18.4)	4 (2.3)	5 (2.9)
	High	48 (15.0)		5 (10.4)	32 (66.7)	10 (20.8)	1 (2.1)
	Very high	10 (3.1)			2 (20.0)	8 (80.0)	
	Missing	1 (0.3)					1 (100.0)
	Total	321 (100.0)	48 (15.0)	177 (55.1)	66 (20.6)	22 (6.9)	8 (2.5)

Abbreviations: % = percentage of subjects with observation. LDL = low density lipoprotein. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.

Notes: The numbers are the number of subjects with a given shift. LDL (high): Normal = ≤ 2.6 mmol/L. Borderline high = >2.6 to 4.1 mmol/L. High = >4.1-4.9 mmol/L. Very high = >4.9 mmol/L. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator.

Source: Applicant response to Information Request dated March 25, 2025

Table 37. Shift Summary for LDL From Baseline to Worst (High) Value, Subjects Continuously Treated With Delgocitinib, 2% for 52 Weeks (SAF)

	Baseline		Worst post-baseline value				
	Grade	n (%)	Normal	Borderline high	High	Very high	Missing
Delgocitinib 20 mg/g (N=198)	Normal	36 (18.2)	11 (30.6)	25 (69.4)			
	Borderline high	121 (61.1)	1 (0.8)	80 (66.1)	34 (28.1)	6 (5.0)	
	High	22 (11.1)		1 (4.5)	11 (50.0)	10 (45.5)	
	Very high	19 (9.6)			2 (10.5)	17 (89.5)	
	Missing						
	Total	198 (100.0)	12 (6.1)	106 (53.5)	47 (23.7)	33 (16.7)	

Abbreviations: % = percentage of subjects with observation. LDL = low density lipoprotein. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.

Notes: The numbers are the number of subjects with a given shift. LDL (high): Normal = ≤ 2.6 mmol/L. Borderline high = >2.6 to 4.1 mmol/L. High = >4.1-4.9 mmol/L. Very high = >4.9 mmol/L. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator.

24MAR2025-/leo/clinical/lp0133/qna/fda_ir_20250315/safety/trf1/safety/programs/t_ib_shift_lyrpat.sas-t_1023
0_shift_ldl_lyrpat.txt

Source: Appendix 1 Table 2.16

Source: Applicant response to Information Request dated March 25, 2025

Triglycerides

For the pooled Trials DELTA 1 and DELTA 2, the shift table for triglycerides from baseline to worst postbaseline grade (active and vehicle) is shown below in [Table 38](#).

CTCAE Grade Shifts in Triglyceride Levels

Two subjects (0.4%) who received delgocitinib shifted from Grade 0 at baseline to Grade 3 at their worst postbaseline grade for triglyceride levels, compared with no subjects who received vehicle. Shifts for other baseline grades to worst postbaseline grade were comparable between subjects who received delgocitinib compared with vehicle. For subjects who received 52 weeks of continuous exposure to delgocitinib, one subject (0.7%) shifted from Grade 0 at baseline to Grade 3 at worst postbaseline grade, and six subjects (12.5%) shifted from Grade 1 at baseline value to Grade 3 at worst postbaseline grade.

Adverse Events

In the primary safety pool to Week 16, AEs of “hypertriglyceridaemia” were reported in 0.1% (1 subject, EAIR 0.46) of subjects who received delgocitinib and in 0.6% (2 subjects, EAIR 1.86) of subjects who received vehicle. Adverse events of “blood triglycerides increased” were reported in 0.6% (four subjects, EAIR 1.80) of subjects who received delgocitinib and in 0.6% (2 subjects, EAIR 1.86) of subjects who received vehicle. In the long-term safety pool, AEs of PT “blood triglycerides increased” were reported in 0.7% (six subjects, EAIR 1.16) of subjects who received delgocitinib and in 0.2% (2 subjects, EAIR 0.9) of subjects who received vehicle or were off treatment. AEs of “hypertriglyceridemia” were reported in 0.3% (3 subjects, EAIR 0.50) of subjects who received delgocitinib and in 0.3% (3 subjects, EAIR 1.81) of subjects who

received vehicle or were off treatment. None of the events were serious, severe, or led to discontinuation or withdrawal from the trials, and none were considered related by the reviewer.

Table 38. Shift Summary for Triglycerides From Baseline to Worst (High) Value, Trials DELTA 1 and DELTA 2, Pooled (SAF)

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=638)	Grade 0	450 (70.5)	296 (65.8)	143 (31.8)	6 (1.3)	2 (0.4)	3 (0.7)
	Grade 1	152 (23.8)	18 (11.8)	97 (63.8)	30 (19.7)	7 (4.6)	
	Grade 2	30 (4.7)		5 (16.7)	17 (56.7)	8 (26.7)	
	Grade 3	6 (0.9)			2 (33.3)	4 (66.7)	
	Missing						
	Total	638 (100.0)	314 (49.2)	245 (38.4)	55 (8.6)	21 (3.3)	3 (0.5)
Vehicle (N=321)	Grade 0	218 (67.9)	145 (66.5)	64 (29.4)	4 (1.8)		5 (2.3)
	Grade 1	86 (26.8)	8 (9.3)	54 (62.8)	20 (23.3)	3 (3.5)	1 (1.2)
	Grade 2	15 (4.7)	2 (13.3)	3 (20.0)	5 (33.3)	4 (26.7)	1 (6.7)
	Grade 3	2 (0.6)			1 (50.0)	1 (50.0)	
	Missing						
	Total	321 (100.0)	155 (48.3)	121 (37.7)	30 (9.3)	8 (2.5)	7 (2.2)

Abbreviations: % = percentage of subjects with observation. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.

Notes: The numbers are the number of subjects with a given shift. Triglycerides (high): Grade 0 = <1.71 mmol/L. Grade 1 = 1.71 mmol/L - 3.42 mmol/L. Grade 2 = >3.42 mmol/L - 5.7 mmol/L. Grade 3 = >5.7 mmol/L. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator.

24MAR2025-/leo/clinical/lp0133/qna/fda_ir_20250318/safety/tfl/safety/programs/t_lb_shift_140102.sas-t_10140_shift_trig_140102.txt

Source: Applicant response to Information Request dated March 25, 2025; Panel 18

Table 39. Shift Summary for Triglycerides From Baseline to Worst (High) Value, Subjects Continuously Treated With Delgocitinib 20 mg/g for a Year (SAF)

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=198)	Grade 0	135 (68.2)	75 (55.6)	55 (40.7)	4 (3.0)	1 (0.7)	
	Grade 1	48 (24.2)	2 (4.2)	25 (52.1)	15 (31.3)	6 (12.5)	
	Grade 2	13 (6.6)		2 (15.4)	6 (46.2)	5 (38.5)	
	Grade 3	2 (1.0)				2 (100.0)	
	Missing						
	Total	198 (100.0)	77 (38.9)	82 (41.4)	25 (12.6)	14 (7.1)	

Abbreviations: % = percentage of subjects with observation. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.

Notes: The numbers are the number of subjects with a given shift. Triglycerides (high): Grade 0 = <1.71 mmol/L. Grade 1 = 1.71 mmol/L - 3.42 mmol/L. Grade 2 = >3.42 mmol/L - 5.7 mmol/L. Grade 3 = >5.7 mmol/L. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator.

Source: Applicant response to Information Request dated March 25, 2025

Cholesterol

CTCAE Grade Shifts in Cholesterol Levels

The cholesterol shift table from baseline to worst (high) value for the pooled Trials DELTA 1 and DELTA 2 (active and vehicle) to Week 16 is shown below in [Table 40](#). Overall, similar proportions of subjects were observed to have abnormal cholesterol levels (>Grade 0) in the delgocitinib and vehicle groups. No subjects treated with delgocitinib in the pooled Trials DELTA 1 and DELTA 2 shifted to cholesterol levels above the Grade 3 threshold of >10.34 mmol/L. The cholesterol shift table from baseline to worst (high) value for subjects continuously treated with delgocitinib for 52 weeks did not reveal any new trend. No subjects had cholesterol levels above the Grade 3 threshold of >10.34 mmol/L with continuous use of delgocitinib.

Adverse Events

In the primary safety pool to Week 16, AEs of “hypercholesterolaemia” were reported in 0.7% (five subject, EAIR 2.24) of subjects who received delgocitinib and in 0.8% (three subjects, EAIR 2.79) of subjects who received vehicle. Adverse events of “blood cholesterol increased” were reported in 0.1% (1 subject, EAIR 0.45) of subjects who received delgocitinib and no subjects who received vehicle. In the long-term safety pool, AEs of “blood cholesterol increased” were reported in 0.3% (three subjects, EAIR 0.50) of subjects who received delgocitinib and in 0.2% (2 subjects, EAIR 0.9) of subjects who received vehicle or were off treatment. Adverse events of “hypercholesterolaemia” were reported in 1% (9 subjects, EAIR 1.66) of subjects who received delgocitinib and in 0.3% (3 subjects, EAIR 1.36) of subjects who received vehicle or were off treatment. None of the events were serious, severe, or led to discontinuation or withdrawal from the trials, and none were considered related by the reviewer.

Table 40. Shift Summary for Cholesterol From Baseline to Worst (High) Value, Trials DELTA 1 and DELTA 2, Pooled (SAF)

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=638)	Grade 0	395 (61.9)	291 (73.7)	101 (25.6)			3 (0.8)
	Grade 1	240 (37.6)	15 (6.3)	224 (93.3)	1 (0.4)		
	Grade 2	3 (0.5)			3 (100.0)		
	Grade 3						
	Missing						
	Total	638 (100.0)	306 (48.0)	325 (50.9)	4 (0.6)		3 (0.5)
Vehicle (N=321)	Grade 0	205 (63.9)	156 (76.1)	43 (21.0)			6 (2.9)
	Grade 1	114 (35.5)	5 (4.4)	105 (92.1)	2 (1.8)	1 (0.9)	1 (0.9)
	Grade 2	1 (0.3)			1 (100.0)		
	Grade 3						
	Missing	1 (0.3)					1 (100.0)
	Total	321 (100.0)	161 (50.2)	148 (46.1)	3 (0.9)	1 (0.3)	8 (2.5)

Abbreviations: % = percentage of subjects with observation. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set. ULN = Upper Limit of Normal.
Notes: The numbers are the number of subjects with a given shift. Cholesterol (high): Grade 0 ≤ ULN. Grade 1 = >ULN - 7.75 mmol/L. Grade 2 = >7.75 - 10.34 mmol/L. Grade 3 = >10.34 mmol/L. ULN = 5.2 mmol/L. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator.

Source: Applicant response to Information Request dated March 25, 2025; Panel 20

Table 41. Shift Summary for Cholesterol From Baseline to Worst (High) Value, Subjects Continuously Treated With Delgocitinib 20 mg/g for a Year (SAF)

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=198)	Grade 0	118 (59.6)	72 (61.0)	46 (39.0)			
	Grade 1	77 (38.9)		77 (100.0)			
	Grade 2	3 (1.5)			3 (100.0)		
	Grade 3						
	Missing						
	Total	198 (100.0)	72 (36.4)	123 (62.1)	3 (1.5)		

Abbreviations: % = percentage of subjects with observation. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set. ULN = Upper Limit of Normal.
Notes: The numbers are the number of subjects with a given shift. Cholesterol (high): Grade 0 ≤ ULN. Grade 1 = >ULN - 7.75 mmol/L. Grade 2 = >7.75 - 10.34 mmol/L. Grade 3 = >10.34 mmol/L. ULN = 5.2 mmol/L. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator.

24MAR2025-/leo/clinical/lp0193/qms/fda_ir_20250318/safety/tfl/safety/programs/t_lb_shift_1yrpat.sas-t_1021
0_shift_chol_1yrpat.txt

Source: Appendix 1 Table 2.14

Source: Applicant response to Information Request dated March 25, 2025

HDL

CTCAE Grade Shifts in HDL

High-density lipoprotein (HDL) shift tables showed similar proportions of subjects with HDL levels above Grade 0 at baseline in the delgocitinib and vehicle groups. The percentages of subjects in the pooled Trials DELTA 1 and DELTA 2 shifting to HDL levels above the “high” threshold of >1.55 mmol/L or below the “low” threshold of <1 mmol/L were similar in subjects treated with delgocitinib and vehicle. The HDL shift table from baseline to worst (high) value for subjects continuously treated with delgocitinib for 52 weeks did not reveal any new trend.

Table 42. Shift Summary for HDL From Baseline to Worst (Low) Value, Trials DELTA 1 and DELTA 2, Pooled (SAF)

Panel 25 Shift summary for HDL from baseline to worst (low) value - Trials 1401 and 1402 pooled - SAF

	Baseline		Worst post-baseline Value			
	Grade	n (%)	Low	Normal	High	Missing
Delgocitinib 20 mg/g (N=638)	Low	36 (5.6)	32 (88.9)	4 (11.1)		
	Normal	328 (51.4)	40 (12.2)	279 (85.1)	8 (2.4)	1 (0.3)
	High	274 (42.9)		105 (38.3)	167 (60.9)	2 (0.7)
	Missing					
	Total	638 (100.0)	72 (11.3)	388 (60.8)	175 (27.4)	3 (0.5)
Vehicle (N=321)	Low	18 (5.6)	17 (94.4)			1 (5.6)
	Normal	166 (51.7)	25 (15.1)	132 (79.5)	4 (2.4)	5 (3.0)
	High	137 (42.7)		44 (32.1)	92 (67.2)	1 (0.7)
	Missing					
	Total	321 (100.0)	42 (13.1)	176 (54.8)	96 (29.9)	7 (2.2)

Abbreviations: % = percentage of subjects with observation. HDL = high density lipoprotein. LLN = Lower Limit of Normal. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.

Notes: The numbers are the number of subjects with a given shift. HDL (low/high): Low = < LLN. Normal = LLN to < 1.55 mmol/L. High = >1.55 mmol/L. LLN = 1 mmol/L. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator.

24MAR2025-/leo/clinical/lp0133/qna/fda_ir_20250318/safety/tf1/safety/programs/t_lb_shift_140102.sas-t_1017
0_shift_hdl_1_140102.txt

Source: Appendix 1 Table 2.9

Source: Applicant response to Information Request dated March 25, 2025

Table 43. Shift Summary for HDL From Baseline to Worst (Low) Value, Subjects Continuously Treated With Delgocitinib for a Year (SAF)

Panel 27 Shift summary for HDL from baseline to worst (low) value - subjects continuously treated with delgocitinib 20 mg/g for a year - SAF

	Baseline		Worst post-baseline Value			
	Grade	n (%)	Low	Normal	High	Missing
Delgocitinib 20 mg/g (N=198)	Low	12 (6.1)	12 (100.0)			
	Normal	106 (53.5)	25 (23.6)	80 (75.5)	1 (0.9)	
	High	80 (40.4)		37 (46.3)	43 (53.8)	
	Missing					
	Total	198 (100.0)	37 (18.7)	117 (59.1)	44 (22.2)	

Abbreviations: % = percentage of subjects with observation. HDL = high density lipoprotein. LLN = Lower Limit of Normal. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.
Notes: The numbers are the number of subjects with a given shift. HDL (low/high): Low = < LLN. Normal = LLN to < 1.55 mmol/L. High = >1.55 mmol/L. LLN = 1 mmol/L. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator.

24MAR2025-/leo/clinical/lp0133/qna/fda_ir_20250318/safety/tfl/safety/programs/t_lb_shift_lyrpat.sas-t_10250_shift_hdl_l_lyrpat.txt

Source: Appendix 1 Table 2.18

Source: Applicant response to Information Request dated March 25, 2025

Hematology

Detailed analyses and a discussion of changes in hematology parameters with exposure to delgocitinib cream, 2% are presented below, including TEAEs related to cytopenia ([Table 44](#), [Table 45](#), and [Table 46](#)). For integrated summary of these findings and labeling recommendations refer to [Summary of Hematologic Findings and Recommendations for Labeling](#). For detailed information on individual subjects who received delgocitinib and had hematologic shifts (including screening, baseline, worst postbaseline values, whether subjects returned to screening/baseline values, whether PK samples were taken, and investigator assessed causality) refer to Section [17.1 Clinical Safety: Additional Information](#).

Table 44. Cytopenia TEAEs in Trials DELTA 1 and DELTA 2, Week 1 to Week 16 Exposure

Category	Delgocitinib 20 mg/g (N=638)		Vehicle (N=321)	
	n (%)	IR	n (%)	IR
MedDRA PT				
Any erythropenia TEAE	2 (0.3)	1.02	0	0
Anaemia	1 (0.2)	0.51	0	0
Normocytic anaemia	1 (0.2)	0.51	0	0
Any neutropenia TEAE	0	0	0	0
Any lymphopenia TEAE	3 (0.5)	1.53	0	0
Lymphocyte count decreased	2 (0.3)	1.02	0	0
Lymphopenia	1 (0.2)	0.51	0	0
Any thrombocytopenia TEAE	0	0	1 (0.3)	1.06
Thrombocytopenia	0	0	1 (0.3)	1.06

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Category MedDRA PT	Delgocitinib 20 mg/g (N=638)		Vehicle (N=321)	
	n (%)	IR	n (%)	IR
Any leukopenia TEAE	3 (0.5)	1.53	0	0
Leukopenia	1 (0.2)	0.51	0	0
Lymphopenia	1 (0.2)	0.51	0	0
White blood cell count decreased	1 (0.2)	0.51	0	0

Source: Applicant response to IR dated June 13, 2025

IR: n/patient years of observation)*100, observation time adjusted incidence rates (EAIRs).

Abbreviations: IR, incidence rate, TEAE; Treatment Emergent Adverse Event; n, number of subjects with TEAE; N, Number of subjects in treatment arm; PT, preferred term; MedDRA, Medical Dictionary for Regulatory Activities

Table 45. Cytopenia TEAEs in Trials DELTA 1, DELTA 2, and DELTA 3, Continuous 52 Weeks Exposure

Category MedDRA PT	Delgocitinib 20 mg/g (N=198)	
	n (%)	IR
Any erythropenia TEAE	0	0
Any neutropenia TEAE	1(0.5)	0.5
Neutropenia	1(0.5)	0.5
Any lymphopenia TEAE	0	0
Any thrombocytopenia TEAE	0	0
Any leukopenia TEAE	1(0.5)	0.5
Leukopenia	1(0.5)	0.5

Source: Applicant response to IR dated June 13, 2025

IR: n/patient years of observation)*100, observation time adjusted incidence rates (EAIRs).

Abbreviations: IR, incidence rate, TEAE; MedDRA, Medical Dictionary for Regulatory Activities; N, Number of subjects in treatment arm; n, number of subjects with TEAE; PT, preferred term; Treatment Emergent Adverse Event

Table 46. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Pooled Trials DELTA 1 and DELTA 2

Laboratory Parameter	DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n/N _w (%)	Vehicle Control N=162 n/N _w (%)	Delgocitinib N=313 n/N _w (%)	Vehicle Control N=159 n/N _w (%)	Delgocitinib N=638 n/N _w (%)	Vehicle Control N=321 n/N _w (%)	Risk Difference % (95% CI)
Complete blood count							
WBC, low (10 ³ cells/μL)							
Level 1 (<3.5)	7/324 (2.2)	6/159 (3.8)	11/311 (3.5)	1/155 (0.6)	18/635 (2.8)	7/314 (2.2)	0.6 (-1.9, 2.6)
Level 2 (<3)	0/324 (0)	2/159 (1.3)	2/311 (0.6)	0/155 (0)	2/635 (0.3)	2/314 (0.6)	-0.3 (-2.0, 0.6)
Level 3 (<1)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
WBC, high (10 ³ cells/μL)							
Level 1 (>10.8)	19/324 (5.9)	12/159 (7.5)	21/311 (6.8)	12/155 (7.7)	40/635 (6.3)	24/314 (7.6)	-1.3 (-5.2, 1.9)
Level 2 (>13)	11/324 (3.4)	1/159 (0.6)	3/311 (1.0)	3/155 (1.9)	14/635 (2.2)	4/314 (1.3)	0.9 (-1.2, 2.6)
Level 3 (>15)	1/324 (0.3)	1/159 (0.6)	1/311 (0.3)	0/155 (0)	2/635 (0.3)	1/314 (0.3)	-0.0 (-1.5, 0.9)
Hemoglobin, low (g/dL)							
Level 2 (>1.5 g/dL dec. from baseline)	7/323 (2.2)	2/159 (1.3)	8/310 (2.6)	3/154 (1.9)	15/633 (2.4)	5/313 (1.6)	0.8 (-1.5, 2.6)
Level 3 (>2 g/dL dec. from baseline)	4/323 (1.2)	0/159 (0)	2/310 (0.6)	1/154 (0.6)	6/633 (0.9)	1/313 (0.3)	0.6 (-0.9, 1.8)
Hemoglobin, high (g/dL)							
Level 2 (>2 g/dL inc. from baseline)	0/323 (0)	1/159 (0.6)	0/310 (0)	2/154 (1.3)	0/633 (0)	3/313 (1.0)	-1.0 (-2.8, -0.3) [*]
Level 3 (>3 g/dL inc. from baseline)	0/323 (0)	0/159 (0)	0/310 (0)	1/154 (0.6)	0/633 (0)	1/313 (0.3)	-0.3 (-1.8, 0.3)
Platelets, low (10 ³ cells/μL)							
Level 1 (<140)	2/324 (0.6)	5/159 (3.1)	7/311 (2.3)	3/155 (1.9)	9/635 (1.4)	8/314 (2.5)	-1.1 (-3.6, 0.6)
Level 2 (<125)	2/324 (0.6)	3/159 (1.9)	3/311 (1.0)	3/155 (1.9)	5/635 (0.8)	6/314 (1.9)	-1.1 (-3.4, 0.3)
Level 3 (<100)	1/324 (0.3)	1/159 (0.6)	2/311 (0.6)	1/155 (0.6)	3/635 (0.5)	2/314 (0.6)	-0.2 (-1.9, 0.9)

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Laboratory Parameter	DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n/N _w (%)	Vehicle Control N=162 n/N _w (%)	Delgocitinib N=313 n/N _w (%)	Vehicle Control N=159 n/N _w (%)	Delgocitinib N=638 n/N _w (%)	Vehicle Control N=321 n/N _w (%)	Risk Difference % (95% CI)
WBC differential							
Lymphocytes, low (10 ³ cells/μL)							
Level 1 (<1)	10/324 (3.1)	5/159 (3.1)	11/311 (3.5)	2/155 (1.3)	21/635 (3.3)	7/314 (2.2)	1.1 (-1.5, 3.2)
Level 2 (<0.75)	4/324 (1.2)	3/159 (1.9)	3/311 (1.0)	0/155 (0)	7/635 (1.1)	3/314 (1.0)	0.1 (-1.7, 1.5)
Level 3 (<0.5)	0/324 (0)	0/159 (0)	1/311 (0.3)	0/155 (0)	1/635 (0.2)	0/314 (0)	0.2 (-1.1, 0.9)
Lymphocytes, high (10 ³ cells/μL)							
Level 1 (>4)	5/324 (1.5)	2/159 (1.3)	6/311 (1.9)	0/155 (0)	11/635 (1.7)	2/314 (0.6)	1.1 (-0.7, 2.6)
Level 2 (>10)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Level 3 (>20)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Neutrophils, low (10 ³ cells/μL)							
Level 1 (<2)	33/324 (10.2)	19/159 (11.9)	29/311 (9.3)	7/155 (4.5)	62/635 (9.8)	26/314 (8.3)	1.5 (-2.6, 5.1)
Level 2 (<1)	1/324 (0.3)	0/159 (0)	1/311 (0.3)	0/155 (0)	2/635 (0.3)	0/314 (0)	0.3 (-0.9, 1.1)
Level 3 (<0.5)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Eosinophils, high (10 ³ cells/μL)							
Level 1 (>0.65)	13/324 (4.0)	5/159 (3.1)	14/311 (4.5)	1/155 (0.6)	27/635 (4.3)	6/314 (1.9)	2.3 (-0.2, 4.5)
Level 2 (>1.5)	0/324 (0)	0/159 (0)	1/311 (0.3)	0/155 (0)	1/635 (0.2)	0/314 (0)	0.2 (-1.1, 0.9)
Level 3 (>5)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)	0.0 (-1.2, 0.6)
Coagulation studies							
PT, high (sec)							
Missing	NA	NA	NA	NA	NA	NA	NA
PTT, high (sec)							
Missing	NA	NA	NA	NA	NA	NA	NA

Source: adlb.xpt; Software: R

* Indicates that 95% confidence interval excludes zero.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CI, confidence interval; dec., decrease; inc., increase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; NA, not applicable; N_w, number of subjects with data; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cells

The previous table ([Table 46](#)) provides analyses of hematology values exceeding prespecified levels for the vehicle-controlled 16-week period of Trials DELTA 1 and DELTA 2. In addition, the review team analyzed shift tables from the primary safety pool for hematology parameters in the same period, and in the subset of subjects who were exposed to continuous delgocitinib for 52 weeks. Shift tables and select narratives for each hematology parameter are presented below. For detailed information on individual subjects who received delgocitinib and had hemoglobin shifts (including screening, baseline, worst postbaseline values, whether subjects returned to screening/baseline values, whether PK samples were taken, and investigator-assessed causality), refer to Section [17.1](#) Clinical Safety: Additional Information.

Hemoglobin

Shift Tables for Subjects Exposed for 16 Weeks

The hemoglobin shifts from baseline to worst (low) value for subjects in the primary safety pool to Week 16 are displayed below. No subjects had hemoglobin levels below the Grade 3 threshold of <80 g/L. A few subjects had hemoglobin levels that shifted to Grade 2, with no difference between treatment groups (two subjects [13.3%] who received delgocitinib cream and one subject [16.7%] who received vehicle).

Adverse Events for Subjects Exposed for 16 Weeks

In the vehicle-controlled 16-week period of Trials DELTA 1 and DELTA 2, two AEs of anemia were reported in two subjects who received delgocitinib cream (incidence rate [IR]: 1.02), while no events were reported in subjects who received vehicle.

- “Anemia” (Grade 1 decrease in hemoglobin, reported term: secondary anemia, Subject (b) (6)).

A 33-year-old male with baseline hemoglobin 145 g/L developed anemia (hemoglobin 127 g/L) on Day 43, 10 days after a COVID-19 infection. He developed COVID-19 interstitial pneumonia on Day 33. Hemoglobin levels subsequently trended upward until the end of treatment, when his hemoglobin level was 144 g/L. Plasma delgocitinib concentrations trended downward throughout the trial. Intermittent exposure to delgocitinib in Trial DELTA 3 showed no trend in hemoglobin levels during “on-treatment” periods compared with “off-treatment” periods. His final hemoglobin level at the end of Trial DELTA 3 was 157 g/L. There was no change to IMP administration. The AE was considered unrelated to study drug by investigator. The clinical reviewer concurs. The decrease was transient, and there was a lack of hemoglobin fluctuations during intermittent delgocitinib treatment (i.e., simulating challenge/dechallenge conditions) in the subsequent trial.

- “Normocytic anemia” (Subject (b) (6): isolated decrease in hemoglobin [Grade 1]).

A 51-year-old male with history of Factor V Leiden deficiency developed decreased hemoglobin from 168 g/L at baseline to 138 g/L at Day 85. At the end of the trial, the hemoglobin level had normalized to 162 g/L. No PK assessments were obtained. After the subject entered Trial DELTA 3 and received continuous delgocitinib, he developed no further decrease in hemoglobin. The investigator deemed the event unrelated to the study drug. The clinical reviewer concurs, in view of the isolated and transient nature of the AE,

spontaneous resolution, and lack of continued drop in hemoglobin despite continued drug exposure in the subsequent trial.

Table 47. Shift Summary for Hemoglobin From Baseline to Worst (Low) Value, Week 0 to 16, Vehicle-Controlled Primary Safety Pool (SAF)

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=691)	Grade 0	671 (97.1)	643 (95.8)	24 (3.6)			4 (0.6)
	Grade 1	15 (2.2)	1 (6.7)	12 (80.0)	2 (13.3)		
	Grade 2	3 (0.4)			3 (100.0)		
	Grade 3						
	Missing	2 (0.3)					2 (100.0)
	Total	691 (100.0)	644 (93.2)	36 (5.2)	5 (0.7)		6 (0.9)
Vehicle (N=371)	Grade 0	364 (98.1)	346 (95.1)	10 (2.7)			8 (2.2)
	Grade 1	6 (1.6)	1 (16.7)	4 (66.7)	1 (16.7)		
	Grade 2						
	Grade 3						
	Missing	1 (0.3)					1 (100.0)
	Total	371 (100.0)	347 (93.5)	14 (3.8)	1 (0.3)		9 (2.4)

Abbreviations: % = percentage of subjects with observation. LLN = Lower Limit of Normal. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.

Notes: The numbers are the number of subjects with a given shift. Hemoglobin: Grade 0 = $\geq$ LLN. Grade 1 = $<$ LLN to 100 g/L. Grade 2 = $<$ 100 to 80 g/L. Grade 3 = $<$ 80 g/L. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator. Reference ranges: LLN (M/F): 130/115 g/L. ULN (M/F): 175/160 g/L.

Source: Applicant response to Information Request dated March 25, 2025; Panel 1

Shift Tables for Subjects Exposed for 52 Weeks

The hemoglobin shift table from baseline to worst (low) value for subjects continuously treated with delgocitinib cream for 52 weeks is below. No subjects continuously treated with delgocitinib cream for 52 weeks had treatment-emergent hemoglobin levels below the Grade 3 threshold of $<$ 80 g/L. During the 0- to 52-week period of continuous delgocitinib cream use, no events of anemia were reported.

Adverse Events for Subjects Exposed for 52 Weeks

In the long-term safety pool, AEs of “anaemia” were reported in 0.3% (3 subjects, EAIR 0.50) of subjects who received delgocitinib and no subjects who received vehicle or were off treatment. AEs “haemoglobin decreased” were reported in 0.1% (1 subject, EAIR 0.45) of subjects who received vehicle or were off treatment and no subjects who received delgocitinib.

Table 48. Shift Summary for Hemoglobin from Baseline to Worst (Low) Value, Subjects Continuously Treated With Delgocitinib Cream 20 mg/g for a Year (SAF)

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=198)	Grade 0	191 (96.5)	183 (95.8)	7 (3.7)	1 (0.5)		
	Grade 1	5 (2.5)		5 (100.0)			
	Grade 2	1 (0.5)			1 (100.0)		
	Grade 3						
	Missing	1 (0.5)	1 (100.0)				
	Total	198 (100.0)	184 (92.9)	12 (6.1)	2 (1.0)		

Abbreviations: % = percentage of subjects with observation. LLN = Lower Limit of Normal. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.

Notes: The numbers are the number of subjects with a given shift. Hemoglobin: Grade 0 = $\geq$ LLN. Grade 1 = $<$ LLN to 100 g/L. Grade 2 = $<$ 100 to 80 g/L. Grade 3 = $<$ 80 g/L. LLN (Male/Female) = 130/115 g/L. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator.

Source: Applicant response to Information Request dated March 25, 2025

A narrative summary of the subject who experienced a Grade 0 to 2 shift in hemoglobin with 52 continuous weeks of treatment is below:

- A 22-year-old female ((b) (6)) with baseline hemoglobin of 117 g/L developed a Grade 1 shift in hemoglobin to 111 g/L on Day 112. On Day 162 of continuous delgocitinib treatment, the subject developed decreased hemoglobin to 98 g/L (Grade 2). The subject's hemoglobin values fluctuated throughout the remainder of the long-term safety trial with a final hemoglobin level of 96 g/L on Day 364.

Because no iron studies were performed, a definite diagnosis for the hemoglobin decrease is not possible. Because no PK samples were obtained, it is not possible to evaluate the relationship between systemic exposure to delgocitinib and the onset of this AE. However, there was no associated AE or shifts in any other hematologic parameters in either Trial DELTA 1 or DELTA 3 with continuous treatment through Day 364 to suggest broad bone marrow suppression. Other hematologic parameters were: baseline lymphocytes 3.9 in trial DELTA 1 and 3.4 at the end of Trial DELTA 3; baseline neutrophils 4 in trial DELTA 1 and unchanged at the end of Trial DELTA 3, baseline thrombocytes 437 in trial DELTA 1 and 432 at the end of Trial DELTA 3, baseline leukocytes 9.7 in trial DELTA 1 and 8.4 (no shift in grade) at the end of Trial DELTA 3. Therefore, the clinical reviewer considers the hemoglobin Grade 0 to 2 shift unlikely to be related to delgocitinib.

Thrombocytes

Shift Tables and Adverse Events for Subjects Exposed for 16 Weeks

The thrombocyte shifts from baseline to worst (low) value for subjects in the primary safety pool to Week 16 are displayed below. Shifts were comparable between subjects who received delgocitinib compared with subjects who received vehicle. For detailed information regarding individual subjects who received delgocitinib and had thrombocyte shifts (including screening, baseline, worst postbaseline values, whether subjects returned to screening/baseline values,

whether PK sampling was performed, and investigator-assessed causality), refer to Section [17.1 Clinical Safety: Additional Information](#).

A total of two subjects in the delgocitinib cream group had thrombocyte counts below $75 \times 10^9/L$ (Grade 2), including one subject with thrombocyte counts below $50 \times 10^9/L$ (Grade 3). Both subjects had a medical history of low platelet counts that confounded the assessment (both subjects with low platelet counts from baseline and throughout the trials). Brief narrative summaries are below:

- Subject (b) (6): A 53-year-old female with a history of “thrombopenic” purpura and an active smoker with a baseline platelet count of $82 \times 10^9/L$ developed thrombocytopenia on Day 85 (platelets decreased to $69 \times 10^9/L$ (Grade 2)). At the end of trial, platelet levels slightly increased to $79 \times 10^9/L$. PK sampling was not performed. After completion of Trial DELTA 1, the subject received continuous treatment with delgocitinib for 52 weeks in Trial DELTA 3, and platelets trended upward. The final platelet count was $147 \times 10^9/L$ at the end of trial. There were no shifts in any other hematology parameters with continuous treatment through 52 weeks to suggest broad bone marrow suppression. The clinical reviewer considers the Grade 2 platelet shift unlikely related delgocitinib.
- Subject (b) (6): A 36-year-old female with a history of idiopathic thrombocytopenic purpura and a screening platelet count of $60 \times 10^9/L$ (Grade 2) and a baseline platelet count of $79 \times 10^9/L$ developed thrombocytopenia on Day 111 (platelet count decreased to $38 \times 10^9/L$ (Grade 3)). No further laboratory data are available after this date since the subject did not participate in the long-term safety trial. Plasma concentrations of delgocitinib fluctuated throughout the trial, though tended to trend downward over time [plasma delgocitinib level 0.48 ng/mL Day 8 → 0.09 ng/mL Day 32 (0.112 ng/mL Day 111)]. The subject developed no concurrent adverse event or shifts in any other hematology parameters in Trial DELTA 2 to suggest broad bone marrow suppression. No follow-up laboratory data are available to determine if the subject returned to her baseline platelet count. However, given the medical history of immune thrombocytopenic purpura and the lower delgocitinib exposure at Day 111 than Day 8, the clinical reviewer considers it unlikely that the platelet shift was related to delgocitinib.

In the primary safety pool, AEs of “thrombocytopenia” were reported in 0.3% (one subject, EAIR 1.94) of subjects who received vehicle, and no subjects who received delgocitinib.

Table 49. Shift Summary for Thrombocytes From Baseline to Worst (Low) Value, Week 0 to 16 Vehicle, Controlled Primary Safety Pool (SAF)

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=691)	Grade 0	686 (99.3)	679 (99.0)	3 (0.4)			4 (0.6)
	Grade 1	2 (0.3)		1 (50.0)	1 (50.0)		
	Grade 2	1 (0.1)				1 (100.0)	
	Grade 3						
	Missing	2 (0.3)					2 (100.0)
	Total	691 (100.0)	679 (98.3)	4 (0.6)	1 (0.1)	1 (0.1)	6 (0.9)
Vehicle (N=371)	Grade 0	369 (99.5)	355 (96.2)	6 (1.6)			8 (2.2)
	Grade 1	1 (0.3)		1 (100.0)			
	Grade 2						
	Grade 3						
	Missing	1 (0.3)					1 (100.0)
	Total	371 (100.0)	355 (95.7)	7 (1.9)			9 (2.4)

Abbreviations: % = percentage of subjects with observation. LLN = Lower Limit of Normal. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.

Notes: The numbers are the number of subjects with a given shift. Thrombocytes: Grade 3 = $<50 \times 10^9/L$. Grade 2 = < 75 to $50 \times 10^9/L$. Grade 1 = $<LLN$ to $75 \times 10^9/L$. Grade 0 = $\geq LLN$. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator. Reference ranges: LLN: $130 \times 10^9/L$. ULN: $400 \times 10^9/L$.

Source: Applicant response to Information Request dated March 25, 2025

Shift Tables and Adverse Events for Subjects Exposed for 52 Weeks

The shift table for thrombocytes from baseline to worst (low) value for subjects continuously treated with delgocitinib cream for 52 weeks is shown below in [Table 50](#). No subjects continuously treated with delgocitinib cream for 52 weeks had thrombocyte levels below the threshold of $<50 \times 10^9/L$ (Grade 3). During the 0- to 52-week period of continuous use, no events of thrombocytopenia were reported. One subject had thrombocyte counts that shifted from Grade 1 ($<130 \times 10^9/L$) in the parent trial at baseline to Grade 2 ($<75 \times 10^9/L$). The subject (b) (6) had a medical history of thrombocytopenic purpura and developed no shifts in any other hematology parameters in either Trial DELTA 1 or DELTA 3 with continuous treatment through Week 52 to suggest broad bone marrow suppression (narrative above).

In the long-term safety pool, AEs of “thrombocytopenia” were reported in 0.3% (one subject, EAIR 0.90) of subjects who received vehicle or off-treatment, and none in subjects who received delgocitinib.

Table 50. Shift Summary for Thrombocytes From Baseline to Worst (Low) Value, Subjects Continuously Treated With Delgocitinib 20 mg/g for a Year (SAF)

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=198)	Grade 0	196 (99.0)	195 (99.5)	1 (0.5)			
	Grade 1	1 (0.5)			1 (100.0)		
	Grade 2						
	Grade 3						
	Missing	1 (0.5)	1 (100.0)				
	Total	198 (100.0)	196 (99.0)	1 (0.5)	1 (0.5)		

Abbreviations: % = percentage of subjects with observation. LLN = Lower Limit of Normal. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.

Notes: The numbers are the number of subjects with a given shift. Thrombocytes: Grade 3 = $<50 \times 10^9/L$. Grade 2 = < 75 to $50 \times 10^9/L$. Grade 1 = $<LLN$ to $75 \times 10^9/L$. Grade 0 = $\geq LLN$. LLN = $130 \times 10^9/L$. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator.

Source: Applicant response to Information Request dated March 25, 2025; Panel 2

Thrombocytosis

During the 16 weeks of treatment in Trials DELTA 1 and DELTA 2, one subject developed thrombocytosis (IR: 0.51) who received delgocitinib cream, while no subjects developed thrombocytosis who received vehicle. The subject had an ongoing AE of gallbladder carcinoma and reported concomitant antineoplastic therapy at the time of the AE. The event was assessed as mild, not related, and did not lead to withdrawal from trial or discontinuation of the IMP. Platelet counts decreased to normal range at the next measurement.

During the 0- to 52-week period of continuous use, no subjects developed thrombocytosis.

Leukocytes

Shift Tables for Subjects Exposed for 16 Weeks

The leukocyte shifts from baseline to worst (low) value for subjects in the primary safety pool to Week 16 are displayed below. For detailed information on individual subjects who received delgocitinib with leukocyte shifts (including screening, baseline, worst postbaseline values, whether subjects returned to screening/baseline values, whether PK sampling was performed, and investigator-assessed causality), refer to Section [17.1](#) Clinical Safety: Additional Information.

No subjects had leukocyte counts below the clinically relevant threshold of $<2.0 \times 10^9$ cells/L (Grade 3). The majority of the worsening grade shifts in leukocyte levels in subjects treated with delgocitinib were shifts to Grade 1 (86 of 89 subjects [96.6%] with worsening shifts). A similar proportion of subjects in the delgocitinib (0.3%) and the vehicle group (0.6%) shifted from Grade 0 to Grade 2.

Table 51. Shift Summary for Leukocytes From Baseline to Worst (Low) Value, Primary Safety Pool (SAF)

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=691)	Grade 0	648 (93.8)	556 (85.8)	86 (13.3)	2 (0.3)		4 (0.6)
	Grade 1	41 (5.9)	5 (12.2)	35 (85.4)	1 (2.4)		
	Grade 2						
	Grade 3						
	Missing	2 (0.3)					2 (100.0)
	Total	691 (100.0)	561 (81.2)	121 (17.5)	3 (0.4)		6 (0.9)
Vehicle (N=371)	Grade 0	342 (92.2)	311 (90.9)	21 (6.1)	2 (0.6)		8 (2.3)
	Grade 1	28 (7.5)	5 (17.9)	23 (82.1)			
	Grade 2						
	Grade 3						
	Missing	1 (0.3)					1 (100.0)
	Total	371 (100.0)	316 (85.2)	44 (11.9)	2 (0.5)		9 (2.4)

Abbreviations: % = percentage of subjects with observation. LLN = Lower Limit of Normal. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.

Notes: The numbers are the number of subjects with a given shift. Leukocytes: Grade 0 = $\geq$ LLN. Grade 1 = $<$ LLN to 3.0×10^9 /L. Grade 2 = <3.0 to 2.0×10^9 /L. Grade 3 = $<2.0 \times 10^9$ /L. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator. Reference ranges: LLN: 4.5×10^9 /L. ULN: 11×10^9 /L.

Source: Applicant response to IR dated March 11, 2025

Adverse Events for Subjects Exposed for 16 Weeks

In the primary safety pool to Week 16, AEs of “leukopenia” were reported in 0.1% (one subject, EAIR 0.46) of subjects who received delgocitinib (considered possibly related by investigator, narrative below), and none in vehicle.

A 64-year-old female ((b) (6)) with a history of leukopenia, hypothyroid, and hyperlipidemia developed leukopenia on Day 113 of delgocitinib. The subject had baseline leukocytes 3.4×10^9 , lymphocytes 0.6×10^9 /L, and neutrophils 2.3×10^9 /L. The subject developed an AE of influenza on Day 109 and an AE of leukopenia (considered possibly related by investigator) on Day 113. The AE of influenza coincided with a leukocyte decrease to 2.5×10^9 /L (shift from baseline Grade 1 to Grade 2), lymphocyte decrease to 0.4×10^9 /L, and neutrophil decrease to 1.5×10^9 /L. Plasma delgocitinib concentrations trended downward throughout the trial (0.74 ng/mL on Day 8 $\rightarrow$ 0.32 ng/mL on Day 29 $\rightarrow$ 0.07 ng/mL on Day 113). After 252 days of continuous delgocitinib, her leukocyte levels were 3.9×10^9 , lymphocyte levels were 0.6×10^9 /L, and neutrophil levels were 2.7×10^9 /L. Laboratory analyses of other hematology parameters did not indicate pancytopenia suggesting broad bone marrow suppression.

The clinical reviewer concludes that a causal association between delgocitinib and the leukopenia cannot be excluded. The causality assessment is confounded by the history of leukopenia and the development of an AE of influenza 4 days prior to the reported AE of

leukopenia with associated decrease in lymphocytes and neutrophils. The systemic concentration of delgocitinib trended downward during the 16-week treatment period. However, the AE of leukopenia occurred while on treatment, and the investigator (most familiar with the subject’s presentation in the context of the clinical trial) assessed the leukopenia as possibly related. Given the known potential of JAK inhibitors to cause leukopenia, these factors suggest that a causal relationship between delgocitinib and the observed leukopenia TEAE (and associated shift) cannot be excluded.

Shift Tables for Subjects Exposed for 52 Weeks

The leukocyte shift table from baseline to worst (low) value for subjects continuously treated with delgocitinib cream for 52 weeks is shown below in [Table 52](#). No subjects continuously treated with delgocitinib cream for 52 weeks had treatment-emergent leukocyte levels below the Grade 3 threshold of $<2.0 \times 10^9$ cells/L.

Adverse Events for Subjects Exposed for 52 Weeks

In the long-term safety pool, AEs of “leukopenia” were reported in 0.3% (three subjects, EAIR 0.50) of subjects who received delgocitinib, and no subjects who received vehicle or off-treatment. AEs of “white blood cell count decreased” were reported in 0.2% (two subjects, EAIR 0.33) of subjects who received delgocitinib, and no subjects who received vehicle or were off treatment.

Table 52. Shift Summary for Leukocytes From Baseline to Worst (Low) Value, Subjects Continuously Treated With Delgocitinib 20 mg/g for a Year (SAF)

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=198)	Grade 0	183 (92.4)	156 (85.2)	27 (14.8)			
	Grade 1	14 (7.1)	1 (7.1)	10 (71.4)	3 (21.4)		
	Grade 2						
	Grade 3						
	Missing	1 (0.5)	1 (100.0)				
	Total	198 (100.0)	158 (79.8)	37 (18.7)	3 (1.5)		

Abbreviations: % = percentage of subjects with observation. LLN = Lower Limit of Normal. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.
Notes: The numbers are the number of subjects with a given shift. Leukocytes: Grade 0 = $\geq$ LLN. Grade 1 = $<$ LLN to 3.0×10^9 /L. Grade 2 = <3.0 to 2.0×10^9 /L. Grade 3 = $<2.0 \times 10^9$ /L. LLN = 4.5×10^9 /L. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator.

Source: Applicant response to Information Request dated March 25, 2025; Panel 5

The review team also analyzed the proportion of subjects with any worsening grade shift in leukocytes, neutrophils, and lymphocytes (refer to [Table 53](#) and [Table 54](#) below). A notable numerical imbalance was observed in subjects developing any worsening grade shift in leukocytes during the 16-week vehicle-controlled period: 13.6% (EAIR 44.2) in the delgocitinib group versus 6.2% (EAIR 21.3) in vehicle (refer to [Table 53](#)). Smaller imbalances were observed for neutrophils (4.4%, EAIR 14.2 in the delgocitinib group versus 3.7%, EAIR 12.8 in the vehicle group) and lymphocytes (2.5%, EAIR 8.1 in the delgocitinib group versus 1.9%, EAIR

6.4 in the vehicle group). The leukocyte imbalance was primarily driven by shifts from Grade 0 at baseline to Grade 1 postbaseline. For subjects with 52 weeks of continuous exposure to delgocitinib: 15.2% had any worsening grade shift in leukocytes, 6.1% had any worsening grade shift in neutrophils, and 3.5% had any worsening grade shift in lymphocytes (refer to [Table 54](#)).

Table 53. Leukopenia: TEAEs (PT: Leukopenia, Neutropenia, Neutrophil Count Decreased, Lymphopenia, Lymphocyte Count Decreased, White Blood Cell Count Decreased) and Worsening Grade Shifts in Leukocyte, Neutrophil, and Lymphocyte Levels, Trials DELTA 1 and DELTA 2

	Delgocitinib 20mg/g (N=638, PYO=196.71)			Vehicle (N=321, PYO=93.91)		
	n	(%)	IR	n	(%)	IR
AEs	5	(0.8)	2.54	0		
Leukopenia	1	(0.2)	0.51	0		
Neutrophil count decreased	0			0		
Neutropenia	0			0		
Lymphopenia	1	(0.2)	0.51	0		
Lymphocyte count decreased	2	(0.3)	1.02	0		
White blood cell count decreased	1	(0.2)	0.51	0		
Any worsening grade shift Leukocytes	87	(13.6)	44.23	20	(6.2)	21.30
Any worsening grade shift Neutrophils	28	(4.4)	14.23	12	(3.7)	12.78
Any worsening grade shift Lymphocytes	16	(2.5)	8.13	6	(1.9)	6.39
Simultaneous worsening grade shift for Neutrophils and Leukocytes	14	(2.2)	7.12	7	(2.2)	7.45
Total	110	(17.2)	55.92	29	(9.0)	30.88

Abbreviations: AE = adverse event. IMP = investigational medicinal product. IR = (n/PYO)*100, observation time adjusted incidence rates (EAIRs). n = number of subjects with observation. PT = preferred term. PYO = patient years of observation. SAF = safety analysis set. TEAE = treatment emergent adverse event. % = percentage of subjects with observation.
Notes: AEs with start date on or after the date of first IMP application or with a worsening in severity after first IMP application are included. Classification according to MedDRA version 24.0. Treatment groups are defined as actual treatment. PYO is calculated as number of days from first IMP application to end of trial divided by 365.25.

Source: Applicant response to IR dated June 12, 2025

Table 54. Leukopenia: TEAE (PT: Leukopenia, Neutropenia, Neutrophil Count Decreased, Lymphopenia, Lymphocyte Count Decreased, White Blood Cell Count Decreased) and Worsening Grade Shifts, Subjects Continuously Treated With Delgocitinib 20 mg/g for a Year

	Delgocitinib 20mg/g (N=198, PYO=207.15)		
	n	(%)	IR
AEs	2	(1.0)	0.97
Leukopenia	1	(0.5)	0.48
Neutrophil count decreased	0		
Neutropenia	1	(0.5)	0.48
Lymphopenia	0		
Lymphocyte count decreased	0		
White blood cell count decreased	0		
Any worsening grade shift Leukocytes	30	(15.2)	14.48
Any worsening grade shift Neutrophils	12	(6.1)	5.79
Any worsening grade shift Lymphocytes	7	(3.5)	3.38
Simultaneous worsening grade shift for Neutrophils and Leukocytes	9	(4.5)	4.34
Total	35	(17.7)	16.90

Abbreviations: % = percentage of subjects with observation. AE = adverse event. IMP = investigational medicinal product. IR = (n/PYO)*100, observation time adjusted incidence rates (EAIRs). n = number of subjects with observation. PT = preferred term. PYO = patient years of observation. SAF = safety analysis set. TEAE = treatment emergent adverse event.
Notes: AEs with start date on or after the date of first IMP application or with a worsening in severity after first IMP application are included, whereas for Trial 1403 AEs with start date after Week 0 (in Trial 1403) or with a worsening in severity after Week 0 (in Trial 1403) are included. Classification according to MedDRA version 24.0. PYO is calculated as number of days from first IMP application in parent trial to end of trial divided by 365.25.

Source: Applicant response to IR dated June 12, 2025

Neutrophils

Shift Tables and Adverse Events for Subjects Exposed for 16 Weeks

Neutrophil shifts from baseline to worst postbaseline (low) value for subjects in the primary safety pool to Week 16 are displayed below in [Table 55](#).

Table 55. Shift Summary for Neutrophils From Baseline to Worst (Low) Value, Week 0 to 16 Vehicle-Controlled Primary Safety Pool (SAF)

Panel 3 Neutrophils - Shift summary from baseline to worst (low) value - Primary pool - SAF

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=691)	Grade 0	678 (98.1)	648 (95.6)	17 (2.5)	7 (1.0)	2 (0.3)	4 (0.6)
	Grade 1	10 (1.4)	3 (30.0)	2 (20.0)	5 (50.0)		
	Grade 2	1 (0.1)			1 (100.0)		
	Grade 3						
	Missing	2 (0.3)					2 (100.0)
	Total	691 (100.0)	651 (94.2)	19 (2.7)	13 (1.9)	2 (0.3)	6 (0.9)
Vehicle (N=371)	Grade 0	365 (98.4)	344 (94.2)	6 (1.6)	7 (1.9)		8 (2.2)
	Grade 1	4 (1.1)	2 (50.0)		2 (50.0)		
	Grade 2	1 (0.3)	1 (100.0)				
	Grade 3						
	Missing	1 (0.3)					1 (100.0)
	Total	371 (100.0)	347 (93.5)	6 (1.6)	9 (2.4)		9 (2.4)

Abbreviations: % = percentage of subjects with observation. LLN = Lower Limit of Normal. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.

Notes: The numbers are the number of subjects with a given shift. Neutrophils: Grade 0 = $\geq$ LLN. Grade 1 = $<$ LLN to $1.5 \times 10^9/L$. Grade 2 = <1.5 to $1.0 \times 10^9/L$. Grade 3 = $<1.0 \times 10^9/L$. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator. Reference ranges: LLN: $1.8 \times 10^9/L$. ULN: $7.7 \times 10^9/L$.

Source: [Appendix 1 Table 1.3](#)

Source: Applicant response to IR dated March 11, 2025

For detailed information on individual subjects who received delgocitinib and had neutrophil shifts (including screening, baseline, worst postbaseline values, whether subjects returned to screening/baseline values, whether PK sampling was performed, and investigator-assessed causality), refer to Section [17.1](#) Clinical Safety: Additional Information.

Two subjects (0.3%) who received delgocitinib shifted from Grade 0 neutrophil values at baseline to Grade 3 neutrophil values at worst postbaseline, versus no such shift observed in subjects in subjects who received vehicle. Brief narrative summaries are below:

- A 52-year-old female (Subject (b) (6)) with a history of a mild nonserious COVID-19 infection 16 days prior to baseline developed neutropenia on Day 15. At screening, the subject had neutrophils of $2.1 \times 10^9/L$ and leukocytes of 4.2×10^9 ; at baseline the subject had neutrophils of $2 \times 10^9/L$ and leukocytes of $3.4 \times 10^9/L$ ($<$ lower limit of normal). On Day 15, neutrophil counts decreased to $0.8 \times 10^9/L$ (Grade 3), and by the next visit (Day 27) had increased to $2.2 \times 10^9/L$. On Day 113, neutrophils were $1.5 \times 10^9/L$, and leukocytes

were $3.3 \times 10^9/L$. No PK sampling was performed. When the subject entered Trial DELTA 3, she received continuous delgocitinib through Day 266 and her neutrophil levels remained stable at $1.51 \times 10^9/L$. The final recorded neutrophil level was $1.6 \times 10^9/L$ on Day 225 (Grade 1, less than baseline of $2.1 \times 10^9/L$ in parent Trial DELTA 1). The final leukocyte count was $3.7 \times 10^9/L$ on Day 225 (stable from baseline of $3.4 \times 10^9/L$ in parent Trial DELTA 1).

The subject did not have any concurrent adverse events, and there were no concurrent shifts in any other hematology parameters either in trial DELTA 1 or with continuous treatment through Day 266 of trial DELTA 3 to suggest broad bone marrow suppression.

The clinical reviewer assessed that a causal association between delgocitinib and the neutrophil shift cannot be excluded based on several factors. The Grade 3 neutrophil decrease occurred during treatment on Day 15, establishing a temporal relationship. Although there was a partial recovery by Day 27, neutrophil levels remained consistently below baseline throughout both trials and did not recover to baseline values at end of 255 days of continuous treatment, suggesting a persistent effect. While the pre-existing low neutrophil count and mild nonserious COVID-19 infection during the screening period introduce some uncertainty, these factors do not fully explain the observed pattern. The lack of PK data prevents a definitive assessment of a dose-response relationship. Given the known association of JAK inhibitors with neutropenia, the preponderance of evidence suggests that a causal relationship between delgocitinib and the observed neutrophil shift cannot be excluded.

- A 43-year-old female (Subject (b) (6)) with a history of COPD, pulmonary tuberculosis (TB), varicose veins, and prior smoker developed neutropenia on Day 30. The subject had baseline neutrophil levels of $2.6 \times 10^9/L$ and shifted to Grade 1 (1.5×10^9) on Day 30. On Day 58, the subject developed an upper respiratory tract infection and then on Day 84 neutrophils shifted to Grade 3 (0.9×10^9). Plasma delgocitinib concentrations trended downward throughout the trial [0.184 ng/mL on Day 7 → 0.168 ng/mL on Day 30 → 0.05 ng/mL on Day 112]. Neutrophil levels normalized to $2.9 \times 10^9/L$ by Week 16. The subject received near-continuous delgocitinib (with a 16-day off-treatment period) until Day 372 in the long-term safety trial. Baseline level neutrophils at Week 16 were $2.9 \times 10^9/L$. Following an AE of mild gastroenteritis on Day 209, her neutrophils decreased to $1.1 \times 10^9/L$ (Grade 2) on Day 225. By Day 372, the subject had neutrophils of $2.4 \times 10^9/L$ (Grade 0). Leukocytes at the beginning of Trial DELTA 2 were $4.03 \times 10^9/L$ and at the end of Trial DELTA 3 were $4.5 \times 10^9/L$. There were no shifts in any other hematology parameters either in Trial DELTA 2 or with near-continuous treatment through Day 372 of trial DELTA 3 to suggest broad bone marrow suppression.

The clinical reviewer assessed that the Grade 3 shift was unlikely related to delgocitinib based on several considerations. Firstly, there is a lack of consistent correlation between drug exposure and neutrophil levels. Plasma delgocitinib levels were trending downward at the time that the subject experienced a Grade 3 neutrophil decrease on Day 84, with the lowest recorded delgocitinib exposure on Day 112. Additionally, neutrophil levels normalized to $2.9 \times 10^9/L$ by Week 16, despite continued delgocitinib treatment. During the long-term safety trial while receiving near continuous delgocitinib treatment for 372 days, neutrophil levels remained mostly stable, with only a transient Grade 2 decrease on Day 225. This decrease in neutrophil level coincided with an adverse event of mild gastroenteritis, suggesting a potential alternative cause. Importantly, neutrophil levels normalized to $2.4 \times 10^9/L$ by the end

of Trial DELTA 3, despite prolonged delgocitinib exposure. The absence of shifts in other hematology parameters in both trials argues against broad bone marrow suppression. Furthermore, the subject's history of COPD, pulmonary TB, and smoking could contribute to fluctuations in neutrophil counts. The temporal relationship between adverse events (upper respiratory tract infection and gastroenteritis) and neutrophil decreases also suggests these infections may have played a role in the observed neutrophil shifts. Collectively, these factors suggest the neutrophil shifts are more likely attributable to other factors, making a causal relationship to delgocitinib unlikely.

Shift Tables and Adverse Events for Subjects Exposed for 52 Weeks

The neutrophils shift table from baseline to worst (low) value for subjects continuously treated with delgocitinib cream, 2% for 52 weeks is shown below in [Table 56](#). A total of two subjects had a shift in neutrophils from Grade 0 to worst postbaseline Grade 3. The narrative for subject (b) (6) is above, and the narrative for the other subject is below:

- A 55-year-old-male ((b) (6)) with a history of allergic contact dermatitis, colon adenoma and active smoking in Trial DELTA 2 developed Grade 3 neutropenia on Day 226. The subject had a neutrophil level at baseline of $3.4 \times 10^9/\text{L}$. Levels stayed stable throughout Trial DELTA 2 and were $5.3 \times 10^9/\text{L}$ at Week 16. Delgocitinib concentrations were 0.191 ng/mL on Day 8 and 0.309 ng/mL on Day 114. After the subject received continuous delgocitinib through Day 366, neutrophil levels trended downward to $3.3 \times 10^9/\text{L}$ on Day 170 and then $0.6 \times 10^9/\text{L}$ (Grade 3) on Day 226. Neutrophils then increased to $3.7 \times 10^9/\text{L}$ on next assessment at Day 282 and remained normal at $3.6 \times 10^9/\text{L}$ on Day 366 at the end of the trial. The subject had no associated AEs. There were no concurrent shifts in any other hematology parameters either in trial DELTA 2 or with near-continuous treatment through Day 366 of trial DELTA 3 to suggest broad bone marrow suppression. The isolated shift is considered unlikely related to delgocitinib by the clinical reviewer.

A total of three subjects shifted from Grade 0 to worst-post baseline Grade 2. All of the treatment-emergent shifts to Grade 2 were transient.

Table 56. Shift Summary for Neutrophils From Baseline to Worst (Low) Value, Subjects Continuously Treated With Delgocitinib 20 mg/g for a Year (SAF)

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=198)	Grade 0	192 (97.0)	182 (94.8)	5 (2.6)	3 (1.6)	2 (1.0)	
	Grade 1	4 (2.0)	1 (25.0)	1 (25.0)	2 (50.0)		
	Grade 2	1 (0.5)			1 (100.0)		
	Grade 3						
	Missing	1 (0.5)	1 (100.0)				
	Total	198 (100.0)	184 (92.9)	6 (3.0)	6 (3.0)	2 (1.0)	

Abbreviations: % = percentage of subjects with observation. LLN = Lower Limit of Normal. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.

Notes: The numbers are the number of subjects with a given shift. Neutrophils: Grade 0 = $\geq$ LLN. Grade 1 = $<$ LLN to $1.5 \times 10^9/L$. Grade 2 = <1.5 to $1.0 \times 10^9/L$. Grade 3 = $<1.0 \times 10^9/L$. LLN = $1.8 \times 10^9/L$. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator.

Source: Applicant response to Information Request dated March 25, 2025; Panel 3

Adverse Events

In the long-term safety pool, AEs of “neutropenia” were reported in 0.1% (one subject, EAIR 0.17) of subjects who received delgocitinib and in no subjects who received vehicle or were off treatment:

- A 45-year-old male ((b) (6)) with a history of irritant contact dermatitis and smoking developed neutropenia on Day 372. The subject had normal neutrophil levels of $2.4 \times 10^9/L$ at baseline. PK sampling was not performed. Neutrophil levels remained stable through Week 16 ($2.5 \times 10^9/L$). The subject received continuous delgocitinib until Day 386. Neutrophils decreased to $1 \times 10^9/L$ at Day 372 (when AE neutropenia was reported). No action was taken with study drug. The subsequent neutrophil level on Day 386 at the end of the trial was increased at $1.4 \times 10^9/L$.

Laboratory findings of other hematology parameters did not indicate pancytopenia suggestive of broad bone marrow suppression in either trial DELTA 1 or with continuous use until Day 386:

- Baseline hemoglobin was 141 in trial DELTA 1 and 140 g/L at the end of Trial DELTA 3.
- Baseline lymphocytes were 1 in trial DELTA 1 and 1 at the end of Trial DELTA 3.
- Baseline thrombocytes were 238 in trial DELTA 1 and 171 at the end of Trial DELTA 3.
- Baseline erythrocytes were $4.77 \times 10^{12}/L$ in trial DELTA 1 and $4.63 \times 10^{12}/L$ at the end of Trial DELTA 3.

The investigator considered the AE neutropenia unrelated to study drug, and the clinical reviewer considers it unlikely related.

Lymphocytes

Shift Tables for Subjects Exposed for 16 Weeks

Lymphocyte shifts from baseline to worst (low) value for subjects in the primary safety pool to Week 16 are displayed below in [Table 57](#).

For detailed information on individual subjects who received delgocitinib and had lymphocyte shifts (including screening, baseline, worst postbaseline values, whether subjects returned to screening/baseline values, whether PK sampling was performed, and investigator-assessed causality), refer to Section [17.1 Clinical Safety: Additional Information](#).

A subject ((b) (6)), full narrative above under “Leukopenias”) with a baseline lymphocyte cell count of 0.6×10^9 cells/L (Grade 2) transiently shifted to clinically relevant values of lymphocyte counts 0.4×10^9 cells/L (Grade 3) on Day 113. A similar proportion of subjects in the delgocitinib cream, 2% (1.0%) and the vehicle groups (0.8%) shifted from Grade 0 to Grade 2.

Table 57. Shift Summary for Lymphocytes From Baseline to Worst (Low) Value, Week 0 to 16 Vehicle-Controlled Primary Safety Pool (SAF)

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=691)	Grade 0	678 (98.1)	657 (96.9)	10 (1.5)	7 (1.0)		4 (0.6)
	Grade 1	7 (1.0)	3 (42.9)	4 (57.1)			
	Grade 2	4 (0.6)	2 (50.0)	1 (25.0)		1 (25.0)	
	Grade 3						
	Missing	2 (0.3)					2 (100.0)
	Total	691 (100.0)	662 (95.8)	15 (2.2)	7 (1.0)	1 (0.1)	6 (0.9)
Vehicle (N=371)	Grade 0	368 (99.2)	354 (96.2)	3 (0.8)	3 (0.8)		8 (2.2)
	Grade 1	2 (0.5)	1 (50.0)	1 (50.0)			
	Grade 2						
	Grade 3						
	Missing	1 (0.3)					1 (100.0)
	Total	371 (100.0)	355 (95.7)	4 (1.1)	3 (0.8)		9 (2.4)

Abbreviations: % = percentage of subjects with observation. LLN = Lower Limit of Normal. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.

Notes: The numbers are the number of subjects with a given shift. Lymphocytes: Grade 0 = $\geq$ LLN. Grade 1 = $<$ LLN to 0.75×10^9 /L. Grade 2 = <0.75 to 0.5×10^9 /L. Grade 3 = $<0.5 \times 10^9$ /L. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator. Reference ranges: LLN: 1×10^9 /L. ULN: 4.8×10^9 /L.

Source: Applicant response to IR dated March 11, 2025

Adverse Events for Subjects Exposed for 16 Weeks

In the primary safety pool to Week 16, AEs of “lymphocyte count decreased” were reported in 0.3% (two subjects, EAIR 0.9) of subjects who received delgocitinib, and no subjects who received vehicle; AEs “lymphopenia” were reported in 0.3% (two subjects, EAIR 0.9) of

subjects who received delgocitinib and no subjects who received vehicle. All four TEAEs were nonserious and mild in severity, none led to interruption or discontinuation of treatment, and none were considered related by the investigator. Of note, laboratory data showed that lymphocyte levels for the four subjects were all within normal range ($>1.0 \times 10^9$ cells/L) throughout the trial.

Narratives for the subjects are below:

- A 64-year-old female ((b) (6)) with a history of hyperlipidemia, hypertension, and polyneuritis developed lymphopenia on Day 113 after initiation of chemotherapy for gallbladder adenocarcinoma. The subject had baseline lymphocyte levels of 2.3×10^9 cells/L. PK sampling was not performed. On Day 30, the subject received the diagnosis of gallbladder adenocarcinoma and on Day 60 initiated chemotherapy with cisplatin and oral glucocorticoids (prednisolone). Lymphocyte levels then began to trend downward: Day 27: 2×10^9 cells/L → Day 72: 1.7×10^9 cells/L → Day 86: 1.4×10^9 cells/L → Day 113: 1.1×10^9 cells/L (when the AE “lymphocyte count decreased” was reported, considered unrelated by the investigator). Platelets and hemoglobin also trended downward during this period. After Week 16, the subject received intermittent delgocitinib until Day 366. Lymphocyte levels fluctuated throughout the trial: on Day 57 they were 2.8×10^9 cells/L and on Day 142 they were 1.2×10^9 cells/L (when the AE “lymphocyte count decreased” was reported again). At the end of the trial, lymphocytes were 1.6×10^9 cells/L. There was no clear pattern of changes in other hematologic parameters while she was on/off treatment with delgocitinib in Trial DELTA 3.

Given the development of adenocarcinoma with concomitant treatment with chemotherapy, the temporal association of lymphocyte changes with the initiation of chemotherapy, and the lack of a clear pattern of changes in hematologic parameters with intermittent treatment with delgocitinib in the long-term safety trial to Day 266 (i.e., under challenge/dechallenge type conditions), the clinical reviewer considered it unlikely that the AEs of “decreased lymphocyte count” were related to delgocitinib.

- A 48-year-old female ((b) (6)) with a history of smoking developed lymphopenia on Day 114 of delgocitinib. The subject had a screening lymphocyte count of 1.7×10^9 cells/L and baseline lymphocyte count of 2×10^9 cells/L. The lymphocyte count on the first day of the long-term safety trial was 1.4×10^9 cells/L. PK sampling was not performed. In Trial DELTA 3, the subject received continuous treatment with delgocitinib. The AE of “lymphocyte count decreased” was considered unrelated by investigator. At the end of Trial DELTA 3, lymphocytes were 1.5×10^9 cells/L (higher than her baseline in Trial DELTA 1). Laboratory analyses of other hematology parameters did not indicate pancytopenia suggestive of broad bone marrow suppression in either trial DELTA 2 or with continuous use in Trial DELTA 3. The AE is considered unlikely related to delgocitinib by the clinical reviewer.
- A 54-year-old female ((b) (6)) with a history of active smoking had lymphopenia on Day 1 of the trial. The subject had a screening lymphocyte count of 1.3×10^9 cells/L and a baseline lymphocyte count of 1.1×10^9 cells. An AE of lymphopenia was documented from Day 1. Counts fluctuated throughout the trial and at the end of the trial were 1.1×10^9 cells/L. PK sampling was not performed. The subject received continuous delgocitinib until Day 251. The lymphocyte count at the end of the trial was 1.2×10^9 cells/L. Laboratory analyses of

- other hematology parameters did not indicate pancytopenia suggestive of broad bone marrow suppression in either trial DELTA 1 nor with continuous use in Trial DELTA 3. The AE is considered unlikely related to delgocitinib by the clinical reviewer.
- A 46-year-old female ((b) (6)) with no relevant medical history had an AE of “lymphopenia” on Day 20 with no documented decline in lymphocyte count. The subject had a lymphocyte count of 1.3×10^9 cells/L at baseline, 1.5×10^9 cells/L on Day 6, 1.5×10^9 cells/L on Day 13, 1.6×10^9 cells/L on Day 27, and a final lymphocyte count at end-of-trial Day 110 of 1.6×10^9 cells/L. Delgocitinib concentrations trended downward to Week 16. The subject did not enter Trial DELTA 3. The AE was considered unlikely related by the clinical reviewer.

Shift Tables and Adverse Events for Subjects Exposed for 52 Weeks

The lymphocyte shift table from baseline to worst (low) value for subjects continuously treated with delgocitinib cream for 52 weeks is shown below in [Table 58](#).

One subject ([Subject](#) (b) (6), narrative above) continuously treated with delgocitinib cream, 2% for 52 weeks, with a Grade 2 baseline lymphocyte cell count of 0.6×10^9 cells/L, transiently shifted to a Grade 3 lymphocyte cell count of 0.4×10^9 cells/L at Week 16 in the parent trial (Trial DELTA 2). Values returned to Grade 2 levels ($<0.75 \times 10^9$ cells/L) at the next assessment and remained at Grade 2 levels until the end of Trial DELTA 3. One subject had lymphocyte levels shifting from Grade 0 at parent trial baseline to Grade 2 ($<0.75 \times 10^9$ cells/L), the shift was transient, and no concurrent AE was reported.

During the 0- to 52-week period of continuous use, no AEs of lymphocytopenia were reported.

Table 58. Shift Summary for Lymphocytes From Baseline to Worst (Low) Value, Subjects Continuously Treated With Delgocitinib 20 mg/g for a Year (SAF)

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=198)	Grade 0	194 (98.0)	188 (96.9)	5 (2.6)	1 (0.5)		
	Grade 1	2 (1.0)	1 (50.0)	1 (50.0)			
	Grade 2	1 (0.5)				1 (100.0)	
	Grade 3						
	Missing	1 (0.5)	1 (100.0)				
	Total	198 (100.0)	190 (96.0)	6 (3.0)	1 (0.5)	1 (0.5)	

Abbreviations: % = percentage of subjects with observation. LLN = Lower Limit of Normal. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.
Notes: The numbers are the number of subjects with a given shift. Lymphocytes: Grade 0 = $\geq$ LLN. Grade 1 = $<$ LLN to 0.75×10^9 /L. Grade 2 = <0.75 to 0.5×10^9 /L. Grade 3 = $<0.5 \times 10^9$ /L. LLN = 1×10^9 /L. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator.

Source: Applicant response to Information Request dated March 25, 2025; Panel 4

Summary of Hematologic Findings and Recommendations for Labeling

The review team conducted a comprehensive analysis of hematologic parameters for subjects in the vehicle-controlled 16-week period and in subjects who received continuous exposure to

delgocitinib for 52 weeks. This included analysis of shifts from baseline to worst postbaseline values, analyses of individual subject narratives, analysis of correlation between hematologic abnormalities and plasma concentrations when collected, cytopenia TEAEs, and detailed subject-level analyses of hematologic lab values at screening/baseline, throughout the trial, and at end of trial (refer to Section [17.1](#) Clinical Safety: Additional Information).

There were no significant imbalances between treatment groups for hemoglobin levels. No subjects developed Grade 3 decreases and only a few subjects developed Grade 2 shifts. Thrombocyte shifts were similar between delgocitinib and vehicle groups. There were isolated cases of Grade 2 or 3 decreases that may have been impacted by other etiologic factors described in their medical histories.

There was a slight imbalance in neutrophil levels between the delgocitinib and vehicle groups: two subjects (0.3%) on delgocitinib shifting from Grade 0 to Grade 3 (versus none in vehicle), for which causality related to delgocitinib could not be excluded in one subject (refer to narrative for [Subject \(b\) \(6\)](#)). Lymphocyte findings showed one transient shift from Grade 2 to Grade 3 in the delgocitinib group, and similar proportions of Grade 0 to Grade 2 shifts between treatment groups. For leukocyte counts, though no subjects in either group had shifts to Grade 3, a greater proportion of subjects who received delgocitinib (13.3%) developed a shift from Grade 0 to Grade 1 than subjects who received vehicle (6.1%). One subject developed a Grade 1 to 2 shift with an associated TEAE of leukopenia, which was considered possibly related by investigator and for which causality related to delgocitinib could not be excluded by the clinical reviewer (refer to narrative for [Subject \(b\) \(6\)](#)).

In the analysis of overall cytopenias, the review team observed a notable numerical imbalance in subjects experiencing any worsening grade shift in leukocytes: 13.6% (EAIR 44.2) in the delgocitinib group versus 6.2% (EAIR 21.3) in the vehicle group during the 16-week vehicle-controlled period (refer to [Table 53](#)). The leukocyte imbalance was primarily driven by shifts from Grade 0 at baseline to Grade 1 postbaseline. Though the clinical significance of these shifts is unclear, since none resulted in drug discontinuation or serious adverse events, there is biologic plausibility the shifts may have been related to JAK inhibition due to known class effects of JAK inhibitors with cytopenias. Smaller imbalances were observed for neutrophils (4.4%, EAIR 14.2 for delgocitinib versus 3.7%, EAIR 12.8 for vehicle) and lymphocytes (2.5%, EAIR 8.1 for delgocitinib versus 1.9%, EAIR 6.4 for vehicle).

Given the totality of these findings – the leukocyte imbalance in the vehicle-controlled period and select cases where a causal relationship with delgocitinib could not be excluded, measurable systemic exposure (refer to Section [5.2](#) of this review), and the known association of JAK inhibitors with cytopenias with biologic plausibility of association – the review team recommends including leukopenia and neutropenia as adverse reactions occurring in <1% of subjects in Section 6 of labeling. Since all Grade 3 shifts across all hematologic parameters observed with 52 weeks of continuous treatment were isolated findings, improved despite continuous treatment, and had a low incidence overall, and since no hematologic shifts were associated with serious adverse events, baseline CBC and intermittent hematologic monitoring is not recommended.

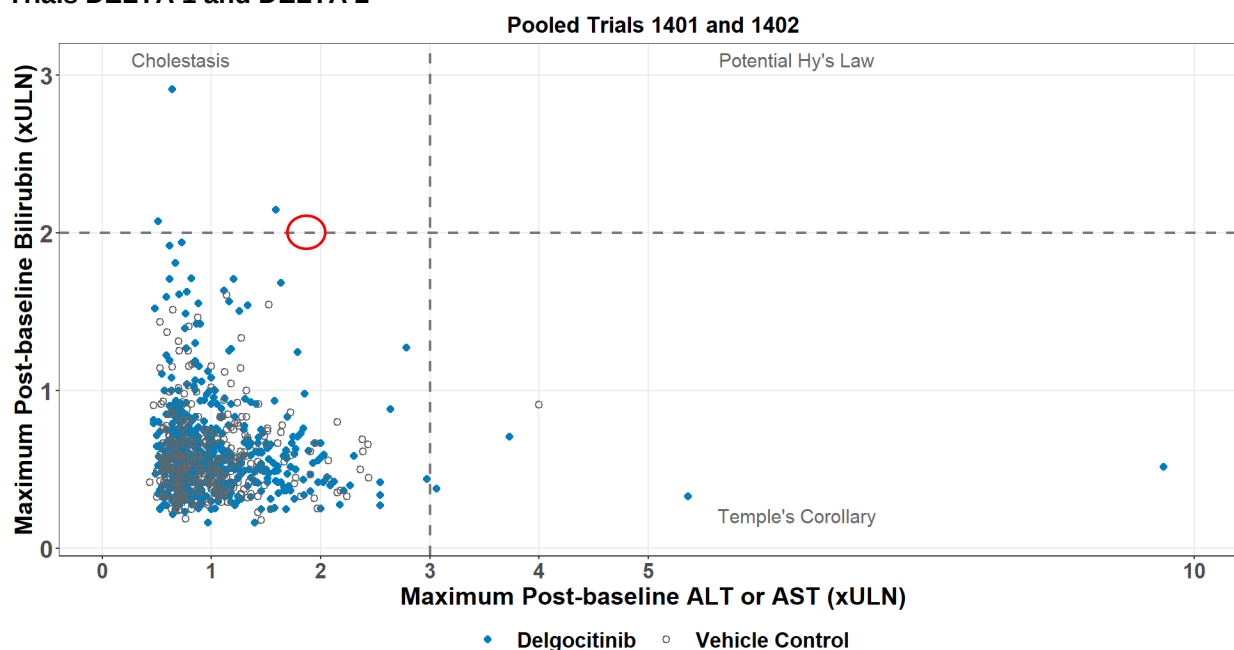
7.6.1.7. Assessment of Drug-Induced Liver Injury, Pooled Analyses, Trials DELTA 1 and DELTA 2

There did not appear to be a safety concern related to hepatic toxicity for subjects who received delgocitinib. In Trials DELTA 1 and DELTA 2, no subjects developed drug-induced liver injury (DILI). A few subjects developed adverse events related to hepatic dysfunction in both treatment groups (<1%). These TEAEs were primarily mild in severity, and none led to change in IMP. [Figure 9](#) and [Table 60](#) show a screening assessment for potential cases of serious DILI. No subjects had Hy's law or concurrent elevations of alanine aminotransferase (ALT)/AST $\geq 3 \times$ upper limit of normal (ULN) with bilirubin $\geq 2 \times$ ULN.

According to the Hepatocellular Drug-Induced Liver Injury Screening Plot below, there were a few subjects with findings suggestive of potential cholestatic DILI and Temple's corollary (refer to [Figure 9](#) and [Table 59](#) below). However, the imbalances between treatment groups were small, and review of the shifts from baseline in hepatic enzymes and individual subject narratives did not support a safety signal.

Of 1,062 subjects enrolled in Trials DELTA 1, DELTA 2, and 1273, five subjects (four subjects who received delgocitinib cream and one subject who received vehicle), developed transient elevations in ALT/AST values exceeding $3 \times$ ULN after baseline with concurrent elevations in bilirubin (bilirubin $< 2 \times$ ULN). All five subjects had isolated aminotransferase elevations during the trial, which normalized at the subsequent assessment despite continued use of the investigational product. Three subjects in the delgocitinib treatment group developed adverse events related to liver parameters. All of these AEs were nonserious and assessed as not related to the trial drug by the investigator and clinical reviewer.

Figure 9. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Trials DELTA 1 and DELTA 2



Source: adlb.xpt; Software: R

Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.

A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN. Those subjects who meet total bilirubin equal to or exceeding 2X ULN criteria within 30 days of the ALT or AST equal to or exceeding 3X ULN criteria are circled in red.

The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.

All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

For number of subjects in each quadrant, see the table "Subjects in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot" and the listing "Listing of Subjects in Hepatocellular Drug-Induced Liver Injury Screening."

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Table 59. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Pooled Trials DELTA 1 and DELTA 2

	DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2	
	Delgocitinib N=325	Vehicle Control N=162	Delgocitinib N=313	Vehicle Control N=159	Delgocitinib N=638	Vehicle Control N=321
Quadrant	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)
Potential Hy's Law (right upper)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)
Cholestasis (left upper)	2/324 (0.6)	0/159 (0)	1/311 (0.3)	0/155 (0)	3/635 (0.5)	0/314 (0)
Temple's corollary (right lower)	2/324 (0.6)	1/159 (0.6)	2/311 (0.6)	0/155 (0)	4/635 (0.6)	1/314 (0.3)
Total	4/324 (1.2)	1/159 (0.6)	3/311 (1)	0/155 (0)	7/635 (1.1)	1/314 (0.3)

Source: adlb.xpt; Software: R

A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN.

The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

Table 60. Subjects in Each Quadrant for Cholestatic DILI Screening Plot, Safety Population, Pooled Trials DELTA 1 and DELTA 2

Quadrant	DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2	
	Delgocitinib N=325	Vehicle Control N=162	Delgocitinib N=313	Vehicle Control N=159	Delgocitinib N=638	Vehicle Control N=321
	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)
Bilirubin ≥2X ULN and ALP ≥2X ULN (right upper)	0/324 (0)	0/159 (0)	0/311 (0)	0/155 (0)	0/635 (0)	0/314 (0)
Bilirubin ≥2X ULN and ALP <2X ULN (left upper)	2/324 (0.6)	0/159 (0)	1/311 (0.3)	0/155 (0)	3/635 (0.5)	0/314 (0)
Bilirubin <2X ULN and ALP ≥2X ULN (right lower)	0/324 (0)	0/159 (0)	1/311 (0.3)	2/155 (1.3)	1/635 (0.2)	2/314 (0.6)
Total	2/324 (0.6)	0/159 (0)	2/311 (0.6)	2/155 (1.3)	4/635 (0.6)	2/314 (0.6)

Source: adlb.xpt; Software: R

A potential cholestatic DILI case was defined as having a maximum postbaseline total bilirubin equal to or exceeding 2X ULN within 30 days after postbaseline ALP became equal to or exceeding 2X ULN. The within 30 days analysis window rule does not apply to cholestatic DILI cases.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

7.6.1.8. Vital Signs, Pooled Analyses, Trials DELTA 1 and DELTA 2

Vital signs (resting blood pressure, pulse, and body temperature) were assessed according to the schedule of trial procedures in Trials DELTA 1 and DELTA 2. Vital signs were measured in a sitting or supine position following at least 5 minutes of rest.

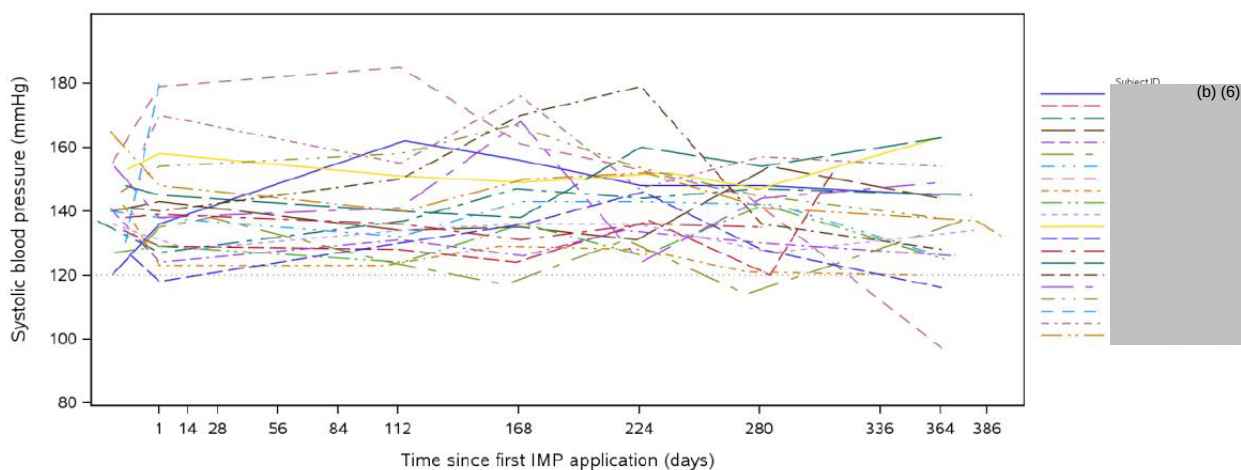
Analysis of shift tables for vital signs showed no clinically relevant differences in vital sign findings between treatment groups from baseline to end of treatment. However, there was an imbalance in adverse event reporting related to hypertension, which was not considered to be causally related to systemic exposure to delgocitinib by the review team, as discussed in detail below.

Hypertension

In Trials DELTA 1 and DELTA 2, there was a numerical difference in the reporting of AEs related to vital signs driven by the PT of “hypertension”: seven events in seven subjects in the delgocitinib group (1.1%) versus no subjects in the vehicle group. There were no increases in the rate of hypertension over time in subjects continuously treated with delgocitinib for 52 weeks (see the spaghetti plots below). Subjects who were randomized to delgocitinib had slightly higher baseline medical history of hypertension (17.4% of subjects on delgocitinib versus 14.3% of subjects on vehicle), but were otherwise comparable in terms of age, gender, body mass index (BMI), and history of diabetes mellitus. All of the subjects with reported AE of hypertension had elevated systolic blood pressure levels at screening and/or baseline.

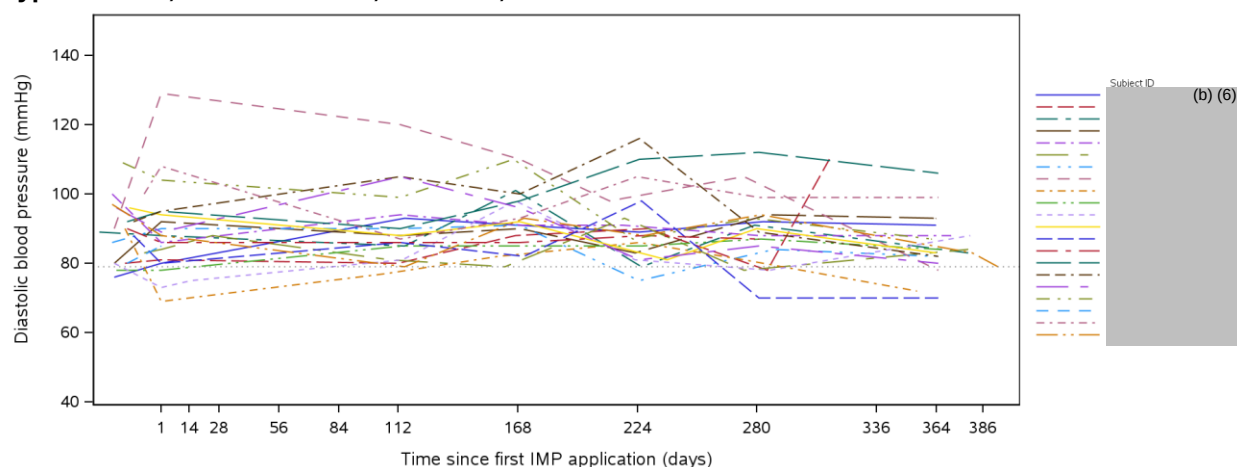
None of the AEs of hypertension were serious or considered related to IMP by investigator or led to discontinuation of IMP or withdrawal from trial. Analysis of individual subject profiles did not suggest a time to onset of hypertension relative to the duration of treatment. (see [Figure 10](#) and [Figure 11](#) below).

Figure 10. Spaghetti Plot of Systolic Blood Pressure Levels in Subjects With an Adverse Event of Hypertension, Trials DELTA 1, DELTA 2, DELTA 3



Source: ISS Panel 122

Figure 11. Spaghetti Plot of Diastolic Blood Pressure Levels in Subjects With an Adverse Event of Hypertension, Trials DELTA 1, DELTA 2, DELTA 3



29MAY2024-/leo/clinical/p0133/iss_update/tfl/safety/programs/f_vs_bp_trajplot.sas-f_250953_dia_bp_prof.png

Source: Applicant response to Information Request dated March 25, 2025

In order to further investigate any hypertension-related safety signal, the review team analyzed the systolic blood pressure shift table from baseline to worst (high) value for the pooled Trials DELTA 1 and DELTA 2, shown in [Table 61](#) below. No subjects who received delgocitinib or vehicle in the pooled Trials DELTA 1 and DELTA 2 had systolic blood pressure shifting from Grade 0 to greater than the Grade 3 (threshold of ≥ 160 mm Hg). In the pooled Trials DELTA 1 and DELTA 2, 11 subjects (1.7%) who received delgocitinib had systolic blood pressure above the Grade 3 threshold of ≥ 160 mm Hg. Of these subjects, four subjects shifted from a Grade 1 abnormal value at baseline, four subjects shifted from Grade 2 abnormal value at baseline, and three subjects already had a Grade 3 abnormal value at baseline. For comparison, two subjects

treated with vehicle had systolic blood pressure above the Grade 3 threshold of ≥ 160 mm Hg. One of these subjects already had a Grade 3 abnormal value at baseline and the other subjects shifted from a Grade 1 abnormal value at baseline.

Table 61. Shift Summary for Systolic Blood Pressure From Baseline to Worst (High) Value, Pooled Trials DELTA 1 and DELTA 2

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=638)	Grade 0	221 (34.6)	154 (69.7)	58 (26.2)	4 (1.8)		5 (2.3)
	Grade 1	322 (50.5)	73 (22.7)	213 (66.1)	29 (9.0)	4 (1.2)	3 (0.9)
	Grade 2	83 (13.0)	4 (4.8)	39 (47.0)	35 (42.2)	4 (4.8)	1 (1.2)
	Grade 3	12 (1.9)		3 (25.0)	5 (41.7)	3 (25.0)	1 (8.3)
	Missing						
	Total	638 (100.0)	231 (36.2)	313 (49.1)	73 (11.4)	11 (1.7)	10 (1.6)
Vehicle (N=321)	Grade 0	113 (35.2)	77 (68.1)	25 (22.1)	2 (1.8)		9 (8.0)
	Grade 1	170 (53.0)	35 (20.6)	112 (65.9)	12 (7.1)	1 (0.6)	10 (5.9)
	Grade 2	32 (10.0)	2 (6.3)	14 (43.8)	16 (50.0)		
	Grade 3	6 (1.9)		2 (33.3)	3 (50.0)	1 (16.7)	
	Missing						
	Total	321 (100.0)	114 (35.5)	153 (47.7)	33 (10.3)	2 (0.6)	19 (5.9)

Abbreviations: % = percentage of subjects with observation. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.

Notes: The numbers are the number of subjects with a given shift. Systolic blood pressure (high): Grade 0 = < 120 mmHg. Grade 1 = $120 - 139$ mmHg. Grade 2 = $140 - 159$ mmHg. Grade 3 = ≥ 160 mmHg. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator. The max. post-baseline table includes unscheduled visits.

Source: Applicant response to IR dated March 25, 2025

Systolic Blood Pressure

The systolic blood pressure shift table from baseline to worst (high) value for subjects continuously treated with delgocitinib for 52 weeks is shown below in [Table 62](#). A total of 10 subjects (5.1%) who received continuous delgocitinib for 52 weeks had systolic blood pressure above the Grade 3 threshold of ≥ 160 mm Hg. Of these, two subjects shifted from Grade 1 at baseline and four subjects shifted from Grade 2 at baseline and four subjects had Grade 3 abnormal values at baseline.

Table 62. Shift Summary for Systolic Blood Pressure From Baseline to Worst (High) Value, Subjects Continuously Treated With Delgocitinib 20 mg/g for a Year

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=198)	Grade 0	47 (23.7)	18 (38.3)	28 (59.6)	1 (2.1)		
	Grade 1	115 (58.1)	5 (4.3)	77 (67.0)	31 (27.0)	2 (1.7)	
	Grade 2	32 (16.2)		11 (34.4)	17 (53.1)	4 (12.5)	
	Grade 3	4 (2.0)				4 (100.0)	
	Missing						
	Total	198 (100.0)	23 (11.6)	116 (58.6)	49 (24.7)	10 (5.1)	

Abbreviations: % = percentage of subjects with observation. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.
Notes: The numbers are the number of subjects with a given shift. Systolic blood pressure (high): Grade 0 = <120 mmHg. Grade 1 = 120 - 139 mmHg. Grade 2 = 140 - 159 mmHg. Grade 3 = ≥160 mmHg. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator.

Source: Applicant response to IR dated March 25, 2025

Diastolic Blood Pressure

Analysis of diastolic blood pressure shift tables for Trials DELTA 1 and DELTA 2 and for subjects who received 52 weeks of continuous treatment did not reveal any new trend.

In addition, the review team analyzed the potassium shift tables from baseline to worst (low) value for the pooled Trials DELTA 1 and DELTA 2. In these pooled trials, no subjects who received delgocitinib or vehicle had potassium levels below the Grade 3 threshold of <3.0 mmol/L, and no subjects continuously treated with delgocitinib cream for 52 weeks had potassium levels below the Grade 3 threshold of <3.0 mmol/L. Shift tables are displayed below in [Table 63](#) and [Table 64](#).

Table 63. Shift Summary for Potassium From Baseline to Worst (Low) Value, Pooled Trials DELTA 1 and DELTA 2

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=638)	Grade 0	636 (99.7)	626 (98.4)	7 (1.1)			3 (0.5)
	Grade 1	2 (0.3)	1 (50.0)	1 (50.0)			
	Grade 2						
	Grade 3						
	Missing						
	Total	638 (100.0)	627 (98.3)	8 (1.3)			3 (0.5)
Vehicle (N=321)	Grade 0	318 (99.1)	307 (96.5)	4 (1.3)			7 (2.2)
	Grade 1	1 (0.3)	1 (100.0)				
	Grade 2						
	Grade 3						
	Missing	2 (0.6)					2 (100.0)
	Total	321 (100.0)	308 (96.0)	4 (1.2)			9 (2.8)

Abbreviations: % = percentage of subjects with observation. LLN = Lower Limit of Normal. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.
Notes: The numbers are the number of subjects with a given shift. Potassium (low): Grade 0 = >= LLN. Grade 1 = <LLN - 3.0 mmol/L. Grade 2 = N/A. Grade 3 = <3.0 mmol/L. LLN = 3.5 mmol/L. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator.

Source: Applicant response to information request

Table 64. Shift Summary for Potassium From Baseline to Worst (Low) Value, Subjects Continuously Treated With Delgocitinib for 52 Weeks

	Baseline		Worst post-baseline value				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Delgocitinib 20 mg/g (N=198)	Grade 0	198 (100.0)	195 (98.5)	3 (1.5)			
	Grade 1						
	Grade 2						
	Grade 3						
	Missing						
	Total	198 (100.0)	195 (98.5)	3 (1.5)			

Abbreviations: % = percentage of subjects with observation. LLN = Lower Limit of Normal. N = number of subjects within a treatment group. n = number of subjects with observation. SAF = safety analysis set.
Notes: The numbers are the number of subjects with a given shift. Potassium (low): Grade 0 = >= LLN. Grade 1 = <LLN - 3.0 mmol/L. Grade 2 = N/A. Grade 3 = <3.0 mmol/L. LLN = 3.5 mmol/L. For each row of worst post-baseline value, the percentages were calculated using the number of subjects with given grade at baseline as the denominator.

Source: Applicant response to information request

Analysis of sodium and potassium shift tables from baseline to worst (high) value for the pooled Trials DELTA 1 and DELTA 2 (active and vehicle) and for subjects who received 52 weeks of continuous treatment did not reveal any new trend.

The review team also compared the total number of measurements by threshold values of sodium and potassium for the primary safety pool and did not identify any imbalance in subjects who received delgocitinib versus vehicle (see [Table 65](#) below).

Table 65. Sodium and Potassium Electrolytes, Number of Measurements Postbaseline, Primary Pool

Category	Delgocitinib 20 mg/g (N=691)	Vehicle (N=371)
	labn (%)	labn (%)
Electrolytes and other parameters		
Sodium	3215 (100.0)	1599 (100.0)
<125 mmol/L		
<LLN	20 (0.6)	7 (0.4)
>=LLN and <=ULN	3171 (98.6)	1589 (99.4)
>ULN	24 (0.7)	3 (0.2)
>155 mmol/L		1 (0.1)
Potassium	3197 (100.0)	1589 (100.0)
<3 mmol/L		
<LLN	15 (0.5)	5 (0.3)
>=LLN and <=ULN	3135 (98.1)	1565 (98.5)
>ULN	47 (1.5)	19 (1.2)
>6 mmol/L		

Source: Adapted from Applicant's Table 3.3.19 Appendix 3 5.2.5.3 ISS

Finally, in cardiac safety Trial LP0133-1409 there were no significant changes in blood pressure observed after oral dosing.

Given the totality of evidence presented above, the observed numerical difference in rates of hypertension between delgocitinib and vehicle appears to be a chance finding and is not considered to be causally related to systemic exposure to delgocitinib. The reported adverse events of hypertension may instead reflect the imbalance of subjects with a history of hypertension at baseline between treatment groups and elevations in blood pressure at baseline rather than a causal association with delgocitinib cream.

7.6.1.9. Subgroups, Pooled Analyses, Trials DELTA 1 and DELTA 2

There are no ADRs that occurred in $\geq 1\%$ in the delgocitinib group and greater than vehicle proposed for labeling (refer to Section [7.6.1.5](#)); therefore, analysis of common ADRs by common demographic subgroups was not performed.

Since there were no common ADRs $\geq 1\%$ proposed for labeling, the review team conducted analyses on adverse events identified during the placebo-controlled periods of Trials DELTA 1 and DELTA 2 for the following subgroups: sex at birth (male, female), age (18 to 64, 65 to 84, ≥ 65 , ≥ 75 , ≥ 85 years of age), race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Multiple, and Other), and ethnicity (Hispanic or Latino, not Hispanic or Latino). There did not appear to be clinically meaningful differences in the frequency of TEAEs by demographic subgroup after accounting for the individual subgroup sample size, as summarized below in [Table 66](#).

Table 66. Overview of Adverse Events by Demographic Subgroup, Safety Population, Studies, Trials DELTA 1 and DELTA 2

Characteristic	DELTA 1		Trial DELTA 2		Pooled Trials DELTA 1 and DELTA 2		
	Delgocitinib N=325 n/Ns (%)	Vehicle Control N=162 n/Ns (%)	Delgocitinib N=313 n/Ns (%)	Vehicle Control N=159 n/Ns (%)	Delgocitinib N=638 n/Ns (%)	Vehicle Control N=321 n/Ns (%)	Risk Difference % (95% CI)
Sex							
Female	95/202 (47.0)	56/104 (53.8)	103/203 (50.7)	50/108 (46.3)	198/405 (48.9)	106/212 (50.0)	-1.1 (-9.4, 7.2)
Male	53/123 (43.1)	26/58 (44.8)	40/110 (36.4)	21/51 (41.2)	93/233 (39.9)	47/109 (43.1)	-3.2 (-14.5, 7.8)
Age group, years							
18 to 64	137/297 (46.1)	78/154 (50.6)	131/285 (46.0)	66/150 (44.0)	268/582 (46.0)	144/304 (47.4)	-1.3 (-8.2, 5.6)
65 to 84	10/27 (37.0)	4/8 (50.0)	12/28 (42.9)	5/8 (62.5)	22/55 (40.0)	9/16 (56.2)	-16.2 (-41.1, 10.9)
≥85	1/1 (100)	0/0 (NA)	0/0 (NA)	0/1 (0)	1/1 (100)	0/1 (0)	100.0 (-58.7, 100.0)
Age group ≥65, years							
≥65	11/28 (39.3)	4/8 (50.0)	12/28 (42.9)	5/9 (55.6)	23/56 (41.1)	9/17 (52.9)	-11.9 (-36.8, 14.3)
Age group ≥75, years							
≥75	3/4 (75.0)	0/0 (NA)	5/6 (83.3)	1/3 (33.3)	8/10 (80.0)	1/3 (33.3)	46.7 (-12.4, 82.9)
Race							
American Indian or Alaska Native	0/1 (0)	0/0 (NA)	0/0 (NA)	0/0 (NA)	0/1 (0)	0/0 (NA)	NA
Asian	6/14 (42.9)	2/5 (40.0)	5/8 (62.5)	6/7 (85.7)	11/22 (50.0)	8/12 (66.7)	-16.7 (-46.5, 18.5)
Black or African American	2/3 (66.7)	1/1 (100)	1/2 (50.0)	0/1 (0)	3/5 (60.0)	1/2 (50.0)	10.0 (-56.3, 70.3)
Multiple	1/2 (50.0)	1/1 (100)	0/1 (0)	0/3 (0)	1/3 (33.3)	1/4 (25.0)	8.3 (-54.6, 68.0)
Native Hawaiian or other Pacific Islander	0/0 (NA)	0/0 (NA)	0/1 (0)	0/0 (NA)	0/1 (0)	0/0 (NA)	NA
White	131/283 (46.3)	71/144 (49.3)	134/294 (45.6)	63/146 (43.2)	265/577 (45.9)	134/290 (46.2)	0.3 (7.3, 6.7)
Not reported	8/20 (40.0)	7/11 (63.6)	1/2 (50.0)	1/1 (100)	9/22 (40.9)	8/12 (66.7)	-25.8 (-54.6, 9.7)
Other	0/2 (0)	0/0 (NA)	2/5 (40.0)	1/1 (100)	2/7 (28.6)	1/1 (100)	-71.4 (-92.4, 23.4)
Ethnicity							
Hispanic or Latino	8/14 (57.1)	2/4 (50.0)	1/2 (50.0)	4/5 (80.0)	9/16 (56.2)	6/9 (66.7)	-10.4 (-45.0, 29.5)
Not Hispanic or Latino	133/292 (45.5)	73/147 (49.7)	141/309 (45.6)	66/152 (43.4)	274/601 (45.6)	139/299 (46.5)	-0.9 (-7.8, 6.0)
Not reported	7/19 (36.8)	7/11 (63.6)	1/2 (50.0)	1/2 (50.0)	8/21 (38.1)	8/13 (61.5)	-23.4 (-52.9, 11.3)

Source: Internal review of Applicant's submitted datasets for DELTA 1 and DELTA 2

Abbreviations: CI, confidence interval; n, number of subjects with characteristic; N, number of subjects in trial arm; Ns, number of subjects in trial arm subgroup; NA, not available

In addition, there did not appear to be meaningful differences in the rates of AEs reported for subjects based on main subtype of CHE (allergic contact dermatitis, irritant contact dermatitis, contact urticaria/contact dermatitis, atopic hand eczema, vesicular hand eczema, and hyperkeratotic eczema), as summarized in [Table 67](#) below. There were also no clinically relevant differences observed on evaluation of AE distribution by SOC and PT.

Table 67. Summary of Adverse Events, by Intrinsic Subgroups, Primary Pool

Intrinsic factor subgroup/ Category	Delgocitinib 20 mg/g					Vehicle				
	N	PYO	n (adj. %)	E	adj. R	N	PYO	n (adj. %)	E	adj. R
Main subtype of hand eczema	691	214.72	328 (48.2)	667	314.97	371	109.91	183 (49.0)	371	334.67
Allergic contact dermatitis	80	24.64	24 (29.5)	46	192.12	57	16.80	23 (40.6)	38	250.02
Irritant contact dermatitis	135	41.83	54 (41.7)	106	265.19	84	25.00	41 (44.0)	74	260.74
Contact urticaria/protein contact dermatitis						1	0.15			
Atopic hand eczema	253	79.90	132 (52.5)	285	350.04	136	40.29	66 (48.1)	149	371.45
Vesicular hand eczema (Pompholyx)	71	21.79	38 (51.3)	76	309.00	21	6.44	14 (68.1)	33	516.05
Hyperkeratotic eczema	152	46.56	80 (55.3)	154	345.50	72	21.24	39 (59.2)	77	384.65

Source: Modified from Applicant's Table 3.1.1 Summary of Clinical Safety Appendix 4

Abbreviations: %, percentage of subjects with events; adj, adjusted; E, number of events; n, number of subjects with events; N, number of subjects within a treatment group; PYO, patient years of observation; R, rate calculated as (E/PYO)*100

7.6.1.10. Exposure-Adjusted Pooled Analyses, Trials DELTA 1 and DELTA 2

Exposure-adjusted incidence rate analysis for pooled trials DELTA 1 and DELTA 2 is presented below in [Table 68](#). Overall EAIRs were comparable between treatment groups, except EAIR for hand dermatitis was markedly lower in the delgocitinib group versus vehicle (2.03 versus 17.04), suggesting an on-treatment benefit consistent with the mechanism of action and efficacy results.

Table 68. Exposure-Adjusted Analysis, Safety Population, Trials DELTA 1 and DELTA 2

SOC/PT	Pooled Trials 1401 and 1402					
	Delgocitinib 20 mg/g (N=638, PYO=196.71)			Vehicle (N=321, PYO=93.91)		
	n (%)	E	R	n (%)	E	R
Infections and infestations						
COVID-19	71 (11.1)	71	36.09	34 (10.6)	34	36.21
Nasopharyngitis	44 (6.9)	49	24.91	26 (7.5)	24	27.69
Pharyngitis	5 (0.8)	5	2.54	5 (1.6)	6	6.39
Urinary tract infection	6 (0.9)	6	3.05	5 (1.6)	5	5.32
Upper respiratory tract infection	9 (1.4)	9	4.28	1 (0.3)	1	1.06
Herpes simplex	1 (0.2)	1	0.51	4 (1.2)	4	4.26
Influenza	7 (1.1)	7	3.56	2 (0.6)	2	2.13
Oral herpes	7 (1.1)	8	4.07	2 (0.6)	2	2.13
Gastroenteritis	6 (0.9)	6	3.05	2 (0.6)	2	2.13
Gastrointestinal infection	5 (0.8)	5	2.54			
Bronchitis	3 (0.5)	3	1.53	3 (0.9)	3	3.19
Skin and subcutaneous tissue disorders						
Hand dermatitis	4 (0.6)	4	2.03	13 (4.0)	16	17.04
Dermatitis contact	7 (1.1)	7	3.56	6 (1.9)	6	6.39
Dermatitis atopic	2 (0.3)	2	1.02	4 (1.2)	5	5.32
Eczema	6 (0.9)	6	3.05	3 (0.9)	3	3.19
Nervous system disorders						
Headache	28 (4.4)	38	19.32	13 (4.0)	17	18.10
Musculoskeletal and connective tissue disorders						
Arthralgia	7 (1.1)	7	3.56	4 (1.2)	4	4.26
Backpain	7 (1.1)	7	3.56	1 (0.3)	1	1.06
Immune system disorders						
Allergy to metals	7 (1.1)	7	3.56	3 (0.9)	3	3.19
Vascular disorders						
Hypertension	7 (1.1)	7	3.56			

Source: Modified from Applicant Panel 11, ISS Appendix 7.

Abbreviations: %, percentage of subjects with events; AE, adverse event; COVID-19, coronavirus disease 2019; E, number of events; IMP, investigational medicinal product; N, number of subjects within a treatment group; n, number of subjects with events; PT, preferred term; PYO, patient years of observation; R, rate calculated as (E/PYO)*100; SOC, system organ class

Refer to [Table 30](#) for a comparison of EAIRs for subjects who received continuous delgocitinib over 52 weeks versus subjects who received vehicle for 16 weeks. This analysis did not suggest any new safety signals emerged over 52 weeks.

7.6.2. Safety Results, Trial 1273

The Applicant submitted additional safety data from a randomized (1:1:1:1), vehicle-controlled, double-blind, dose-ranging Trial LP0133-1273, that evaluated the efficacy and safety of multiple concentrations [1 mg/g (n=52), 3 mg/g (n=51), 8 mg/g (n=52), and 20 mg/g (n=53)] of delgocitinib cream compared with vehicle n=50) in the treatment of 258 subjects with mild to severe CHE.

Key differences in the study population and study design between Trial 1273 and Trials DELTA 1 and DELTA 2:

- Trial 1273 enrolled a broader study population. Trial 1273 evaluated subjects with mild to severe CHE, whereas Trials DELTA 1 and DELTA 2 evaluated subjects with moderate to severe CHE. Of the 24 subjects with mild CHE enrolled in the relevant groups of Trial 1273, 12 of 53 subjects received delgocitinib cream, 2%, and 12 of 50 subjects received vehicle.
- Trial 1273 utilized a different IGA scale than in Trials DELTA 1 and DELTA 2.
- Trial 1273 evaluated a different formulation than Trials DELTA 1 and DELTA 2, specifically containing a reduced concentration of the (b) (4) from (b) (4) to (b) (4)

The review team analyzed safety data from Trial 1273 both individually and pooled with data from Trials DELTA 1 and DELTA 2 and identified no new safety signals (see [Table 69](#) below).

Table 69. Most Frequent AEs (≥1%) by System Organ Class and Preferred Term, Pooled Trials DELTA 1 and DELTA 2 and Primary Pool (Which Includes Subjects Who Received Delgocitinib Cream, 2% in Trial 1273)

SOC/PT	Pooled Trials 1401 and 1402						Primary pool					
	Delgocitinib 20 mg/g (N=638, PYO=196.71)			Vehicle (N=321, PYO=93.91)			Delgocitinib 20 mg/g (N=691, PYO=214.72)			Vehicle (N=371, PYO=109.91)		
	n (%)	E	R	n (%)	E	R	n (adj. %)	E	adj. R	n (adj. %)	E	adj. R
Infections and infestations												
COVID-19	71 (11.1)	71	36.09	34 (10.6)	34	36.21	71 (9.9)	71	32.23	34 (9.4)	34	32.46
Nasopharyngitis	44 (6.9)	49	24.91	26 (7.5)	24	27.69	58 (9.0)	69	34.18	44 (11.0)	46	38.04
Pharyngitis	5 (0.8)	5	2.54	5 (1.6)	6	6.39	6 (0.9)	6	2.87	5 (1.4)	6	5.83
Urinary tract infection	6 (0.9)	6	3.05	5 (1.6)	5	5.32	8 (1.2)	8	3.93	6 (1.6)	6	5.41
Upper respiratory tract infection	9 (1.4)	9	4.28	1 (0.3)	1	1.06	11 (1.7)	11	5.28	1 (0.3)	1	0.93
Herpes simplex	1 (0.2)	1	0.51	4 (1.2)	4	4.26	1 (0.1)	1	0.46	5 (1.3)	5	4.56
Influenza	7 (1.1)	7	3.56	2 (0.6)	2	2.13	11 (1.8)	11	5.28	2 (0.6)	2	1.90
Oral herpes	7 (1.1)	8	4.07	2 (0.6)	2	2.13	8 (1.2)	9	4.23	3 (0.8)	3	2.57
Gastroenteritis	6 (0.9)	6	3.05	2 (0.6)	2	2.13	8 (1.2)	8	3.92	2 (0.6)	2	1.94
Gastrointestinal infection	5 (0.8)	5	2.54				7 (1.1)	7	3.48	1 (0.2)	1	0.67
Bronchitis	3 (0.5)	3	1.53	3 (0.9)	3	3.19	4 (0.6)	4	1.95	4 (1.0)	4	3.50
Skin and subcutaneous tissue disorders												
Hand dermatitis	4 (0.6)	4	2.03	13 (4.0)	16	17.04	4 (0.6)	4	1.83	13 (3.6)	16	15.14
Dermatitis contact	7 (1.1)	7	3.56	6 (1.9)	6	6.39	7 (1.0)	7	3.17	6 (1.7)	6	5.67
Dermatitis atopic	2 (0.3)	2	1.02	4 (1.2)	5	5.32	2 (0.3)	2	0.90	4 (1.1)	5	4.73
Eczema	6 (0.9)	6	3.05	3 (0.9)	3	3.19	12 (2.1)	13	6.90	11 (2.6)	12	8.92
Nervous system disorders												
Headache	28 (4.4)	38	19.32	13 (4.0)	17	18.10	32 (4.7)	43	20.30	15 (4.0)	19	17.61
Musculoskeletal and connective tissue disorders												
Arthralgia	7 (1.1)	7	3.56	4 (1.2)	4	4.26	8 (1.2)	8	3.79	4 (1.1)	4	3.76
Backpain	7 (1.1)	7	3.56	1 (0.3)	1	1.06	10 (1.6)	10	4.95	2 (0.5)	2	1.60
Immune system disorders												
Allergy to metals	7 (1.1)	7	3.56	3 (0.9)	3	3.19	7 (1.0)	7	3.14	3 (0.8)	3	2.79
Vascular disorders												
Hypertension	7 (1.1)	7	3.56				7 (1.0)	7	3.15			

Abbreviations: Adj. = adjusted; AE = adverse event; COVID-19 = coronavirus disease 2019; E = number of events; IMP = investigational medicinal product; N = number of subjects within a treatment group; n = number of subjects with events; PT = preferred term; PYO = patient years of observation; R = rate; SOC = system organ class; % = percentage of subjects with events.
Note: For the Primary pool, adj. % and rates are weighted and summed based on number of subjects in each trial to avoid Simpson's paradox.

Source: Applicant's Panel 11, Summary of Clinical Safety Appendix 7

Table 70. Summary of Safety Focus Areas, Pooled Trials DELTA 1 and DELTA 2 and Primary Pool Which Includes Trial 1273 (SAF)

	Pooled Trials 1401 and 1402						Primary pool					
	Delgocitinib 20 mg/g (N=638, PYO=196.71)			Vehicle (N=321, PYO=93.91)			Delgocitinib 20 mg/g (N=691, PYO=214.72)			Vehicle (N=371, PYO=109.91)		
	n (%)	E	R	n (%)	E	R	n (adj. %)	E	adj. R	n (adj. %)	E	adj. R
Dermal safety	14 (2.2)	16	8.13	11 (3.4)	13	13.84	14 (2.0)	16	7.30	12 (3.3)	14	12.93
Application site reactions	7 (1.1)	9	4.58	9 (2.8)	11	11.71	7 (1.0)	9	4.11	9 (2.5)	11	10.40
Acnes	2 (0.3)	2	1.02				2 (0.3)	2	0.92			
Local skin infections	5 (0.8)	5	2.54	3 (0.9)	3	3.19	5 (0.7)	5	2.26	4 (1.0)	4	3.50
Skin atrophy												
Hypersensitivity reactions	27 (4.2)	31	15.76	29 (9.0)	39	41.53	35 (5.4)	41	20.05	38 (10.0)	51	45.05
Serious or severe infections	7 (1.1)	8	4.07	2 (0.6)	2	2.13	7 (1.1)	8	3.62	2 (0.6)	2	1.90
Opportunistic infections	4 (0.6)	4	2.03	3 (0.9)	3	3.19	4 (0.6)	4	1.80	3 (0.8)	3	2.87
Herpes viral infections	8 (1.3)	9	4.58	6 (1.9)	7	7.45	9 (1.3)	10	4.69	8 (2.1)	9	8.10
Eczema herpeticum												
Abnormal blood cell counts ^a	8 (1.3)	14	7.12	1 (0.3)	2	2.13	8 (1.1)	14	6.32	1 (0.3)	2	1.94
Lymphocytopenia	3 (0.5)	3	1.53				3 (0.4)	3	1.36			
Abnormal lipid parameters ^b	15 (2.4)	18	9.15	5 (1.6)	7	7.45	15 (2.1)	18	8.12	5 (1.4)	7	6.51
Gastrointestinal perforations										1 (0.2)	1	0.67
Vaccination side effects, including COVID-19 vaccination	5 (0.8)	5	2.54	2 (0.6)	5	5.32	5 (0.7)	5	2.26	2 (0.6)	5	4.82
Hepatic safety	10 (1.6)	17	8.64	6 (1.9)	6	6.39	11 (1.6)	18	8.31	6 (1.7)	6	5.71
Renal safety	1 (0.2)	1	0.51				1 (0.1)	1	0.46			

Abbreviations: Adj. = adjusted; AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease 2019; CRF = case report form; E = number of events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects within a treatment group; n = number of subjects with events; PYO = patient years of observation; R = rate calculated as (E/PYO)*100; SAF = safety analysis set; % = percentage of subjects with events.

Notes: ^a The search abnormal blood cell count includes increases and decreases in blood cell counts, although the safety focus area is low blood cell count.

^b The search for abnormal lipid parameters includes increases and decreases in lipids, however all AEs reported were associated with increases or high levels of lipids.

AEs with start date on or after the date of first IMP application or with a worsening in severity after first IMP application are included. Classification according to MedDRA version 24.0. The safety focus areas are captured as defined in M2.7.4 Appendix 1. Some searches overlap. AEs may therefore appear in more than one search. The AESIs are captured by CRF form. Treatment groups are defined as actual treatment. PYO is calculated as number of days from first IMP application to end of trial divided by 365.25. For the Primary pool, adj. % and rates are weighted and summed based on number of subjects in each trial to avoid Simpson's paradox.

Source: Applicant's Panel 21, Summary of Clinical Safety Appendix 7

7.6.3. Safety Results, Trial DELTA FORCE

7.6.3.1. Overview of Treatment-Emergent Adverse Events Summary, Trial DELTA FORCE

Alitretinoin (marketed in several European countries, Canada, Israel, and South Korea as Tocrino) was first approved in 2008 for the treatment of severe CHE in adults who are unresponsive to treatment with potent topical corticosteroids. The Applicant conducted Trial DELTA FORCE outside the United States in adult subjects ≥ 18 years of age with severe CHE.

Design and Study Population

Trial DELTA FORCE was a phase 3, randomized, assessor-blinded, active-controlled, parallel-group, 2-arm trial that compared the efficacy and safety of delgocitinib cream, 2% twice daily with alitretinoin capsules 30 mg (or 10 mg) once daily. Approximately 500 adult subjects with severe CHE who had a documented recent history of inadequate response to treatment with TCS or for whom TCS was medically inadvisable were randomized in a 1:1 ratio to receive delgocitinib cream twice daily or alitretinoin capsules 30 mg once daily for up to 24 weeks (refer to [Figure 12](#) below). Randomization was stratified by subtype (hyperkeratotic/nonhyperkeratotic) and region (North America/Europe).

The primary endpoint was change in HECSI score from baseline to Week 12.

Safety monitoring included physical examinations, AEs, clinical laboratory data, vital signs, pregnancy testing, and ECGs.

Figure 12. Schematic of Trial DELTA FORCE

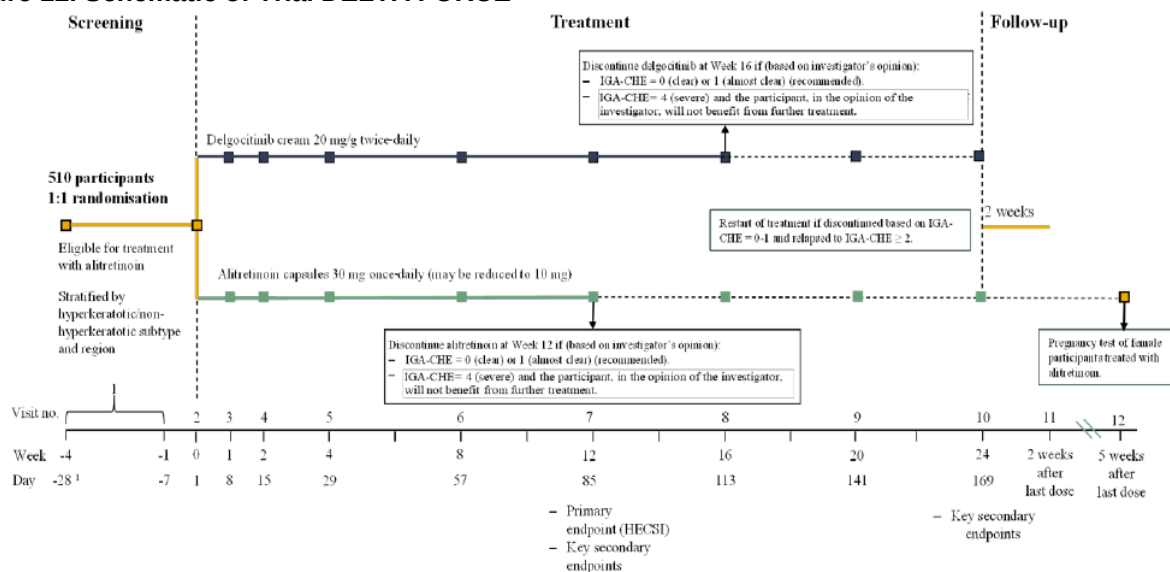


Table 71. Clinical Trial DELTA FORCE Submitted in Support of Efficacy and Safety Determinations for Delgocitinib

Trial Identifier	Trial Population	Trial Design	Regimen, Duration	Primary and Key Secondary Endpoints	No. of Subjects Planned; Actual Randomized	No. of Centers and Countries
LP0133-1528	Adults with severe CHE.	Control Type: Active-controlled Randomization: Standard Randomization Ratio: 2:1 Blinding: Randomized, Assessor-blinded Biomarkers: No biomarkers Innovative design features: None	Drug, Dose: Delgocitinib cream, 20 mg/g Alitretinoin capsule, 30 (or 10) mg Number treated: • Delgocitinib: 313 • Alitretinoin: 159 Duration: 24 weeks	Primary: Change in HECSI from baseline to Week 12. Secondary: • HECSI-90 at Week 24 • IGA-CHE TS at Week 12 • AUC of HECSI-90 from baseline up to Week 24 • Change in HECSI score from baseline to Week 24 • Change in HESD itch score (weekly average) from baseline to Week 12 • Change in HESD pain score (weekly average) from baseline to Week 12 • AUC of change from baseline in DLQI score up to Week 24	Planned: 510 Actual: 513	Centers: 103 Countries: 9

Source: Synopses of individual trials, Clinical Study Report, Protocol, and adsl.xpt
Abbreviations: AUC, area under the concentration-time curve; CHE, chronic hand eczema; DLQI, Dermatology Life Quality Index; HECSI, Hand Eczema Severity Index; HECSI-90, at least 90% improvement in HECSI from baseline; HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for CHE; No., number; TS, treatment success

Results

A total of 513 adult subjects with severe CHE received delgocitinib cream or alitretinoin for up to 24 weeks. Results for delgocitinib cream did not identify any new safety concerns. The safety analysis for delgocitinib cream compared to alitretinoin demonstrated fewer AEs, SAEs, severe AEs, related AEs, and AEs leading to investigational product discontinuation.

These results are summarized in [Table 72](#) through [Table 76](#) below.

Table 72. Overview of Adverse Events, Safety Population, Trial DELTA FORCE (Weeks 0 to 12)

Event Category	Delgocitinib Cream 20 mg/g N=253 n (%)	Alitretinoin Capsule 30 mg N=247 n (%)	Risk Difference % (95% CI)
SAE	4 (1.6)	6 (2.4)	-0.8 (-3.8, 1.9)
SAEs with fatal outcome	0	0	0.0 (-1.5, 1.5)
Life-threatening SAEs	0	0	0.0 (-1.5, 1.5)
SAEs requiring hospitalization	2 (0.8)	3 (1.2)	-0.4 (-2.8, 1.8)
Other	2 (0.8)	3 (1.2)	-0.4 (-2.8, 1.8)
AE leading to permanent discontinuation of study drug	3 (1.2)	20 (8.1)	-6.9 (-11.1, -3.5)*
AE leading to dose modification of study drug	0	36 (14.6)	-14.6 (-19.5, -10.7)*
AE leading to interruption of study drug	0	0	0.0 (-1.5, 1.5)
AE leading to reduction of study drug	0	36 (14.6)	-14.6 (-19.5, -10.7)*
AE leading to dose delay of study drug	0	0	0.0 (-1.5, 1.5)
Any AE	101 (39.9)	170 (68.8)	-28.9 (-37.0, -20.4)*
Severe and worse	4 (1.6)	11 (4.5)	-2.9 (-6.4, 0.1)
Moderate	47 (18.6)	76 (30.8)	-12.2 (-19.7, -4.7)*
Mild	50 (19.8)	83 (33.6)	-13.8 (-21.5, -6.1)*

Source: adae.xpt; Software: R

* Indicates that 95% confidence interval excludes zero.

Treatment-emergent adverse events defined as AE that begins or that worsens in severity after at least one dose of the study drug has been administered until Week 12.

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

Table 73. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial DELTA FORCE (Weeks 0 to 12)

System Organ Class Preferred Term	Delgocitinib Cream 20 mg/g N=253 n (%)	Alitretinoin Capsule 30 mg N=247 n (%)	Risk Difference % (95% CI)
Any SAE	4 (1.6)	6 (2.4)	-0.8 (-3.8, 1.9)
Infections and infestations (SOC)	1 (0.4)	0	0.4 (-1.1, 2.2)
Gastroenteritis norovirus	1 (0.4)	0	0.4 (-1.1, 2.2)
Investigations (SOC)	1 (0.4)	1 (0.4)	-0.0 (-1.9, 1.8)
Blood potassium increased	1 (0.4)	0	0.4 (-1.1, 2.2)
International normalized ratio increased	0	1 (0.4)	-0.4 (-2.3, 1.1)
Musculoskeletal and connective tissue disorders (SOC)	1 (0.4)	0	0.4 (-1.1, 2.2)
Intervertebral disc protrusion	1 (0.4)	0	0.4 (-1.1, 2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.4)	1 (0.4)	-0.0 (-1.9, 1.8)
Basal cell carcinoma	1 (0.4)	1 (0.4)	-0.0 (-1.9, 1.8)
Nervous system disorders (SOC)	0	1 (0.4)	-0.4 (-2.3, 1.1)
Headache	0	1 (0.4)	-0.4 (-2.3, 1.1)
Reproductive system and breast disorders (SOC)	0	1 (0.4)	-0.4 (-2.3, 1.1)
Prostatitis	0	1 (0.4)	-0.4 (-2.3, 1.1)

System Organ Class	Delgocitinib Cream 20 mg/g N=253 n (%)	Alitretinoin Capsule 30 mg N=247 n (%)	Risk Difference % (95% CI)
Preferred Term			
Skin and subcutaneous tissue disorders (SOC)	0	2 (0.8)	-0.8 (-2.9, 0.7)
Hand dermatitis	0	1 (0.4)	-0.4 (-2.3, 1.1)
Skin ulcer	0	1 (0.4)	-0.4 (-2.3, 1.1)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AE that begins or that worsens in severity after at least one dose of the study drug has been administered until Week 12.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: AE, adverse event; CI, confidence interval; incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

Table 74. Subjects With Serious Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term, Safety Population, DELTA FORCE (Weeks 0 to 12)

System Organ Class	Delgocitinib Cream 20 mg/g N=253 n (%)	Alitretinoin Capsule 30 mg N=247 n (%)	Risk Difference % (95% CI)
OCMQ (Narrow)			
Preferred Term			
Infections and infestations (SOC)			
Viral infection (OCMQ)	1 (0.4)	0	0.4 (-1.1, 2.2)
Gastroenteritis norovirus	1 (0.4)	0	0.4 (-1.1, 2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)			
Malignancy (OCMQ)	1 (0.4)	1 (0.4)	-0.0 (-1.9, 1.8)
Basal cell carcinoma	1 (0.4)	1 (0.4)	-0.0 (-1.9, 1.8)
Nervous system disorders (SOC)			
Headache (OCMQ)	0	1 (0.4)	-0.4 (-2.3, 1.1)
Headache	0	1 (0.4)	-0.4 (-2.3, 1.1)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AE that begins or that worsens in severity after at least one dose of the study drug has been administered until Week 12.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

See the table "Subjects With Adverse Events by Preferred Term Not Captured in FDA Medical Query (Narrow)"

Abbreviations: AE, adverse event; CI, confidence interval; OCMQ, OND custom medical query; incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class

A greater number of subjects discontinued treatment in the alitretinoin group compared with the delgocitinib group (8.1% versus 1.2%) as tabulated below in [Table 75](#).

Table 75. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial DELTA FORCE (Weeks 0 to 12)

System Organ Class Preferred Term	Delgocitinib Cream 20 mg/g N=253 n (%)	Alitretinoin Capsule 30 mg N=247 n (%)	Risk Difference % (95% CI)
Any AE leading to discontinuation	3 (1.2)	20 (8.1)	-6.9 (-11.1, -3.5)*
Cardiac disorders (SOC)	0	1 (0.4)	-0.4 (-2.3, 1.1)
Palpitations	0	1 (0.4)	-0.4 (-2.3, 1.1)
Eye disorders (SOC)	0	1 (0.4)	-0.4 (-2.3, 1.1)
Vision blurred	0	1 (0.4)	-0.4 (-2.3, 1.1)
Gastrointestinal disorders (SOC)	0	4 (1.6)	-1.6 (-4.1, -0.1)*
Diarrhoea	0	2 (0.8)	-0.8 (-2.9, 0.7)
Nausea	0	3 (1.2)	-1.2 (-3.5, 0.3)
General disorders and administration site conditions (SOC)	2 (0.8)	1 (0.4)	0.4 (-1.5, 2.5)
Application site pain	1 (0.4)	0	0.4 (-1.1, 2.2)
Pain	1 (0.4)	0	0.4 (-1.1, 2.2)
Oedema peripheral	0	1 (0.4)	-0.4 (-2.3, 1.1)
Immune system disorders (SOC)	1 (0.4)	0	0.4 (-1.1, 2.2)
Drug hypersensitivity	1 (0.4)	0	0.4 (-1.1, 2.2)
Investigations (SOC)	0	1 (0.4)	-0.4 (-2.3, 1.1)
Weight decreased	0	1 (0.4)	-0.4 (-2.3, 1.1)
Nervous system disorders (SOC)	0	14 (5.7)	-5.7 (-9.3, -3.4)*
Dizziness	0	1 (0.4)	-0.4 (-2.3, 1.1)
Idiopathic intracranial hypertension	0	1 (0.4)	-0.4 (-2.3, 1.1)
Migraine	0	1 (0.4)	-0.4 (-2.3, 1.1)
Headache	0	11 (4.5)	-4.5 (-7.8, -2.5)*
Psychiatric disorders (SOC)	0	3 (1.2)	-1.2 (-3.5, 0.3)
Affective disorder	0	1 (0.4)	-0.4 (-2.3, 1.1)
Aggression	0	1 (0.4)	-0.4 (-2.3, 1.1)
Anger	0	1 (0.4)	-0.4 (-2.3, 1.1)
Anxiety	0	1 (0.4)	-0.4 (-2.3, 1.1)
Depressed mood	0	1 (0.4)	-0.4 (-2.3, 1.1)
Mood swings	0	1 (0.4)	-0.4 (-2.3, 1.1)
Respiratory, thoracic and mediastinal disorders (SOC)	0	2 (0.8)	-0.8 (-2.9, 0.7)
Cough	0	1 (0.4)	-0.4 (-2.3, 1.1)
Epistaxis	0	1 (0.4)	-0.4 (-2.3, 1.1)
Skin and subcutaneous tissue disorders (SOC)	1 (0.4)	4 (1.6)	-1.2 (-3.7, 0.7)
Pain of skin	1 (0.4)	0	0.4 (-1.1, 2.2)
Dermatitis atopic	0	1 (0.4)	-0.4 (-2.3, 1.1)
Hand dermatitis	0	1 (0.4)	-0.4 (-2.3, 1.1)
Hyperhidrosis	0	1 (0.4)	-0.4 (-2.3, 1.1)
Rash maculo-papular	0	1 (0.4)	-0.4 (-2.3, 1.1)
Urticaria	0	1 (0.4)	-0.4 (-2.3, 1.1)
Vascular disorders (SOC)	0	1 (0.4)	-0.4 (-2.3, 1.1)
Hypertension	0	1 (0.4)	-0.4 (-2.3, 1.1)

Source: adae.xpt; Software: R

* Indicates that 95% confidence interval excludes zero.

Treatment-emergent adverse events defined as AE that begins or that worsens in severity after at least one dose of the study drug has been administered until Week 12.

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

Table 76. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class, FDA Medical Query (Narrow) and Preferred Term, Safety Population, Trial DELTA FORCE (Weeks 0 to 12)

System Organ Class OCMQ (Narrow) Preferred Term	Delgocitinib Cream 20 mg/g N=253 n (%)	Alitretinoin Capsule 30 mg N=247 n (%)	Risk Difference % (95% CI)
Cardiac disorders (SOC)			
Palpitations (OCMQ)	0	1 (0.4)	-0.4 (-2.3, 1.1)
Palpitations	0	1 (0.4)	-0.4 (-2.3, 1.1)
Systemic hypertension (OCMQ)	0	1 (0.4)	-0.4 (-2.3, 1.1)
Hypertension	0	1 (0.4)	-0.4 (-2.3, 1.1)
Gastrointestinal disorders (SOC)			
Diarrhea (OCMQ)	0	2 (0.8)	-0.8 (-2.9, 0.7)
Diarrhoea	0	2 (0.8)	-0.8 (-2.9, 0.7)
Nausea (OCMQ)	0	3 (1.2)	-1.2 (-3.5, 0.3)
Nausea	0	3 (1.2)	-1.2 (-3.5, 0.3)
General disorders and administration site conditions (SOC)			
Local administration reaction (OCMQ)	1 (0.4)	0	0.4 (-1.1, 2.2)
Application site pain	1 (0.4)	0	0.4 (-1.1, 2.2)
Dizziness (OCMQ)	0	1 (0.4)	-0.4 (-2.3, 1.1)
Dizziness	0	1 (0.4)	-0.4 (-2.3, 1.1)
Peripheral edema (OCMQ)	0	1 (0.4)	-0.4 (-2.3, 1.1)
Oedema peripheral	0	1 (0.4)	-0.4 (-2.3, 1.1)
Immune system disorders (SOC)			
Hypersensitivity (OCMQ)	1 (0.4)	0	0.4 (-1.1, 2.2)
Drug hypersensitivity	1 (0.4)	0	0.4 (-1.1, 2.2)
Nervous system disorders (SOC)			
Headache (OCMQ)	0	12 (4.9)	-4.9 (-8.3, -2.8)*
Migraine	0	1 (0.4)	-0.4 (-2.3, 1.1)
Headache	0	11 (4.5)	-4.5 (-7.8, -2.5)*
Psychiatric disorders (SOC)			
Anxiety (OCMQ)	0	1 (0.4)	-0.4 (-2.3, 1.1)
Anxiety	0	1 (0.4)	-0.4 (-2.3, 1.1)
Depression (OCMQ)	0	1 (0.4)	-0.4 (-2.3, 1.1)
Depressed mood	0	1 (0.4)	-0.4 (-2.3, 1.1)
Respiratory, thoracic and mediastinal disorders (SOC)			
Cough (OCMQ)	0	1 (0.4)	-0.4 (-2.3, 1.1)
Cough	0	1 (0.4)	-0.4 (-2.3, 1.1)

System Organ Class	Delgocitinib Cream 20 mg/g N=253 n (%)	Alitretinoin Capsule 30 mg N=247 n (%)	Risk Difference % (95% CI)
OCMQ (Narrow)			
Preferred Term			
Skin and subcutaneous tissue disorders (SOC)			
Rash (OCMQ)	0	1 (0.4)	-0.4 (-2.3, 1.1)
Rash maculo-papular	0	1 (0.4)	-0.4 (-2.3, 1.1)
Urticaria	0	1 (0.4)	-0.4 (-2.3, 1.1)
Urticaria (OCMQ)	0	1 (0.4)	-0.4 (-2.3, 1.1)
Urticaria	0	1 (0.4)	-0.4 (-2.3, 1.1)
Vascular disorders (SOC)			
Hemorrhage (OCMQ)	0	1 (0.4)	-0.4 (-2.3, 1.1)
Epistaxis	0	1 (0.4)	-0.4 (-2.3, 1.1)

Source: adae.xpt; Software: R

* Indicates that 95% confidence interval excludes zero.

Treatment-emergent adverse events defined as AE that begins or that worsens in severity after at least one dose of the study drug has been administered until Week 12.

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

See the table "Subjects With Adverse Events by Preferred Term Not Captured in FDA Medical Query (Narrow)."

Abbreviations: AE, adverse event; CI, confidence interval; OCMQ, OND custom medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class

7.6.3.2. Treatment-Emergent Adverse Events, Trial DELTA FORCE

The safety profile of delgocitinib cream in Trial DELTA FORCE was similar to the safety profile observed in phase 3 trials DELTA 1, DELTA 2, and DELTA 3. No new safety signals were identified. Overall, subjects who received delgocitinib developed fewer TEAEs compared to subjects who received alitretinoin in Trial DELTA FORCE, as illustrated in [Table 77](#), [Table 78](#), and [Table 79](#) below.

Table 77. Subjects With Common Adverse Events Occurring at ≥1% Frequency, Safety Population, Trial 1528 (Weeks 0 to 12)

Preferred Term	Delgocitinib Cream 20 mg/g N=253 n (%)	Alitretinoin Capsule 30 mg N=247 n (%)	Risk Difference % (95% CI)
Any AE	101 (39.9)	170 (68.8)	-28.9 (-37.0, -20.4)*
Low density lipoprotein increased	4 (1.6)	1 (0.4)	1.2 (-0.8, 3.6)
Sinusitis	4 (1.6)	2 (0.8)	0.8 (-1.5, 3.3)
Blood cholesterol increased	3 (1.2)	2 (0.8)	0.4 (-1.8, 2.7)
Influenza	3 (1.2)	2 (0.8)	0.4 (-1.8, 2.7)
Pharyngitis	3 (1.2)	2 (0.8)	0.4 (-1.8, 2.7)
Oral herpes	3 (1.2)	3 (1.2)	-0.0 (-2.5, 2.4)
Pruritus	3 (1.2)	3 (1.2)	-0.0 (-2.5, 2.4)
Nasopharyngitis	22 (8.7)	22 (8.9)	-0.2 (-5.3, 4.9)
Blood thyroid stimulating hormone decreased	2 (0.8)	3 (1.2)	-0.4 (-2.8, 1.8)
Fatigue	2 (0.8)	3 (1.2)	-0.4 (-2.8, 1.8)
Abdominal pain upper	1 (0.4)	3 (1.2)	-0.8 (-3.2, 1.1)
Dermatitis atopic	1 (0.4)	3 (1.2)	-0.8 (-3.2, 1.1)
Pain in extremity	1 (0.4)	3 (1.2)	-0.8 (-3.2, 1.1)
Vomiting	1 (0.4)	3 (1.2)	-0.8 (-3.2, 1.1)
Eczema	2 (0.8)	4 (1.6)	-0.8 (-3.4, 1.4)
COVID-19	3 (1.2)	5 (2.0)	-0.8 (-3.6, 1.7)
Back pain	0	3 (1.2)	-1.2 (-3.5, 0.3)
Toothache	0	3 (1.2)	-1.2 (-3.5, 0.3)
Dizziness	1 (0.4)	4 (1.6)	-1.2 (-3.7, 0.7)
Dyspepsia	1 (0.4)	4 (1.6)	-1.2 (-3.7, 0.7)
Hypertriglyceridaemia	2 (0.8)	5 (2.0)	-1.2 (-4.0, 1.1)
Upper respiratory tract infection	5 (2.0)	8 (3.2)	-1.3 (-4.5, 1.7)
Epistaxis	0	4 (1.6)	-1.6 (-4.1, -0.1)*
Vision blurred	0	4 (1.6)	-1.6 (-4.1, -0.1)*
Migraine	1 (0.4)	5 (2.0)	-1.6 (-4.3, 0.4)
Dry skin	3 (1.2)	7 (2.8)	-1.6 (-4.7, 1.0)
Diarrhoea	0	5 (2.0)	-2.0 (-4.7, -0.5)*
Flushing	0	5 (2.0)	-2.0 (-4.7, -0.5)*
Urinary tract infection	0	5 (2.0)	-2.0 (-4.7, -0.5)*
Blood triglycerides increased	1 (0.4)	6 (2.4)	-2.0 (-4.9, 0.0)
Dry eye	0	6 (2.4)	-2.4 (-5.2, -0.9)*
Hypercholesterolaemia	0	6 (2.4)	-2.4 (-5.2, -0.9)*
Erythema	1 (0.4)	8 (3.2)	-2.8 (-5.9, -0.7)*
Lip dry	0	8 (3.2)	-3.2 (-6.3, -1.6)*
Nausea	1 (0.4)	14 (5.7)	-5.3 (-8.9, -2.7)*

Preferred Term	Delgocitinib Cream 20 mg/g N=253 n (%)	Alitretinoin Capsule 30 mg N=247 n (%)	Risk Difference % (95% CI)
Headache	8 (3.2)	75 (30.4)	-27.2 (-33.5, -21.2)*

Source: adae.xpt; Software: R

* Indicates that 95% confidence interval excludes zero.

Treatment-emergent adverse events defined as AE that begins or that worsens in severity after at least one dose of the study drug has been administered until Week 12.

Duration is 24 weeks.

Coded as MedDRA preferred terms.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 78. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial DELTA FORCE (Weeks 0 to 12)

System Organ Class OCMQ (Narrow)	Delgocitinib Cream 20 mg/g N=253 n (%)	Alitretinoin Capsule 30 mg N=247 n (%)	Risk Difference % (95% CI)
Blood and lymphatic system disorders (SOC)			
Thrombocytopenia	1 (0.4)	0	0.4 (-1.1, 2.2)
Leukopenia	0	1 (0.4)	-0.4 (-2.3, 1.1)
Cardiac disorders (SOC)			
Palpitations	1 (0.4)	1 (0.4)	-0.0 (-1.9, 1.8)
Systemic hypertension	1 (0.4)	1 (0.4)	-0.0 (-1.9, 1.8)
Arrhythmia	0	2 (0.8)	-0.8 (-2.9, 0.7)
Tachycardia	0	2 (0.8)	-0.8 (-2.9, 0.7)
Ear and labyrinth disorders (SOC)			
Vertigo	0	2 (0.8)	-0.8 (-2.9, 0.7)
Endocrine disorders (SOC)			
Hyperglycemia	0	2 (0.8)	-0.8 (-2.9, 0.7)
Gastrointestinal disorders (SOC)			
Vomiting	1 (0.4)	3 (1.2)	-0.8 (-3.2, 1.1)
Abdominal pain	1 (0.4)	5 (2.0)	-1.6 (-4.3, 0.4)
Diarrhea	0	5 (2.0)	-2.0 (-4.7, -0.5) *
Dyspepsia	2 (0.8)	7 (2.8)	-2.0 (-5.0, 0.4)
Dry mouth	0	9 (3.6)	-3.6 (-6.8, -1.9) *
Nausea	1 (0.4)	14 (5.7)	-5.3 (-8.9, -2.7) *
General disorders and administration site conditions (SOC)			
Pyrexia	3 (1.2)	0	1.2 (-0.4, 3.4)
Local administration reaction	1 (0.4)	0	0.4 (-1.1, 2.2)
Peripheral edema	0	1 (0.4)	-0.4 (-2.3, 1.1)
Decreased appetite	0	2 (0.8)	-0.8 (-2.9, 0.7)
Fatigue	3 (1.2)	6 (2.4)	-1.2 (-4.2, 1.3)
Dizziness	1 (0.4)	6 (2.4)	-2.0 (-4.9, 0.0)
Hepatobiliary disorders (SOC)			
Hepatic injury	2 (0.8)	1 (0.4)	0.4 (-1.5, 2.5)
Immune system disorders (SOC)			
Hypersensitivity	1 (0.4)	0	0.4 (-1.1, 2.2)

System Organ Class	Delgocitinib Cream 20 mg/g N=253 n (%)	Alitreinoin Capsule 30 mg N=247 n (%)	Risk Difference % (95% CI)
OCMQ (Narrow)			
Infections and infestations (SOC)			
Viral infection	12 (4.7)	12 (4.9)	-0.1 (-4.1, 3.8)
Fungal infection	0	1 (0.4)	-0.4 (-2.3, 1.1)
Purulent material	1 (0.4)	2 (0.8)	-0.4 (-2.6, 1.5)
Nasopharyngitis	31 (12.3)	33 (13.4)	-1.1 (-7.1, 4.8)
Bacterial infection	7 (2.8)	18 (7.3)	-4.5 (-8.8, -0.7)*
Metabolism and nutrition disorders (SOC)			
Lipid disorder	6 (2.4)	17 (6.9)	-4.5 (-8.6, -0.9)*
Musculoskeletal and connective tissue disorders (SOC)			
Tendinopathy	1 (0.4)	0	0.4 (-1.1, 2.2)
Arthritis	2 (0.8)	1 (0.4)	0.4 (-1.5, 2.5)
Fracture	2 (0.8)	1 (0.4)	0.4 (-1.5, 2.5)
Arthralgia	1 (0.4)	1 (0.4)	-0.0 (-1.9, 1.8)
Myalgia	1 (0.4)	2 (0.8)	-0.4 (-2.6, 1.5)
Back pain	0	4 (1.6)	-1.6 (-4.1, -0.1)*
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)			
Malignancy	1 (0.4)	1 (0.4)	-0.0 (-1.9, 1.8)
Nervous system disorders (SOC)			
Somnolence	0	1 (0.4)	-0.4 (-2.3, 1.1)
Paresthesia	0	2 (0.8)	-0.8 (-2.9, 0.7)
Headache	9 (3.6)	79 (32.0)	-28.4 (-34.8, -22.3)*
Psychiatric disorders (SOC)			
Anxiety	0	1 (0.4)	-0.4 (-2.3, 1.1)
Study agent abuse potential	0	1 (0.4)	-0.4 (-2.3, 1.1)
Depression	0	2 (0.8)	-0.8 (-2.9, 0.7)
Renal and urinary disorders (SOC)			
Renal & urinary tract infection	0	7 (2.8)	-2.8 (-5.7, -1.3)*
Reproductive system and breast disorders (SOC)			
Abnormal uterine bleeding	1 (0.4)	0	0.4 (-1.1, 2.2)
Amenorrhea	0	1 (0.4)	-0.4 (-2.3, 1.1)
Decreased menstrual bleeding	0	1 (0.4)	-0.4 (-2.3, 1.1)
Respiratory, thoracic and mediastinal disorders (SOC)			
Bronchospasm	0	1 (0.4)	-0.4 (-2.3, 1.1)
Cough	1 (0.4)	2 (0.8)	-0.4 (-2.6, 1.5)
Skin and subcutaneous tissue disorders (SOC)			
Pruritus	4 (1.6)	3 (1.2)	0.4 (-2.1, 2.9)
Rash	3 (1.2)	4 (1.6)	-0.4 (-3.0, 2.0)
Urticaria	0	2 (0.8)	-0.8 (-2.9, 0.7)
Erythema	1 (0.4)	13 (5.3)	-4.9 (-8.5, -2.3)*

System Organ Class	Delgocitinib Cream 20 mg/g N=253 n (%)	Alitretinoin Capsule 30 mg N=247 n (%)	Risk Difference % (95% CI)
OCMQ (Narrow)			
Vascular disorders (SOC)			
Thrombosis	1 (0.4)	0	0.4 (-1.1, 2.2)
Thrombosis venous	1 (0.4)	0	0.4 (-1.1, 2.2)
Hemorrhage	2 (0.8)	6 (2.4)	-1.6 (-4.5, 0.7)

Source: adae.xpt; Software: R

* Indicates that 95% confidence interval excludes zero.

Treatment-emergent adverse events defined as AE that begins or that worsens in severity after at least one dose of the study drug has been administered until Week 12.

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

For specific preferred terms under each OCMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term."

Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

See the table "Subjects With Adverse Events by Preferred Term Not Captured in FDA Medical Query (Narrow)."

Abbreviations: AE, adverse event; CI, confidence interval; OCMQ, OND custom medical query; incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class

Table 79. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Broad), Safety Population, Trial DELTA FORCE (Weeks 0 to 12)

System Organ Class	Delgocitinib Cream 20 mg/g N=253 n (%)	Alitretinoin Capsule 30 mg N=247 n (%)	Risk Difference % (95% CI)
OCMQ (Broad)			
Blood and lymphatic system disorders (SOC)			
Thrombocytopenia	1 (0.4)	0	0.4 (-1.1, 2.2)
Leukopenia	0	1 (0.4)	-0.4 (-2.3, 1.1)
Cardiac disorders (SOC)			
Palpitations	1 (0.4)	1 (0.4)	-0.0 (-1.9, 1.8)
Systemic hypertension	1 (0.4)	1 (0.4)	-0.0 (-1.9, 1.8)
Heart failure	0	1 (0.4)	-0.4 (-2.3, 1.1)
Tachycardia	0	2 (0.8)	-0.8 (-2.9, 0.7)
Arrhythmia	2 (0.8)	7 (2.8)	-2.0 (-5.0, 0.4)
Ear and labyrinth disorders (SOC)			
Vertigo	1 (0.4)	6 (2.4)	-2.0 (-4.9, 0.0)
Endocrine disorders (SOC)			
Hyperglycemia	0	2 (0.8)	-0.8 (-2.9, 0.7)
Gastrointestinal disorders (SOC)			
Diarrhea	5 (2.0)	8 (3.2)	-1.3 (-4.5, 1.7)
Abdominal pain	1 (0.4)	5 (2.0)	-1.6 (-4.3, 0.4)
Dyspepsia	4 (1.6)	9 (3.6)	-2.1 (-5.4, 0.8)
Dry mouth	0	9 (3.6)	-3.6 (-6.8, -1.9)*
Nausea	2 (0.8)	17 (6.9)	-6.1 (-10.0, -3.1) *
Vomiting	2 (0.8)	18 (7.3)	-6.5 (-10.5, -3.4) *

System Organ Class	Delgocitinib Cream 20 mg/g N=253 n (%)	Alitretinoin Capsule 30 mg N=247 n (%)	Risk Difference % (95% CI)
OCMQ (Broad)			
General disorders and administration site conditions (SOC)			
Local administration reaction	1 (0.4)	0	0.4 (-1.1, 2.2)
Pyrexia	3 (1.2)	2 (0.8)	0.4 (-1.8, 2.7)
Peripheral edema	0	1 (0.4)	-0.4 (-2.3, 1.1)
Decreased appetite	0	2 (0.8)	-0.8 (-2.9, 0.7)
Fatigue	3 (1.2)	7 (2.8)	-1.6 (-4.7, 1.0)
Dizziness	1 (0.4)	6 (2.4)	-2.0 (-4.9, 0.0)
Fall	1 (0.4)	6 (2.4)	-2.0 (-4.9, 0.0)
Hepatobiliary disorders (SOC)			
Cholecystitis	0	1 (0.4)	-0.4 (-2.3, 1.1)
Hepatic injury	2 (0.8)	5 (2.0)	-1.2 (-4.0, 1.1)
Immune system disorders (SOC)			
Anaphylactic reaction	1 (0.4)	0	0.4 (-1.1, 2.2)
Angioedema	1 (0.4)	0	0.4 (-1.1, 2.2)
Hypersensitivity	11 (4.3)	25 (10.1)	-5.8 (-10.6, -1.3)*
Infections and infestations (SOC)			
Pneumonia	3 (1.2)	3 (1.2)	-0.0 (-2.5, 2.4)
Fungal infection	0	1 (0.4)	-0.4 (-2.3, 1.1)
Purulent material	1 (0.4)	2 (0.8)	-0.4 (-2.6, 1.5)
Nasopharyngitis	31 (12.3)	33 (13.4)	-1.1 (-7.1, 4.8)
Viral infection	20 (7.9)	23 (9.3)	-1.4 (-6.5, 3.6)
Bacterial infection	14 (5.5)	23 (9.3)	-3.8 (-8.6, 0.8)
Metabolism and nutrition disorders (SOC)			
Cachexia	0	1 (0.4)	-0.4 (-2.3, 1.1)
Lipid disorder	6 (2.4)	17 (6.9)	-4.5 (-8.6, -0.9) *
Musculoskeletal and connective tissue disorders (SOC)			
Arthritis	5 (2.0)	3 (1.2)	0.8 (-1.8, 3.5)
Tendinopathy	1 (0.4)	0	0.4 (-1.1, 2.2)
Fracture	2 (0.8)	1 (0.4)	0.4 (-1.5, 2.5)
Arthralgia	3 (1.2)	2 (0.8)	0.4 (-1.8, 2.7)
Myalgia	2 (0.8)	2 (0.8)	-0.0 (-2.2, 2.1)
Back pain	3 (1.2)	5 (2.0)	-0.8 (-3.6, 1.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)			
Malignancy	1 (0.4)	1 (0.4)	-0.0 (-1.9, 1.8)
Nervous system disorders (SOC)			
Confusional state	0	1 (0.4)	-0.4 (-2.3, 1.1)
Dysgeusia	0	1 (0.4)	-0.4 (-2.3, 1.1)
Somnolence	2 (0.8)	4 (1.6)	-0.8 (-3.4, 1.4)
Paresthesia	0	3 (1.2)	-1.2 (-3.5, 0.3)
Syncope	1 (0.4)	4 (1.6)	-1.2 (-3.7, 0.7)
Headache	9 (3.6)	79 (32.0)	-28.4 (-34.8, -22.3)*

System Organ Class OCMQ (Broad)	Delgocitinib Cream 20 mg/g N=253 n (%)	Alitretinoin Capsule 30 mg N=247 n (%)	Risk Difference % (95% CI)
Psychiatric disorders (SOC)			
Anxiety	0	1 (0.4)	-0.4 (-2.3, 1.1)
Insomnia	0	1 (0.4)	-0.4 (-2.3, 1.1)
Parasomnia	0	1 (0.4)	-0.4 (-2.3, 1.1)
Psychosis	0	2 (0.8)	-0.8 (-2.9, 0.7)
Mania	0	3 (1.2)	-1.2 (-3.5, 0.3)
Study agent abuse potential	0	3 (1.2)	-1.2 (-3.5, 0.3)
Depression	0	5 (2.0)	-2.0 (-4.7, -0.5) *
Renal and urinary disorders (SOC)			
Urinary retention	0	1 (0.4)	-0.4 (-2.3, 1.1)
Renal & urinary tract infection	0	7 (2.8)	-2.8 (-5.7, -1.3)*
Reproductive system and breast disorders (SOC)			
Abnormal uterine bleeding	1 (0.4)	0	0.4 (-1.1, 2.2)
Amenorrhea	0	1 (0.4)	-0.4 (-2.3, 1.1)
Decreased menstrual bleeding	0	1 (0.4)	-0.4 (-2.3, 1.1)
Bacterial vaginosis	1 (0.4)	2 (0.8)	-0.4 (-2.6, 1.5)
Respiratory, thoracic and mediastinal disorders (SOC)			
Bronchospasm	0	1 (0.4)	-0.4 (-2.3, 1.1)
Cough	1 (0.4)	2 (0.8)	-0.4 (-2.6, 1.5)
Skin and subcutaneous tissue disorders (SOC)			
Pruritus	4 (1.6)	3 (1.2)	0.4 (-2.1, 2.9)
Urticaria	1 (0.4)	4 (1.6)	-1.2 (-3.7, 0.7)
Rash	5 (2.0)	12 (4.9)	-2.9 (-6.6, 0.3)
Erythema	1 (0.4)	13 (5.3)	-4.9 (-8.5, -2.3)*
Vascular disorders (SOC)			
Thrombosis	2 (0.8)	0	0.8 (-0.7, 2.8)
Thrombosis venous	2 (0.8)	0	0.8 (-0.7, 2.8)
Thrombosis arterial	1 (0.4)	0	0.4 (-1.1, 2.2)
Hemorrhage	2 (0.8)	6 (2.4)	-1.6 (-4.5, 0.7)

Source: adae.xpt; Software: R

* Indicates that 95% confidence interval excludes zero.

Treatment-emergent adverse events defined as AE that begins or that worsens in severity after at least one dose of the study drug has been administered until Week 12.

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.

Abbreviations: AE, adverse event; CI, confidence interval; OCMQ, OND custom medical query; incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class

7.7. Key Safety Review Issues

Refer to list from Section [3.1](#).

7.7.1. Impact of the Formulation Change on the Assessment of Pharmacokinetics and Safety

The Applicant evaluated the final to-be-marketed formulation in most of the trials in the clinical development program, including maximal use studies (LP0133-2285 and DELTA 2). However,

the Applicant also used an early formulation in the development program. The difference between the final formulation and the early formulation is the amount of (b) (4), which was (b) (4) mg/g in the final formulation compared to (b) (4) mg/g in the early formulation.

Per the Drug Product review, (b) (4) is used as (b) (4). Based on the submitted stability data, the formulation with the reduced (b) (4) met the desired stability criteria (b) (4), which indicated that the reduced level of (b) (4) is sufficient (b) (4). The change in the formulation did not warrant any PK or clinical bridging study as determined by Biopharmaceutics review. Furthermore, Biopharmaceutics determined the change in the formulation to be minor and the bridge established based on chemistry, manufacturing, and controls (CMC) information submitted.

Refer to the Office of Pharmaceutical Quality (OPQ) drug product review for the detailed information on the assessment of formulation change and supporting data.

7.7.2. Impact of the Lack of Run-In Period on the Assessment of Safety

The proposed inclusion criteria for the phase 3 trials (DELTA 1, DELTA 2, and DELTA 3) specified enrollment of subjects with “a recent history of inadequate response to treatment with TCS within 1 year prior to screening, or for whom TCS therapy was medically inadvisable (e.g., due to safety concerns or side effects).”

At the End-of-Phase 2 meeting, the Agency advised that an inadequate response to TCS therapy may not be reliably determined based on medical history alone. To address this, the Agency recommended incorporating a run-in period with standard care measures (e.g., moisturizers, irritant avoidance) and TCS therapy to prospectively confirm inadequate response.

The Applicant, however, did not incorporate a run-in-period and expressed concern that such a run-in period would unnecessarily re-expose subjects to therapies previously deemed ineffective and delay access to an investigational product in a setting with limited treatment options. In their NDA submission, the Applicant further argued that defining inadequate response based on a single short course of TCS with limited follow-up does not appropriately reflect the chronic, relapsing nature of CHE. The Applicant noted that while patients may experience temporary improvement with a short course of potent TCS, the durability of response, timing of relapse, need for retreatment, and cumulative treatment burden remain uncertain. Therefore, the Applicant concluded that selection based on documented medical history was more reflective of the target patient population.

To support their decision to omit a run-in period from the study design and to confirm that their enrollment criteria adequately defined a study population with “inadequate response to treatment with topical corticosteroids,” the Applicant conducted post hoc analyses of the safety and efficacy data from their phase 3 trials. Their analyses compared data from subjects who discontinued daily TCS no earlier than 2, 4, or 8 weeks prior to screening, with subjects who used daily TCS on the hands after screening, up to 2 weeks before baseline (“run-in-like” exposure). The Applicant conducted post hoc subgroup analyses of the primary and key secondary endpoints at Week 16 by these TCS run-in-like periods. Based on AE distribution by SOC and PT, the Applicant concluded that the incidence of AEs was comparable between the

delgocitinib and vehicle groups, with no clinically meaningful differences observed between subjects with or without TCS run-in-like exposure. The data presented in the review team's [Table 80](#) and [Table 81](#) below suggest that the impact of the lack of a formal run-in period on the assessment of safety appears low, with no meaningful differences observed in SAEs or TEAEs between subjects with and without run-in-like periods. Therefore, the review team's analyses confirmed the Applicant's conclusions.

Table 80. Overview of Adverse Events in Subjects With and Without Run-In Like Period, Pooled Trials DELTA 1 and DELTA 2

Event Category	TCS With Run-In Like Period			TCS Without Run-In Like Period		
	Delgocitinib 20 mg/g N=253 n (%)	Vehicle Control N=121 n (%)	Risk Difference % (95% CI)	Delgocitinib 20 mg/g N=385 n (%)	Vehicle Control N=200 n (%)	Risk Difference % (95% CI)
SAE	3 (1.2)	1 (0.8)	0.4 (-3.4, 2.7)	8 (2.1)	5 (2.5)	-0.4 (-3.8, 2.0)
SAEs with fatal outcome	0	0	0.0 (-3.1, 1.5)	0	0	0.0 (-1.9, 1.0)
Life-threatening SAEs	0	0	0.0 (-3.1, 1.5)	0	0	0.0 (-1.9, 1.0)
SAEs requiring hospitalization	3 (1.2)	1 (0.8)	0.4 (-3.4, 2.7)	8 (2.1)	5 (2.5)	-0.4 (-3.8, 2.0)
AE leading to permanent discontinuation of study drug	1 (0.4)	4 (3.3)	-2.9 (-7.8, -0.4) *	2 (0.5)	7 (3.5)	-3.0 (-6.6, -0.9) *
AE leading to dose modification of study drug	0	0	0.0 (-3.1, 1.5)	0	0	0.0 (-1.9, 1.0)
AE leading to interruption of study drug	0	0	0.0 (-3.1, 1.5)	0	0	0.0 (-1.9, 1.0)
AE leading to reduction of study drug	0	0	0.0 (-3.1, 1.5)	0	0	0.0 (-1.9, 1.0)
AE leading to dose delay of study drug	0	0	0.0 (-3.1, 1.5)	0	0	0.0 (-1.9, 1.0)
Any AE	117 (46.2)	60 (49.6)	-3.3 (-14.1, 7.4)	174 (45.2)	93 (46.5)	-1.3 (-9.8, 7.2)
Severe and worse	3 (1.2)	2 (1.7)	-0.5 (-4.7, 2.1)	12 (3.1)	7 (3.5)	-0.4 (-4.2, 2.5)
Moderate	48 (19.0)	21 (17.4)	1.6 (-7.3, 9.5)	60 (15.6)	35 (17.5)	-1.9 (-8.7, 4.2)
Mild	66 (26.1)	37 (30.6)	-4.5 (-14.6, 5.0)	102 (26.5)	51 (25.5)	1.0 (-6.7, 8.3)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as an event that started after the first application of IMP or if started before the first application of IMP and worsened in severity after first dose of IMP.

Duration is 16 weeks.

TCS With Run-in Like Period refers to subjects who discontinued daily TCS no earlier than 2 weeks (≤ 14 days) before screening and included subjects who used daily TCS on the hands after screening and until 2 weeks before randomization (as allowed by the protocol).

TCS Without Run-in Like Period refers to subjects who did not have record of administration of TCS earlier than 2 weeks (≤ 14 days) before screening.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Severity as assessed by the investigator.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medical product; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event; TCS; topical corticosteroid

Table 81. Overview of Adverse Events by System Organ Class and Preferred Term in ≥1% Subjects With and Without Run-In Like Period, Pooled Trials DELTA 1 and DELTA 2

System Organ Class Preferred Term	TCS With Run-In Like Period			TCS Without Run-In Like Period		
	Delgocitinib 20 mg/g N=253 n (%)	Vehicle Control N=121 n (%)	Risk Difference % (95% CI)	Delgocitinib 20 mg/g N=385 n (%)	Vehicle Control N=200 n (%)	Risk Difference % (95% CI)
Any AE	117 (46.2)	60 (49.6)	-3.3 (-14.1, 7.4)	174 (45.2)	93 (46.5)	-1.3 (-9.8, 7.2)
Blood and lymphatic system disorders (SOC)	1 (0.4)	0	0.4 (-2.7, 2.2)	3 (0.8)	3 (1.5)	-0.7 (-3.6, 1.0)
Lymphadenopathy	0	0	0.0 (-3.1, 1.5)	0	2 (1.0)	-1.0 (-3.6, -0.0) *
Gastrointestinal disorders (SOC)	7 (2.8)	3 (2.5)	0.3 (-4.5, 3.6)	10 (2.6)	7 (3.5)	-0.9 (-4.7, 1.9)
Abdominal pain	1 (0.4)	2 (1.7)	-1.3 (-5.5, 0.8)	2 (0.5)	0	0.5 (-1.4, 1.9)
General disorders and administration site conditions (SOC)	7 (2.8)	3 (2.5)	0.3 (-4.5, 3.6)	9 (2.3)	13 (6.5)	-4.2 (-8.6, -0.9) *
Influenza like illness	3 (1.2)	0	1.2 (-1.9, 3.4)	0	3 (1.5)	-1.5 (-4.3, -0.5) *
Application site paraesthesia	1 (0.4)	0	0.4 (-2.7, 2.2)	2 (0.5)	2 (1.0)	-0.5 (-3.1, 1.0)
Application site pruritus	0	0	0.0 (-3.1, 1.5)	1 (0.3)	2 (1.0)	-0.7 (-3.3, 0.6)
Immune system disorders (SOC)	3 (1.2)	2 (1.7)	-0.5 (-4.7, 2.1)	9 (2.3)	6 (3.0)	-0.7 (-4.2, 2.0)
Drug hypersensitivity	0	0	0.0 (-3.1, 1.5)	1 (0.3)	2 (1.0)	-0.7 (-3.3, 0.6)
Perfume sensitivity	0	0	0.0 (-3.1, 1.5)	3 (0.8)	2 (1.0)	-0.2 (-2.8, 1.4)
Allergy to metals	2 (0.8)	2 (1.7)	-0.9 (-5.1, 1.5)	5 (1.3)	1 (0.5)	0.8 (-1.6, 2.6)
Allergy to chemicals	1 (0.4)	2 (1.7)	-1.3 (-5.5, 0.8)	1 (0.3)	1 (0.5)	-0.2 (-2.5, 1.0)
Infections and infestations (SOC)	76 (30.0)	34 (28.1)	1.9 (-8.2, 11.4)	95 (24.7)	53 (26.5)	-1.8 (-9.5, 5.4)
Nasopharyngitis	24 (9.5)	10 (8.3)	1.2 (-5.7, 6.9)	20 (5.2)	14 (7.0)	-1.8 (-6.6, 2.1)
Influenza	3 (1.2)	0	1.2 (-1.9, 3.4)	4 (1.0)	2 (1.0)	0.0 (-2.6, 1.8)
Oral herpes	3 (1.2)	0	1.2 (-1.9, 3.4)	4 (1.0)	2 (1.0)	0.0 (-2.6, 1.8)
Sinusitis	3 (1.2)	0	1.2 (-1.9, 3.4)	1 (0.3)	3 (1.5)	-1.2 (-4.1, 0.2)
Gastroenteritis	2 (0.8)	0	0.8 (-2.3, 2.8)	4 (1.0)	2 (1.0)	0.0 (-2.6, 1.8)
Upper respiratory tract infection	2 (0.8)	0	0.8 (-2.3, 2.8)	7 (1.8)	1 (0.5)	1.3 (-1.1, 3.3)
Gastrointestinal infection	1 (0.4)	0	0.4 (-2.7, 2.2)	4 (1.0)	0	1.0 (-0.9, 2.6)
Herpes simplex	1 (0.4)	0	0.4 (-2.7, 2.2)	0	4 (2.0)	-2.0 (-5.0, -0.8) *
Bronchitis	2 (0.8)	1 (0.8)	-0.0 (-3.8, 2.1)	1 (0.3)	2 (1.0)	-0.7 (-3.3, 0.6)
COVID-19	33 (13.0)	16 (13.2)	-0.2 (-8.2, 6.7)	38 (9.9)	18 (9.0)	0.9 (-4.6, 5.6)
Rhinitis	2 (0.8)	2 (1.7)	-0.9 (-5.1, 1.5)	4 (1.0)	0	1.0 (-0.9, 2.6)
Urinary tract infection	2 (0.8)	2 (1.7)	-0.9 (-5.1, 1.5)	4 (1.0)	3 (1.5)	-0.5 (-3.4, 1.4)
Cystitis	1 (0.4)	2 (1.7)	-1.3 (-5.5, 0.8)	2 (0.5)	0	0.5 (-1.4, 1.9)
Pharyngitis	1 (0.4)	2 (1.7)	-1.3 (-5.5, 0.8)	4 (1.0)	3 (1.5)	-0.5 (-3.4, 1.4)

System Organ Class Preferred Term	TCS With Run-In Like Period			TCS Without Run-In Like Period		
	Delgocitinib 20 mg/g N=253 n (%)	Vehicle Control N=121 n (%)	Risk Difference % (95% CI)	Delgocitinib 20 mg/g N=385 n (%)	Vehicle Control N=200 n (%)	Risk Difference % (95% CI)
Investigations (SOC)	11 (4.3)	3 (2.5)	1.9 (-3.0, 5.6)	20 (5.2)	9 (4.5)	0.7 (-3.5, 4.2)
Alanine aminotransferase increased	1 (0.4)	0	0.4 (-2.7, 2.2)	2 (0.5)	2 (1.0)	-0.5 (-3.1, 1.0)
Low density lipoprotein increased	1 (0.4)	0	0.4 (-2.7, 2.2)	5 (1.3)	0	1.3 (-0.6, 3.0)
Metabolism and nutrition disorders (SOC)	4 (1.6)	3 (2.5)	-0.9 (-5.6, 2.0)	8 (2.1)	1 (0.5)	1.6 (-0.8, 3.6)
Hypercholesterolaemia	2 (0.8)	2 (1.7)	-0.9 (-5.1, 1.5)	3 (0.8)	1 (0.5)	0.3 (-2.0, 1.8)
Musculoskeletal and connective tissue disorders (SOC)	10 (4.0)	6 (5.0)	-1.0 (-6.8, 3.2)	16 (4.2)	6 (3.0)	1.2 (-2.6, 4.2)
Back pain	3 (1.2)	0	1.2 (-1.9, 3.4)	4 (1.0)	1 (0.5)	0.5 (-1.8, 2.2)
Arthralgia	0	2 (1.7)	-1.7 (-5.8, -0.1) *	7 (1.8)	2 (1.0)	0.8 (-1.9, 2.9)
Nervous system disorders (SOC)	12 (4.7)	7 (5.8)	-1.0 (-7.1, 3.5)	25 (6.5)	11 (5.5)	1.0 (-3.6, 4.8)
Headache	9 (3.6)	4 (3.3)	0.3 (-4.9, 4.0)	19 (4.9)	9 (4.5)	0.4 (-3.8, 3.9)
Psychiatric disorders (SOC)	6 (2.4)	2 (1.7)	0.7 (-3.6, 3.7)	3 (0.8)	1 (0.5)	0.3 (-2.0, 1.8)
Insomnia	3 (1.2)	0	1.2 (-1.9, 3.4)	0	0	0.0 (-1.9, 1.0)
Depression	1 (0.4)	2 (1.7)	-1.3 (-5.5, 0.8)	1 (0.3)	0	0.3 (-1.6, 1.5)
Skin and subcutaneous tissue disorders (SOC)	10 (4.0)	12 (9.9)	-6.0 (-12.9, -0.8) *	29 (7.5)	18 (9.0)	-1.5 (-6.8, 3.0)
Eczema	3 (1.2)	0	1.2 (-1.9, 3.4)	3 (0.8)	3 (1.5)	-0.7 (-3.6, 1.0)
Dermatitis atopic	1 (0.4)	1 (0.8)	-0.4 (-4.2, 1.5)	1 (0.3)	3 (1.5)	-1.2 (-4.1, 0.2)
Dermatitis contact	0	2 (1.7)	-1.7 (-5.8, -0.1) *	7 (1.8)	4 (2.0)	-0.2 (-3.4, 2.1)
Hand dermatitis	0	6 (5.0)	-5.0 (-10.4, -2.3) *	4 (1.0)	7 (3.5)	-2.5 (-6.1, -0.1) *
Vascular disorders (SOC)	5 (2.0)	1 (0.8)	1.1 (-2.7, 3.9)	5 (1.3)	0	1.3 (-0.6, 3.0)
Hypertension	4 (1.6)	0	1.6 (-1.5, 4.0)	3 (0.8)	0	0.8 (-1.1, 2.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as an event that started after the first application of IMP or if started before the first application of IMP and worsened in severity after first dose of IMP.
Duration is 16 weeks.
TCS With Run-In Like Period refers to subjects who discontinued daily TCS no earlier than 2 weeks (≤ 14 days) before screening and included subjects who used daily TCS on the hands after screening and until 2 weeks before randomization (as allowed by the protocol).
TCS Without Run-In Like Period refers to subjects who did not have record of administration of TCS earlier than 2 weeks (≤ 14 days) before screening.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medical product; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; TCS; topical corticosteroid

7.7.3. Evaluation of JAK Inhibitor Class Safety Labeling for Inflammatory Conditions in Context of the Delgocitinib Development Program

Infection

Based on the safety considerations associated with the class of JAK inhibitors and the existing Boxed Warning for serious infections in JAK inhibitor labeling for inflammatory conditions, the Applicant identified infection as a safety review focus area.

Serious and opportunistic infections, including tuberculosis, have been reported in patients receiving JAK inhibitors, including both topical (e.g., ruxolitinib) and systemic agents (e.g., abrocitinib, baricitinib, tofacitinib). An increased risk of herpes zoster and other serious infections associated with JAK inhibitor therapy is hypothesized to be related, in part, to the suppression of NK cell function. Natural killer cells play a key role in antiviral immunity, particularly in controlling varicella zoster virus reactivation ([Meudec et al. 2023](#); [Winthrop et al. 2023](#)).

The following subjects were excluded in the phase 3 clinical trials for delgocitinib: those with clinically significant infection (e.g., “impetiginized hand eczema”) on the hands, systemic infection or serious skin infection requiring systemic treatment within 28 days prior to baseline, and those with history of any known primary immunodeficiency disorder, including a positive HIV test at screening.

Serious Infections

No serious infections at the application site were observed in Trials DELTA 1, DELTA 2, DELTA 3, and 1273 in subjects who received delgocitinib. The following serious infections were reported in Trials DELTA 1, DELTA 2, DELTA 3, and 1273 in subjects who received delgocitinib: peritonsillar abscess (2 cases), tonsillitis, chronic sinusitis, bacterial keratitis, paranasal sinus abscess, chest infection, pneumonia, right maxillary sinusitis due to aspergillosis, periappendicular abscess, gastroenteritis, urinary tract infection, bilateral interstitial COVID-19 pneumonia, appendicitis, severe pyelonephritis, pseudomembranous colitis, and streptococcal infection. Most of the serious infections were single events (except when noted). There was no clustering of events. Opportunistic infections included vulvovaginal mycotic infection, fungal genital infection, herpes simplex (27 cases), herpes zoster (3 cases), and eczema herpeticum (1 case). There were no reported cases of tuberculosis. There were no reported imbalances in serious infections between subjects who received delgocitinib versus vehicle.

In open-label extension Trial DELTA 3, there were cases of eczema herpeticum (one subject delgocitinib, zero vehicle) and herpes zoster (two subjects delgocitinib, zero vehicle). Narratives for these subjects are presented below.

Eczema Herpeticum

A 34-year-old female ((b) (6)) with a history of atopic dermatitis, asthma, contact dermatitis, allergic rhinitis, and hypertension developed eczema herpeticum affecting the right side of the neck and bilateral eyelids on Day 144 of near-continuous treatment with delgocitinib. She received antiviral therapy, with resolution of EH in 20 days. The investigator

considered the event possibly related to the investigational product. No PK samples were obtained. Neutrophil levels [$10^9/L$] at baseline of Trial DELTA 1 → end of DELTA 1 → and end of Trial DELTA 3 were 4.1 → 4.3 → 3.3 (i.e., lower than baseline).

Given the timing of onset during active treatment and the known pathophysiology of eczema herpeticum, a causal relationship with delgocitinib cannot be excluded. Janus kinase inhibitors may impair antiviral immune responses by disrupting cytokine signaling critical for the function of NK cells. Natural killer cells play a central role in early host defense against HSV, and their suppression may increase susceptibility to disseminated HSV infection (i.e., eczema herpeticum), particularly in patients with atopic dermatitis and other underlying skin barrier defects. This mechanistic plausibility, in combination with the temporal association and downward trend of neutrophils over time, supports the conclusion that the investigational product may have contributed to the event ([Traidl et al. 2021](#); [Wang et al. 2021](#)).

Herpes Zoster

- A 42-year-old male ((b) (6)) with a history of diabetes, hyperlipidemia, hypertension, and hyperthyroidism developed moderate HZ on the face adjacent to the lips on Day 252 of continuous treatment with delgocitinib. The narrative did not include family history or other risk factors for HZ. The subject received antiviral therapy. Levels for hematologic parameters (leukocytes, lymphocytes, and neutrophils) remained stable from baseline to the end of treatment:
 - Leukocytes [$10^9/L$]: 11 → 10 → 12
 - Lymphocytes [$10^9/L$]: 2.7 → 2.2 → 2.4
 - Neutrophils [$10^9/L$]: 7.4 → 6.9 → 8.4

The investigator assessed the AE as not related to the investigational product. Given the subject's age <50 years of age (with advanced age a risk factor for HZ) and the timing of onset during active treatment, a causal role for delgocitinib cannot be excluded.

- A 49-year-old female ((b) (6)) with a history of atopic dermatitis developed mild herpes zoster on the back on Day 121 of delgocitinib. Family history was unknown, and the subject had no documented risk factors for HZ. The subject received antiviral therapy and continued delgocitinib uninterrupted. Levels for hematologic parameters (leukocytes, lymphocytes, and neutrophils) remained stable from baseline to the end of treatment:
 - Leukocytes [$10^9/L$]: 5.9 → 4.9 → 6.5
 - Lymphocytes [$10^9/L$]: 1.9 → 1.5 → 2.1
 - Neutrophils [$10^9/L$]: 3.3 → 2.7 → 3.5

PK levels of delgocitinib remained stable in Trial DELTA 2 (0.26 ng/ml on Day 8 → 0.19 ng/ml on Day 29 → 0.16 ng/mL on Day 113). The investigator assessed the AE as not related to the investigational product. Patients with AD have a greater risk of developing HZ. However, given the absence of traditional HZ risk factors and the timing of onset during active treatment, a causal role for delgocitinib cannot be excluded.

Tuberculosis and Nontuberculosis Atypical Mycobacterial Infection

The Boxed Warning in JAK inhibitor labeling for inflammatory conditions includes a warning for increased risk of TB and provides specific instructions to test for latent TB before and during

therapy and to treat latent TB prior to use. The warning also instructs clinicians to monitor all patients for active TB during treatment, even patients with initial negative latent TB tests.

TB was not assessed at baseline nor actively in the phase 3 trials for delgocitinib. No cases of tuberculosis or nontuberculosis atypical mycobacterial infection were reported in the phase 3 trials. While no TB cases were observed in the delgocitinib clinical trials, the absence of systematic TB screening and monitoring in these trials limits the ability to fully characterize the TB risk profile.

Cases of EH and HZ were observed and will be included in Warning and Precaution section of the product labeling. In addition, although cases of TB were not observed in the pivotal clinical trials, labeling will include potential risks for serious infection will be included in the Warnings and Precautions section of labeling.

Mortality

Class labeling for JAK inhibitors indicated for the treatment of inflammatory conditions includes a boxed warning for all-cause mortality. In a large, randomized, postmarketing safety study of another oral JAK inhibitor in subjects with rheumatoid arthritis ages 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed in subjects treated with the JAK inhibitor compared with subjects treated with TNF blockers.

In the development program for CHE, there were three deaths among subjects who received delgocitinib and none among subjects who received only vehicle. Investigators assessed all three deaths as not related to delgocitinib (refer to Section [7.6.1.2](#) of this review). Two cases did not have a persuasive temporal association with the drug product and one case lacked sufficient information to support any conclusion. Overall, delgocitinib did not appear to increase the risk of all-cause mortality compared to vehicle.

Although higher rates of all-cause mortality were not observed in the pivotal clinical trials, potential risks related to JAK inhibition will be included in the Warnings and Precautions section of labeling.

Malignancy and Lymphoproliferative Disorders

Class labeling for JAK inhibitors indicated for the treatment of inflammatory conditions includes a boxed warning for lymphoma and other malignancies. The literature supports a key role for the JAK-STAT signaling pathway in the development of cancer cells and their proliferation, differentiation, and survival ([Harrison 2012](#)). In a large, randomized, postmarketing safety study of a systemic JAK inhibitor in subjects with rheumatoid arthritis, a higher rate of malignancies (including lymphomas and lung cancer) was observed in subjects treated with the JAK inhibitor compared to those treated with TNF blockers.

There were no reports of lymphomas or lung cancers in the development program for delgocitinib. However, there are reports of the development of nonmelanoma skin cancers in trials for both topical and systemic JAK inhibitors.

There were no imbalances between treatment groups in the development of malignancies in Trials DELTA 1, DELTA 2, and DELTA 3. The following malignancies were reported in subjects who received delgocitinib: gallbladder adenocarcinoma (one in delgocitinib, zero in

vehicle), metastatic esophageal cancer (one in delgocitinib, zero in vehicle), basal cell carcinoma (one in delgocitinib, zero in vehicle), and intraductal proliferative breast lesion (one in delgocitinib, zero in vehicle).

Although malignancy and lymphoproliferative adverse reactions were not observed in the pivotal clinical trials, potential risks related to JAK inhibition will be included in the Warnings and Precautions section of labeling.

Basal Cell Carcinoma

A 77-year-old male with a history of chronic sun exposure developed a nodular basal cell carcinoma on the left ear on Day 57 of delgocitinib. Biopsy on Day 92 confirmed nodular basal cell carcinoma, and the lesion was surgically excised on Day 113. The event was classified as serious. Delgocitinib treatment continued without interruption, and the event was considered resolved. The investigator did not attribute the event to delgocitinib. Based on subject risk factors, lesion location outside of treatment area, and timing, this reviewer considers it unlikely that the AE was related to the investigational product.

Gallbladder Cancer

A 64-year-old female with no relevant medical history was diagnosed with adenocarcinoma of the gallbladder on Day 29 of treatment with delgocitinib. The subject presented with “colic pain” on Day 1, and an escalation of symptoms (not defined) on Day 20. Biliary magnetic resonance imaging on Day 27 revealed 2 gallstones and cholecystectomy was performed on the following day. Pathology showed gallbladder adenocarcinoma. Delgocitinib was continued without interruption. On Day 49, subject received chemotherapy. The investigator assessed the SAE as not related. In view of the long latency period for the development of gallbladder cancer and diagnosis early in the course of the trial, the review team agrees that the SAE of gallbladder cancer is likely unrelated to delgocitinib.

Metastatic Esophageal Cancer

Metastatic esophageal cancer from Trial DELTA 2: see narrative under death.

Breast Cancer

A 55-year-old female with a history of basal cell carcinoma, obesity (BMI 46.7), and two prior pregnancies (with two children but no breastfeeding) developed ductal carcinoma in situ on Day 286. The subject had a routine mammogram with ultrasound on Day 174 that showed calcifications in upper right breast. The subject was diagnosed with right breast ductal carcinoma in situ (DCIS). Pathology report from the lumpectomy showed no residual DCIS. The subject completed delgocitinib without interruption. The subject’s family history for breast cancer was unknown. The investigator concluded the event was unlikely to be related to delgocitinib. Because the subject developed breast cancer ~9.5 months after first dose of delgocitinib and had several known risk factors (female, obesity, history of other cancer, i.e., basal cell carcinoma), the review team concludes that it is less likely that this AE was related to delgocitinib. DCIS tends to be slow-growing and takes many years to develop (some studies suggest anywhere between 3 to 9 years).

In the Exposure pool (Trials DELTA 1, DELTA 2, DELTA 3, 1273, DELTA FORCE, 2285, 1275, 1181), cases of malignancy also included a malignant melanoma that developed in a subject with AD who received vehicle (Trial 1275). The 120-day Safety Report included two additional reports of malignancy in subjects who received delgocitinib, including pancreatic carcinoma and papillary thyroid cancer, considered unrelated by the review team.

Major Adverse Cardiovascular Events

Class labeling for JAK inhibitors indicated for the treatment of chronic inflammatory conditions includes a Boxed Warning for MACE, defined as cardiovascular death, myocardial infarction, and stroke. In a large, randomized, postmarketing safety study of another JAK inhibitor in subjects with rheumatoid arthritis who were 50 years of age and older with at least one cardiovascular risk factor, a higher rate of MACE was observed with the JAK inhibitor compared to those treated with TNF blockers. Subjects who were current or past smokers were at additional increased risk.

Baseline risk factors for MACE (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) were well balanced between the treatment arms of trials DELTA 1 and DELTA 2:

- Male: 36.4% delgocitinib versus 33.9% vehicle
- Mean BMI: 27 delgocitinib versus 27.6 vehicle
- Medical histories of:
 - Diabetes mellitus: 4.2% delgocitinib versus 5.6% vehicle
 - Hypertension: 17.4% delgocitinib versus 14.3% vehicle
 - Myocardial infarction: 0.6% delgocitinib versus none vehicle
 - Stroke: 0.2% delgocitinib versus none vehicle
 - Thrombosis: 0.2% delgocitinib versus 1.2% vehicle

In the phase 3 trials for the evaluation of delgocitinib for the treatment of CHE, a 71-year-old male subject developed a serious adverse event of MI and died 2 weeks later. This SAE occurred approximately 7 months after the last dose of delgocitinib. The subject received antihypertensive medication for 3 months prior to the event. Given the timing of the event and risk factors (age >50 years, male gender, and history of hypertension) for MACE, this event was unlikely related to delgocitinib, though causal association cannot be ruled out (refer to Section [7.6.1.2](#) of this review).

No clinically relevant differences in vital sign assessments (blood pressure and pulse) or ECGs were observed during the treatment period in either the delgocitinib or vehicle group in the phase 3 trials.

Finally, cardiac safety was supported by Trial LP0133-1409, a phase 1, randomized, double-blind, placebo-controlled, parallel-group, single-dose clinical trial in healthy subjects. An oral (capsule) formulation was used for this trial. Forty subjects received single-dose treatment, with 8 subjects in each dose group (placebo and delgocitinib 1.5 mg, 3 mg, 6 mg, and 12 mg). Delgocitinib did not have a clinically relevant effect on ECG parameters as assessed in this trial, and there were no AEs of SMQ Torsade de pointes or QT prolongation. In this trial the mean C_{max} was 96.4 ng/mL for the highest oral dose assessed (12 mg), compared to a mean C_{max} of 0.5 ng/mL anticipated therapeutic exposure for the topical cream. Therefore, the highest dose of

12 mg after oral administration covers the maximum anticipated therapeutic exposure (C_{max}) by 193-fold, and for Section 12.2 of labeling the following language is recommended: “At 193 times the mean maximal concentration provided by the recommended topical dose, clinically significant corrected QT interval (QTc) prolongation was not observed.” Refer to the review by the Cardiac-Safety Interdisciplinary Review Team dated March 3, 2025, for details.

Although cardiovascular adverse reactions are not observed in the pivotal clinical trials, potential risks related to JAK inhibition will be included in the Warnings and Precautions section of labeling.

Thrombosis

Labeling for JAK inhibitors that treat inflammatory conditions carry a Boxed Warning for thrombosis, including increased incidence of pulmonary embolism and venous and arterial thrombosis.

Deep vein thrombosis and pulmonary embolism were prespecified as AESIs in the trial protocols to capture additional information on such events. No AESIs of deep vein thrombosis, pulmonary embolism, or arterial thrombosis were reported with delgocitinib in the development program.

Superficial thrombophlebitis was reported in two subjects who received delgocitinib cream. A 43-year-old female ((b) (6)) with history of bilateral varicose veins developed an AE of superficial thrombophlebitis of the right thigh on Day 135. In addition, a 54-year-old female who was enrolled in Trial DELTA FORCE with history of hypertension developed superficial thrombophlebitis on Day 52. Both events were assessed as nonserious, of moderate severity, did not lead to withdrawal from trial, and were not considered related to the IMP by the review team.

One subject who received delgocitinib developed one event (IR: 0.51) of thrombocytosis in the phase 3 trials up to 16 weeks, while no subjects who received vehicle developed such events. The subject had an ongoing AE of gallbladder carcinoma and reported concomitant antineoplastic medications at the time of the AE. The event was assessed as mild and not related and did not lead to withdrawal from trial or discontinuation of the IMP. Platelet counts decreased to normal range at the next assessment. During the 0- to 52-week period of continuous use, no events of thrombocytosis were reported. There did not appear to be any meaningful increases in thrombocyte counts in subjects who received delgocitinib in the Week 0 to 16 period and in subjects who received 52 weeks of continuous delgocitinib.

Although cases of thrombosis are not observed in the pivotal clinical trials, potential risks related to JAK inhibition will be included in the Warnings and Precautions section of labeling.

Gastrointestinal Perforation

Gastrointestinal perforation is a known risk associated with treatment with other JAK inhibitors, and reflected in labeling under Warnings and Precautions for JAK inhibitors that treat certain chronic inflammatory conditions. Patients with underlying inflammatory bowel conditions, diverticulitis, or other GI disorders may be at increased risk of GI perforation. There were no reports of GI perforation in the delgocitinib development program. Additionally, review of GI-related adverse events that could potentially signal underlying perforation risk showed no cases of acute abdominal pain requiring hospitalization, peritonitis or signs of intra-abdominal

infection, bowel obstruction or ileus of unclear etiology, severe GI bleeding requiring intervention, or emergency abdominal surgical procedures to suggest that delgocitinib increases the risk of GI perforation. Therefore, GI perforation is not proposed for inclusion in labeling.

Liver Enzyme Elevations

Warnings regarding the potential for “elevated liver enzymes” are included in Warnings and Precautions, Laboratory Abnormalities, and Adverse Reactions of labeling for certain JAK inhibitors indicated for the treatment of inflammatory conditions (e.g., baricitinib, tofacitinib, upadacitinib).

In the phase 3 trials for delgocitinib, subjects with positive hepatitis B surface antigen or hepatitis C virus antibody serology at screening and screening ALT or AST level $\geq 2.0 \times \text{ULN}$ were excluded. In the phase 3 trials there were no clinically relevant changes or differences between treatment groups in liver parameters (alkaline phosphatase, ALT, AST, bilirubin, or albumin), there were no reported adverse events suggesting hepatotoxic effects, and no subjects met Hy’s law criteria or had concurrent elevations of ALT/AST $\geq 3 \times \text{ULN}$ with bilirubin $\geq 2 \times \text{ULN}$. Refer to Section [7.6.1.7](#) of this review.

The clinical trials and long-term safety data also did not show signs of drug-induced liver injury, hepatic failure, or any patterns suggesting hepatotoxic effects from delgocitinib cream, 2%, and “elevated liver enzymes” are not proposed for inclusion in labeling.

Hematologic Abnormalities

Erythropoietin, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor are modulated by JAK2 signaling. Therefore, inhibition of JAK2 may result in reduced production of erythrocytes and leukocytes ([Brizzi et al. 1996](#)). Hematologic abnormalities are known risks associated with treatment with other JAK inhibitors to treat inflammatory conditions (e.g., thrombocytopenia, anemia, and neutropenia for topical ruxolitinib; thrombocytopenia and lymphopenia for abrocitinib). The clinical trials for delgocitinib did not have predefined exclusion criteria based on hematologic parameters, and hematologic parameters were monitored periodically.

The review team conducted a comprehensive analysis of hematologic parameters for subjects in the vehicle-controlled 16-week period and in subjects who received continuous exposure to delgocitinib for 52 weeks. This included analysis of shifts from baseline to worst postbaseline values (refer to [Hematology](#) above), analyses of individual subject narratives, analysis of correlation between PK samples and shifts and AEs (refer to Section [17.1](#) Clinical Safety: Additional Information), cytopenia TEAEs (refer to [Table 44](#)), and detailed subject-level analyses of hematologic lab values at screening/baseline, throughout the trial, and at end of trial (refer to Section [17.1](#) Clinical Safety: Additional Information).

No significant imbalances were observed for hemoglobin levels, with no subjects experiencing Grade 3 decreases and only a few subjects showing Grade 2 shifts, comparable between treatment groups. Thrombocyte shifts were similar between delgocitinib and vehicle groups, with isolated cases of Grade 2 or 3 decreases attributed to confounding medical histories.

Neutrophil findings showed two subjects (0.3%) on delgocitinib shifting from Grade 0 to Grade 3 (versus none in vehicle), for which causality attributable to delgocitinib could not be ruled out in one subject (refer to narrative for [Subject \(b\) \(6\)](#)). Lymphocyte findings

showed one transient shift from Grade 2 to Grade 3 in the delgocitinib group, and similar proportions of Grade 0 to Grade 2 shifts between treatment groups. For leukocyte counts, though no subjects in either arm had shifts to Grade 3, a greater proportion of subjects who received delgocitinib (13.3%) experienced a shift to Grade 1 than subjects who received vehicle (6.1%), and one subject experienced a Grade 1 to 2 shift with associated TEAE of leukopenia which was considered possibly related by investigator and for which causality to delgocitinib could not be ruled out by the clinical reviewer (refer to narrative for [Subject \(b\) \(6\)](#)).

In the analysis of overall cytopenias, the review team observed a notable numerical imbalance in subjects experiencing any worsening grade shift in leukocytes: 13.6% (EAIR 44.2) for delgocitinib versus 6.2% (EAIR 21.3) for vehicle during the 16-week vehicle-controlled period (refer to [Table 53](#)). Smaller imbalances were observed for neutrophils (4.4%, EAIR 14.2 for delgocitinib versus 3.7%, EAIR 12.8 for vehicle) and lymphocytes (2.5%, EAIR 8.1 for delgocitinib versus 1.9%, EAIR 6.4 for vehicle). The leukocyte imbalance was primarily driven by shifts from Grade 0 at baseline to Grade 1 postbaseline. Given these collective findings – the leukocyte imbalance and select cases where a causal relationship with delgocitinib could not be ruled out, non-negligible systemic exposure (refer to Section [5.2](#) Clinical Pharmacology of this review), and the known association of JAK inhibitors with cytopenias – the review team recommends including leukopenia and neutropenia as adverse reactions occurring in <1% of subjects in Section 6 of labeling. Since all Grade 3 shifts across all hematologic parameters observed with 52 weeks of continuous treatment were isolated measurements and improved despite continuous treatment, and because of the overall low incidence of the observed cytopenias, baseline CBC and hematologic monitoring is not recommended.

Hyperlipidemia

Warnings regarding the potential for lipid elevations are included in labeling for JAK inhibitors indicated for the treatment of inflammatory conditions, as JAK inhibition can affect lipid metabolism through interference with cytokine signaling pathways involved in cholesterol and triglyceride regulation. During the delgocitinib clinical trials, the Applicant evaluated lipid profiles periodically under nonfasted conditions to monitor for potential changes in lipid parameters that could indicate emerging hyperlipidemia.

The review team analyzed subject narratives and shift tables for lipid parameters (triglycerides, cholesterol, LDL, HDL) from baseline to worst value for subjects treated for 16 weeks in phase 3 trials DELTA 1 and DELTA 2 and for subjects treated continuously with delgocitinib cream 20 mg/g for 52 weeks (refer to Section [7.6.1.6](#) of this review). Of note, the collection of lipid parameters in a nonfasted state limited the interpretability of these findings and precludes meaningful clinical assessment of lipid changes. In that context, analyses of shift tables, hyperlipidemia-related adverse events, and subject narratives revealed no apparent clinically significant change in lipid parameters in either the placebo-controlled phase 3 safety pool or in the 0-to-52-week long-term exposure pool. Given the limitations described above, potential risks related to JAK inhibition will be included in the Warnings and Precautions section of labeling.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Organ Impairment

Studies in subjects with renal or hepatic impairment were not conducted due to low systemic exposures and the lack of a relationship between plasma concentration and adverse events, including AESIs.

Age

No studies were conducted to establish safety and efficacy in pediatric patients. Based on the clinical trials, no overall differences in safety or effectiveness were observed between subjects 65 years of age and older and younger adult subjects.

Race

No studies were conducted to determine therapeutic individualization based on race.

Gender

No studies were conducted to determine therapeutic individualization based on gender.

Genetics

The proposed product is intended to be indicated in general population. No genetic factors were considered in the clinical development.

8.2. Extrinsic Factors

Drug-Drug Interactions

In vitro drug-drug interaction (DDI) data demonstrated no potential for cytochrome P-450 (CYP)- or transporter-mediated DDIs and therefore, no clinical DDI studies were conducted.

Food

The drug product is intended to be administered via topical route; therefore, the issue of a food-drug interaction is not relevant.

Alcohol and Smoking

The drug product is intended to be administered via topical route; therefore, the issue of any alcohol and smoking are not relevant.

8.3. Plans for Pediatric Drug Development

To support the evaluation of delgocitinib cream in the pediatric population ages 12 years and older with CHE, the Applicant conducted the following juvenile toxicity studies:

- Preliminary one-month dermal dose toxicity study in juvenile minipigs (Study 77052).
- Ten-week oral dose toxicity study in juvenile rats with a 12-week recovery period (Study SB95TY).
- Pre- and postnatal developmental toxicity study in rats (Study R-1208).
- Pharmacokinetics in juvenile rats (Study B160168) including metabolite profiling of biological samples (Study JE052PK043).
- Milk excretion in rats (Study B150159).
- Tissue concentrations in pregnant rats (Study B150158).

In addition, the development program included two juvenile toxicity studies, mass balance in juvenile rats, feto-placental transfer, milk excretion, and a pre- and postnatal developmental toxicity study. No unique or new toxicities were identified in juvenile animals, and the NOAELs in juvenile rats and minipigs were similar to NOAELs obtained in adult animals. Refer to Section [13.1.4.4](#) Reproductive and Developmental Toxicology.

The product triggers the Pediatric Research Equity Act as a new active ingredient. The Applicant initiated development of their product in the pediatric population ages 12 to 17 years by conducting a non-IND trial outside of the United States. However, the Applicant experienced challenges in the recruitment of adolescents and requested a deferral of pediatric assessments. Therefore, with this initial NDA submission, the Applicant is seeking approval of delgocitinib cream for the topical treatment of moderate to severe CHE in adults because adult studies are completed and ready for approval. The requested waiver and deferral in the current pediatric plan are the same as the agreed initial pediatric study plan.

The agreed initial pediatric study plan (dated July 22, 2024) provided for a partial waiver of required pediatric assessments in the pediatric population <12 years of age. Since the number of patients with CHE in this age group is small, studies are impossible or highly impracticable to conduct (Section 505B(a)(4)(B)(i) of the Act). In accordance with 505(a)(d)(A)(ii) of the Pediatric Research Equity Act, the Applicant requested a deferral of the submission of the results of assessments from ongoing Trial 1426 for the treatment of CHE in adolescents aged 12 to 17 years “to avoid delaying the initial NDA submission for the CHE indication in adults.” The Applicant intends to submit the data from Trial 1426 as an efficacy supplement.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

8.4.1. Animal Data

The following nonclinical information was used in support of product labeling (see Section [13.1.4](#) for detailed information).

Fertility and early embryonic development (FEED) studies were conducted in male and female rats. In the male FEED study, delgocitinib (0, 3, 10, or 30 mg/kg) was administered daily by oral gavage to male rats for 2 weeks before mating, throughout the mating period, and up to the day before necropsy. In the female FEED study, delgocitinib (0, 3, 10, 30, and 100 mg/kg) was administered daily by oral gavage to female rats for 14 days prior to mating and throughout the mating period to gestation day (GD) 7.

Embryo-fetal development studies were conducted in rats and rabbits. Delgocitinib (0, 3, 10, and 30 mg/kg) was administered orally to pregnant female rats from GD 7 to 17. On GD 20, all the animals were euthanized for cesarean section and the effects on the embryos/fetuses were examined. Delgocitinib (0, 1, 3, and 10 mg/kg) was administered orally to pregnant female rabbits from GD 6 to 18. On GD 29, all animals were euthanized for cesarean section and the effects on the embryos/fetuses were examined.

A pre- and postnatal development study was conducted in rats. Delgocitinib (0, 3, 10, and 30 mg/kg) was administered orally to pregnant female rats once daily from GD 7 to lactation day 20, which was the period from implantation to the day before weaning (total maximum dosing period: 37 days).

Juvenile animal studies were conducted in rats and minipigs. Delgocitinib (0, 3, 10, and 30 mg/kg) was administered orally once daily to juvenile rats (Day 21 of age) for 10 weeks. In a preliminary study in minipigs, delgocitinib was administered by a single intravenous injection (0.1 mg/kg), a single dermal application of JTE-052 ointment (3%), and 28 days of repeated dermal application of JTE-052 ointment (5%) (400 mg/kg ointment/day) (12 and 20 mg/kg/day of JTE-052 for JTE-052 ointment 3% and 5%, respectively) to juvenile minipigs (30 days old).

A lactation study was conducted to examine the milk secretion of radioactivity in lactating rats. A single dose of ^{14}C -delgocitinib was administered orally at 1 mg/kg to lactating rats on day 12 postpartum under nonfasting conditions. Radioactivity was excreted in the milk and the area under the concentration-time curve ($\text{AUC}_{0-\text{inf}}$) of radioactivity in the milk was 2.59 times the value in the plasma. The radioactivity concentrations in the milk decreased over time in a similar manner to those in the plasma.

The results of these studies are shown in Section 7.1 including NOAELs, systemic exposure, multiples of exposures, and major findings (see Sections 13.1.3 and 13.1.4 for detailed information).

9. Product Quality

Approval

The drug substance, delgocitinib, is a white to almost white, nonhygroscopic powder, freely soluble in aqueous solution at pH 3, sparingly soluble at pH 5, and slightly soluble in aqueous solution at pH 7.4. Delgocitinib bulk drug substance is packaged in (b) (4) with a retest period of (b) (4) months.

The Applicant evaluated multiple dosage forms, formulations, and concentrations of delgocitinib during product development. A cream formulation of the proposed product was evaluated in a phase 1 clinical trial, an ointment formulation was evaluated in a phase 2a trial, and a cream formulation was evaluated in phase 2b and 3 trials. Different strengths of delgocitinib cream

were tested in the phase 2b trial, i.e., vehicle, 1 mg/g, 3 mg/g, 8 mg/g and 20 mg/g. For the phase 3 trials, 20 mg/g was the selected strength, which is also the commercial drug product composition. During the course of the phase 2b trial, the final optimization of the formulation was performed and the amount of the (b) (4) was reduced from (b) (4) mg/g to (b) (4) mg/g in phase 3.

Delgocitinib is formulated as a semisolid cream mixed

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

ANZUPGO® (delgocitinib) cream, 2% is packaged with three configurations: 15 g, 30 g and 60 g, in laminated aluminum tubes. Three primary registration batches (Batch MDTR3965, MDTR3966 and MDTR4119) for each package manufactured at LEO Laboratories Limited have been provided with their COAs. The Applicant has also provided a couple of supportive stability batches.

The Applicant provided up to 36 months of long-term stability data at 25°C/60% relative humidity and 6 months accelerated data at 40°C/75% relative humidity for three primary registration batches for three package configurations. The proposed expiry period for the drug product is 36 months when stored at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) (see United States Pharmacopeia Controlled Room Temperature). Do not freeze.

The OPQ review team has assessed NDA 219155 with respect to CMC and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, OPQ recommends approval of this NDA from a quality perspective.

9.1. Device or Combination Product Considerations

Not applicable.

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

According to the Applicant, the phase 3 trials were conducted in compliance with the clinical trial protocol, International Council for Harmonisation (ICH) Guideline for good clinical practice (GCP), and the applicable regulatory requirement(s). The Applicant submitted the relevant financial certification and disclosure forms per 21 CFR 54.4 (Form FDA 3454 and 3455). Refer to Section [25](#) Financial Disclosure of this review.

The review team requested that the Office of Scientific Investigations conduct clinical trial site inspections to ensure the quality and reliability of the data from Trials LP0133-1401 (DELTA 1) and LP0133-1402 (DELTA 2) that was submitted in support of NDA 219155. The sites were

selected using a risk-based approach. The criteria for the selection of sites included high treatment effect compared to placebo (CAN1568 and POL0771), financial disclosures of 25000 or more (CAN1568), larger size and high treatment effect (ESP1017), high treatment effect for its size (DEU0751), and GCP issue (DEU0995). The following five sites were inspected by Office of Scientific Investigations representatives.

Table 82: Clinical Inspection Sites

Name, Address, Phone Number, Email	Protocol ID Site #	Number of Subjects (SAFPOP)	Study Title	Endpoint
Devani, Alim Dermatology Research Institute Inc. 8500 Blackfoot Trail Se, Suite 310 Calgary, Alberta, Canada T2J 7E1 Phone: 403-263-3376 alim@dermatologyresearch.ca	DELTA 1 CAN1568	18	Efficacy and Safety of Delgocitinib Cream in Adults With Moderate to Severe Chronic Hand Eczema	IGA-CHE TS at Week 16
Lesiak, Aleksandra Dermoklinika Centrum Medyczne Ul. Kosciuszki 93 Lodz, Lodzkie, 90-346, Poland Phone: +4842230-96-57 lesiak_ola@interia.pl	DELTA 1 POL0771	15	Efficacy and Safety of Delgocitinib Cream in Adults With Moderate to Severe Chronic Hand Eczema	IGA-CHE TS at Week 16
Radny, Peter Derma-Study-Center Friedrichshafen GmbH Charlottenstrasse 12/1 Friedrichshafen, Baden-wuerttemberg, 88045 Germany Phone: +491774248728 radny@dsc-fn.de	DELTA 2 DEU0751	14	Efficacy and Safety of Delgocitinib Cream in Adults With Moderate to Severe Chronic Hand Eczema	IGA-CHE TS at Week 16
Leitz, Nicolas Dr. Leitz Treatment Marienstrasse 1 Stuttgart, Baden-wuerttemberg, 70178 Germany Phone: +49(1)71122931689 nicolas.leitz@gmail.com	DELTA 2 DEU0995	26	Efficacy and Safety of Delgocitinib Cream in Adults With Moderate to Severe Chronic Hand Eczema	IGA-CHE TS at Week 16
Silvestre, Juan Francisco Hospital General Universitario Dr. Balmis Avenida Pintor Baeza 12, Edif Consultas Externas, 6ª Planta, Eecc Dermatología Alicante, Spain 3010 Phone: +34965913723 silvestre_jfr@gva.es	DELTA 2 ESP1017	22	Efficacy and Safety of Delgocitinib Cream in Adults With Moderate to Severe Chronic Hand Eczema	IGA-CHE TS at Week 16

Source: Reviewer's Table

Abbreviations: Investigator's Global Assessment for chronic hand eczema; SAFPOP, safety population; TS, treatment success

According to the Clinical Inspection Summary, "The inspections did not find significant concerns regarding the conduct of the clinical trial or GCP or regulatory compliance. Based on the results of these inspections, data generated by the inspected clinical investigators appear acceptable in support of the proposed indication." (Clinical Inspection Summary dated April 8, 2025)

11. Advisory Committee Summary

The FDA did not hold an Advisory Committee meeting, because the review team identified no unexpected or significant safety/efficacy issue or controversial/challenging issue that would benefit from discussion with external experts. However, the review team sought advice from the Medical Policy and Program Review Committee regarding communication of the benefits and risks of delgocitinib cream in labeling.

III. Additional Analyses and Information

12. Summary of Regulatory History

Delgocitinib, a topical therapeutic agent, was initially synthesized and formulated as an ointment by Japan Tobacco. The compound received regulatory approval in Japan on January 27, 2020, under the proprietary name CORECTIM, for the topical management of atopic dermatitis in both adult and pediatric populations (≥ 6 months of age). In November 2014, Japan Tobacco and LEO Pharma established a licensing agreement, conferring upon LEO Pharma the global rights (excluding Japan) to investigate, develop, and commercialize delgocitinib for topical application in various dermatological conditions.

LEO Pharma then demonstrated clinical proof of concept for CHE treatment utilizing the ointment formulation in a phase 2a clinical trial. LEO Pharma also developed a cream formulation to help with patient compliance and to enhance the pharmacokinetic profile. This formulation was initially evaluated in a phase 2b trial and subsequently evaluated in multiple clinical trials for CHE, including a phase 1 pharmacokinetic trial and comprehensive phase 3 development program. It should be noted that delgocitinib is also referred to as JTE-052 and LEO 124249 in various scientific and regulatory documentation.

The U.S. FDA granted fast track designation for the investigation of delgocitinib cream in the treatment of moderate to severe CHE on June 12, 2020, following a fast-track request submission on May 5, 2020. The Applicant originally requested fast track designation on February 17, 2020, but was denied due to the development plan being inadequate. In addition, the Applicant submitted a breakthrough designation request on August 26, 2020, but was denied due to lack of preliminary clinical evidence showing that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.

Key regulatory interactions with the FDA included:

- Pre-IND meeting (July 2017; Meeting Minutes dated August 2, 2017)
- IND 135351 submission dated May 25, 2018, and Study May Proceed letter issued on November 2, 2018
- End-of-Phase 2 meetings (December 2019 and September 2020)
 - December 2019 teleconference (Preliminary Comments dated December 2, 2019) related to nonclinical and CMC issues
 - September 2020 teleconference (Meeting Minutes dated October 23, 2020)
 - December 2020 informal teleconference to discuss phase 3 protocol inclusion of “run-in” period (Memo to File dated January 14, 2021)
- Pre-NDA meeting (September 2023; Meeting Minutes dated October 27, 2023)

During these meetings, the FDA provided recommendations to the Applicant about various aspects of the clinical development program. At the September 2020 End-of-Phase 2 meeting,

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

FDA provided feedback for phase 3 trials DELTA 1 and DELTA 2 and long-term extension trial DELTA 3. The Applicant conducted their phase 3 trials as non-IND trials outside the United States. At the Pre-NDA meeting, the FDA and Applicant agreed on the content and format of the submission of a comprehensive data package to support the proposed NDA.

The NDA for delgocitinib cream cross-references two INDs: IND 135351 for the cream formulation (submitted May 25, 2018) and IND 128008 for the ointment formulation (submitted October 19, 2015). The cream formulation has been the primary focus of the clinical development program for CHE. The Applicant requested priority review designation with this NDA; however, that request was denied. The Agency denied the priority review request because the Applicant did not provide clinical evidence indicating that the drug demonstrates substantial improvement over existing therapies on one or more clinically significant efficacy or safety endpoints. Therefore, this NDA review followed a standard review clock.

The Applicant proposed proprietary name ANZUPGO, on July 23, 2024, and on September 23, 2024, this was determined to be conditionally acceptable.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

The nonclinical studies conducted to support delgocitinib were originally submitted to and reviewed under IND 135351. All pertinent studies were also submitted to the present NDA. Delgocitinib was coded as JTE-052 or JTP-105319 in nonclinical study reports.

13.1.1. Pharmacology (Primary and Secondary)

Delgocitinib is a JAK inhibitor that targets the activity of all four members of the JAK family of enzymes, consisting of JAK1, JAK2, JAK3, and TYK2. The established pharmacologic class for delgocitinib is JAK inhibitor. Delgocitinib exhibits inhibitory activity against human JAK1, JAK2, JAK3, and TYK2, thereby inhibiting signal transduction in many inflammatory processes. Delgocitinib inhibits the phosphorylation of STATs stimulated by cytokines IL-2, IL-6, GM-CSF, and IL-23 and inhibits IL-13 and TNF- α production. Delgocitinib inhibits human T cell and B cell proliferation. Tabulated summaries of the in vitro and in vivo pharmacology studies in animals conducted in support of delgocitinib are listed below.

Table 83. Summary of In Vitro and In Vivo Pharmacology Studies

Study/Study Number	Major Findings
<i>In Vitro Pharmacodynamics</i>	
Inhibitory Effect on JAK/10B052EN01	JTE-052 inhibited human recombinant JAK1, JAK2, JAK3 and TYK2 in a concentration-related manner, with IC ₅₀ values of 0.00280, 0.00264, 0.0125 and 0.0578 μ M/L, respectively.
Inhibitory Effects on Cytokine Signaling/10B052SG01, 11B052SG01	In human PBMCs, JTE-052 inhibited the phosphorylation of STATs stimulated by cytokines (IL-2, IL-6, GM-CSF and IL-

Study/Study Number	Major Findings
	23) in a concentration-related manner. The IC ₅₀ values of JTE-052 on IL-2, IL-6, GM-CSF, and IL-23 were 0.0396, 0.0325, 0.304, and 0.0843μM/L, respectively.
	In human PBMCs, JTE-052 inhibited the phosphorylation of STAT1 induced by IFN-α in a concentration-related manner. The IC ₅₀ value was 0.0181μM/L.
Inhibitory Effect on T Cell Activation and Proliferation Induced by IL-2/10B052HT01, 11B052MT01, 11B052RT01	JTE-052 inhibited human T cell proliferation in a concentration-related manner, with an IC ₅₀ value of 0.0089μM/L. JTE-052 inhibited mouse T cell proliferation in a concentration-related manner, with an IC ₅₀ value of 0.0109μM/L. JTE-052 inhibited rat T cell proliferation in a concentration-related manner with an IC ₅₀ value of 0.0153μM/L.
Inhibitory Effect on B Cell Activation and Proliferation Induced by IL-21/11B052HB01	JTE-052 inhibited IL-21 stimulated human B cell proliferation in a concentration-related manner, with an IC ₅₀ value of 0.0492μM/L.
Inhibitory Effect on Mast Cell Activation Induced by IL-4/11B052HH01	JTE-052 inhibited IL-13 production by human cord blood mast cells in a concentration-related manner, with an IC ₅₀ value of 135 nmol/L, demonstrating that JTE-052 inhibits the activation of human mast cells stimulated with IL-4.
Inhibitory Effect on Monocyte Activation Induced by GM-CSF / 11B052HM01	JTE-052 inhibited TNF-α production from human monocytes stimulated by GM-CSF in a concentration-related manner with an IC ₅₀ value of 0.277μM/L.
Effect on The Expression of Skin Barrier Function Related Molecules/11BJAKVT01-02, 11B052HK01	JTE-052 increased the mRNA levels of filaggrin, loricrin, involucrin, and B-defensin 3 in IL-4/IL-13-stimulated human epidermal keratinocytes in a concentration-related manner. JTE-052 also increased these mRNA levels in unstimulated human epidermal keratinocytes in a concentration-related manner. JTE-052 suppressed the decrease in the mRNA levels of filaggrin and loricrin in human epidermal keratinocytes stimulated with IL-4 and IL-13 in a concentration-related manner.
<i>In Vivo Pharmacodynamics</i>	
Effect on Dermal Inflammation And Antibody Production/11B052MH01	JTE-052 inhibited skin inflammation (based on ear thickness) at doses of 3 mg/kg and above in DNFB-induced dermatitis in mice. JTE-052 inhibited the production of total IgE and anti-DNP IgE in this model. JTE-052 decreased the increase in ear tissue cytokine levels at 3 mg/kg and above.
Effect on Dermal Inflammation/13B052RH01	JTE-052 ointments were considered to inhibit DNCB-induced skin inflammation at 0.3% and above in rats. JTE-052 ointments significantly inhibited ear swelling at concentrations of 0.3% and above and decreased the incidence or severity of histopathological changes in a concentration-related manner.

Study/Study Number	Major Findings
Effect on IL-31 Induced Scratching Behavior/12BJAKVV01-02, 17B052MI01	Mice were treated with 5-day-continuous infusion of IL-31 and JTE-052 was administered orally for 5 days from the first day of infusion. JTE-052 decreased scratching with significant differences at 30 mg/kg. Mice were treated with IL-31 by single injection into the right cheek. JTE-052 was applied on the right cheek 15 minutes before IL-31 injection. JTE-052 decreased scratching in a concentration dependent manner at concentrations of 0.3% and above.

Source: Nonclinical overview, Pharmacology Written and Tabulated Summaries, Individual Study Reports
Abbreviations: JTE-052, delgocitinib; IgE, Immunoglobulin E; DNCB, dinitrochlorobenzene; DNP, dinitrophenol; DNFB; dinitrofluorobenzene; TNF, tumor necrosis factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; mRNA, messenger ribonucleic acid; IC₅₀, half-maximal inhibitory concentration; JAK, Janus kinase; PMBC, peripheral blood mononuclear cells; STAT, signal transducer and activator of transcription

Table 84. Summary of Secondary Pharmacology Studies

Study/Study Number	Major Findings
Inhibitory Effects on Various Kinases/10B052KP01	JTE-052 inhibited ROCK-II with an IC ₅₀ value of 0.141 μM/L. The IC ₅₀ values of JTE-052 for the other 49 kinases tested were above 1 μM/L.
Inhibitory Effects on Various Receptors and Enzymes/AL-4447-G	The inhibition ratios of JTP-105319 were less than 50% for all receptors and enzyme reactions examined.

Source: Nonclinical overview, Pharmacology Written and Tabulated Summaries, Individual Study Reports
Abbreviations: IC₅₀, half-maximal inhibitory concentration; JTE-052, delgocitinib; JTP-105319, delgocitinib

13.1.2. Safety Pharmacology

Delgocitinib:

- Had no effect on cardiovascular, respiratory, or neurological parameters at clinically relevant doses in rats and dogs.
- Had no inhibitory effect on hERG current at clinically relevant concentrations.
- Had an inhibitory effect on gastrointestinal transport (↓27%) in rats at an oral dose of 30 mg/kg.

Table 85. Summary of Safety Pharmacology Studies

Study/Study Number	Major Findings
CNS General Condition and Behavior/P100984	JTE-052 was administered orally to rats and effects on the central and the peripheral nervous systems were examined through observation of general condition and behavior. No CNS abnormalities or changes were observed 2-8 hours or 24 hours after administration at any dose.
hERG Current/P100986	JTE-052 did not affect the hERG current at concentrations up to 3×10^{-6} mol/L.
Blood Pressure, Heart Rate, and ECG/P100985	JTE-052 was administered orally to beagle dogs and effects on cardiovascular parameters (blood pressure, heart rate, and ECG) were investigated. JTE-052 had no effect on blood pressure or heart rate up to 1 mg/kg or on ECG up to 3 mg/kg.
Blood Pressure and Heart Rate/11B052P05	JTE-052 was administered orally to rats and effects on blood pressure and heart rate were examined. JTE-052 at 30 mg/kg had a decreasing effect on blood pressure and an increasing effect on

Study/Study Number	Major Findings
	heart rate in rats. 3 and 10 mg/kg produced no effects attributable to the test article on blood pressure or heart rate.
Vascular Smooth Muscle Contraction/11B052SP01	The effects of JTE-052 on the vascular smooth muscle in rat was assessed using ring preparations of the thoracic aorta. JTE-052 had a direct, reversible relaxant effect on vascular smooth muscle in rat. The IC ₅₀ of JTE-052 was 3.6×10 ⁻⁶ mol/L for phenylephrine-induced contraction and 3.5×10 ⁻⁶ mol/L for KCl-induced contraction.
Cardiac Function/11B052SP04	The effects of JTE-052 on cardiac function were evaluated using isolated rat hearts. JTE-052 increased coronary flow at a concentration of 30μM/L, but had no clear effect on cardiac contractility at concentrations up to 30μM/L.
Respiratory Rate, and Blood Gas/P100985	JTE-052 was administered orally to beagle dogs and effects on respiratory parameters (respiratory rate and blood gas) were investigated. JTE-052 had no effect on the respiratory system up to 3 mg/kg.
Gastrointestinal Transport of Charcoal/11B052SP02	The effect of JTE-052 on gastrointestinal transport was investigated in rats. Oral administration of 30 mg/kg JTE-052 had an inhibitory effect on gastrointestinal transport (↓27%) in rats via the gastrointestinal system.
Urine Volume and Urinary Electrolyte Excretion/11B052SP03	The effects of JTE-052 on urine volume and urinary electrolyte (Na ⁺ , K ⁺ and Cl ⁻) excretion was investigated in saline-loaded rats. Oral administration of 30 mg/kg JTE-052 had an increasing effect on the urinary potassium excretion via the renal/urinary system.

Source: Nonclinical overview, Pharmacology Written and Tabulated Summaries, Individual Study Reports
Abbreviations: Cl⁻, chloride ion; CNS, central nervous system; ECG, electrocardiogram; hERG, human ether-à-go-go-related gene; IC₅₀, half-maximal inhibitory concentration; JTE-052, delgocitinib; K⁺, potassium ion; KCl, potassium chloride; Na⁺, sodium ion

13.1.3. Pharmacokinetics

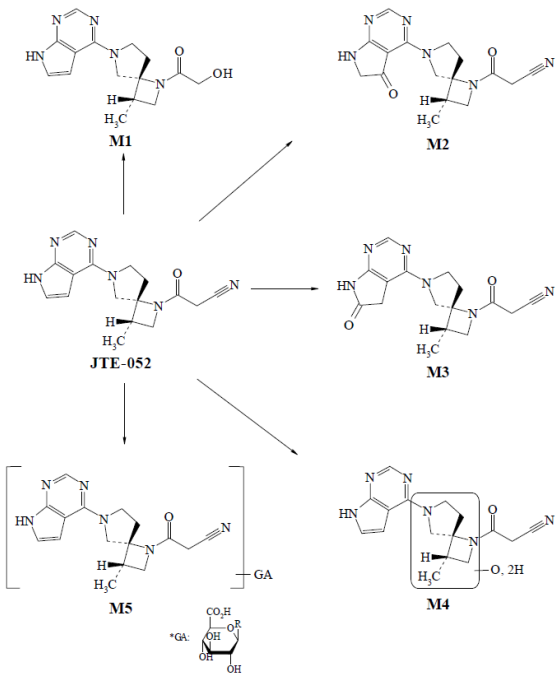
The absorption, distribution, metabolism, excretion, and in vitro drug-drug interaction potential of delgocitinib (also referred to as JTE-052) were investigated in mice, rats, rabbits, dogs, and minipigs.

Table 86. Summary of Pharmacokinetics Studies

Study/Study Number	Major Findings
Absorption	
LEO 124249: Pharmacokinetic Study by Single Dose Dermal Administration to Sedated Minipigs/BA2972	All formulations were applied topically at 0.4 g formulation/kg body weight (approx. 10% body surface area) 30 mg/g ointment • C_{max}: 0.752 ng/mL • T_{max}: 4 hours • AUC_{0-inf}: 4.33 ng.h/mL 20 mg/g cream (formulation A) • C_{max}: 0.370 ng/mL • T_{max}: 4 hours • AUC_{0-inf}: 5.43 ng.h/mL

Study/Study Number	Major Findings
	20 mg/g cream (formulation B) • C_{max}: 2.12 ng/mL • T_{max}: 4 hours • AUC_{0-inf}: 17.2 ng.h/mL
	20 mg/g cream (formulation C) • C_{max}: 6.69 ng/mL • T_{max}: 4 hours • AUC_{0-inf}: 40.2 ng.h/mL
LEO 124249: Pharmacokinetic Study by Dermal Administration to Minipigs for 7 Days/XP98RC	12 mg/kg delgocitinib ointment (30 mg/g) • C_{max}: Day 1: 3.54 ng/mL; Day 7: 22.8 ng/mL • AUC_{0-inf}: Day 1: 16.6 ng.hr/mL; Day 7: 119 ng.hr/mL 8 mg/kg delgocitinib cream (20 mg/g) • C_{max}: Day 1: 3.51 ng/mL; Day 7: 5.00 ng/mL • AUC_{0-inf}: Day 1: 27.6 ng.hr/mL; Day 7: 44.2 ng.hr/mL
Distribution	
Pharmacokinetics of ¹⁴ C- JTE-052 Ointment in Rats After Single Dermal Application/B130379	¹⁴ C-JTE-052 Ointment 3% (2.4 mg/body) At 24-hour postdose, the highest radioactivity concentration was detected in the applied skin. Radioactivity concentrations were noted in the cecum, large intestine, liver, pancreas, and kidney. At 168-hour postdose, radioactivity concentration was detected only in the applied skin. Whole-body Autoradiography: In normal skin rat, at 24-hour postdose, a high radioactivity level was detected in the applied skin, and low levels of radioactivity were also observed in the contents of gastrointestinal tracts. At 168 hr postdose, a high radioactivity level was detected only in the applied skin.
Plasma Protein Binding	
In Vitro Protein Binding of ¹⁴ C-JTE-052/B101262	In vitro protein binding of ¹⁴ C-JTE-052 was determined in rat, dog, and human plasma. The degrees of plasma protein binding of ¹⁴ C-JTE-052 in the concentration range of 30 to 100,000 ng/mL were low and comparable: 23.5% to 27.1% in rats, 17.7% to 22.2% in dogs, and 21.8% to 29.1% in humans.
In Vitro Plasma Protein Binding of ¹⁴ C-JTE-052 in Mice, Rabbits, and Minipigs/B150157	In vitro protein binding of ¹⁴ C-JTE-052 was determined in mouse, rabbit, and minipig plasma. The degrees of plasma protein binding of ¹⁴ C-JTE-052 in the concentration range of 30 to 100,000 ng/mL were low and comparable: 28.4% to 29.4% in mice, 26.1% to 27.5% in rabbits, and 20.7% to 23.0% in minipigs.
Pregnant or Nursing Animal PK	
Feto-Placental Transfer of ¹⁴ C-JTE-052 in Rats/B150158	¹⁴ C-JTE-052 (1 mg/kg) was administered orally to pregnant rats on day 18 of pregnancy. Radioactivity after oral administration of ¹⁴ C-JTE-052 was transferred into the fetus; however, the radioactivity was not readily distributed to the fetus body due to the placental barrier. At 0.5-hour postdose, the highest radioactivity concentration in maternal tissue was detected in the small intestine at a level 28.43-fold higher than that in the maternal plasma. Radioactivity concentrations were noted in the kidney, stomach, liver, and adrenal, which were 9.60-, 9.14-, 5.45-, and 3.90-fold higher than that in the maternal plasma, respectively. The highest radioactivity

Study/Study Number	Major Findings
	concentration in fetal tissue at 0.5-hour postdose was detected in the spleen at a level 3.59-fold higher than that in the maternal plasma. At 8-hour postdose, the highest radioactivity concentration in maternal tissue was detected in the cecum at a level 220.05-fold higher than that in the maternal plasma. Radioactivity concentrations were noted in the large intestine, small intestine, liver, kidney, adrenal, artery, and pancreas, which were 148.67-, 16.36-, 6.83-, 6.03-, 4.47-, 3.64-, and 3.39-fold higher than that in the maternal plasma, respectively. In fetal tissues, the highest radioactivity concentration was detected in the kidney, followed by the gastrointestinal tract and heart, which were 1.18-, 1.07-, and 1.01-fold that in the maternal plasma. At 24-hour postdose, the highest radioactivity concentration in maternal tissue was detected in the cecum, which was 73.80-fold higher than that in the maternal plasma. Radioactivity concentrations were noted in the large intestine, liver, artery, thyroid, adrenal, skin, small intestine, stomach, and kidney, which were 51.60-, 19.80-, 17.00-, 15.60-, 14.00-, 10.20-, 9.20-, 6.60-, and 6.40-fold higher than that in the maternal plasma, respectively. In fetal tissues, the highest radioactivity concentration was detected in the liver, followed by the lung, gastrointestinal tract, whole body, skin, and blood, which were 2.40-, 2.00-, 2.00-, 1.40-, 1.40-, and 1.20-fold that in the maternal plasma, respectively. At 48-hour postdose, the highest radioactivity concentration in maternal tissue was detected in the cecum, which was 32.25-fold higher than that in the maternal plasma. Radioactivity concentrations were noted in the artery, large intestine, small intestine, skin, adrenal, liver, thyroid, kidney, amnion, and spleen, which were 23.25-, 21.75-, 21.50-, 20.00-, 17.50-, 15.50-, 13.75-, 7.50-, 6.25-, and 6.00-fold higher than that in the maternal plasma, respectively. In fetal tissues, the highest radioactivity concentration was detected in the lung, liver, and gastrointestinal tract, followed by the whole body, kidney, skin, blood, and brain, which were 2.00-, 2.00-, 2.00-, 1.50-, 1.50-, 1.50-, 1.25-, and 1.00-fold that in the maternal plasma, respectively.
Milk Secretion of ¹⁴ C-JTE-052 in Rats/B150159	¹⁴C-JTE-052 (1 mg/kg) was administered orally to lactating rats on day 12 postpartum. The C_{max} in milk was 368.6 ng eq./mL at 0.5-hour postdose (t_{max}), and the radioactivity concentrations in milk decreased with the t_{1/2} of 6.3 hr. The AUC_{inf} was 1443 ng eq.·hr/mL. The ratios of milk to plasma (M/P ratios) calculated from the radioactivity concentrations were 1.68, 2.63, 2.73, 3.53, 6.80, and 4.50 at 0.5, 2, 4, 8, 24, and 48-hour postdose, respectively.
Metabolism	
Identification and Characterization of the Metabolites of JTE-052/JE052PK013	JTE-052 was oxidized at the side chain of the azetidine ring to form M1; JTE-052 was oxidized at the pyrrolo-pyrimidine ring to form M2 or M3; JTE-052 was oxidized at the spiro ring to form M4; and JTE-052 was conjugated to a glucuronide (M5).
Metabolite Profiling of JTE-052 in Human Plasma After Multiple Oral Dose of JTE-052 (Phase 1 Clinical Study of JTE-052 –Single	The proposed metabolic pathway is shown below.

Study/Study Number and Multiple Dose Study– (NBX1-1)/JE052PK032	Major Findings
	Figure 13. Postulated Metabolic Pathways of Delgocitinib  Source: Pharmacokinetics Written Summary, Study JTE052-AD-016 Study Report Abbreviation: JTE-052, delgocitinib
Identification of Human CYP Isoforms Involved in the Metabolism of ¹⁴C-JTE-052/B101265	¹⁴C-JTE-052 was metabolized by CYP2C19, 2D6, and 3A4. M1, M2 and M3 were formed by CYP3A4, and M3 was formed by CYP2C19 and 2D6. The metabolites generated by CYP3A4 were the same as those formed in the human liver microsomes. No metabolite was detected after incubation with CYP1A2, 2A6, 2B6, 2C8, 2C9, 2E1, or 3A5. The metabolism of ¹⁴C-JTE-052 and the formation of M1, M2, and M3 in human liver microsomes were completely inhibited by 1μM/L ketoconazole. Sulfaphenazole, (S)-(+)-N-3-benzylirvanol, and quinidine also inhibited the metabolism of ¹⁴C-JTE-052; however, the inhibition was weak and not concentration-dependent. These results suggest that CYP3A4 plays a major role in the oxidative metabolism of JTE-052.
In Vitro Metabolism Study of ¹⁴C-JTE-052 in Human Skin Microsomes and Recombinant Human CYP Enzymes/B130479	¹⁴C-JTE-052 was not metabolized by human skin microsomes in the presence or absence of NADPH. ¹⁴C-JTE-052 was metabolized to M3 by CYP1A1. The metabolic degradation rate of ¹⁴C-JTE-052 and the formation rate of M3 during 1 hour incubation was 30.9pM/min/nmol CYP. ¹⁴C-JTE-052 was not metabolized by CYP1B1. These results suggest that CYP1A1 is involved in the oxidative metabolism of JTE-052.
Excretion	
Pharmacokinetics of ¹⁴C-JTE-052 Ointment in Rats After Single Dermal Application/B130379	¹⁴C-JTE-052 Ointment was applied dermally at 3% (2.4 mg/body). At 168-hour postdose, 0.82% and 0.44% of the applied radioactivity were excreted into urine and feces, respectively. Radioactivity in the ointment removed from the application site at 24-hour postdose accounted for 96.84% of the applied radioactivity.

Study/Study Number	Major Findings
Toxicokinetics	
TK Data From General Toxicology Studies	
A 9-Month Dermal Toxicity Study of JTE-052 Ointments in Minipigs with a 1-Month Recovery Period/77057	<u>Minipig dermal; once daily for 9 months</u> AUC₀₋₂₄ (ng.hr/mL Week 36 (mean of both sexes): 1% (4 mg/kg/day): 12.89 3% (12 mg/kg/day): 85.50 5% (20 mg/kg/day): 114.38 Dose proportionality: The AUC increase was roughly dose proportional. Accumulation: Systemic exposure to JTE-052 was higher in Week 13 than those in Week 1 in almost all treated animals. Most animals reached steady-state exposure at Week 13. No sex effect was observed.
Nine-Month Oral Dose Toxicity Study of JTE-052 in Dogs with a 3-Month Recovery Period (b) (4) 0013	<u>Dog oral; once daily for 9 months</u> AUC₀₋₂₄ ng.h/mL Week 39: 0.1 mg/kg/day: M: 171.6; F: 224.3 0.6 mg/kg/day: M: 1536.1; F: 1507.8 1.5 mg/kg/day: M: 2929.3; F: 3596 Dose proportionality: The AUC increase was roughly dose proportional. No accumulation occurred at 0.1 and 0.6 mg/kg/day. There were no significant sex differences in the systemic exposure to JTE-052 at any dose level.
TK Data From Reproductive Toxicology Studies	
Oral Dose Study for the Effects of JTE-052 on Male Fertility and Early Embryonic Development to Implantation in Rats/R-1179	<u>Rat oral; once daily for 2 weeks before mating and through the mating period</u> AUC₀₋₂₄ µg.h/mL Day 27 [from a 3-month oral toxicity study (Study# B-7187)]: 3 mg/kg/day: 0.794 10 mg/kg/day: 2.91 30 mg/kg/day: 9.685
Oral Dose Study for the Effects of JTE-052 on Fertility and Early Embryonic Development to Implantation in Female Rats/P110952	<u>Rat oral; once daily for 2 weeks before mating and through GD7</u> AUC₀₋₂₄ µg.h/mL Day 28: 3 mg/kg/day: 0.8 10 mg/kg/day: 3.2 30 mg/kg/day: 8.1 100 mg/kg/day: 43.6 Dose proportionality: The AUC increase was roughly dose proportional. No accumulation occurred at 3, 10, and 30 mg/kg/day. At 100 mg/kg/day, systemic exposure reached steady state by Day 14.
Oral Dose Study for the Effects of JTE-052 on Embryo-Fetal Development in Rats/P110949	<u>Rat oral; once Daily for 11 days (GD 7-17)</u> AUC₀₋₂₄ µg.h/mL GD 17: 3 mg/kg/day: 0.9 10 mg/kg/day: 3.8 30 mg/kg/day: 10.7 Dose proportionality: The AUC increase was roughly dose proportional. Accumulation: No accumulation occurred at 3 and 10 mg/kg/day. Slight accumulation seen at 30 mg/kg/day.
Oral Dose Study for the Effects of JTE-052 on Embryo-Fetal Development in Rabbits/P110951	<u>Rabbit oral; once daily for 13 days (GD 6-18)</u> AUC₀₋₂₄ µg.h/mL GD 18: 1 mg/kg/day: 0.6 3 mg/kg/day: 1.4 10 mg/kg/day: 7.3

Study/Study Number	Major Findings
	Dose proportionality: The AUC increase was roughly dose proportional. Accumulation: No accumulation occurred at any dose.
Oral Dose Study for the Effects of JTE-052 on Pre- and Postnatal Development, Including Maternal Function in Rats/R-1208	<u>Rat oral; once Daily from GD 7 to LD 20</u> AUC ₀₋₂₄ µg.h/mL Day 27 [from a 3-month oral toxicity study (Study# B-7187)]: 3 mg/kg/day: 0.739 10 mg/kg/day: 2.801 30 mg/kg/day: 11.51
TK Data From Juvenile Animal Studies	
Ten-Week Oral Dose Toxicity Study of JTE-052 in Juvenile Rats with a 12-Week Recovery Period/SB95TY	<u>Juvenile rat oral; once daily for 10 weeks from PND 21</u> AUC ₀₋₂₄ ng.h/mL Week 10: 3 mg/kg/day: M: 645; F: 962.1 10 mg/kg/day: M: 2964.8; F: 3589.4 30 mg/kg/day: M: 9598.5; F: 12550 Dose proportionality: The AUC increase was roughly dose proportional. Accumulation: No accumulation occurred at any dose. There were no significant sex differences in the extent of systemic exposure.
Preliminary One-Month Dermal Dose Toxicity Study of JTE-052 ointment in Juvenile Minipigs with Pharmacokinetic Analyses/77052	<u>Juvenile minipig IV; single dose</u> AUC _{0-last} ng.hr/mL: 0.1 mg/kg: 134.2 <u>Juvenile minipig dermal; single dose</u> JTE-052 ointment 3%: plasma concentrations at or below LLOQ JTE-052 ointment 5%: plasma concentrations at or below LLOQ
TK Data From Carcinogenicity Studies	
104-Week Oral Gavage Carcinogenicity Study of JTE-052 in Rats/B-7981	<u>Rat oral; once daily for 104 weeks</u> AUC ₀₋₂₄ µg.h/mL Day 177: 3 mg/kg/day: M: 1.19; F: 1.17 10 mg/kg/day: M: 4.48; F: 4.29 30 mg/kg/day: M: 13.83; F: 16.83 Dose proportionality: The AUC increase was roughly dose proportional. There were no significant sex differences in plasma concentrations at any dose level.
104-Week Dermal Dose Carcinogenicity Study of JTE-052 Ointments in Mice/B-7982	<u>Mouse dermal; once daily for 104 weeks</u> AUC ₀₋₂₄ µg.h/mL Day 178: 1% (6 mg/kg/day): M: 0.66; F: 0.73 3% (18 mg/kg/day): M: 2.44; F: 2.45 5% (30 mg/kg/day): M: 4.79; F: 4.37 Dose proportionality: The AUC increase was roughly dose proportional. Accumulation: No accumulation occurred at any dose. There were no significant sex differences in the systemic exposure to JTE-052 at any dose level.

Source: Nonclinical overview, Pharmacokinetics and Toxicology Written and Tabulated Summaries, Individual Study Reports
Abbreviations: ¹⁴C, carbon-14; AUC, area under the concentration-time curve; AUC₀₋₂₄, area under the concentration-time curve from 0 to 24 hours PND, postnatal day; AUC_{0-last}, area under the concentration-time curve to the last measurable concentration; CYP, cytochrome; delgocitinib; F, Female; GD, gestation day; LD, lactation day; LLOQ, lower limit of quantitation JTE-052; M, male; NADPH, nicotinamide adenine dinucleotide phosphate

13.1.4. Toxicology

13.1.4.1. General Toxicology

Pivotal 9-month repeat dose toxicity studies were conducted in beagle dogs administered oral delgocitinib (0.1, 0.6, 3.0 mg/kg/day) and in minipigs administered topical delgocitinib (1, 3, 5%). The findings from these pivotal studies are summarized below.

Study Title/Number

A 9-Month Dermal Toxicity Study of JTE-052 Ointments in Minipigs with a 1-Month Recovery Period / 77057

Key study findings:

- The NOAEL was 5% JTE-052 ointment (20 mg/kg/day as a dose level of JTE-052).
- No treatment-related changes were observed in clinical signs, body weights, food consumption, hematology including bone marrow examinations, clinical chemistry, urinalysis, ECG, or ophthalmoscopy during the dosing and recovery periods.
- Skin reactions consisted of very slight to well defined erythema with only a few observations of moderate to severe erythema.
- Plasma concentrations of JTE-052 increased dose-dependently at up to the highest dose level. There were no marked sex differences in the plasma JTE-052 concentrations.

Table 87. Study Information, Study JTE052-TX-037

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	JTE-052 ointment 1%, 3%, 5%; Once Daily (4, 12, and 20 mg/kg/day)
Route of administration	Dermal (10% BSA)
Formulation/vehicle	JTE-052 ointment placebo (b) (4)
Species/strain	Göttingen SPF minipigs
Number/sex/group	4/sex/group
Age	3-4 months
Satellite groups/unique design	Recovery animals (2/sex/group) in control and 5% treated groups for 1-month recovery period
Deviation from study protocol affecting interpretation of results	None

Source: Study JTE052-TX-037 study report

Abbreviations: BSA, body surface area; GLP, good laboratory practice; JTE-052, delgocitinib; SPF, specific pathogen-free

Table 88. Observations and Results, Study JTE052-TX-037

Parameters	Major Findings
Mortality	No deaths occurred in either sex at any dose level.
Clinical signs	No treatment-related changes were observed in clinical signs.
Body weights	No treatment-related changes were observed in body weights.
Ophthalmoscopy	No treatment-related changes were observed in ophthalmoscopy.
Electrocardiogram	No treatment-related changes were observed in the ECG.
Hematology	No treatment-related changes were observed in hematology.

Parameters	Major Findings
Clinical chemistry	No treatment-related changes were observed in clinical chemistry.
Urinalysis	No treatment-related changes were observed in urinalysis.
Gross pathology	Red discoloration of the skin was observed in two animals in Group 4 (5%). Nodules up to 3 mm in diameter were described in two animals in Group 3 (3%) and in one animal from Group 4. Red foci up to 4 mm in diameter were reported in two animals in Group 2 (1%), in seven animals in Group 3 and in six animals in Group 4. In Group 3 and 4, there was an increased incidence and/or severity of epidermal hyperplasia. Infiltration in the epidermis/dermis/subcutaneous tissue of mixed inflammatory cells was observed in several animals in Group 3 and 4 and were considered treatment-related.
Organ weights	Increased weight of the pituitary was observed in Group 4 in animals of both sexes in both absolute values (34%) and as percentage of body weight (24%).
Histopathology Adequate Battery: Yes	No treatment-related histopathology findings.
Other Evaluations	Skin reactions consisted of very slight to well defined erythema with only a few observations of moderate to severe erythema. The incidence of erythema was lower in the treated groups (Groups 2, 3 and 4) when compared to the placebo control group (Group 1) in both sexes, indicating a treatment-related effect.

Source: Study JTE052-TX-037 study report
Abbreviations: ECG, electrocardiogram

Study Title/Number

Nine-Month Oral Dose Toxicity Study of JTE-052 in Dogs with a 3-Month Recovery Period/IMW0013

Key study findings:

- The NOAEL was 0.6 mg/kg/day.
- Skin lesions were observed in the 3.0 mg/kg/day group and the dose was lowered to 1.5 mg/kg/day from Week 24.

Table 89. Study Information, Study JTE052-TX-033

Study Features and Methods	Details
GLP compliance	GLP compliant
Dose and frequency of dosing	0.1, 0.6 and 3.0 mg/kg; Once Daily
Route of administration	Oral Gavage
Formulation/vehicle	0.5 w/v% methylcellulose aqueous solution
Species/strain	Beagle Dogs
Number/sex/group	4/sex/group
Age	7-9 months
Satellite Groups/Unique Design	2/sex/group in control and 3/mg/kg/day groups for 3-month recovery period
Deviation from study protocol affecting interpretation of results	None

Source: JTE052-TX-033 study report
Abbreviations: GLP, good laboratory practice; w/v%, weight/volume percent

Table 90. Observations and Results, Study JTE052-TX-033

Parameters	Major Findings
Mortality	Skin lesions during the course of the treatment period at 3.0 mg/kg/day necessitated the early sacrifice of three animals in Week 21.
Clinical signs	Severe skin lesions were observed in HD dogs causing the HD level to be lowered to 1.5 mg/kg/day during Week 24. The cause of the lesions was determined to be <i>Demodex canis</i> (mites). HD dogs were treated with Advocate anti-demodex treatment; however, skin condition of the surviving dogs continued to deteriorate. Dosing was stopped in Week 25 and the 13-week recovery period began at this point for this dose group.
Body weights	No treatment-related changes were observed in body weights.
Ophthalmoscopy	No treatment-related ophthalmic findings.
Electrocardiogram	The electrophysiology of the heart was not affected by treatment.
Hematology	Reduced lymphocyte counts were observed in LD (18-26%), MD (22-34%), and HD (21-33%) males and HD (13-31%) females starting at Week 13. Decreased eosinophil counts were observed in weeks 13 (male: -60%; female: -63%), 22 (male: -71%; female: -85%) and 25 (male: -54%; female: -45%) in HD animals and in Week 39 in MD males (-39%). Increased monocyte counts were observed in HD males (50-108%). Hematocrit was decreased in Weeks 13 (male: -13%; female: -8%), 22 (male: -6%) and 25 (male: -12%; female: -12%) in HD animals. Hemoglobin concentration was decreased in Weeks 13 (male: -16%; female: -8%), 22 (male: -8%) and 25 (male: -14%; female: -12%) in HD animals. Erythrocyte count was decreased in Weeks 13 (male: -14%; female: -10%), 22 (male: -5%) and 25 (male: -9%; female: -10%) in HD animals. An increase in platelet counts was observed in Weeks 13 (male: 26%; female: 28%), 22 (male: 29%; female: 33%) and 25 (male: 43%; female: 40%) in HD animals and in Weeks 13 (16%), 22 (14%), 30 (15%) and 39 (13%) in MD females.
Clinical chemistry	Increased C-reactive protein concentrations were observed in four female HD animals (mean: 197%). Decreased total cholesterol concentrations were observed in Weeks 13 (male: -22%; female: -38%), 22 (male: -29%; female: -26%) and 25 (male: -30%; female: -27%) in HD animals.
Urinalysis	No treatment-related urinalysis findings.
Gross pathology	Hair loss was observed in all HD animals.
Organ weights	No treatment-related organ weight findings
Histopathology	Minimal to slight, multifocal demodicosis was observed in the haired skin (including extremities and/or head) of three recovery HD males and one recovery HD female. Multifocal pyogranulomas/granulomas were associated with mite fragments. Demodex mites were not present within the hair follicles or adnexal glands.

Source: JTE052-TX-033 study report
Abbreviations: HD, high dose; MD, mid-dose

13.1.4.2. Genetic Toxicology

Table 91. Genetic Toxicology Studies

Study Title/Number	Major Findings
Bacterial Reverse Mutation Test of JTE-052/11905 GLP compliant	<u>Tester strains:</u> <i>Salmonella typhimurium</i> (TA98, TA1537, TA100 and TA1535) and <i>Escherichia coli</i> (WP2uvrA) <u>Highest dose:</u> 5000 µg/plate <u>Treatment duration:</u> 2 days ± S9 metabolic activation Delgocitinib was negative for any potential to induce reverse mutations in bacterial tester strains regardless of the presence or absence of S9 mix.
Chromosomal Aberration Test of JTE-052 in Human Peripheral Blood Lymphocytes/TN10466 GLP Compliant	<u>Test system:</u> Human peripheral blood lymphocytes (2 donors) <u>Highest dose and treatment duration:</u> 2000 µg/mL, 3-hour-treatment with S9 mix 2000 µg/mL, 3-hour-treatment without S9 mix 200 µg/mL, 24-hour-treatment without S9 mix Chromosomal numerical aberrations (polyploidy) were significantly increased at concentrations of 125 µg/mL and above after a 3-hour treatment without S9 mix and at concentrations of 50 µg/mL and above after a 24-hour treatment without S9 mix. No increases in the incidence of structural aberrations at any concentrations under either treatment condition were observed.
In Vivo Chromosomal Aberration Test of JTE-052 in Rat Bone Marrow Cells/TN10467 GLP compliant	<u>Test system:</u> Bone marrow cells from delgocitinib treated rats <u>Doses and treatment duration:</u> Oral administration to rats at dose levels of 37.5, 75, 150 and 300 mg/kg. Bone marrow chromosomal preparations were made at approximately 24 or 48 hours after dosing. At 300 mg/kg, 6/12 animals died up to 48 hours after dosing and this dose level was not evaluated for chromosomal aberrations. There were no statistically significant increases in the incidences of chromosomal aberrations (structural aberrations or polyploidy) at any other dose level at 24 or 48 hours posttreatment when compared with those in the negative control groups. JTE-052 was considered not to have any potential to induce chromosomal aberrations (structural aberrations or polyploidy). The C_{max} were 5.237, 8.536 and 13.725 µg/mL at 37.5, 75 and 150 mg/kg, respectively. The AUC_{0-24hr} were 20.659, 52.647 and 123.529 µg·hr/mL at 37.5, 75 and 150 mg/kg, respectively. At 300 mg/kg, the t_{max}, C_{max}, AUC_{0-24hr} and AUC_{0-48hr} were 4.4 hours, 20.582 µg/mL, 285.794 µg·hr/mL, and 346.535 µg·hr/mL, respectively.
Skin Micronucleus Test of JTE-052 in Hairless Mice/G-15-053 Non-GLP	<u>Test system:</u> Epidermal cells from the skin of male hairless mice administered delgocitinib ointment or solution topically <u>Doses and duration of treatment:</u> Delgocitinib ointment 3% or delgocitinib ointment 5% (0.035 mL), or 5% solution (0.2 mL) by dermal application to the dorsal skin once daily for 3 days. Animals in all dosing groups were euthanized at 18 to 24 hours after the last dosing and the dorsal skin from the application site was isolated. There were no increases in the frequency of micronucleated epidermal cells in JTE-052 ointment 3%, JTE-052 ointment 5% or 5% JTE-052 solution groups when compared with the matched control group.

Source: Nonclinical overview, Toxicology Written and Tabulated Summaries, Individual Study Reports
Abbreviations: AUC_{0-24hr}, area under the concentration-time curve from 0 to 24 hours; AUC_{0-48hr}, area under the concentration-time curve from 0 to 48 hours; C_{max}, maximum plasma concentration; GLP, good laboratory practice; JTE-052, delgocitinib; t_{max}, time to maximum concentration

13.1.4.3. Special Toxicity Studies

In a skin irritation study with delgocitinib ointment in rabbits (delgocitinib ointment placebo and 3%), both delgocitinib ointment, 3% and placebo were found to be mild irritants to rabbit skin. In a primary skin irritation study with delgocitinib ointment in minipigs (delgocitinib ointment placebo, 1, and 3%), none of the delgocitinib ointments or placebo were irritant to the minipig skin. The skin reactions observed in the primary skin irritation study in rabbits were considered attributable to (b) (4), the main component of delgocitinib ointment; delgocitinib ointment was considered unlikely to be irritant to the human skin. Delgocitinib cream (2%) administered by dermal application for 28 consecutive days to minipigs was well tolerated and no test item related skin reactions were observed.

In a BCOP test, delgocitinib ointment placebo, 1%, and 3% were all classified as nonirritants and considered to have no eye irritation potential.

In a skin sensitization study with delgocitinib ointment in guinea pigs (delgocitinib ointment placebo, 0.3%, 1%, and 3%), delgocitinib ointment did not show skin reactions at any challenge site and was determined to have no skin sensitization potential.

In a skin photosensitization study with delgocitinib ointment in guinea pigs (delgocitinib ointment placebo, 0.3%, 1%, and 3%), delgocitinib ointment did not show skin reactions at any challenge site with or without ultraviolet irradiation and was determined to have no skin photosensitization potential.

In a single oral dose phototoxicity study with delgocitinib in mice (dose levels: 25, 50, and 100 mg/kg), no findings suggestive of phototoxicity were observed.

In a dermal single dose phototoxicity study with delgocitinib ointment in guinea pigs (dose levels: placebo, 0.3%, 1%, and 3%), neither delgocitinib ointment placebo nor delgocitinib 0.3%, 1%, or 3% showed phototoxicity.

In a 4-week oral dose immunotoxicity study in rats (dose levels: 3, 10 and 30 mg/kg/day), dose-dependent suppression of T cell-dependent antibody response, decreases in all lymphocyte subsets (mainly cytotoxic T lymphocytes and NK cells) in the peripheral blood, and decreases in immature and mature lymphocyte counts in the thymus were observed from the lowest dose level (3 mg/kg) in both sexes. All the changes were considered attributable to the pharmacological action of delgocitinib.

13.1.4.4. Reproductive and Developmental Toxicity

Fertility and Early Embryonic Development

Study Title/Number

Oral Dose Study for the Effects of JTE-052 on Male Fertility and Early Embryonic Development to Implantation in Rats/R-1179.

The NOAEL was 30 mg/kg/day for general toxicity in males, male fertility, and early embryonic development.

Table 92. Study Information, Study JTE052-TX-038

Study Features and Methods	Details
Conducting laboratory and location	(b) (4)
GLP compliance	GLP-compliant
Dose and frequency of dosing	0, 3, 10, 30 mg/kg/day, once daily for 2 weeks before mating and through the mating period
Route of administration	Oral gavage (5 mL/kg)
Formulation/vehicle	0.5 w/v% methylcellulose solution
Species/strain	Sprague-Dawley rats
Number/sex/group	20 males/group
Age	8 weeks
Satellite Groups/Unique Design	Nondosed females were used for mating purposes at the same number as the treated male animals (20 females/group).
Deviation from study protocol affecting interpretation of results	None

Source: Study JTE052-TX-038 Study Report
Abbreviations: GLP, good laboratory practice; w/v%, weight/volume percent

Table 93. Observations and Results, Study JTE052-TX-038

Parameters	Major Findings
Mortality	No deaths occurred in any male at any dose level.
Clinical signs	Reddening of the skin was observed transiently 0.5 to 1 hours after daily dosing at 10 mg/kg and above throughout the premating period.
Body weights	There were no significant differences in body weights between the control and any treated groups.
Food Consumption	Food consumption during the premating period at 30 mg/kg was increased by 8% on Days 7 and 11 when compared with the control group. Total food consumption throughout the premating period at 30 mg/kg was increased by 6% when compared with the control group.
Gross pathology	Small thymus was observed in 2 of 20 males at 10 mg/kg and in 5 of 20 males at 30 mg/kg. Small spleen was observed in 3 of 20 males at 30 mg/kg.
Mating, Fertility, Embryonic Development	There were no statistically significant differences in the numbers of days until copulation, copulation index or fertility index between the control group and any treated group. There were no statistically significant differences in the number of corpora lutea, number of implantations, preimplantation loss index, implantation index, number of dead embryos, postimplantation loss index, or number of live embryos between the control group and any treated group.

Source: Study JTE052-TX-038 Study Report

Study Title/Number

Oral Dose Study for the Effects of JTE-052 on Fertility and Early Embryonic Development to Implantation in Female Rats/P110952.

- The NOAEL was 30 mg/kg/day for general toxicity and female fertility, and 3 mg/kg/day for early embryonic development.
- Embryonic deaths occurred after implantation at 10 mg/kg/day and above and inhibition of ovulation and implantation disturbance were observed at 100 mg/kg/day. The female fertility index was also decreased at 100 mg/kg/day.
- Body weight, body weight gain, and food consumption were slightly decreased at 100 mg/kg/day.

Table 94. Study Information, Study JTE052-TX-015

Study Features and Methods	Details
Conducting laboratory and location	(b) (4)
GLP compliance	GLP-compliant
Dose and frequency of dosing	0, 3, 10, 30, 100 mg/kg/day; once daily for 2 weeks prior to mating through GD 7 (3-5 weeks total)
Route of administration	Oral gavage (5.0 mL/kg)
Formulation/vehicle	0.5 w/v% methylcellulose solution
Species/strain	Sprague-Dawley rat
Number/sex/group	20 females/group
Age	10 weeks
Satellite Groups/Unique Design	Nondosed males were used for mating purposes at the same number as the treated female animals (20 males/group). Satellite groups of 5 females/group for each dose were used for toxicokinetic analysis (28-day dosing period).
Deviation from study protocol affecting interpretation of results	None

Source: Study JTE052-TX-015 Study Report
Abbreviations: GLP, good laboratory practice; w/v%, weight/volume percent, GD, gestation day

Table 95. Observations and Results, Study JTE052-TX-015

Parameters	Major Findings
Mortality	No deaths occurred at any dose level.
Clinical signs	Reddening of the skin was observed every day throughout the dosing period at 10 mg/kg and above. This finding was observed between 0.5 and 1 hour after dosing and disappeared by the next morning. The incidence of the findings increased with a dose dependency.
Body weights	Body weights were decreased on GD 13 at 100 mg/kg (-4%). Body weight gain was decreased on Day 4 (-119%) and GDs 10 (-47%) and 13 (-63%) at 100 mg/kg when compared with the control group.
Food Consumption	Food consumption was decreased on Day 2 (-17%), GDs 1 (-14%) and 13 (-19%) at 100 mg/kg when compared with the control group.
Estrous Cycle	No significant differences were observed in the count of estrus or the estrous cycle at any dose level.
Gross pathology	There were no treatment-related findings at any dose level.

Parameters	Major Findings														
Mating, fertility, embryonic development	The number of pregnant females was decreased at 100 mg/kg. There were no treatment-related effects in the copulation index or the number of days required for successful copulation. <table> <tr> <th>Parameter</th><th>Findings</th></tr> <tr> <td>Number of corpora lutea</td><td>Decreased at 100 mg/kg (-21%)</td></tr> <tr> <td>Number of implantations</td><td>Decreased at 100 mg/kg (-47%)</td></tr> <tr> <td>Preimplantation loss index</td><td>Increased at 100 mg/kg (6.3 times control)</td></tr> <tr> <td>Resorption of all embryos</td><td>Observed in 14/15 dams at 100 mg/kg and only 3 live embryos were obtained from one litter</td></tr> <tr> <td>Postimplantation loss index</td><td>Increased at 10 mg/kg and above (10 mg/kg: 2.3 times control; 30 mg/kg: 5.9 times control; 100 mg/kg: 20.8 times control)</td></tr> <tr> <td>Number of live embryos</td><td>Decreased at 30 mg/kg and above (30 mg/kg: -28%; 100 mg/kg: -99%)</td></tr> </table> Source: Study JTE052-TX-015 Study Report There were no treatment-related effects in the number of corpora lutea, implantations, pre-implantation loss index and the number of live embryos at 3 mg/kg.	Parameter	Findings	Number of corpora lutea	Decreased at 100 mg/kg (-21%)	Number of implantations	Decreased at 100 mg/kg (-47%)	Preimplantation loss index	Increased at 100 mg/kg (6.3 times control)	Resorption of all embryos	Observed in 14/15 dams at 100 mg/kg and only 3 live embryos were obtained from one litter	Postimplantation loss index	Increased at 10 mg/kg and above (10 mg/kg: 2.3 times control; 30 mg/kg: 5.9 times control; 100 mg/kg: 20.8 times control)	Number of live embryos	Decreased at 30 mg/kg and above (30 mg/kg: -28%; 100 mg/kg: -99%)
Parameter	Findings														
Number of corpora lutea	Decreased at 100 mg/kg (-21%)														
Number of implantations	Decreased at 100 mg/kg (-47%)														
Preimplantation loss index	Increased at 100 mg/kg (6.3 times control)														
Resorption of all embryos	Observed in 14/15 dams at 100 mg/kg and only 3 live embryos were obtained from one litter														
Postimplantation loss index	Increased at 10 mg/kg and above (10 mg/kg: 2.3 times control; 30 mg/kg: 5.9 times control; 100 mg/kg: 20.8 times control)														
Number of live embryos	Decreased at 30 mg/kg and above (30 mg/kg: -28%; 100 mg/kg: -99%)														

Source: Study JTE052-TX-015 Study Report
Abbreviation: GD, gestation day

Embryo-Fetal Development

Study Title/Number

Oral Dose Study for the Effects of JTE-052 on Embryo-Fetal Development in Rats/P110949

- The NOAEL for general toxicity in the dams was 30 mg/kg/day and for embryo-fetal development the NOAEL was 3 mg/kg/day.
- Embryos/fetuses showed a decrease in fetal weights and an increase in wavy ribs as a skeletal variation at 10 mg/kg/day and above, and a tendency toward an increase in the postimplantation loss index, an increase in skeletal variations, delayed sternum ossification and an increase in thymic remnants in the neck at 30 mg/kg/day.

Table 96. Study Information, Study JTE052-TX-016

Study Features and Methods	Details
Conducting laboratory and location	(b) (4)
GLP compliance	GLP-compliant
Dose and frequency of dosing	0, 3, 10, 30 mg/kg/day; once daily from GD 7 to GD 17
Route of administration	Oral gavage (5 mL/kg)
Formulation/vehicle	0.5 w/v% methylcellulose aqueous solution
Species/strain	Sprague-Dawley rat
Number/sex/group	20 pregnant females/group
Age	12-14 weeks

Study Features and Methods Details	
Satellite groups/unique design	Satellite groups of 5 females/group for each dose were used for toxicokinetic analysis.
Deviation from study protocol affecting interpretation of results	None

Source: Study JTE052-TX-016 Study Report

Abbreviations: GLP, good laboratory practice; w/v%, weight/volume percent, GD, gestation day

Table 97. Observations and Results, Study JTE052-TX-016

Parameters	Major Findings
Mortality	No deaths occurred at any dose level.
Clinical signs	Reddening of the skin was observed transiently after dosing from GDs 7 to 17 (days 1 to 11 of the dosing period) at 10 and 30 mg/kg. This finding was observed between 0.5 and 1 hour after dosing and disappeared by the next morning.
Body weights	Body weight gain was slightly decreased at 30 mg/kg on GD 8 when compared with the control group.
Food consumption	No significant differences in food consumption were observed between the control group and any dose groups.
Gross pathology	There were no treatment-related findings at any dose level.
Embryo-fetal development	A decrease in fetal weights was observed at 10 mg/kg and above (Males at 10 mg/kg: -5.5%; Males and Females at 30 mg/kg: -16%), and a tendency toward an increase in postimplantation loss index was observed at 30 mg/kg (1.8 times control). There were no treatment-related effects on the number of corpora lutea, the number of implantations, the number of preimplantation losses, the number of live fetuses, the sex ratio, placental weights, or the external or placental findings. In the visceral examination, an increase in the incidence of thymic remnants in the neck was observed at 30 mg/kg/day. Skeletal variations included: Increased incidence of wavy ribs at 10 mg/kg/day and above (0.71%, 0%, 3.75%, and 7.2% at 0, 3, 10, and 30 mg/kg/day, respectively) Increased incidence of asymmetry of the sternebrae at 30 mg/kg/day (2.14%, 0.71%, 2.89%, and 11.01% at 0, 3, 10, and 30 mg/kg/day, respectively). Increased incidence of splitting of the sternebrae at 30 mg/kg/day (0%, 0%, 1.43%, and 3.98% at 0, 3, 10, and 30 mg/kg/day, respectively) Increased incidence of splitting of the thoracic vertebral body at 30 mg/kg/day (0%, 1.25%, 1.25%, and 4.81% at 0, 3, 10, and 30 mg/kg/day, respectively). Increase incidence of 7 lumbar vertebrae at 30 mg/kg/day (0%, 0%, 0%, and 3.57% at 0, 3, 10, and 30 mg/kg/day, respectively). At 30 mg/kg, the number of ossified sternebrae was decreased (-9%). Findings in the visceral and skeletal examinations were considered to be changes related to fetal growth retardation because a decrease in fetal weights was observed at 10 mg/kg and above.

Source: Study JTE052-TX-016 Study Report

Abbreviation: GD, gestation day

Study Title/Number

Oral Dose Study for the Effects of JTE-052 on Embryo-Fetal Development in Rabbits/ P110951

- The NOAEL for maternal toxicity in the dams was 10 mg/kg/day and for embryo-fetal development the NOAEL was 3 mg/kg/day.
- An increase in postimplantation loss index, reduced number of live fetuses, and a decrease in fetal weights were observed at 10 mg/kg/day.

Table 98. Study Information, Study JTE052-TX-017

Study Features and Methods	Details
Conducting laboratory and location	(b) (4)
GLP compliance	GLP-compliant
Dose and frequency of dosing	0, 1, 3, 10 mg/kg/day; once daily from GD 6 to GD 18
Route of administration	Oral Gavage (5.0 mL/kg)
Formulation/vehicle	0.5 w/v% aqueous solution
Species/strain	New Zealand White Rabbits
Number/sex/group	20 pregnant females/group
Age	20 weeks
Satellite groups/unique design	None
Deviation from study protocol affecting interpretation of results	None

Source: Study JTE052-TX-017 Study Report

Abbreviations: GD, gestation day; GLP, good laboratory practice; w/v%, weight/volume percent,

Table 99. Observations and Results, Study JTE052-TX-017

Parameters	Major Findings
Mortality	No deaths occurred at any dose level.
Clinical signs	The auricular blood vessels were observed more clearly and reddening of the auricular skin was observed. These findings were noted after dosing from GDs 7 to 18 (days 2 to 13 of the dosing period) at 10 mg/kg. These findings occurred at 2 hours after dosing and disappeared by 4 hours after dosing.
Body weights	No significant body weight changes occurred at any dose level.
Food consumption	No significant food consumption changes occurred at any dose level.
Gross pathology	There was no treatment-related finding at any dose level.
Embryo-fetal development	At 10 mg/kg, the postimplantation loss index (late resorption) was increased (6.6 times control), there was a decrease in the number of live fetuses (-31%) and there was a decrease in fetal weights (Male: -3.4%; Female -10%) compared to control. There were no treatment-related changes in the number of corpora lutea or implantations, the preimplantation loss index, placental weights, or placental findings. There were no treatment-related findings in the fetal external, skeletal, or visceral examinations and no teratogenic potential was observed.

Source: Study JTE052-TX-017 Study Report

Abbreviation: GD, gestation day

Pre- and Postnatal Development

Study Title/Number

Oral Dose Study for the Effects of JTE-052 on Pre- and Postnatal Development, Including Maternal Function in Rats/R-1208.

- The NOAEL was determined as 30 mg/kg/day for maternal toxicity and 10 mg/kg/day for developmental toxicity.
- Decreased viability, decreased birth index, an increase in the number of dead newborns, and reduced pup weights were observed during the early postnatal period in newborns at 30 mg/kg/day.

Table 100. Study Information, Study JTE052-TX-047

Study Features and Methods	Details
Conducting laboratory and location	(b) (4)
GLP compliance	GLP-compliant
Dose and frequency of dosing	0, 3, 10, 30 mg/kg/day; once Daily from GD 7 to LD 20
Route of administration	Oral gavage (5 mL/kg)
Formulation/vehicle	0.5 w/v% methylcellulose aqueous solution
Species/strain	Sprague Dawley rat
Number/sex/group	20 pregnant females/group
Age	11-12 weeks
Satellite groups/unique design	Six females were used for microbiological monitoring. All animals for microbiological monitoring were observed for clinical signs once every day. Microbiological tests were conducted twice: before the initiation of dosing and after the end of mating in the F1 animals.
Deviation from study protocol affecting interpretation of results	None

Source: Study JTE052-TX-047 Study Report

Abbreviations: GLP, good laboratory practice; LD, lactation day; w/v%, weight/volume percent, GD, gestation day

Table 101. Observations and Results, Study JTE052-TX-047

Parameters	Major Findings
F₀ Dams	
Mortality	No deaths occurred in any female at any dose level.
Clinical signs	In all females at 10 and 30 mg/kg, reddening of the skin was observed transiently 0.5 to 1 hours after daily dosing throughout the dosing period.
Body weights	There were no treatment-related changes in body weights throughout the gestation and lactation periods at any dose level.
Food consumption	During the gestation period, there were no treatment-related changes at any dose level. During the lactation period, statistically significant decreases were noted at 30 mg/kg in food consumption from LD 4 to LD 21 (Day 4: -18%, Day 7: -17%, Day 11: -19%, Day 14: -21%, Day 17: -13%, Day 21: -26%) and in total food consumption (-19%) when compared with the control group.

Parameters	Major Findings
Observations at delivery and nursing	At 30 mg/kg, statistically significant differences were noted in the following parameters: prolongation of the gestation period (2.3%), a decrease in the birth index (0.8 times control), and an increase in the number of dead newborns (600%). At 30 mg/kg, the number of live newborns (total, both sexes) was lower than that in the control group (~20%). In one female at 30 mg/kg, the time required for delivery was prolonged (the delivery was initiated on GD 22 and completed on GD 24).
Gross pathology	At 30 mg/kg, small thymus and small spleen were noted in 12 of 20 dams and two of 20 dams, respectively.
F₁ Offspring	
Observation at birth	There were no treatment-related abnormalities in the external examinations in the F ₁ newborns at any dose level.
Viability	At 30 mg/kg, a significant decrease in the viability index on PND 4 was noted when compared with the control group (0.86 times control). For the weaning index at PND 21, there were no statistically significant differences when compared with the control group. In one dam at 30 mg/kg, the viability index on PND 4 was very low and the dam had only one live pup (male) on PND 4. The body weight of the live pup (body weight on PND 21: 14 g) was much lower than that of other pups (mean body weight at 30 mg/kg on PND 21: 43.7 g). This pup was found dead on PND 27.
Body weight	At 30 mg/kg, statistically significant decreases in body weights of both sexes were noted after birth until weaning when compared with the control group. After weaning, statistically significant decreases in body weights of both sexes were noted from PND 28 to PND 70 when compared with the control group. In males at this dose level, a statistically significant decrease in total body weight gain from PND 28 to PND 70 was noted when compared with the control group (~11%).
External differentiation	There were no treatment-related effects on external differentiation (pinna detachment, eruption of the lower incisors, opening of eyelids, vaginal opening, or cleavage of the balanopreputial gland) at any dose level.
Sensory and reflex function	There were no treatment-related effects on the reaction time for righting reflex in either sex at any of the treated groups. All pups at all dose levels showed normal reactions for the pupillary reflex, Preyer's reflex, and pain reflex.
Macroscopic findings	At 30 mg/kg, small spleen was noted in twenty-seven of 32 males and twenty-two of 32 females at weaning.
Open field test	There were no treatment-related effects on the time of latency, distance of ambulation, number of rearing or grooming, or fecal boluses in either sex at any dose level.
Rotarod test	There were no treatment-related effects on the counts of falling in either sex at any dose level.
Water-filled multiple T-Maze test	There were no treatment-related effects on the elapsed time and counts of error in either sex at any dose level.
Macroscopic findings after behavioral test	Large spleen was observed in one F ₁ female at 3 mg/kg and one F ₁ female at 30 mg/kg. There were no changes in the shape, texture, and color tone of the spleen in these animals.
Organ weights after behavioral test	There were no treatment-related effects on the weights of the thymus or spleen in either sex at any dose level.
Mating and fertility	There were no treatment-related effects on the elapsed day of conceiving, copulation index or fertility index in either sex at any dose level.
F₁ Dams	
Body weights	There were no treatment-related effects on body weights during the gestation period.

Parameters	Major Findings
Examinations at the mid stage of gestation	There were no treatment-related effects on the number of corpora lutea, number of implantations, preimplantation loss index, implantation index, number of dead embryos, postimplantation loss index, or number of live embryos at any dose level.
Macroscopic findings after reproductive performance test	There were no macroscopic abnormalities in any animal at any dose level.
Macroscopic findings of F ₁ animals found dead after weaning	In the animal found dead on PND 27 at 30 mg/kg (F ₁ male), small thymus, small spleen and emaciation were noted. In one animal found dead on PND 66 in the control group (F ₁ male), there were no macroscopic abnormalities.

Source: Study JTE052-TX-047 Study Report
Abbreviations: GD, gestation day; LD, lactation day; PND, postnatal day

Juvenile Animal Studies

Study Title/Number

Ten-Week Oral Dose Toxicity Study of JTE-052 in Juvenile Rats with a 12-Week Recovery Period/SB95TY

- The NOAEL was determined as 30 mg/kg/day.
- Changes related to the pharmacological action of delgocitinib (including effects on lymphocyte subsets and T-cell dependent antibody response) were observed from the lowest dose level, 3 mg/kg/day; there were no changes suggestive of systemic or target organ toxicity at up to the highest dose level.
- There were no effects on the timing of sexual maturity in either sex and the estrous cycle in females at up to 30 mg/kg/day and no reproductive toxicity was observed in either sex after the 6-week recovery period.

Table 102. Study Information, Study JTE052-TX-036

Study Features and Methods	Details
Conducting laboratory and location	(b) (4)
GLP compliance	GLP-compliant
Dose and frequency of dosing	0, 3, 10, 30 mg/kg/day; once daily for 10 weeks
Route of administration	Oral gavage (5 mL/kg)
Formulation/vehicle	0.5% methylcellulose aqueous solution
Species/strain	Sprague-Dawley rat
Number/sex/group	Main: 12/sex/group Recovery: 6/sex/group Reproductive and Toxicokinetics: 24/sex/group Immunology: 22/sex/group
Age	21 days

Study Features and Methods	
Methods	Details
Satellite groups/unique design	Immunology Phase animals: 30 µg/animal/occasion (0.1 mL per animal) Days 78 and 85 of age, Immunology Phase 1 animals (11 animals/sex/group). Days 162 and 169 of age, Immunology Phase 2 animals (11 animals/sex/group). Recovery animals were analyzed following a 12-week recovery period.
Deviation from study protocol affecting interpretation of results	None
Source: Study JTE052-TX-036 Study Report Abbreviations: GLP, good laboratory practice	

Table 103. Observations and Results, Study JTE052-TX-036

Parameters	Major Findings
Mortality	There were five unexpected deaths during the course of the study; none of these deaths were related to JTE-052 administration.
Clinical signs	The primary signs associated with dose administration comprised reddening of the skin for some or all of the extremities, which was observed transiently after dosing.
Body weights	When compared with controls, males and females administered JTE-052 showed a slight and generally dose-dependent reduction in mean body weight gain from Week 2 of treatment (Day 28 of age); this persisted throughout the dosing period for males but was generally apparent in females during Weeks 2-4 and Week 8 of treatment only. Overall mean body weight gain from Days 21-91 of age was lower than the control in all groups of treated males and females, in a statistically significant and dose-dependent manner (males: 97%, 94% and 87% of the control, respectively and females: 94%, 94% and 90% of the control, respectively).
Food consumption	The mean amount of food consumed by males given 10 or 30 mg/kg was slightly higher than the controls during Days 21-27 of age (Week 1) and was similar to the control in Week 2. From Day 35 of age (start of Week 3) there was a decrease in food consumption for males given 30 mg/kg compared to the controls, which persisted to the end of the treatment period. From Days 80-89 of age, mean food consumption was also low for males given 3 or 10 mg/kg when compared to the controls. Among females, at 30 mg/kg mean food consumption was lower than the controls from Day 38 of age to the end of the treatment period. From Days 70-89 of age, food consumption was low for females given 3 or 10 mg/kg when compared to the controls. During the recovery period, mean food consumption was lower than the controls during Weeks 1-6 for males and females previously given 30 mg/kg, during Weeks 1-4 for males previously given 10 mg/kg, and during Weeks 1-3 for females in the 3 or 10 mg/kg groups. Thereafter, mean food intake was similar to that of the control animals.

Parameters	Major Findings
Ulna length	Overall growth of the ulna during the treatment period (Day 21-91 of age) in all treated animals was reduced compared with the controls, with a clear dose response apparent in males. This reduction in ulna growth in both sexes predominantly occurred during the first 6 weeks of treatment (Days 21-63 of age), with growth being similar to the control during the final 4 weeks of the dosing period. Following the cessation of treatment, overall mean growth of the ulna during the first 6 weeks of the recovery period (Day 91-133 of age; prior to the mating trial for the Reproductive phase animals) was greater than the controls for all the groups of previously treated males and for females previously given 30 mg/kg, although the ulna length in males at 30 mg/kg at the end of the recovery period was still shorter than that in the control group. Thereafter, from Day 133 of age until termination of the Recovery phase and Immunology phase animals, mean ulna growth was similar to the controls.
Urinalysis	A non-dose-dependent decrease in urine volume was observed in males given 30 mg/kg. Urinary output of electrolytes (sodium, potassium, and chloride) was decreased in all the groups of treated males and females. The decrease in sodium concentration was seen in males given 30 mg/kg, decreased potassium concentration was seen in males at all dose levels and females at 10 or 30 mg/kg, and low chloride concentration was seen in males given 10 or 30 mg/kg. The analysis of urinary parameters during Week 12 of the recovery period did not reveal any differences from the controls, indicating full recovery.
Blood chemistry	Biochemical examination of plasma performed after 10 weeks of treatment showed, when compared with the controls, decreases in mean plasma urea in males and females given 30 mg/kg and creatinine in females given 10 or 30 mg/kg. Cholesterol concentrations were increased in females given 30 mg/kg. Sodium concentrations were high in females in all the treated groups and chloride concentrations were high in females given 10 or 30 mg/kg. A decrease in plasma calcium concentration was seen in females given 10 or 30 mg/kg and phosphorus concentration was high in females given 30 mg/kg. There was no effect on plasma electrolytes in the males. Further biochemical examination of plasma performed after 12 weeks of the recovery period did not reveal any differences from the controls, indicating full recovery.

Parameters	Major Findings
Hematology	Analysis of the erythrocytic parameters after 10 weeks of treatment showed, when compared with the controls, a decrease in hematocrit and hemoglobin concentrations and low erythrocyte counts in females given 30 mg/kg. Red cell distribution width was high in both sexes at all dose levels with the exception of females at 3 mg/kg and a clear dose-relationship apparent in the females. Erythrocyte counts were low in males previously given 10 or 30 mg/kg. The analysis of erythrocytic parameters during Week 8 of the recovery period and at termination of the recovery period did not reveal any differences from the controls, indicating full recovery. Assessment of leukocytic parameters after 10 weeks of treatment revealed, when compared to the controls, low lymphocyte and basophil counts in all the treated groups of males and females, low large unstained cell counts in males given 10 or 30 mg/kg and in all the groups of treated females, and low eosinophil counts for all the groups of treated males and for females given 30 mg/kg. There was a decrease in neutrophil counts for males given 30 mg/kg. Monocyte counts were low in males and females given 10 or 30 mg/kg. These changes resulted in low total leukocyte counts in both sexes at all dose levels, with the magnitude of the change demonstrating a clear relationship to treatment. Further investigations performed during Week 4 of the recovery period revealed low lymphocyte and basophil counts in males previously given 3, 10 or 30 mg/kg. Total leukocyte counts were decreased in males at all dose levels. The analysis performed at termination of the recovery phase did not reveal any differences from the control and it is therefore considered that full recovery from the treatment-related changes in leukocytic parameters had occurred. The examination of platelet counts and clotting times performed after 10 weeks of treatment and after 12 weeks of the recovery period did not reveal any test article-related differences from the control.
Hematology, bone marrow	The examination of the bone marrow performed after 10 weeks of treatment revealed, when compared with the controls, an increase in total erythroid cell ratio in both sexes at 10 mg/kg and above and in females at 3 mg/kg, and a decrease in the total other cell ratios for males at 10 mg/kg and above and for all the groups of treated females, with a statistical significance in males at 30 mg/kg and in females at all dose levels. The analysis of the bone marrow at termination of the recovery period did not reveal any differences from the controls, indicating full recovery.
Organ weights	The analysis of organ weights performed for the Main phase animals killed after 10 weeks of treatment revealed, when compared with the controls, low absolute adrenal gland and spleen weights in males and females at all dose levels. When considered relative to terminal body weight, changes in adrenal gland weights were limited to males at 10 mg/kg and above and in females at 30 mg/kg, but changes in spleen weights were apparent for both sexes in all the treated groups. Low thymus weights were seen in males and females given 10 or 30 mg/kg.
Gross pathology	No macroscopic findings were seen in any animal at any dose.

Parameters	Major Findings
Histopathology	Histopathological changes related to treatment with JTE-052 occurred in the thymus, spleen, bone marrow (sternum and femur including the joint) and adrenal glands. A decrease in cellular density and size of the cortex of the thymus was observed in animals of both sexes treated with 30 mg/kg and in one male treated with 10 mg/kg. Similar changes were observed in the medulla of males and females at 10 mg/kg and above with a dose-response pattern. The changes of cellular density/size of the cortex and medulla correlated with a reduction in organ weight. A decreased size of the PALS and marginal zones in the spleen was observed in both sexes given 10 mg/kg and above, with a dose-response pattern, correlating with a reduction of organ weight. Changes in the bone marrow consistent with increased adipocytes were observed in the sternum and femur in males at all dose levels. In females, similar changes were observed in the sternum at 10 mg/kg and above and in the femur at 30 mg/kg only. Minimal hypertrophy of the zona glomerulosa was observed in both sexes at 30 mg/kg; affected cells appeared larger with pale/foamy cytoplasm.
Immunotoxicology	The following changes in the immunophenotyping parameters were observed at the end of the dosing period: decreases in the absolute counts of T, B and NK cells in both sexes at all dose levels, a dose-dependent decrease in CD8+ T cells in both sexes at all dose levels, and dose-dependent decreases in the proportions of NK cells and CD8+ T cells in both sexes at all dose levels. The proportion of CD4+ T cells also showed a concomitant increase; however, as the absolute count of this population did not change, this is expected to be a result of the decrease in the CD8+ T cells. These changes had recovered at Week 4 of the recovery period and no further changes were observed in subsequent recovery period occasions. In the TDAR assessment at the end of the dosing period, the levels of IgM at Day 84 of age (primary response) and the levels of IgG or IgM at Day 91 of age (secondary response) decreased dose-dependently in both sexes at all dose levels when compared with the control group. This was not seen at the end of the recovery period (Day 175).
Sexual maturation	The age and body weights of the Reproductive phase animals at attainment of vaginal opening and balanopreputial separation were not affected by treatment with JTE-052.
Estrous cycle, precoital interval, mating performance and fertility	There was no effect of treatment with JTE-052 upon estrous cycle regularity during Week 6-7 of treatment or during Week 5-6 of the recovery period (prior to pairing for mating). The majority of females in all the groups demonstrated a regular 4- to 5-day cycle. In order to establish the reproductive capacity of the Reproductive phase males and females which had previously received JTE-052, the animals were paired with naive animals (study males with untreated females, study females with stock males) after at least 6 weeks recovery. All mating pairs showed positive evidence of mating at the first estrus opportunity after pairing, and the conception and fertility indices among males and females previously treated with JTE-052 were 96-100%.

Parameters	Major Findings
Reproductive assessment	There was no indication of any effect of previous treatment of males with JTE-052 on their reproductive performance as judged by the litter size and survival of the conceptuses in the litters of their untreated female partners. There was no effect of previous treatment of females with JTE-052 on their reproductive performance, as supported by the fact that treatment was not associated with any delay in the timing of female sexual maturity or regularity of estrous cycles during treatment, on female reproductive organ weights, or the macroscopic or microscopic appearance of female reproductive organs, and that there was no effect of previous treatment on estrous cycles, mating performance and fertility during recovery.

Source: Study JTE052-TX-036 Study Report
Abbreviations: CD, cluster of differentiation; Ig, immunoglobulin; JTE-052, delgocitinib; NK, natural killer; PALS, periaarterial lymphoid sheath; TDAR, T-dependent antibody response

Study Title/Number

Preliminary One-Month Dermal Dose Toxicity Study of JTE-052 ointment in Juvenile Minipigs with Pharmacokinetic Analyses/77052

Juvenile Göttingen minipigs (30 days of age, 3 males) were administered a single intravenous dose of delgocitinib at 0.1 mg/kg. For the general toxicity investigation, a single dose of delgocitinib ointment (3%) at a dose volume of 400 mg/kg (12 mg/kg) was applied dermally to clipped dorsal skin (approximately 10% BSA) of the same animals (32 days of age) on Day 3 and repeated doses of delgocitinib ointment (5%) at a dose volume of 400 mg/kg (20 mg/kg) were then applied dermally to the clipped dorsal skin (approximately 10% BSA) of the same animals (35 days of age) once daily for 28 days starting on Day 6 (on Days 6 to 33).

- The NOAEL was determined as 5% delgocitinib ointment.
- There were no findings considered related to treatment with JTE-052 in the skin reactions, clinical signs, body weights or clinical pathology throughout the dosing period.
- In the single intravenous injection of JTE-052 at 0.1 mg/kg, the mean AUC_{0-last} was 134.2 ng.hr/mL.
- Exposure after a single dermal application (plasma concentration 24 hours postdosing) appeared to increase proportional to dose level.
- In the single dermal dose of JTE-052 ointment 3%, plasma JTE-052 concentrations were very low (below or close to LLOQ: 0.5 ng/mL) for up to 24 hours after dose.
- After 28 days' repeated dermal dosing of JTE-052 ointment 5%, plasma JTE-052 concentrations were very low (below or close to LLOQ) for all JTE-052 treated animals.

13.1.5. Excipients/Impurities

There are no novel excipients in the clinical formulation. All the inactive ingredients are below approved levels for the dermal route of administration listed in the FDA's inactive ingredient database. The Applicant provided an impurity characterization and control strategy, or the impurities have been qualified in studies described below. The potential impurities that are evaluated and controlled include product-related impurities, process-related impurities, (b) (4)

(b) (4), elemental impurities, and contaminants. The proposed control strategy is considered acceptable. There are no safety concerns for potential impurities contained in this product.

Sprague Dawley rats were administered delgocitinib + impurities (30 mg/kg/day) by oral gavage for 4 weeks in a study investigating the toxicity of impurities in the delgocitinib drug substance. The impurities included (b) (4)

(b) (4) each at a dose of (b) (4) mg/kg/day (b) (4) of each impurity; 27 mg delgocitinib + (b) (4) mg impurities). Delgocitinib + impurities at 27+(b) (4) mg/kg/day to Sprague-Dawley rats administered for 4 weeks resulted in nonadverse changes in the spleen, thymus and bone marrow, associated changes in organ weights, and changes in leukocyte counts and erythrocyte indices. All findings were considered to be related to JAK inhibition, and there were no significant differences in the findings between animals that were treated with delgocitinib alone or with delgocitinib + impurities, which indicates that the impurities administered at dose levels of (b) (4) mg/kg/day (corresponding to approximately (b) (4) % in the formulation) induced no additional effects or systemic toxicity.

The (b) (4) was shown in PK studies to be present at higher amounts in nonclinical toxicology studies following metabolism of the parent compound than in human studies. This qualifies (b) (4) at the proposed $\leq$ (b) (4) % release limit and $\leq$ (b) (4) % shelf-life limit.

The (b) (4) impurity (b) (4) has a proposed acceptable intake (AI) of (b) (4) ng/day. (b) (4) was determined as nonmutagenic in an Ames assay in five strains (TA98, TA100, TA1535, TA1537 and TA102) of *Salmonella typhimurium* at concentrations up to 5000 µg/plate. The Center for Drug Evaluation and Research/Office of Translational Sciences/Office of Clinical Pharmacology/Division of Applied Regulatory Science Computational Toxicology Consultation Service was consulted to apply the Carcinogenic Potency Categorization Approach to calculate the carcinogenic potency category (PC) and associated AI limit of (b) (4) as well. (b) (4) (b) (4) is a (b) (4) form of the active pharmaceutical ingredient, delgocitinib. The Computational Toxicology Consultation Service concluded that (b) (4) is assigned to PC 5 and has an associated recommended AI limit of (b) (4) ng/day, which agrees with the calculated PC and AI limit.

13.1.6. Extractables/Leachables

The container closure system for the drug product, consisting of 15 g, 30 g and 60 g tubes, is a laminate tube with an inner layer of (b) (4) fitted with a (b) (4) flip-top cap.

An extractables study was completed using the 15 g tube size of the container closure system. The tube, with seal and cap, was filled with 15 mL simulation solvent and stored for 7 months at 40°C. The simulation solvent was chosen to mimic the extractable power of the drug product; hence, a combination of water and organic solvents was used in combination with acid to mimic the drug product. To mimic the acidity of the drug product formulation in the simulation solvent, (b) (4) used for drug product vehicle composition was used. The maximum daily dose (MDD) for the drug product is (b) (4). The mean amount of cream used in the phase 3 clinical study was 1.4 g/day. Twice-daily treatment is not expected to continue on

a long-term basis, but a duration of more than 10 years for the treatment of CHE (as for atopic dermatitis) is considered a conservative worst-case duration.

Justification of the levels of extractables and leachables found in the study are shown below.

Unidentified Impurities

Two unidentified compounds were detected in tube samples of the container closure system above the safety control threshold (SCT) of 1.5 µg/day. The estimated amounts of these unidentified compounds in the tube samples are (b) (4) µg/tube and (b) (4) µg/tube, respectively.

Equation 1. Unknown #1 MDE

$$(b) (4) \text{ µg impurity/tube in 15 g tube} = (b) (4) \text{ µg impurity/g product} \times 1.4 \text{ g/day} = (b) (4) \text{ µg impurity/day}$$

Abbreviation: MDE, maximum daily exposure

Equation 2. Unknown #2 MDE

$$(b) (4) \text{ µg impurity/tube in 15 g tube} = (b) (4) \text{ µg impurity/g product} \times 1.4 \text{ g/day} = (b) (4) \text{ µg impurity/day}$$

Abbreviation: MDE, maximum daily exposure

Both impurities are below the 1.5 µg/day SCT at both the MDD and normal use doses. These impurities do not present a significant toxicological risk at these levels in the final drug product.

(b) (4)

(b) (4) categorized as Cramer Class II in a quantitative structure-activity relationship assessment, indicating a potential for moderate skin irritation and sensitization, was identified as a potential contaminant from packaging materials at a maximum concentration of (b) (4) µg/tube. Based on the Product Quality Research Institute recommendations for parenteral drug products, irritants and sensitizers have an SCT of 5 µg/day maximum daily exposure (MDE).

Equation 3. (b) (4) MDE

$$(b) (4) \text{ µg (b) (4) tube in 15 g tube} = (b) (4) \text{ µg (b) (4) /g cream} \times 1.4 \text{ g/day} = (b) (4) \text{ µg (b) (4) day}$$

Abbreviation: MDE, maximum daily exposure

The MDE at the mean phase 3 dose is below the Product Quality Research Institute SCT of 5 µg/day. Based on this, the level of (b) (4) is acceptable.

(b) (4)

(b) (4) is a Class 2 mutagenic impurity formed from (b) (4) present in the excipient (b) (4). The excipient contains (b) (4) ppm (b) (4) % of (b) (4) resulting in a concentration of (b) (4) ppm of (b) (4) in the final formulation. The acceptable limit for (b) (4) in the cream is (b) (4) ppm. Theoretically, if all (b) (4) were to convert to (b) (4) it would exceed the acceptable limit. The (b) (4) µg/g limit for (b) (4) is based on the MDD of (b) (4) day of the drug product.

At the mean clinical use dose of 1.4 g/day of the drug product, the limit at a 1.5 µg/day acceptable intake would be 1.1 µg/g.

Equation 4. (b) (4)

(b) (4) µg (b) (4) /g cream = (b) (4) µg (b) (4) /g cream in a worst-case scenario

(b) (4) µg (b) (4) /g cream × 1.4 g cream/day = (b) (4) /day

Abbreviation: MDE, maximum daily exposure

The development of (b) (4) has been monitored during the first weeks/months after manufacture. The (b) (4) level is below the limit of (b) (4) µg/g after about 1 month at long-term storage conditions. All stability datapoints, for up to 36 months at long-term and 6 months at accelerated storage conditions, show (b) (4) levels below the (b) (4) µg/g limit. During the first month after manufacture, varying levels of (b) (4) between (b) (4) µg/g are observed, all well below the limit of (b) (4) µg/g applied for a treatment duration of more than 10 years. Based on the available data, an (b) (4) limit of (b) (4) ppm is estimated to generate a peak level of (b) (4) below (b) (4) µg/g. The concentration of (b) (4) would then rapidly decrease to a level below the ICH M7 (R2) ([April 2023](#)) limit of (b) (4) µg/g. When the content of (b) (4) decreases, (b) (4), a Class 5 impurity, is formed. (b) (4) is controlled according to the specification limit for any unspecified organic impurities. The toxicological assessment of (b) (4) showed no risk associated with the observed level because of rapid degradation of (b) (4) in blood and skin to nonmutagenic metabolites, and it is therefore highly unlikely that (b) (4) will be present in the body to generate any mutagenic or carcinogenic effects. When applied topically, degradation of (b) (4) will take place before it reaches the viable epidermis (with a pH of approximately 7) as the degradation is pH-dependent. Additionally, based on the timeframe for release and distribution of the drug product, it is unlikely that patients would receive the drug product within a month of its manufacture. Based on the factors of degradation of (b) (4) in long-term storage, topical degradation, the low likelihood of total conversion of (b) (4) to (b) (4) and the acceptable ppm and MDE levels compared to limits at the mean clinical dose, the level of (b) (4) is acceptable.

(b) (4)

The estimated total (b) (4) content in the drug product is (b) (4) ppm. This level exceeds the calculated limit of (b) (4) ppm based on the acceptable daily intake for Class 3 impurities as per ICH M7(R2) ([April 2023](#)).

Equation 5. (b) (4) MDE

(b) (4) µg (b) (4) g cream × 1.4 g/day cream = (b) (4) µg (b) (4) /day

Abbreviation: MDE, maximum daily exposure

The MDE is below the SCT of 1.5 µg/day at the mean clinical dose amount. (b) (4) (b) (4) as a compound with endogenous and/or environmental exposure. Based on these factors, the level of (b) (4) in the drug product is acceptable.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

13.2.1. Carcinogenicity

Dermal mouse and oral rat carcinogenicity studies were submitted and reviewed under the NDA.

Study Title/Number

104-Week Dermal Dose Carcinogenicity Study of JTE-052 Ointments in Mice / B-7982.

- There were no treatment-related neoplastic findings.
- The NOAEL for this study was 5% for both sexes (30 mg/kg/day).

Table 104. Study Information, Study JTE052-TX-039

Study Features and Methods Details	
Conducting laboratory and location	(b) (4)
GLP compliance	GLP-compliant
Dose and frequency of dosing	JTE-052 ointment 1 (6 mg/kg), 3 (18 mg/kg), and 5% (30 mg/kg); once daily for 104 weeks
Route of administration	Topical (600 mg/kg; 10% BSA)
Formulation/vehicle	JTE-052 ointment placebo ((b) (4)
Species/strain	CD1 Mouse
Number/sex/group	60/sex/group
Age	4 weeks
Satellite groups/unique design	Satellite groups for toxicokinetic analysis: Nontreated: 5/sex/group Placebo and treated animals: 25/sex/group
Deviation from study protocol affecting interpretation of results	None

Source: Study JTE052-TX-039 Study Report

Abbreviations: BSA, body surface area; GLP, good laboratory practice; JTE-052, delgocitinib

Table 105. Observations and Results, Study JTE052-TX-039

Parameters	Major Findings
Mortality	JTE-052 did not increase the number of deaths attributable to specific tumors or nontumor lesions in either sex at any dose level.
Clinical signs	There were no treatment-related findings in either sex at any dose level.
Body weights	There were no treatment-related changes in either sex at any dose level during the dosing period.
Food consumption	There were no treatment-related changes in either sex at any dose level during the dosing period.

Parameters	Major Findings
Hematology	In satellite animals at the week 28 time point, white blood cell (3% ointment: 0.62× in males; 5% ointment: 0.9× in males and 0.61× in females) and lymphocyte counts (1% ointment: 0.7× in males; 3% ointment: 0.56× in males and 1.07× in females; 5% ointment: 0.54× in males and 0.42× in females) were decreased in both sexes at all dose levels when compared with the placebo control group. Eosinophil counts were decreased in both sexes at 5% (0.71× in females). Large unstained cell counts were decreased in males at 5% (0.5×). At terminal necropsy, white blood cell counts were decreased in males at 3% (0.62×) and 5% (0.9×) and in females at 5% (0.61×) when compared with the placebo control group. Lymphocyte counts were decreased in males at all dose levels (1% ointment: 0.7×; 3% ointment: 0.56×; 5% ointment: 0.54×) and in females at 5% (0.42×). Eosinophil counts were decreased in females at 5% (0.71×). Large unstained cell counts were decreased in males at 3% (0.5×) and 5% (0.67×) and in females at 5% (0.43×). Reticulocyte counts were decreased in females at 5% (0.61×).
Blood chemistry	Plasma total bilirubin levels were increased in males at all dose levels compared with the placebo control group. Plasma albumin levels (3% and 5% ointment: 1.10×) and albumin/globulin ratio (3% and 5% ointment: 1.33×) were increased in males at 3% and 5%. Plasma triglyceride levels were increased in both sexes at 3% (1.33× in males and 1.51× in females) and 5% (1.3× in males and 1.7× in females). Glucose levels were increased in both sexes at 3% (1.24× in males and 1.09× in females) and 5% (1.2× in males and 1.11× in females).
Gross pathology	There were no treatment-related changes in either sex at any dose level.
Ophthalmology	There were no treatment-related changes in either sex at any dose level.
Histopathology	There were no treatment-related increases in the incidences of any tumor, benign or malignant, in either sex at any dose level. Increased adipocytes were observed in the sternal bone marrow (females at 5%) and femoral bone marrow (both sexes at 3% and above). Increased dermal adipose tissue was observed in the inguinal skin (females at 5%) and treated/untreated area of the dorsal skin (females at 3% and above).

Source: Study JTE052-TX-039 Study Report
Abbreviation: JTE-052, delgocitinib

Study Title/Number

104-Week Oral gavage Carcinogenicity Study of JTE-052 in Rats/B-7981

- There was no evidence of drug-related neoplasms in male rats.
- In female rats, benign thymoma was significantly increased at the 30 mg/kg/day dose compared to vehicle and showed a dose-response relationship trend.

Table 106. Study Information, Study JTE052-TX-040

Study Features and Methods Details

Conducting laboratory and location	(b) (4)
GLP compliance	GLP-compliant
Dose and frequency of dosing	0, 3, 10, 30 mg/kg/day; once daily for 104 weeks
Route of administration	Oral gavage (5 mL/kg)
Formulation/vehicle	0.5 w/v% methylcellulose aqueous solution
Species/strain	Sprague Dawley rat
Number/sex/group	66/sex/group
Age	4 weeks
Satellite groups/unique design	None
Deviation from study protocol affecting interpretation of results	None

Source: JTE052-TX-040 Study Report

Abbreviations: GLP, good laboratory practice; w/v%, weight/volume percent

Table 107. Observations and Results, Study JTE052-TX-040

Parameters	Major Findings
Mortality	There were no treatment-related effects on the survival rate in either sex at any dose level.
Clinical signs	Reddening of the skin was observed transiently at 1 to 3 hours after daily dosing in both sexes at 30 mg/kg throughout the dosing period.
Body weights	In males at 10 mg/kg and above, body weights decreased from Day 21. The mean body weights at the end of the dosing period (week 104) in males at 10 and 30 mg/kg/day were 7% and 15% lower than those in the control group, respectively. Body weight gain in these groups was also lower than that in the control group.
Food consumption	In males at 30 mg/kg/day, food consumption was increased on Days 7 and 14. Food consumption was slightly decreased in males at 10 mg/kg/day and above from Day 28. In females at 30 mg/kg/day, food consumption was increased on Day 7, but was comparable to the control group thereafter.
Urinalysis	Urine samples were collected in Week 52 (Day 359 for males and Day 358 for females) and Week 104 (Day 723 for males and Day 722 for females) of the dosing period. A decrease in the urine volume and increases in the osmotic pressure, sodium, potassium, and chloride concentrations were observed in females at 30 mg/kg/day in Week 104.

Parameters	Major Findings
Hematology	At terminal necropsy, white blood cell counts were decreased in both sexes at all dose levels (3 mg/kg/day: 0.64× in males, 0.57× in females; 10 mg/kg/day: 0.59× in males, 0.96× in females; 30 mg/kg/day: 0.81× in males, 0.59× in females). Lymphocyte (3 mg/kg/day: 0.41× in males, 0.49× in females; 10 mg/kg/day: 0.43× in males, 0.52× in females; 30 mg/kg/day: 0.54× in males, 0.45× in females), eosinophil (3 mg/kg/day: 0.46× in males, 0.75× in females; 10 mg/kg/day: 0.54× in males, 0.75× in females; 30 mg/kg/day: 0.38× in males, 0.5× in females), basophil, and large unstained cell counts (3 mg/kg/day: 0.5× in males, 0.3× in females; 10 mg/kg/day: 0.4× in males, 0.5× in females; 30 mg/kg/day: 0.6× in males, 0.3× in females) were decreased in both sexes at all dose levels. Red blood cell counts (3 mg/kg/day: 0.87× in males; 10 mg/kg/day: 0.94× in males; 30 mg/kg/day: 0.81× in males, 0.86× in females), hemoglobin concentration (3 mg/kg/day: 0.89× in males; 10 mg/kg/day: 0.95× in males; 30 mg/kg/day: 0.82× in males, 0.87× in females), and hematocrit value (3 mg/kg/day: 0.91× in males; 10 mg/kg/day: 0.96× in males; 30 mg/kg/day: 0.86× in males, 0.89× in females) were slightly decreased in males at all dose levels and in females at 30 mg/kg/day. A slight increase in platelet counts was also observed in females at 30 mg/kg/day (1.21×).
Blood chemistry	Plasma potassium levels were increased in both sexes at 30 mg/kg/day (1.06× in male, 1.12× in female). Plasma total cholesterol was decreased in males at 30 mg/kg/day (0.8×) and triglyceride levels were decreased in females at 30 mg/kg/day (0.57×). Plasma alkaline phosphatase levels were increased (1.47×) in females at 30 mg/kg/day. Plasma inorganic phosphorus levels were decreased in females at all dose levels (3 mg/kg/day: 0.84x; 10 mg/kg/day: 0.89x; 30 mg/kg/day: 0.86×).
Gross pathology	Treatment-related changes were observed in the skin/subcutis, lung, eye, and seminal vesicle. Skin/subcutis: The incidence of subcutaneous nodules was increased in males at 3 mg/kg/day and above. Three out of the 7 nodules, 7 out of the 13 nodules, 3 out of the 11 nodules corresponded to lipoma in males at 3, 10 and 30 mg/kg/day, respectively. Lung: White focus was increased in males at 30 mg/kg/day and females at 3 mg/kg/day and above. The majority of the white foci corresponded to alveolar proteinosis histopathologically. Eye: Opacity was increased in males at 30 mg/kg/day. Opacity corresponded to corneal inflammation histopathologically. Seminal vesicle: Dark area or dark red focus was observed in males at 10 mg/kg/day and above, associated with microscopic vesicular dilatation.
Ophthalmology	There were no test article-related changes in either sex at any dose level.
Histopathology	The only tumor finding with statistically significant findings in both the pairwise comparison and dose relationship trend data was benign thymoma in the thymus of females at the high dose of 30 mg/kg/day. Following the multiple testing adjustment method, analysis showed statistically significant increasing dose-response relationships across the vehicle control and the treated groups in male rats for the incidence of malignant astrocytoma in the brain (cerebrum) and in female rats for the incidence of the benign thymoma in the thymus (p-value=0.0089 and =0.0006, respectively). The pairwise comparisons showed statistically significant increases in the medium dose group, for the incidences of adenoma hepatocellular in the liver and the incidence of the lipoma in the skin/subcutis, in male rats, when compared to the vehicle control group (p-value=0.0078 and =0.0078, respectively). In female rats, the pairwise comparisons showed statistically significant increases in the medium dose group for the incidences of the malignant astrocytoma in

Parameters	Major Findings
	the brain (cerebrum), and in the high-dose group for the incidence of benign thymoma in the thymus, when compared to the vehicle control group (p-value=0.0384 and =0.0072, respectively).
	Treatment-related changes were observed in the lung, eye, skin/subcutis, liver, seminal vesicle, kidney, spleen, Peyer's patch, mesenteric lymph node, submandibular lymph node, and thymus.
	Lung: The incidence and severity of alveolar proteinosis were increased in both sexes at 3 mg/kg/day and above.
	Eye: The incidence and severity of corneal inflammation were increased in males at 30 mg/kg/day. Moderate and severe inflammation was observed in males at 30 mg/kg/day. In most cases including control animals, the lesion was unilateral, not bilateral.
	Skin/subcutis: The incidence of increased dermal adipose tissue in the inguinal region was increased in males at 10 mg/kg/day and above and in females at 3 mg/kg/day and above, although there was no dose response in females. Pyogranulomatous inflammation was observed in both sexes at 30 mg/kg/day.
	Liver: The incidence of clear altered cell foci was increased in females at 3 mg/kg/day and above; however, the severity in most of the foci was very slight and there was no apparent dose response.
	Seminal vesicle: The incidence of vesicular dilatation was increased in males at 10 mg/kg/day and above.
	Kidney: Intraluminal mineralization was observed in males at 10 mg/kg/day and above and females at 3 mg/kg/day and above. This lesion was mainly observed in animals that died or were euthanized in moribund condition.
	Spleen: The incidence and severity of lymphoid atrophy were increased in both sexes at 10 mg/kg/day and above.
	Peyer's patch: The incidence and severity of lymphoid atrophy were increased in both sexes at 10 mg/kg/day and above.
	Mesenteric lymph node: The incidence and severity of lymphoid atrophy were increased in males at 30 mg/kg/day and females at 10 mg/kg/day and above.
	Submandibular lymph node: Lymphoid atrophy was increased in females at 30 mg/kg/day.
	Thymus: The severity of atrophy was increased in both sexes at 30 mg/kg/day.

Source: JTE052-TX-040 Study Report

The carcinogenic potential of JTE-052 (delgocitinib) ointment was evaluated in ICR mice in a 2-year dermal study with JTE-052 ointments (1%, 3% and 5%) and in Sprague-Dawley rats in a 2-year oral gavage study (0, 3, 10 and 30 mg/kg/day). The AUC values and human multiples for the mouse and rat carcinogenicity studies are shown in Section [7.1](#).

The carcinogenicity studies were presented to the Executive Carcinogenicity Assessment Committee (ECAC) and the conclusions were as follows:

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

2-year mouse dermal study:

- The ECAC concluded that the carcinogenicity study was adequate.
- The ECAC concluded that there was no evidence of drug-related neoplasms in male and female mice in the 2-year study.

2-year rat oral study:

- The ECAC concluded that the carcinogenicity study was adequate.
- The ECAC concluded that there was no evidence of drug-related neoplasms in male rats in the 2-year study. Benign thymoma was significantly increased in females at the 30 mg/kg/day dose compared to vehicle and showed a dose-response relationship trend.

Based on the results of the two carcinogenicity studies, the dermal route of administration, human multiples, and concurrence of the ECAC, the carcinogenic potential of JTE-052 appears to be low for the treatment of CHE.

13.3. Labeling

Recommended revisions to the Applicant's proposed wording for the nonclinical portions of labeling are provided below. It is recommended that the underlined wording be inserted into and the ~~strike through~~ wording be deleted from the text of the ANZUPGO label proposed by the Applicant.

(b) (4)

14. Clinical Pharmacology

14.1. In Vitro Studies

Metabolism

Limited metabolism of delgocitinib was observed in vitro and in vivo with no major human-specific metabolites. Delgocitinib was the main component in human plasma and in the plasma, urine, bile, and feces of rats and dogs. No metabolites were detected in plasma from juvenile rats. Metabolism occurred by oxidation and through glucuronide conjugation.

Delgocitinib was mainly metabolized by CYP3A4/5 and with minor contribution from CYP2C9, CYP2C19, and CYP2D6.

In Vitro Drug Interaction Assessments

Delgocitinib was evaluated for potential drug interactions across series of CYP enzymes and transporters under in vitro conditions. The key findings from the reported in vitro studies are summarized below.

Delgocitinib as Inhibitor of CYP (Study JE052-PK-021)

Delgocitinib was investigated for inhibitory effects on human CYP isoform-specific activities of CYP1A2 (phenacetin), CYP2A6 (coumarin), CYP2B6 (bupropion), CYP2C8 (amodiaquine), CYP2C9 (diclofenac), CYP2C19 (mephenytoin), CYP2D6 (bufuralol), and CYP3A4/5 (testosterone and midazolam) at concentrations of 0, 0.1, 0.3, 1, 3, 10, and 30 $\mu\text{M/L}$ using human liver microsomes. The time-dependent inhibitory effect of delgocitinib was also evaluated after preincubation with microsomes for 30 minutes in the presence of NADPH.

The results indicated that the IC_{50} of delgocitinib was $>30\mu\text{M/L}$ for all the CYP isoforms investigated. After preincubation for 30 minutes, the extent of inhibition was almost the same as that without preincubation for all the CYP isoforms examined, indicating no potential for time-dependent inhibition of the tested CYP isoforms.

Delgocitinib as Inducer of CYP (Study JTE052-AD-014)

The study was designed to evaluate the CYP-inducing potential of delgocitinib using fresh human hepatocytes. The effects of CYP1A2, CYP2B6, or CYP3A4 activity was studied in the fresh preparations of cultured human hepatocytes from three separate livers treated once daily for 3 consecutive days with dimethyl sulfoxide (DMSO, 0.1% v/v, vehicle control), one of five concentrations of delgocitinib (0.3, 1, 3, 10, or $30\mu\text{M}$) or one of three known human CYP

inducers, namely, omeprazole (50 μ M), phenobarbital (750 μ M), and rifampin (10 μ M) and with the marker substrates for the analysis of phenacetin O-deethylation (marker for CYP1A2), bupropion hydroxylation (marker for CYP2B6), and testosterone 6 β -hydroxylation (marker for CYP3A4/5).

The results showed that delgocitinib, at concentrations up to 30 μ M, is not an inducer of CYP1A2, CYP2B6, or CYP3A4 activity or mRNA expression. It is noted that concentration-dependent decreases were observed in CYP3A4/5 activity; however, since this drug is applied topically at the target site (skin), the potential effect of enzyme induction on the systemic exposure of delgocitinib is unlikely to cause any effect on efficacy.

Transporter Study (Study JTE052-AD-015)

The study was designed to investigate the potential of delgocitinib as a substrate or inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) and substrate/inhibitor of organic cation transporter (OCT)2, OAT1, and OAT3. The inhibitory effect of delgocitinib on uptake of model substrates in OAT1- and OAT3-expressing S2 cells and OCT2-, organic anion transporting polypeptide (OATP)1B1- and OATP1B3-expressing HEK293 cells was also investigated to examine whether delgocitinib was an inhibitor of OAT1, OAT3, OCT2, OATP1B1, or OATP1B3.

The results showed that delgocitinib is a substrate of P-gp but not a substrate of BCRP and not an inhibitor of P-gp or BCRP, and is a weak substrate of OCT2 and OAT3, but not a substrate of OAT1. In addition, delgocitinib showed inhibition of OAT1 and OAT3 with IC₅₀ values of 1.59 μ M/L (493 ng/mL) and 6.38 μ M/L (1980 ng/mL), respectively. Due to the low systemic exposure observed in the maximal use study in subjects with CHE, there is no concern for delgocitinib to inhibit OAT1 and OAT3. Delgocitinib exhibited little to no inhibition of the OATP1B1, OATP1B3 and the OCT2-mediated uptakes, indicating that delgocitinib showed no inhibition of OCT2, OATP1B1, or OATP1B3.

Solute Carrier Transporter Potential in Cells (Study (b) (4) 208059)

The study was designed to evaluate inhibitory and substrate potential of delgocitinib of the human transporters multidrug and toxin extrusion (MATE)1 and MATE2-K.

Table 108. Summary of Solute Carrier Transporter Inhibition/Substrate in Cell (Study (b) (4) 208059)

Transporter	Test system	Substrate	Experimental design	[Delgocitinib] (μM)	IC ₅₀ (μM)
MATE1	HEK293 cells	[¹⁴ C]-Metformin (10 μM)	Accumulation of substrate in cells	0.002, 0.006, 0.02, 0.06, 0.2, 0.6, 2	> 2
MATE2-K					

Substrate

Transporter	Test system	Experimental design	[Delgocitinib] (μM)	Potential substrate ^a
MATE1	HEK293 cells	Accumulation of test article in cells	0.002, 0.02, 0.2, 2	No
MATE2-K ^b			0.002, 0.02, 0.2, 2	No
			2	

^a Uptake ratio ≥ 2 and reduced $> 50\%$ in presence of inhibitor

^b In the initial assay, only the 2 μM results were above the lower limit of quantitation; however, this concentration was not evaluated in the presence of inhibitors and the substrate potential of delgocitinib could not be determined. An additional assay was performed at 2 μM in the absence and presence of inhibitors to confirm substrate potential.

Source: Page No 12 of 42, Study report (b) (4) 208059

Abbreviations: ¹⁴C, carbon-14; HEK, human embryonic kidney; IC₅₀, half-maximal inhibitory concentration; MATE, multidrug and toxin extrusion transporter

The results showed that delgocitinib is not an inhibitor or substrate of MATE1 or MATE2-K.

Overall, based on the in vitro DDI studies, no DDI potential of delgocitinib is observed and therefore, the Applicant did not perform any clinical drug interaction studies. The Applicant's justification is that as delgocitinib showed limited metabolism, and low systemic exposure of topically applied delgocitinib, a low potential for any drug interaction is anticipated. The Applicant's justifications are reasonable.

14.2. In Vivo Studies

Delgocitinib is a pan-JAK inhibitor and acts on the JAK family of enzymes (JAK1, JAK2, JAK3), and TYK2 in a concentration-dependent manner. JAKs are intracellular enzymes associated with different cytokine receptors (heterodimeric or homodimeric complex) and are essential for cytokine signaling. Activation of JAKs upon cytokine-receptor interaction leads to initiation of phosphorylation and activation of STATs. The activated STATs activate the expression of cytokine-responsive genes to induce specific biological responses in target cells. Delgocitinib, by inhibiting the JAK-STAT pathway, attenuates the signaling of proinflammatory cytokines (IL-2, IL-4, IL-6, IL-13, IL-21, IL-23, GM-CSF), and IFN- α , downregulating the immune and inflammatory responses in cells of relevance to CHE pathology. The proposed indication for delgocitinib cream is for the topical treatment of moderate-to-severe CHE in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable.

The Applicant's clinical development program involved:

- Five phase 1 trials (four studies in healthy volunteers, one in adults, adolescents/children with moderate-to-severe AD (1181) (maximal use trial [MuST], one trial in subjects with moderate-to-severe CHE [MuST], and one trial in adults, adolescents, and children with moderate-to-severe atopic dermatitis).
- Three phase 2 trials (two in subjects with mild-to-severe CHE and one in subjects with AD).
- Three phase 3 trials in subjects with moderate-to-severe CHE (DELTA 3) along with two phase 3 ongoing trials in subjects with moderate-to-severe CHE.

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

The pharmacokinetics of delgocitinib was assessed in the following trials:

- Phase 1 trial under maximal use conditions with twice-daily administration of delgocitinib cream to evaluate pharmacokinetics and safety in adult subjects with moderate-to-severe CHE (LP0133-2285).
- Phase 3 clinical trial to assess efficacy and evaluate safety for 16 weeks in adult subjects with moderate-to-severe chronic hand eczema (DELTA 2).
- Phase 1 trial under maximal use conditions in subjects with AD (LP0133-1181) for 8 weeks in adults, adolescents, and children with moderate-to-severe AD.
- Phase 2a trial with twice-daily applications of delgocitinib ointment 30 mg/g in the treatment of chronic hand eczema (LP0133-1180).
- Phase 2b dose-ranging trial to evaluate delgocitinib cream for 16 weeks in adult subjects with chronic hand eczema (LP0133-1273).
- Phase 2b dose-ranging trial for 8 weeks in adult subjects with atopic dermatitis (LP0133-1275).
- Phase 1 trial to evaluate QT interval using Fridericia's correction (QTcF) prolongation and proarrhythmic potential evaluation for delgocitinib following oral administration in healthy subjects (LP0133-1409).
- Phase 1 trial to evaluate oral pharmacokinetics of delgocitinib in healthy subjects as single and multiple doses (NBX1-1).

Recommendation

NDA 219155 is acceptable from a clinical pharmacology perspective.

Postmarketing Commitment/PMR

None.

Summary of Clinical Pharmacology

The summary of pharmacokinetics, pharmacodynamics, and pharmacokinetic/ pharmacodynamic relationships of delgocitinib provided by the Applicant is based on the following clinical pharmacology studies conducted in subjects with CHE and AD:

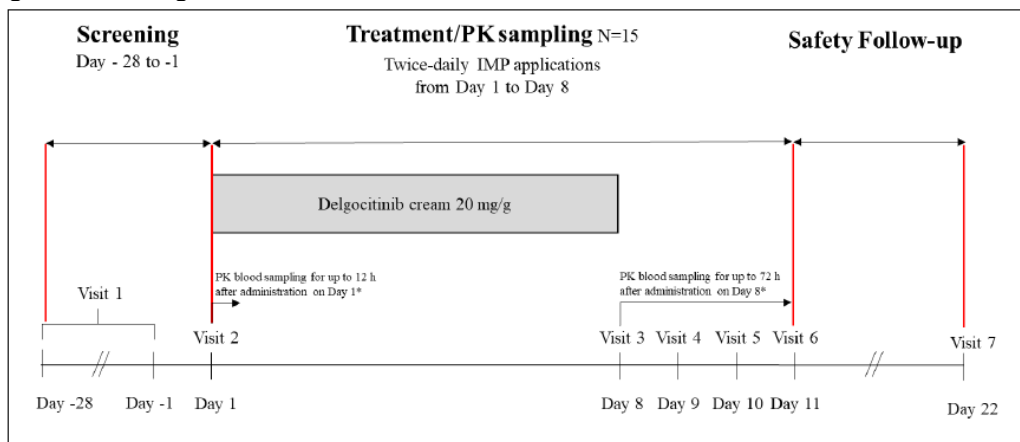
- Maximal use trial in adult subjects with moderate-to-severe CHE with final formulation (LP0133-2285).
- Maximal use trial in pediatric and adult subjects with AD (LP0133-1181) with earlier formulation.
- Phase 3 trial in adult subjects with moderate-to-severe CHE (DELTA 2) with the final formulation (subgroup of subjects treated under maximal use conditions).

Phase 1 Trial in Subjects With Moderate-to-Severe CHE (LP0133-2285)

Trial Design

This was a phase 1, open-label, single-site trial to evaluate the pharmacokinetics and safety of delgocitinib cream 20 mg/g (2%) in subjects with moderate-to-severe CHE.

Figure 14. Design for Phase 1 Pharmacokinetic Trial LP0133-2285



Source: Panel 2, Page 16 of 146, clinical study report LP0133-2285

Abbreviations: IMP, investigational medicinal product; N, number of subjects; h, hours; PK, pharmacokinetic

Trial Population

The trial was conducted in adult subjects (N=15; age range of 22 to 69 years) with moderate-to-severe CHE (according to IGA-CHE [i.e., an IGA-CHE score of 3 or 4]) who have had an inadequate response to, or for whom topical corticosteroids were medically inadvisable. The median BSA was 1%, range 0.25 to 3%.

Formulation

The formulation of delgocitinib cream, 20 mg/g (2%), was the same as the final formulation. The product was applied as a thin layer covering the affected areas, twice daily for 1 week (Days 1 to 7 plus one application on Day 8). The average IMP use during the 1-week treatment period was 13.07 g which corresponds to 0.87 g per application (15 applications in total during the trial) (Table 1.4.1: Summary of Exposure, Page No 61 of 146, clinical trial report LP0133-2285).

Pharmacokinetic Assessment

Pharmacokinetic assessment was performed on Day 1 and Days 8 to 11; Day 1: 0 hour (predose), 1 hour, 2 hours, 4 hours, 8 hours, 12 hours post-morning dose and Days 8 to 11: 0 hour (predose), 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours post-Day 8 morning dose.

Pharmacokinetic Results

The PK results and demographics are shown below.

Table 109. Demographic Parameters of Subjects, Trial LP0133-2285

	FAS N=16	SAF N=16	PKS N=15
Age [years]			
n	16	16	15
Mean (SD)	38.4 (14.6)	38.4 (14.6)	38.9 (14.9)
Median (Q1;Q3)	39.0 (24.0; 48.0)	39.0 (24.0; 48.0)	40.0 (23.0; 48.0)
Min; max	22; 69	22; 69	22; 69
Age group, n (%)			
n	16	16	15
18-64	15 (93.8)	15 (93.8)	14 (93.3)
65-84	1 (6.3)	1 (6.3)	1 (6.7)
>=85	0 (0.0)	0 (0.0)	0 (0.0)
Sex, n (%)			
n	16	16	15
Male	8 (50.0)	8 (50.0)	8 (53.3)
Female	8 (50.0)	8 (50.0)	7 (46.7)
Ethnic origin, n (%)			
n	16	16	15
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)
Not Hispanic or Latino	16 (100.0)	16 (100.0)	15 (100.0)
Race, n (%)			
n	16	16	15
White	14 (87.5)	14 (87.5)	13 (86.7)
Asian	1 (6.3)	1 (6.3)	1 (6.7)
Black or African American	1 (6.3)	1 (6.3)	1 (6.7)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: FAS = full analysis set; max = maximum; min = minimum; N = number of subjects; n = number of subjects with observation; PKS = pharmacokinetics analysis set; Q1 = 1st quartile; Q3 = 3rd quartile; SAF = safety analysis set; SD = standard deviation; % = percentage of subjects with observation.

Source: Panel 5, Page no 24 of 146, clinical trial report. LP0133-2285

A total of 16 subjects were screened and enrolled in the trial, 16 subjects completed the treatment, and 15 subjects completed the trial. It is noted that one subject prematurely discontinued during the pharmacokinetic sampling period on Day 9 due to the reason of “withdrawal by subject.” The subject performed an early termination visit on Day 9 and a safety follow-up visit on Day 50.

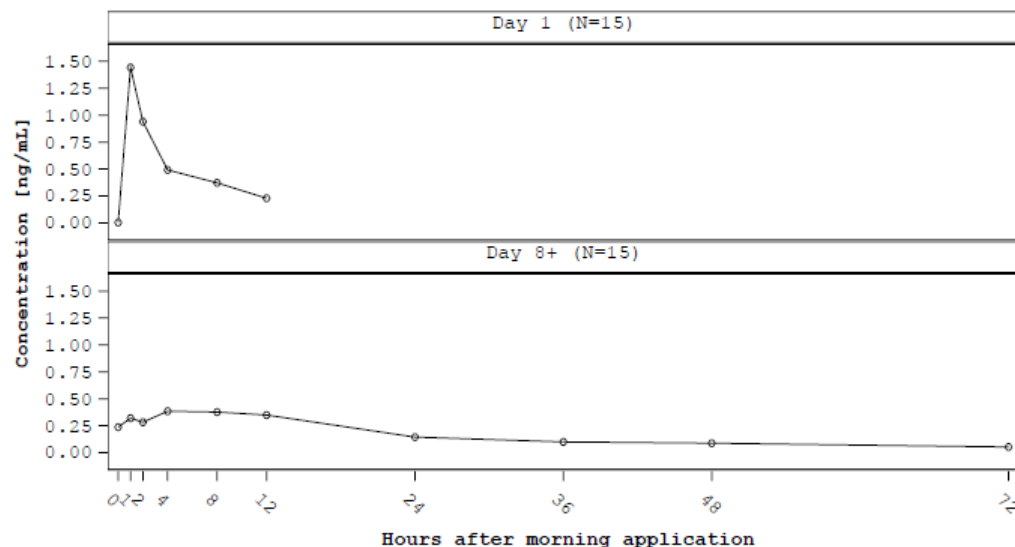
Table 110. Pharmacokinetic Results (AUC₀₋₁₂) and C_{max}, Trial LP0133-2285

PK Parameter	Delgocitinib Cream 20 mg/g (N=15)	
	Day 1	Day 8
C _{max} (ng/mL)		
N	15	15
Geometric mean (GSD)	0.50 (6.17)	0.46 (1.74)
Mean (SD)	1.53 (2.34)	0.53 (0.28)
CV, %	153.07	52.68
Min; max	0.01; 7.30	0.17; 1.08
AUC ₀₋₁₂ (h*ng/mL)		
N	15	15
Geometric mean (GSD)	2.5 (5.21)	3.7 (1.74)
Mean (SD)	6.1 (8.14)	4.2 (1.88)
CV, %	134.4	45.1
Min; max	0.0; 30.7	1.0; 7.6
T _{max} (h)		
N	15	15
Mean (SD)	3.4 (4.17)	6.4 (4.36)
Median (Q1; Q3) (1.9; 11.9)	0.9 (0.8; 7.8)	7.9
Min; max	0.8; 11.8	0.0; 12.1
T _{1/2} (h)		
N	NA	6
Geometric mean (GSD)		20.3 (1.31)
Mean (SD)		21.0 (5.98)
CV, %		28.5
Min; max		15.8; 30.9

Source: Panel 9, 10 and 11, clinical trial report. LP0133-2285

Abbreviations: AUC₀₋₁₂; C_{max}, area under the concentration-time curve from 0 to 12 hours; C_{max}, maximum plasma concentration; CV, coefficient of variation; GSD, geometric standard deviation; max, maximum; min, minimum; N, number of subjects receiving treatment; PK, pharmacokinetic; SD, standard deviation, T_{1/2}, half-life; T_{max}, time to maximum concentration

Figure 15. Mean Concentration Profile for Delgocitinib With Time in Pharmacokinetic Trial LP0133-2285



Source: Figure 2.3.5, Page 100 of 146, clinical trial report LP0133-2285

Abbreviations: N, number of subjects receiving treatment; PK, pharmacokinetic

Safety Assessments

Delgocitinib was well-tolerated and there were no AEs, deaths, or other SAEs reported. No abnormal vital signs or abnormal physical findings were noted at the final examination on Day 8. No clinically significant changes were observed for clinical chemistry, hematology, and urinalysis parameters from Day 1 (baseline) to Day 8 and none of the abnormal clinical chemistry, hematology, or urinalysis values were assessed to be clinically significant.

Delgocitinib competitively inhibited JAK1, JAK2, JAK3, and TYK2 with respect to adenosine triphosphate. The K_i values for delgocitinib on JAK1, JAK2, JAK3, and TYK2 were 2.08, 1.71, 5.45, and 13.9 nmol/L, respectively. Furthermore, delgocitinib inhibited the JAKs activity of JAK1, JAK2, JAK3 and TYK2 with IC_{50} mean values of 2.8 nmol/L, 2.6 nmol/L, 12.5 nmol/L, and 57.8 nmol/L, respectively. The C_{max} in this maximal use study in subjects with CHE was 1.53 ng/mL (4.93 nmol/L) and 0.53 ng/mL (1.71 nmol/L) on Day 1 and 8, respectively. Overall, the C_{max} is on par with IC_{50} of JAK1 and JAK2. While the systemic concentration/ IC_{50} ratio is much lower than oral JAK inhibitors, the systemic safety concern cannot be ruled out based on systemic exposure/ IC_{50} comparison.

It is noted that approximately 33% of subjects on Day 1 and 20% subjects on Day 8 in the study showed concentrations in the subnanomolar range.

Phase 1 Trial Under Maximal Use Conditions in Subjects With Moderate-to-Severe AD (LP0133-1181)

Trial Objectives

To investigate safety and pharmacokinetics in adults, adolescents (12 to 17 years) and children (2 to 11 years) with moderate-to-severe AD.

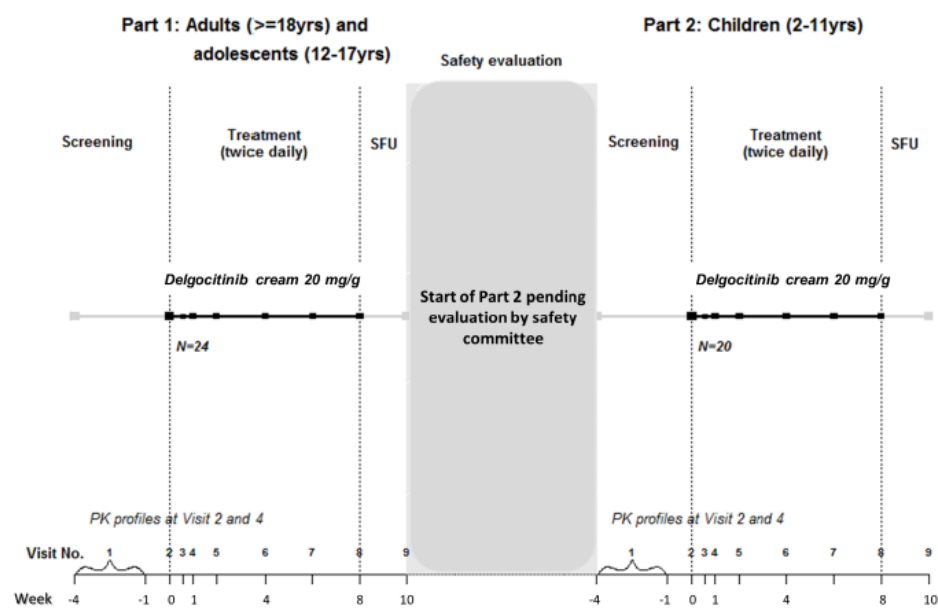
Trial Design

This was a phase 1 open-label, multicenter, single-arm, 8-week trial in adults, adolescents, and children with moderate-to-severe AD.

The trial consisted of two parts:

- Part 1 enrolled adolescents (12 to 17 years) and adults (≥ 18 years) only.
- Part 2 enrolled children (2 to 11 years).

Figure 16. Trial Design for Maximal Use Conditions in Subjects With AD, Trial LP0133-1181



Abbreviations: PK: pharmacokinetic; SFU: safety follow-up; N: number of subjects.
Source: Clinical trial report (LP0133-1181), Panel 3, Page No.19

Each part contained a screening period (Week 4 to Week 1), treatment period (Week 0 to Week 8) and a safety follow-up (Week 8 to Week 10). In Part 2 of the trial, the data monitoring committee assessed patient safety for children (age 2 to 11 years) during conduct.

Trial Population and Body Surface Area

The eligible subjects had a diagnosis with AD, with the severity of moderate-to-severe at screening and baseline according to the Validated Investigator's Global Assessment for Atopic Dermatitis (score ≥3).

- Part 1: Adolescents (12 to 17 years; mean %BSA: 31.8 [range: 25.0 to 47.0]) and adults (≥18 years; mean %BSA of 33.6 [range: 29.0 to 50.0])
- Part 2: Children (2 to 11 years) with ≥35% treatable BSA at screening and a history of AD for ≥3 months (children 2 to 5 years) and for ≥12 months (children 6 to 11 years); mean %BSA of 46.0 (range: 30.0 to 78.0)

It is noted that the Applicant changed the inclusion criterion from 25 to 50% to ≥35% treatable BSA during the conduct of Part 2.

Formulation

The formulation of delgocitinib cream, 20 mg/g, that was used in the trial is not the final formulation. The difference in the formulation from the final formulation relates to the concentration of (b) (4) ((b) (4) in the early formulation is (b) (4) mg/g whereas the final formulation contained (b) (4) of (b) (4) mg/g).

Per the email communication with Biopharmaceutics and Drug Product reviewers,

“(b) (4). Based on the submitted stability data, the formulation with the reduced (b) (4) met the desired stability criteria throughout its shelf life, (b) (4). This change in the formulation did not require any pharmacokinetic or clinical bridging trial as determined by Biopharmaceutics. Furthermore, Biopharmaceutics determined the change in the formulation to be minor and a bridge was established based on CMC information submitted. Hence, pharmacokinetic data obtained using the old formulation would apply.”

Refer to OPQ drug product review for the detailed information on the assessment of formulation change and supporting data.

Pharmacokinetic Assessment

Pharmacokinetic samples were collected on Day 1 and Day 8 at 1-, 2-, 4-, 8- and 12-hours postdose, followed by a second dose administration. Blood samples were drawn from a skin area not treated with product.

Pharmacokinetic Results

A total of 20 children, 12 adolescents, and 14 adults were enrolled in the trial. Children enrolled in the trial had numerically higher Eczema Area and Severity Index score and %BSA compared to adults and adolescents. The demographics of subjects is shown in [Table 111](#) and the disease characteristics are shown in [Table 112](#).

Table 111. Summary of Demographic and Baseline Characteristics, Trial LP0133-1181

Demographic	Children 2-11 Years (N=20)	Adolescents 12-17 Years (N=12)	Adults ≥18 Years (N=14)	All Subjects (N=46)
Sex				
n	20	12	14	46
Male	13 (65.0%)	4 (33.3%)	8 (57.1%)	25 (54.3%)
Female	7 (35.0%)	8 (66.7%)	6 (42.9%)	21 (45.7%)
Race				
n	20	12	14	46
White	8 (40.0%)	7 (58.3%)	12 (85.7%)	27 (58.7%)
Black or African American	7 (35.0%)	2 (16.7%)	0	9 (19.6%)
Asian	3 (15.0%)	2 (16.7%)	2 (14.3%)	7 (15.2%)
Native Hawaiian or other Pacific islander	0	0	0	0
	0	1 (8.3%)	0	1 (2.2%)
American Indian or Alaska Native	2 (10.0%)	0	0	2 (4.3%)
Other				
Ethnicity				
n	20	12	14	46
Hispanic or Latino	3 (15.0%)	0	2 (14.3%)	5 (10.9%)
Not Hispanic or Latino	17 (85.0%)	12 (100%)	12 (85.7%)	41 (89.1%)

Demographic	Children 2-11 Years (N=20)	Adolescents 12-17 Years (N=12)	Adults ≥18 Years (N=14)	All Subjects (N=46)
Country				
n	20	12	14	46
United States	15 (75.0%)	6 (50.0%)	10 (71.4%)	31 (67.4%)
Canada	5 (25.0%)	6 (50.0%)	4 (28.6%)	15 (32.6%)

Source: Panel 1, Page No 43 of 72, Clinical trial report (LP0133-1181)

Abbreviations: N, number of subjects in age group; n, number of subjects with demographic characteristic

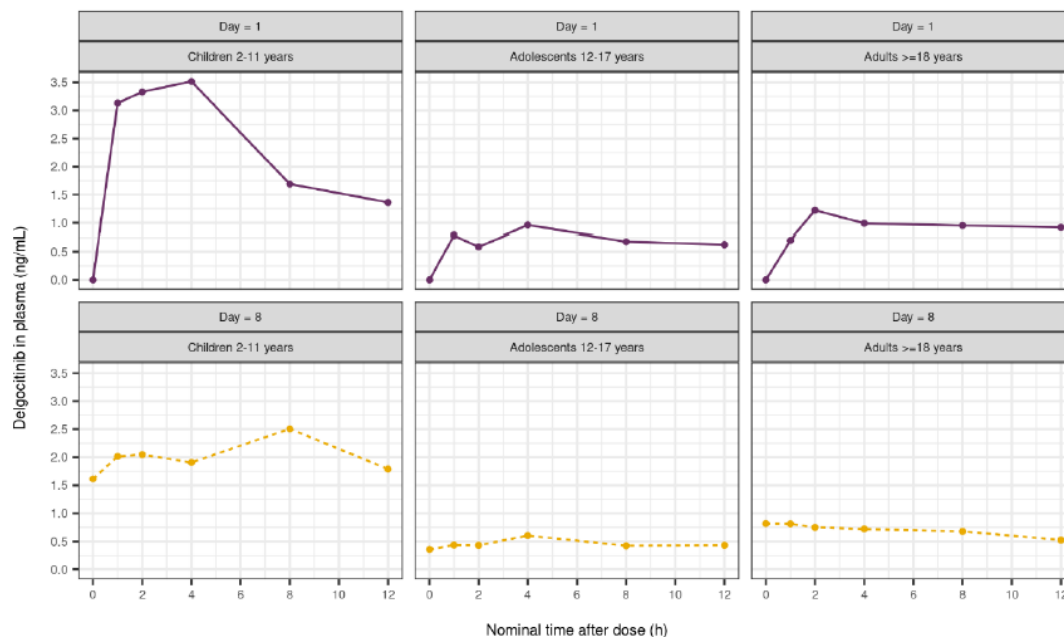
Table 112. Summary of Baseline EASI Score, vIGA-AD Score, and BSA Involved for Enrolled Subjects

Baseline Parameters	Children 2-11 Years (N=20)	Adolescents 12-17 Years (N=12)	Adults ≥18 Years (N=14)	All Subjects (N=46)
EASI total				
n	20	12	14	46
Mean (SD)	27.2 (9.9)	20.1 (7.4)	19.9 (7.4)	23.1 (9.1)
Median	26.7	19.2	18.6	21.4
Q1; Q3	17.5; 32.6	15.5; 25.8	15.4; 23.6	16.2; 30.1
Min; max	13.0; 46.6	9.0; 33.0	9.1; 36.0	9.0; 46.6
vIGA-AD				
n	20	12	14	46
0: clear	0	0	0	0
1: almost clear	0	0	0	0
2: mild	0	0	0	0
3: moderate	10 (50.0%)	7 (58.3%)	12 (85.7%)	29 (63.0%)
4: severe	10 (50.0%)	5 (41.7%)	2 (14.3%)	17 (37.0%)
BSA (%)				
n	20	12	14	46
Mean (SD)	46.0 (13.1)	31.8 (6.3)	33.6 (5.8)	38.5 (11.7)
Median	43.5	29.5	31.5	33.5
Q1; Q3	34.5; 53.5	28.5; 34.0	30.0; 36.0	30.0; 45.0
Min; max	30.0; 78.0	25.0; 47.0	29.0; 50.0	25.0; 78.0

Source: Panel 12, Page No. 44 of 72, Clinical trial report (LP0133-1181)

Abbreviations: BSA, body surface area; EASI, Eczema Area and Severity Index; max, maximum; N, number of subjects in age group; n, number of subjects with the disposition; Q1, first quartile; Q3, third quartile, min, minimum; SD, standard deviation; vIGA-AD, Validated Investigator's Global Assessment for Atopic Dermatitis

Figure 17. Geometric Mean Concentrations of Delgocitinib by Treatment Day and Age Cohort in Subjects With Atopic Dermatitis



Source: Panel 9, Page No.58 of 72, Clinical trial report (LP0133-1181)
Abbreviation: h, hour

Overall, the systemic exposure of delgocitinib tended to be higher in subjects with higher treatable %BSA involvement, with a more-than-proportional increase in AUC and C_{max} observed, compared with %BSA. It is noted that the systemic exposure in children 2- to 11-years-old was much higher than in adults and adolescents ([Table 113](#)) and this might be explained by a higher treatable %BSA ([Table 112](#)), a higher ratio of BSA/body weight, and the different disease severity ([Table 112](#)) compared with adults and adolescents.

The pharmacokinetic parameters C_{max} , AUC, and time to maximum concentration (T_{max}) values at Day 1 and Day 8 are presented in [Table 113](#). The T_{max} values for the individual subjects ranged between 0.83 to 12.22 hours at Day 1 and from 0.00 to 12.03 hours at Day 8, indicating variability in the absorption profiles. However, for the majority of the subjects, the T_{max} was reached during the first hour after administration, with a median T_{max} of 1 to 2 hours in the different age groups. The mean exposure was low, but few subjects, mainly in the children group, showed higher exposure, with values for C_{max} ranging from 0.01 to 79.80 ng/mL at Day 1 and from 0.04 to 54.70 ng/mL at Day 8.

The reported AEs in the trial did not identify safety concerns for the subjects with higher exposure.

Table 113. Pharmacokinetic Parameters of Delgocitinib by Age Group, Trial LP0133-1181

PK Parameter (Mean ± SD)	Children 2-11 Years N=17	Adolescents 12-17 Years N=10	Adults ≥18 Years N=12	All Subjects N=39
Day 1				
C _{max} (ng/mL)	15.82 (22.25)	4.06 (8.21)	3.33 (4.75)	8.96 (16.38)
AUC _{0-t} (ng.h/mL)	71.30 (103.91)	32.58 (67.01)	21.59 (24.93)	46.08 (79.45)
T _{max} (h)	1.98 (0.83-12.22)	2.04 (0.98-8.17)	2.04 (0.92-12.17)	2.03 (0.83-12.22)
Day 8				
C _{max} (ng/mL)	9.81 (14.94)	1.77 (3.27)	1.78 (1.22)	5.07 (10.35)
AUC _{0-t} (ng.h/mL)	54.68 (64.93)	16.33 (28.06)	12.56 (7.77)	31.59 (48.47)
T _{max} (h)	1.99 (0.00-11.98)	1.02 (0.00-12.03)	1.02 (0.00-8.10)	1.03 (0.00-12.03)

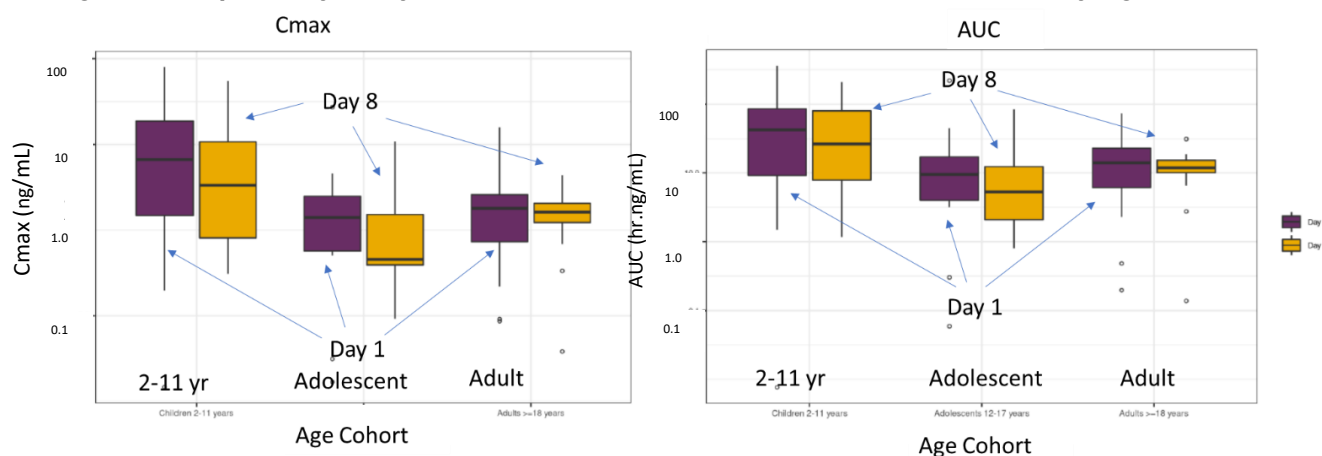
Source: Panel 20, Page 59 of 72, Clinical trial report LP0133-1181

Abbreviations: AUC_{0-t}, area under the concentration-time curve from dosing (time 0) to time t; C_{max}, maximum plasma concentration; N, number of subjects in age group; SD, standard deviation; T_{max}, time to maximum concentration

The Agency noticed an error in the Applicant-submitted pharmacokinetic data, specifically for the C_{max} for the adults (≥18 years) which was mentioned as 33.33 ng/mL, whereas the Agency's verified value was 3.33 ng/mL. The Applicant submitted a revised pharmacokinetic data table in response to an information request dated February 11, 2025.

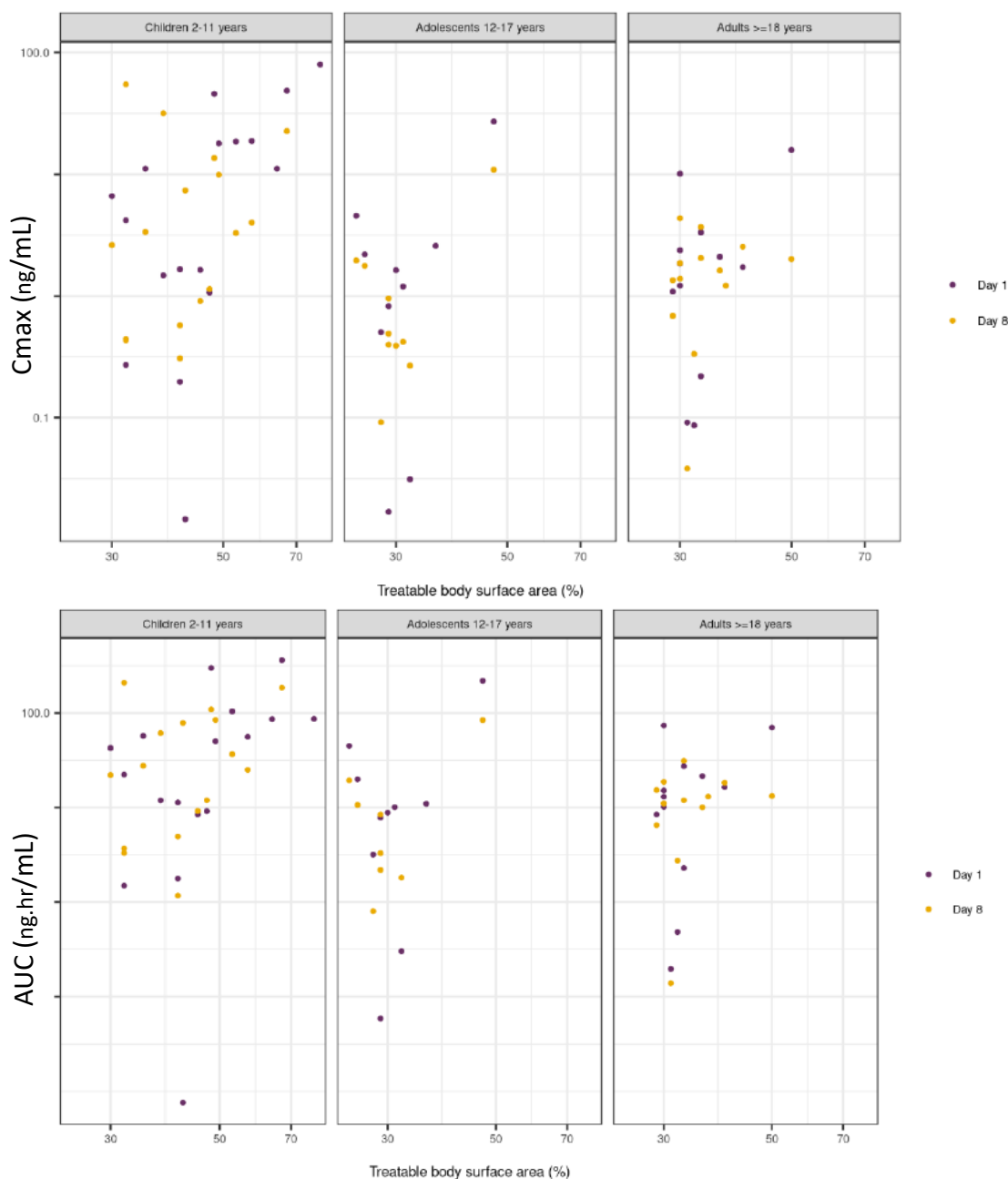
The Applicant also reported exploratory analysis of exposure by age group ([Figure 18](#)) and impact of exposure by treatment area ([Figure 19](#)) group. The exploratory analyses showed that the systemic exposure increased with increase in %BSA especially in children.

Figure 18. Exploratory Analysis: C_{max} and AUC of Plasma Concentration Profile by Age Cohorts



Source: Panel 21, Page No.61 of 72, Clinical trial report LP0133-1181

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration

Impact of Treatment Area Exposure: Per-Protocol Analysis Set**Figure 19. Exploratory Analysis: Treatment Area Exposure by Age Cohorts**

Source: Panel 22, Page No. 62 of 72, Clinical trial report LP0133-1181

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration

Based on the exploratory analysis, the systemic exposure on Day 1 and Day 8 are higher in 2- to 11-year-age group compared to adolescents and adult groups for both C_{max} and AUC. The increase in C_{max} and AUC seemed to be more than proportional compared with %BSA as children (2 to 11) had higher treatable BSA than adolescent and adults. Higher treatable %BSA observed in children was due to different inclusion criterion; AD involvement in children (AD

involvement of $\geq 35\%$ treatable BSA) compared with adults and adolescents (AD involvement of 25 to 50% treatable BSA). As noted earlier, the mean BSA was 46% in 2- to 11-year-age group, whereas it was 32% and 34% respectively in adolescents and adults, which accounts for the higher exposure of delgocitinib in younger children than other age group subjects.

To further characterize the exposure in the children age group, the group was split into two age subgroups, i.e., 2- to 5- and 6- to 11-year-age groups. The mean $C_{\max}$ and AUC showed a tendency of higher exposure in the 2- to 5-year-age group. At Day 1, there was a tendency to higher $C_{\max}$ in the 2- to 5-year-age group compared with the 6- to 11-year-age group, while at Day 8 the $C_{\max}$ values were more comparable, as shown below.

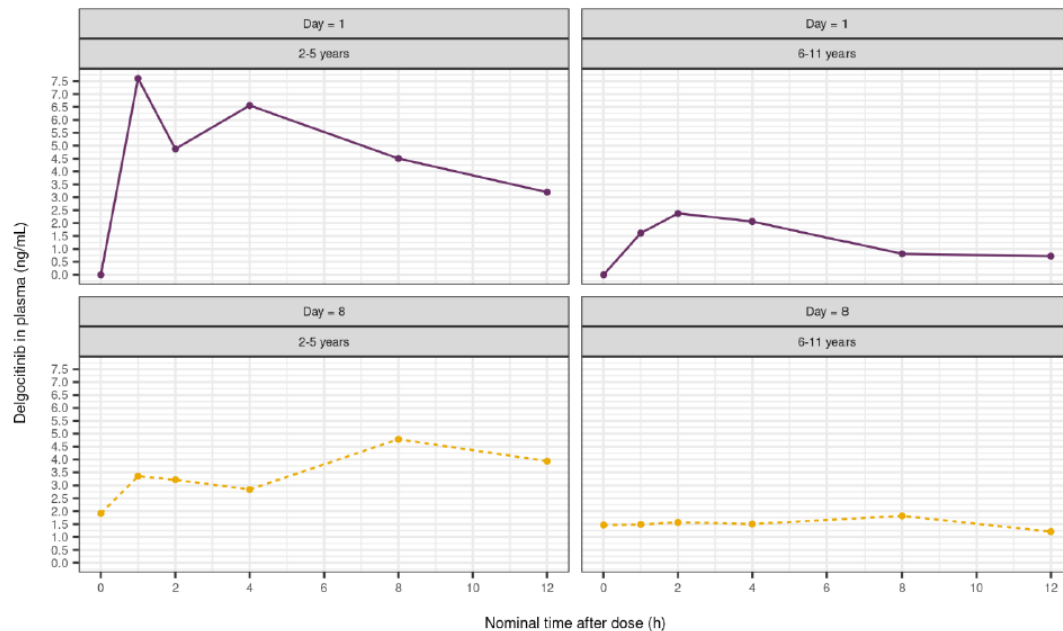
Table 114. Pharmacokinetic Parameters of Delgocitinib by Age Group, Trial LP0133-1181

Parameter (Mean $\pm$ SD)	Children 2-5 Years N=8	Children 6-11 Years N=9	All Children N=17
Day 1			
$C_{\max}$ (ng/mL)	25.91 (29.13)	6.85 (7.42)	15.82 (22.25)
AUC _{0-t} (ng*h/mL)	119.91 (137.67)	28.09 (23.41)	71.30 (103.91)
Day 8			
$C_{\max}$ (ng/mL)	8.02 (8.68)	10.88 (18.08)	9.81 (14.94)
AUC _{0-t} (ng*h/mL)	70.10 (70.14)	45.44 (63.57)	54.68 (64.93)

Source: Panel 23, Page 63 of 72, Clinical trial report LP0133-1181

Abbreviations: AUC_{0-t}, area under the concentration-time curve from dosing (time 0) to time t; $C_{\max}$, maximum plasma concentration

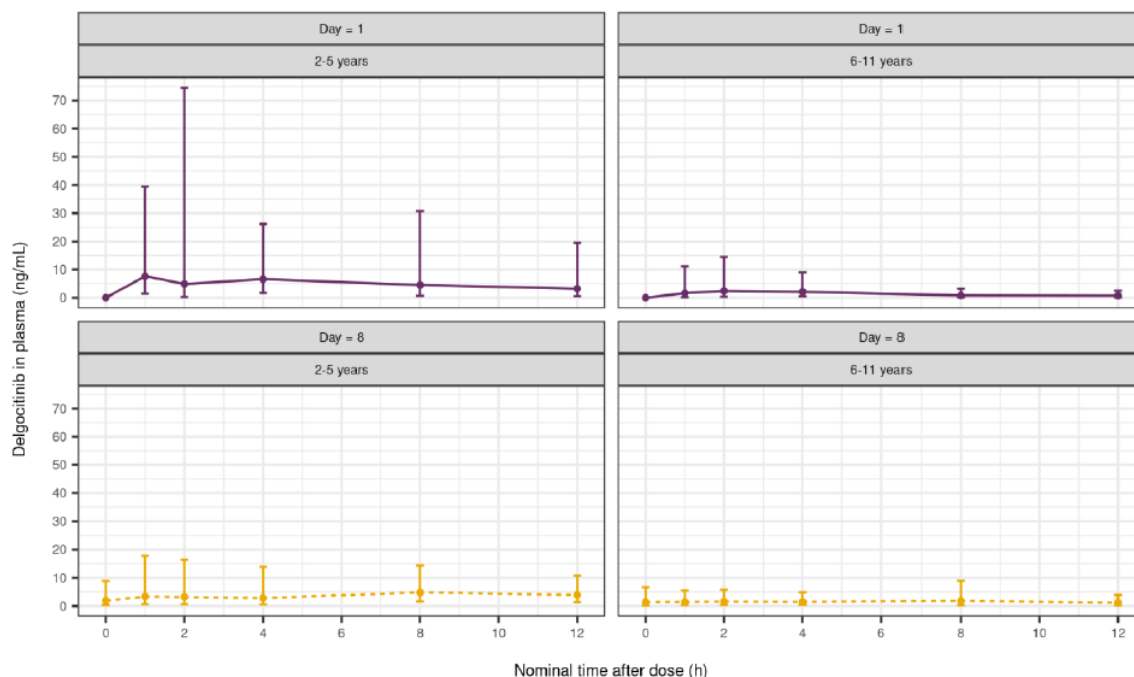
Figure 20. Geometric Mean Profiles of Systemic Concentration of Delgocitinib in Children



Source: Figure 3.6.13, Clinical trial report LP0133-1181

Abbreviation: h, hour

Figure 21. Geometric Mean Profiles of Delgocitinib With Geometric Standard Deviation in Children



Source: Figure 3.6.14, Clinical trial report LP0133-1181
Abbreviation: h, hour

The MuST data from AD is supportive for the CHE indication as the disease is similar and the %BSA involved in CHE is smaller than AD. Furthermore, the difference in the formulation used in that trial is considered minor, and the data supported the exploration to the CHE indication.

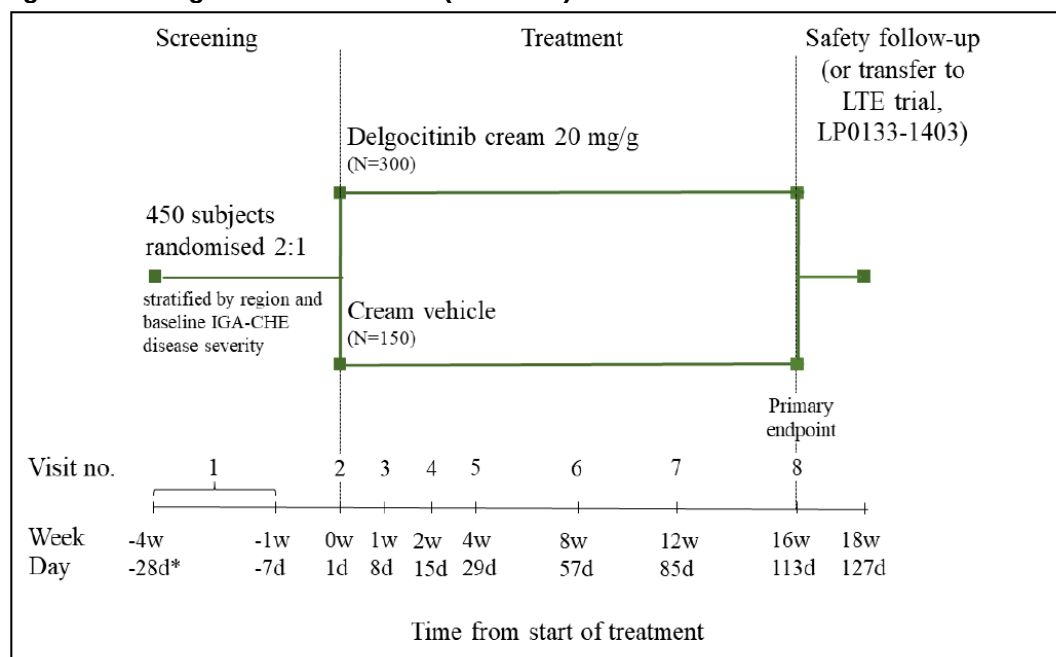
Phase 3 Trial in Adult Subjects With Moderate-to-Severe CHE (DELTA 2)

Trial Design

The Applicant conducted additional pharmacokinetic assessments of delgocitinib cream under maximal use conditions in a subset of subjects with moderate-to-severe CHE in the current phase 3 trial.

This trial was designed as randomized (2:1), double-blind, vehicle-controlled, parallel-group, multisite, phase 3 trial to assess the efficacy and safety of twice-daily delgocitinib cream compared with vehicle for 16 weeks in adult subjects with moderate-to-severe CHE.

Figure 22. Design for Phase 3 Trial (DELTA 2)



Source: Panel 3, Page No, 27 of 695, Clinical trial report LP0133-1402

Abbreviations: d, day; LTE, long-term extension; w, week, IGA-CHE, Investigator's Global Assessment for chronic hand eczema

Trial Population

The trial population was adults with moderate-to-severe CHE who had an inadequate response to, or for whom TCS were not advisable.

Out of the total number of subjects exposed to delgocitinib (N=313), 75 subjects had severe CHE (IGA-CHE score=4) at baseline; 19 of 75 subjects were in the upper quartile of IMP use. The mean IMP use was 0.98 g delgocitinib cream per application and mean %BSA was 2.17% in these 19 subjects and are considered to be under maximal use conditions. Remaining 294 subjects (238 subjects with moderate CHE and 56 subjects with severe disease but a lower IMP use) were not under MuST (mean IMP use of 0.52 g per application and mean %BSA of 1.48%).

The specific inclusion criteria included the following.

- Diagnosis of CHE, defined as hand eczema that has persisted for more than 3 months or returned twice or more within the last 12 months.
- Disease severity graded as moderate-to-severe at screening and baseline according to IGA-CHE (i.e., an IGA-CHE score of 3 or 4).
- HESD itch score (weekly average) of ≥ 4 points at baseline. The baseline weekly average will be calculated from daily assessments of itch severity during the 7 days immediately preceding the baseline visit (Day 7 to Day 1). A minimum of 4 itch scores out of the 7 days is required to calculate the baseline average score.
- Subjects who have a documented recent history of inadequate response to treatment with TCS (at any time within 1 year before the screening visit) or for whom TCS are documented to be otherwise medically inadvisable (e.g., due to important side effects or safety risks).

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Formulation

The final to-be-marketed formulation of delgocitinib cream, 20 mg/g, was used in the trial.

Pharmacokinetic Assessment

The pharmacokinetic blood samples were taken 2 to 6 hours post-application of IMP at Week 1, Week 4, and Week 16.

Pharmacokinetic Results

Table 115. Summary of Subjects Pharmacokinetic Parameters, Trial DELTA 2

Delgocitinib plasma concentration	Delgocitinib 20 mg/g Maximal use conditions (N = 19)	Delgocitinib 20 mg/g Remaining subjects (N = 294)	Delgocitinib 20 mg/g Total (N = 313)
Week 1			
n	19	268	287
Geometric mean, ng/mL	0.58	0.19	0.21
CV (%)	147.40	213.97	218.28
Min; max	0.10; 4.46	0.00; 5.65	0.00; 5.65
Week 4			
n	17	259	276
Geometric mean, ng/mL	0.58	0.19	0.21
CV (%)	95.91	241.49	239.82
Min; max	0.19; 3.69	0.00; 29.20	0.00; 29.20
Week 16			
n	16	246	262
Geometric mean, ng/mL	0.51	0.10	0.11
CV (%)	143.21	454.55	459.68
Min; max	0.07; 2.98	0.00; 4.63	0.00; 4.63

Abbreviations: CV = coefficient of variation; max = maximum; min = minimum; N = number of subjects within a treatment group; n = number of subjects with data.

Source: Panel 20, Module 2.7.2 Summary of Clinical Pharmacology, Page No. 48 of 74

Table 116. Summary of Demographic and Baseline Characteristics, Trial DELTA 2

	Delgocitinib 20 mg/g Severe IGA-CHE and high IMP consumption (N=19)	Delgocitinib 20 mg/g Moderate IGA-CHE or lower IMP consumption (N=294)	Delgocitinib 20 mg/g Total (N=313)
Age (years)			
n	19	294	313
Mean (SD)	50.7 (10.8)	44.9 (14.8)	45.3 (14.6)
Median (Q1;Q3)	54.0 (41.0;59.0)	45.0 (33.0;56.0)	46.0 (34.0;57.0)
Min;max	33;66	18;83	18;83
Sex, n (%)			
n	19 (100.0)	294 (100.0)	313 (100.0)
Male	6 (31.6)	104 (35.4)	110 (35.1)
Female	13 (68.4)	190 (64.6)	203 (64.9)
BMI (kg/m ²)			
n	19	294	313
Mean (SD)	28.72 (6.25)	27.15 (5.38)	27.24 (5.44)
Median (Q1;Q3)	27.64 (23.83;31.91)	26.55 (22.77;30.63)	26.97 (22.96;30.69)
Min;max	21.4;47.0	16.8;46.7	16.8;47.0
Race, n (%)			
n	19 (100.0)	294 (100.0)	313 (100.0)
White	18 (94.7)	276 (93.9)	294 (93.9)
Black or African American		2 (0.7)	2 (0.6)
Asian other		8 (2.7)	8 (2.6)
Native Hawaiian or Other Pacific Islander	1 (5.3)		1 (0.3)
Other		5 (1.7)	5 (1.6)
White,Black or African American		1 (0.3)	1 (0.3)
Not reported		2 (0.7)	2 (0.6)
IGA-CHE, n (%)			
n	19 (100.0)	294 (100.0)	313 (100.0)
3 - Moderate		238 (81.0)	238 (76.0)
4 - Severe	19 (100.0)	56 (19.0)	75 (24.0)
HECSI score			
n	19	294	313
Mean (SD)	112.0 (68.2)	61.2 (33.0)	64.3 (37.9)
Median (Q1;Q3)	77.0 (60.0;171.0)	57.0 (37.0;80.0)	59.0 (38.0;82.0)
Min;max	48;272	7;260	7;272
CHE subtype, n (%)			
n	19 (100.0)	294 (100.0)	313 (100.0)
Allergic contact dermatitis	2 (10.5)	25 (8.5)	27 (8.6)
Irritant contact dermatitis	8 (42.1)	66 (22.4)	74 (23.6)
Atopic hand eczema	3 (15.8)	79 (26.9)	82 (26.2)
Pompholyx	4 (21.1)	40 (13.6)	44 (14.1)
Hyperkeratotic eczema	2 (10.5)	84 (28.6)	86 (27.5)
eGFR (mL/min/1.73m ²)			
n	19	294	313
Mean (SD)	92.9 (16.8)	98.4 (17.2)	98.1 (17.2)
Median (Q1;Q3)	94.9 (85.1;104.3)	99.4 (87.0;111.8)	99.1 (86.8;111.7)
Min;max	59;120	42;136	42;136
Country, n (%)			
n	19 (100.0)	294 (100.0)	313 (100.0)
Belgium	3 (15.8)	8 (2.7)	11 (3.5)
Canada	5 (26.3)	59 (20.1)	64 (20.4)
Denmark		19 (6.5)	19 (6.1)
Germany	4 (21.1)	94 (32.0)	98 (31.3)
Netherlands		13 (4.4)	13 (4.2)
Poland	5 (26.3)	59 (20.1)	64 (20.4)
Spain	2 (10.5)	42 (14.3)	44 (14.1)

Source: Table 3.4, Summary of Clinical pharmacology Appendix, Pane 65 of 78
Abbreviations BMI; body mass index; CHE, chronic hand eczema; HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; IMP, investigational medicinal product; N, number of subjects in treatment arm; n, number of subjects with characteristic; Q1, first quartile; Q3, third quartile; SD, standard deviation

Table 117. Pharmacokinetic Parameters of Delgocitinib Under Maximal Use Conditions at Week 1, Week 4 and Week 16

Delgocitinib plasma concentration (ng/mL)	Delgocitinib 20 mg/g Severe IGA-CHE and high IMP consumption (N=19)	Delgocitinib 20 mg/g Moderate IGA-CHE or lower IMP consumption (N=294)	Delgocitinib 20 mg/g Total (N=313)
Week 1			
n	19	268	287
Mean	1.01	0.38	0.42
Geometric mean	0.58	0.19	0.21
CV (%)	147.40	213.97	218.28
Median	0.72	0.21	0.22
Q1;Q3	0.28 ; 1.02	0.11 ; 0.43	0.11 ; 0.47
Min;Max	0.10 ; 4.46	0.00 ; 5.65	0.00 ; 5.65
Week 4			
n	17	259	276
Mean	0.81	0.48	0.50
Geometric mean	0.58	0.19	0.21
CV (%)	95.91	241.49	239.82
Median	0.56	0.22	0.23
Q1;Q3	0.30 ; 0.97	0.11 ; 0.47	0.12 ; 0.53
Min;Max	0.19 ; 3.69	0.00 ; 29.20	0.00 ; 29.20
Week 16			
n	16	246	262
Mean	0.83	0.32	0.35
Geometric mean	0.51	0.10	0.11
CV (%)	143.21	454.55	459.68
Median	0.50	0.13	0.14
Q1;Q3	0.31 ; 1.14	0.05 ; 0.34	0.05 ; 0.37
Min;Max	0.07 ; 2.98	0.00 ; 4.63	0.00 ; 4.63
Early termination			
n	1	12	13
Mean	0.06	0.51	0.47
Geometric mean	0.06	0.02	0.02
CV (%)		5146.30	3868.89
Median	0.06	0.00	0.00
Q1;Q3	0.06 ; 0.06	0.00 ; 0.11	0.00 ; 0.08
Min;Max	0.06 ; 0.06	0.00 ; 2.99	0.00 ; 2.99

Source: Table 3.9, Summary of Clinical pharmacology Appendix, Pane 71 of 78

Abbreviations BMI; body mass index; CHE, chronic hand eczema; HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; IMP, investigational medicinal product; N, number of subjects in treatment arm; n, number of subjects with characteristic; Q1, first quartile; Q3, third quartile; SD, standard deviation

The mean plasma concentration of delgocitinib (one sample, 2 to 6 hours postmorning dose) under maximal use conditions was generally comparable between Week 1, 4, and 16 and was higher compared to the other population indicating that the degree of disease severity could impact the systemic exposure.

It is noted that approximately 62% of subjects at Week 1, 64% subjects at Week 4 and 81% subjects at Week 16 in the study showed concentrations in the subnanomolar range.

Phase 2a Trial in Adult Subjects With Chronic CHE (LP0133-1180)

Trial Design

This was a phase 2a, prospective, randomized, double-blind, two arms, vehicle-controlled, parallel-group, 8 weeks, phase 2a trial in subjects with CHE. A total of 91 male and female subjects with at least mild disease severity were randomized into this clinical trial, conducted across Germany at 13 clinical sites. The trial subjects were administered with twice-daily over a 56-day treatment period (8 weeks) to delgocitinib ointment 30 mg/g or vehicle (1.7 mg/cm²) in 2:1 ratio.

Trial Population

The subjects for the trial had the diagnosis of chronic CHE with:

- Clinical diagnosis of CHE with or without atopic etiology/background with a history of not adequately controlled disease activity with cutaneously applied corticosteroids.
- Physician Global Assessment of disease severity graded as at least mild at baseline (Week 0).

Formulation

The formulation of delgocitinib ointment, 30 mg/g that was used in the trial is different than the final formulation.

Table 118. Delgocitinib Ointment Formulation Composition

Name of component	Delgocitinib ointment	
	Vehicle	30 mg/g
Delgocitinib	-	30
(b) (4)		

^a Contains the (b) (4)

Source: Table 2-3, Quality Overall Summary, Page No. 10, Module: 2.3P
Abbreviation: (b) (4)

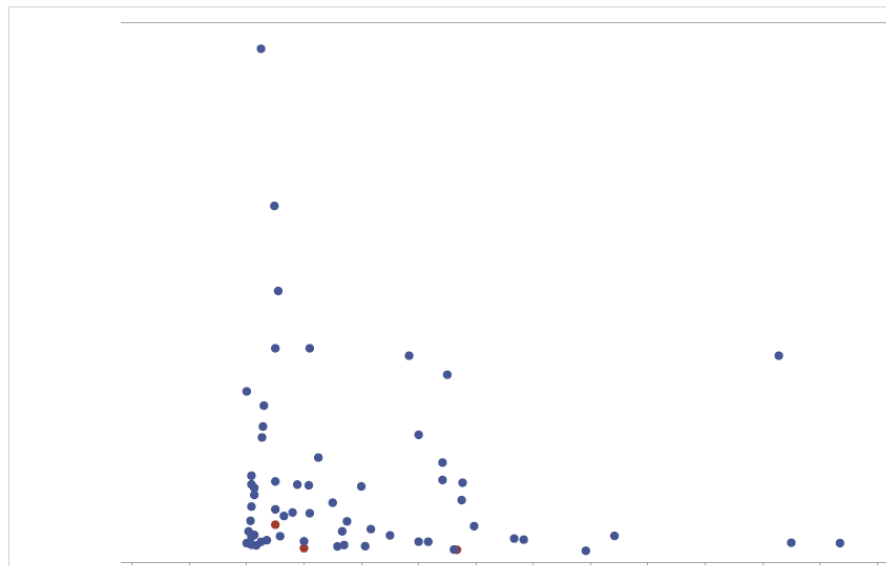
Pharmacokinetic Assessment

Pharmacokinetic assessment was performed to evaluate systemic concentrations of delgocitinib at 1 week (2 to 6 hours after the morning application).

Pharmacokinetic Results

Out of 91 subjects, 86 (94.5%) subjects completed the trial (delgocitinib group: 59 [98.3%] subjects; vehicle group: 27 [87.1%] subjects). In the 60 samples obtained from subjects treated with delgocitinib ointment 30 mg/g, plasma concentrations above LLOQ of (5.00 pg/mL) were measured in all subjects. The measured concentrations in the 60 samples were between 5.01 and 2720 pg/mL with a mean value of 385 pg/mL. The systemic exposure of delgocitinib was low as very few samples were above 1 ng/mL.

Figure 23. Plasma Concentrations of Delgocitinib in Subjects With Chronic Hand Eczema, Trial LP0133-1180



Source: Figure 5, Page No. 137 of 366, Clinical trial report LP0133-1180

Delgocitinib was found to be more efficacious compared to vehicle as confirmed by Physician Global Assessment (45.7% versus 14.9%) at Week 8. The improvement in the disease severity seen for both secondary measures HECSI assessment and Patient's Global Assessment (PaGA) of disease severity supports this conclusion, showing a lower mean HECSI score (12.3 versus 27.9) and a greater percentage of subjects achieving treatment success according to PaGA (31.0% versus 17.6%) in the delgocitinib group than the vehicle group at Week 8.

The most common AEs reported for the delgocitinib group included nasopharyngitis (25.0%), postoperative wound infection and headache (6.7%, each), as well as hand dermatitis (5.0%). The only AEs reported more frequently in the delgocitinib group than in the vehicle group were nasopharyngitis and headache. An AE of worsening of CHE was reported more frequently in the vehicle group than in the delgocitinib group.

Phase 2b Dose-Ranging Trial in Adult Subjects With Chronic CHE (LP0133-1273)

Trial Design

This was a phase 2b, double-blind, randomized, five-arm, vehicle-controlled, parallel-group, multicenter, dose-ranging trial to establish a dose-response relationship and to investigate the efficacy and safety of delgocitinib cream in the treatment of adult subjects with mild-to-severe CHE. A total of 250 subjects were randomized in a 1:1:1:1:1 ratio (delgocitinib cream 1, 3, 8, or 20 mg/g or placebo).

The randomization was stratified by the severity of CHE according to the Investigator's Global Assessment for CHE (IGA-CHE score of 2 [mild], 3 [moderate], or 4 [severe]) and region (Europe and North America).

Trial Population

The subjects for the trial had chronic CHE with:

- Diagnosis of chronic hand eczema defined as hand eczema that has persisted for more than 3 months or returned twice or more within the last 12 months.
- Disease severity graded as mild-to-severe according to Investigator's Global Assessment for chronic hand eczema (i.e., an IGA-CHE score of 2 or more).
- Recent history (within 1 year before the screening visit) of inadequate response to topical corticosteroid treatment or topical corticosteroid treatment being medically inadvisable.

Formulation

Delgocitinib cream at 1, 3, 8, or 20 mg/g or placebo were administered twice daily via cutaneous application for 16 weeks.

The applications were performed approximately 12 hours apart. The formulation of delgocitinib (20-mg/g cream) used in the trial is different than the final to-be-marketed formulation in terms of the (b) (4) concentration (similar for the formulation used in MuST in AD subjects; Trial LP0133-1181), where the change in the formation was deemed minor.

Pharmacokinetic Assessment

One blood sample from each subject was collected for pharmacokinetic assessments 2 to 6 hours after the morning application of IMP.

Pharmacokinetic/Pharmacodynamic Assessment

Skin swabs were collected on Day 1 and Week 16 to investigate the effect of treatment with delgocitinib on the skin microbiome in general and on colonization with *Staphylococcus aureus*. These results will not be described in detail as this pharmacodynamic assessment is not considered relevant to this program.

Pharmacokinetic Results

Delgocitinib showed low systemic exposure across all doses, although with a tendency to increase with dose (geometric mean range: 0.02 to 0.26 ng/mL), as shown below.

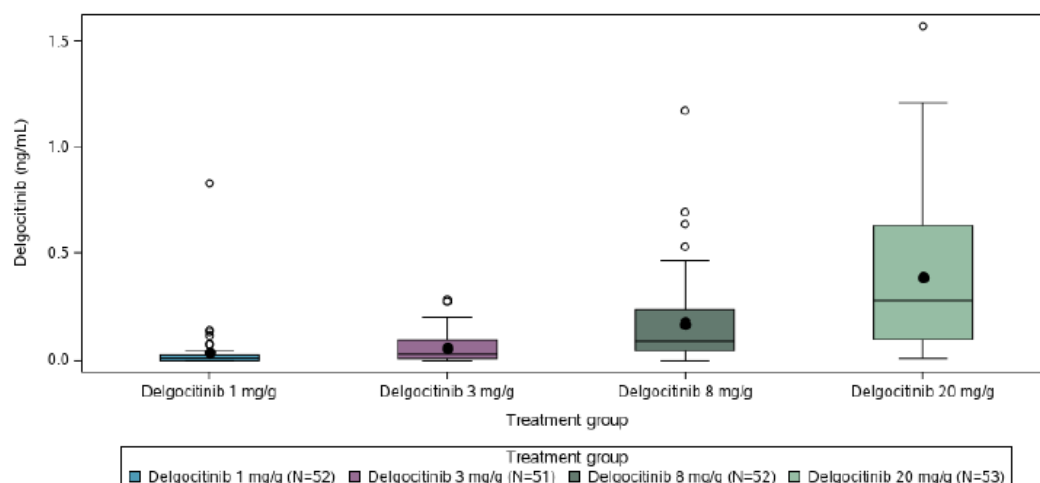
Table 119. Systemic Concentration (ng/mL) of Delgocitinib: Safety Analysis Set

Delgocitinib Plasma Concentration	Delgocitinib 1 mg/g (N=52)	Delgocitinib 3 mg/g (N=51)	Delgocitinib 8 mg/g (N=52)	Delgocitinib 20 mg/g (N=53)
Week 1				
n	49	51	51	51
Geometric mean	0.02	0.04	0.10	0.26
CV (%)	157.61	143.49	158.34	194.19
Median	0.01	0.03	0.09	0.29
Q1; Q3	0.00; 0.02	0.01; 0.09	0.05; 0.23	0.10; 0.63
Min; max	0.00; 0.83	0.00; 0.28	0.00; 1.17	0.01; 20.80

Source: Table 3.6.1, Page No, 1430 of 1441, Clinical trial report LP0133-1273

Abbreviations: CV, coefficient of variation; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with samples analyzed; Q1, first quartile; Q3, third quartile

Figure 24. Delgocitinib Plasma Concentration at Week 1 by Treatment Group, Safety Analysis Set



Source: Panel 59, Page No, 155 of 1441, Clinical trial report LP0133-1273
Abbreviations: N, number of subjects in treatment group

Phase 1 QT Prolongation and Proarrhythmic Trial in Healthy Subjects (LP0133-1409)

Trial Design

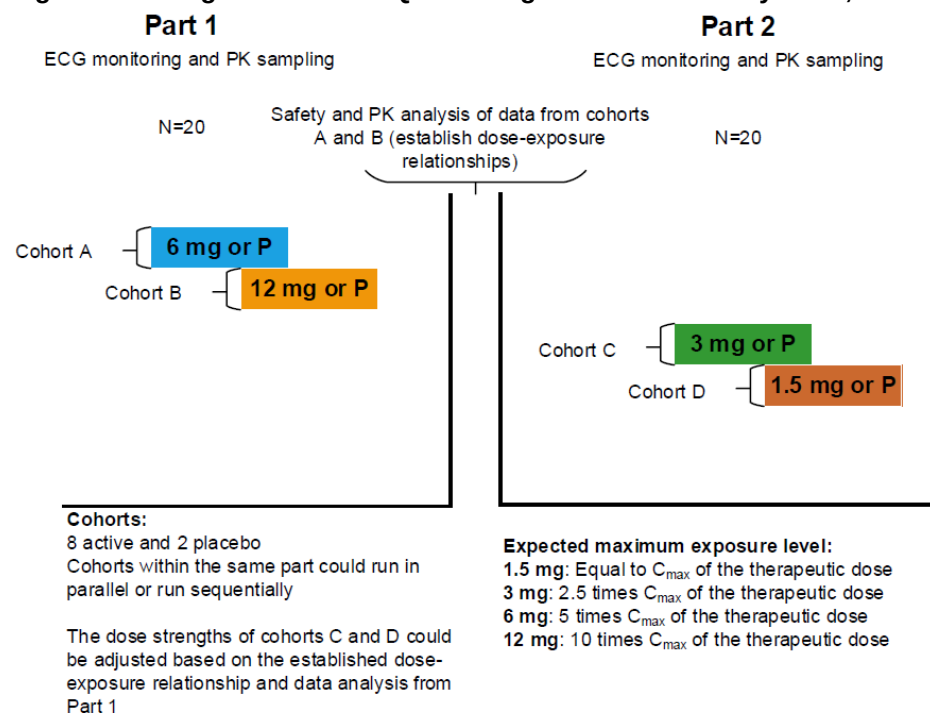
Randomized, phase 1, double-blind, placebo-controlled, parallel-group, single-dose, single-center trial to evaluate QTcF prolongation and proarrhythmic potential of delgocitinib following oral administration in healthy subjects.

The trial consisted of a screening (between 28 and 2 days before IMP administration), an in-clinic treatment period (Days 1 to 2), and a safety follow-up phone call 2 weeks after dosing. Dosing was done on Day 1 and PK blood sampling and 12-lead ECG monitoring were performed from predose until 24 hours postdose.

The trial subjects received a single oral dose at one-dose level. The trial included four-dose cohorts; 6- and 12-mg dose levels were dosed in Part 1 and following evaluation of Part 1 data, the planned dose levels of 1.5 and 3 mg delgocitinib were administered in Part 2.

The trial consisted of four-dose cohorts in two parts, as shown below ([Figure 25](#)).

Figure 25. Design for Phase 1 QT Prolongation and Proarrhythmic, Trial LP0133-1409



Source: Panel 2, Page 14 of 246, Clinical trial report LP0133-1409

Abbreviations: C_{max} , maximum plasma concentration; ECG, electrocardiogram; N, number of subjects in cohort; PK, pharmacokinetic

Formulation

Delgocitinib capsules of 1.5 mg, 3 mg, 6 mg, and 12 mg were administered as a single dose in the morning of Day 1 under fasted condition.

Pharmacokinetic Assessment

Predose (–30 min), 20, 40 minutes, 1 hour, 1 hour and 20 minutes, 1 hour and 40 minutes, 2, 2.5, 3, 4, 6, 8, 12 hours and 24-hour postdose after single dosing on Day 1 (up to three additional PK blood samples may have been taken from each subject).

Pharmacokinetic Results

Following single-ascending oral doses of 1.5- to 12-mg delgocitinib, a rapid absorption phase was observed, with a median T_{max} of 0.83 to 1.00 hour. Delgocitinib profile declined in a multiphasic manner, post- C_{max} . The elimination half-life was below 3 hours in all dose groups (2.02 to 2.85 hours), with individual subject values not exceeding 5 hours.

Geometric mean $AUC_{0-\infty}$ was approximately 10.3-fold higher following the 8-fold increase in dose from 1.5- to 12-mg delgocitinib, and geometric mean C_{max} was approximately 13.8-fold higher following the 8-fold increase in the delgocitinib dose.

Table 120. Summary of the Pharmacokinetic Parameters for Delgocitinib Following Single Oral Doses

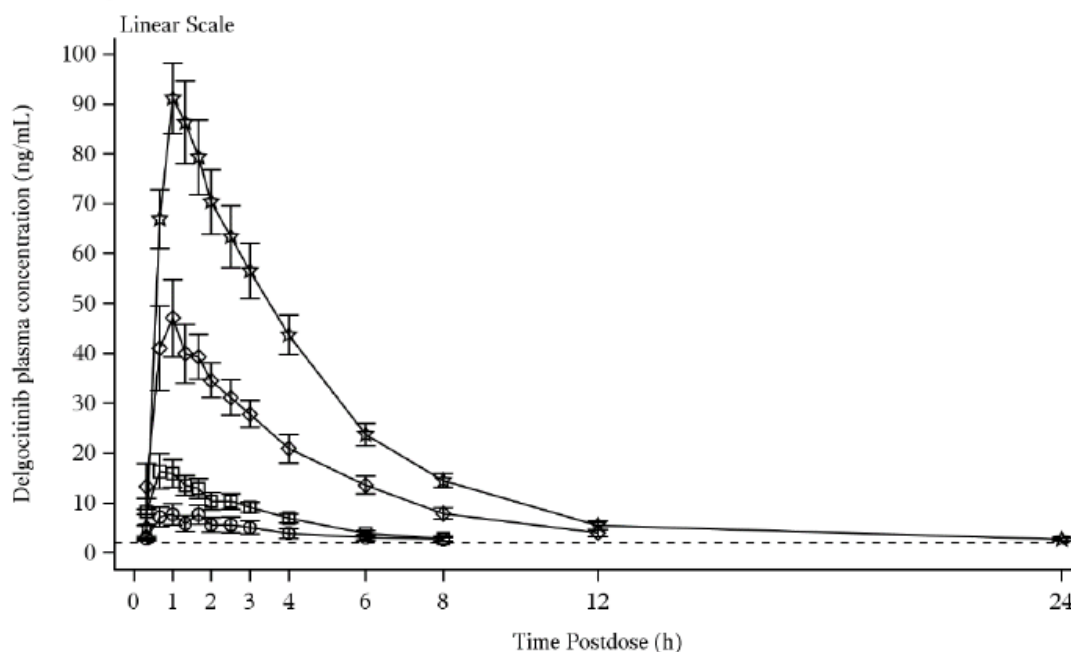
Parameter	1.5 mg delgocitinib (N = 8)	3 mg delgocitinib (N = 8)	6 mg delgocitinib (N = 8)	12 mg delgocitinib (N = 8)
AUC ₀₋₂₄ (h*ng/mL)	32.4 (72.6) [6]	66.5 (35.2) [8]	210 (35.7) [8]	405 (20.0) [8]
AUC _{0-t} (h*ng/mL)	19.4 (123.8) [7]	55.8 (39.1) [8]	193 (37.9) [8]	389 (22.1) [8]
AUC _{0-∞} (h*ng/mL)	39.6 (53.2) [5]	66.6 (35.1) [8]	211 (35.8) [8]	408 (20.5) [8]
C _{max} (ng/mL)	7.22 (89.6) [8]	18.4 (42.6) [8]	51.0 (41.9) [8]	99.3 (17.0) [8]
t _{max} (h)	1.00 (0.667-1.33) [8]	0.842 (0.667-1.67) [8]	0.833 (0.667-1.72) [8]	1.00 (0.667-1.33) [8]
t _{1/2} (h)	2.02 (39.9) [6]	2.32 (11.5) [8]	2.85 (15.7) [8]	2.75 (25.4) [8]
CL/F (L/h)	37.9 (53.2) [5]	45.1 (35.1) [8]	28.4 (35.8) [8]	29.4 (20.5) [8]
V _z /F (L)	118 (30.0) [5]	151 (34.8) [8]	117 (29.1) [8]	117 (31.7) [8]

Source: Panel 17, Page 49 of 246, Clinical trial report LP0133-1409

Abbreviations: AUC₀₋₂₄, area under the concentration-time curve from time 0 to 24 h; AUC_{0-t}, area under the concentration-time curve from dosing (time 0) to time t; AUC_{0-∞}, area under the concentration-time curve estimated to infinity; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; N, number of subjects in treatment arm; t_{1/2}, half-life; t_{max}, time to maximum concentration; V_z/F, apparent volume of distribution during terminal phase

Figure 26. Geometric Mean (±Standard Error) Plasma Concentration Profiles of Delgocitinib

Trial Analysis Set: Pharmacokinetic



Source: Panel 16, Page 48 of 246, Clinical trial report LP0133-1409

QT Prolongation Potential (Safety ECGs)

No clinically relevant changes from baseline in the 12-lead ECG parameters were observed measured and no clinically significant abnormalities in the morphology of the 12-lead ECG for any subject. None of the subjects showed postdose QTcF >450 msec. A single subject had a postdose increase from baseline in QTcF >30 msec following a single 3-mg dose of delgocitinib. This subject had an increase of 33 msec on Day 1, 1-hour postdose, at which time the investigator considered the ECG to be abnormal, not clinically significant.

The estimated population slope of the concentration-QTc relationship was 0.016 msec per ng/mL (90% CI: -0.0124 to 0.0442) with a treatment effect-specific intercept of 1.26 msec (90% CI: -0.971 to 3.482). Neither the treatment effect-specific intercept (p-value of 0.3444) nor the slope (p-value of 0.3405) were statistically significant at the 10% level.

Based on the consult response from IRT QT team, the data did not suggest that delgocitinib is associated with large mean QTcF interval prolongation and the results of the primary analysis are further supported by the lack of QTc prolongation in by-time analysis and categorical analysis at the highest studied dose of 12 mg (oral) that covers the maximum anticipated therapeutic exposure (C_{max}) by 193-fold. The QT team also provided language for the labelling.

Phase 1 Oral Administration, Single and Multiple Doses (Study NBX1-1)

Trial Design

The trial was designed to investigate the safety and pharmacokinetics of orally administered delgocitinib in healthy Japanese male adult volunteers and designed as a placebo-controlled, single-blind trial. In addition, pharmacokinetics of delgocitinib administered under fasted and fed conditions was investigated to determine the food effect.

Part 1 is designed as randomized, single-blind, single-dose, placebo-controlled trial with delgocitinib doses of 1 mg, 5 mg, 25 mg, 50 mg, 100 mg, or placebo (fasted) (N=40), whereas Part 2 is designed as a randomized, single-blind, multiple-dose, placebo-controlled trial; it consists of three steps; under steps 2-1 and 2-2, delgocitinib administered as multiple doses once daily after standard breakfast for 14 days. In step 2-3, delgocitinib was administered as multiple doses twice daily after standard breakfast and dinner for 14 days (on Day 14, after breakfast only).

Pharmacokinetic Assessments (Plasma)

- Part 1: Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 hours postdose
- Part 2: Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 hours postdose, 0 hour after dosing on Day 2, 3, 7, and 10 and on Day 14 at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 hours

Pharmacokinetic Assessments (Urine)

- Part 1: Predose, 0 to 6, 6 to 12 and 12 to 24 hours, 24 to 36 and 36 to 48 hours
- Part 2: Predose, 0 to 6, 6 to 12 and 12 to 24 hours and 24 to 36 hours

Pharmacokinetic Results

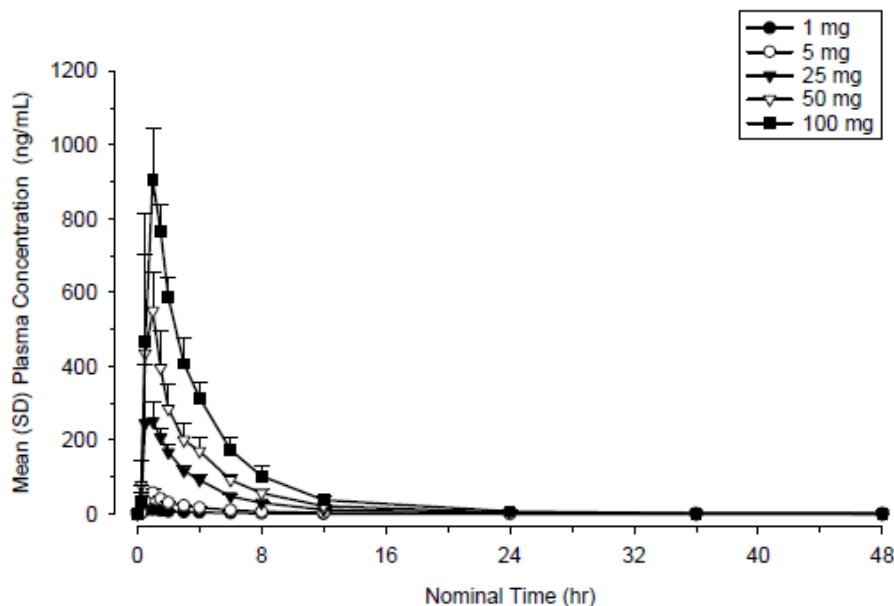
After a single-dose administration of delgocitinib at the above doses under fasted conditions, the T_{max} was 0.75, 1.00, 1.00, 1.00, and 1.00 hour, respectively, and the C_{max} was 11.0, 56.5, 313, 619, and 956 ng/mL, respectively. After the T_{max} , the plasma concentrations of delgocitinib decreased in a biphasic manner. In the 5, 25, 50, and 100-mg groups, the $t_{1/2}$ was 2.71, 3.82, 3.96, and 4.45 hours, respectively, the AUC_{inf} was 175, 957, 1815, and 3212 ng hr/mL, respectively, the apparent clearance at steady-state was 28.80, 26.40, 28.35, and 31.16 L/hour, respectively,

NDA 219155

ANZUPGO (delgocitinib) cream, 2%

and the apparent volume of distribution during terminal phase was 112.7, 147.5, 164.0, and 199.7 L, respectively.

Figure 27. Plasma Concentrations Profile of Delgocitinib After Single Dose Administration Under the Fasted Condition



Source; Figure 12-1, Page 111 or 1474, clinical trial report NBX1-1

Table 121. Pharmacokinetic Parameters of Delgocitinib After Single Dose Administration (Fasted State)

Pharmacokinetic parameters	Fasted					Fed
	1 mg	5 mg	25 mg	50 mg	100 mg	25 mg
N	6	6	6	6	6	6
t_{max}^a (hr)	0.75 (0.50 - 1.00)	1.00 (1.00 - 1.00)	1.00 (0.50 - 1.50)	1.00 (0.50 - 1.00)	1.00 (0.50 - 1.50)	1.50 (0.50 - 2.00)
C_{max} (ng/mL)	11.0 ± 2.43	56.5 ± 9.85	313 ± 94.6	619 ± 115	956 ± 129	275 ± 110
$t_{1/2}$ (hr)	NC ± NC ^b	2.71 ± 0.32	3.82 ± 0.83 ^c	3.96 ± 1.00	4.45 ± 1.21 ^d	4.09 ± 0.95
AUC_{last} (ng·hr/mL)	29 ± 6	167 ± 16	951 ± 92	1799 ± 339	3238 ± 279	988 ± 136
AUC_{inf} (ng·hr/mL)	NC ± NC ^b	175 ± 16	957 ± 105 ^c	1815 ± 341	3212 ± 94 ^d	997 ± 139
CL_F (L/hr)	NC ± NC ^b	28.80 ± 2.65	26.40 ± 3.08 ^c	28.35 ± 5.15	31.16 ± 0.94 ^d	25.49 ± 3.60
V_z/F (L)	NC ± NC ^b	112.7 ± 19.9	147.5 ± 44.7 ^c	164.0 ± 59.1	199.7 ± 53.4 ^d	147.7 ± 22.9

Source; Table 12-1, Page 112 or 1474, clinical trial report NBX1-1

Abbreviations: AUC_{inf}, area under the concentration-time curve estimated to infinity; AUC_{last}, area under the concentration-time curve to the last measurable concentration; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; N, number of subjects; NC, not calculated; t_{1/2}, half-life; t_{max}, time to maximum concentration; V_z/F, apparent volume of distribution during terminal phase

The pharmacokinetics of delgocitinib was not affected by food intake, as there was no change in the pharmacokinetics with or without food.

Urinary Excretion Levels

Table 122. Pharmacokinetic Parameters of Delgocitinib in Urine After Single Dose

Pharmacokinetic parameters	JTE-052					
	Fasted					Fed
	1 mg	5 mg	25 mg	50 mg	100 mg	25 mg
N	6	6	6	6	6	6
Ae _{total} (mg)	0.7743 ± 0.05076	3.981 ± 0.2119	20.23 ± 1.176	37.46 ± 2.722	70.85 ± 7.260	19.33 ± 0.5545
fe _{total} (%)	77.4 ± 5.1	79.6 ± 4.2	80.9 ± 4.7	74.9 ± 5.4	70.8 ± 7.3	77.3 ± 2.2
CL _r (L/hr)	NC ± NC ^a	22.84 ± 1.01	21.53 ± 3.38 ^b	21.15 ± 3.54	22.57 ± 1.75 ^c	19.70 ± 2.71

Mean ± standard deviation

Source: Table 12-4, Page 116 or 1474, clinical trial report NBX1-1
Abbreviations N, number of subjects; Ae_{total}, total amount excreted; Fe_{total}, total fraction excreted; CL, clearance; JTE-052, delgocitinib

Multiple-Dose Pharmacokinetics

Table 123. Pharmacokinetic Parameters of Delgocitinib in Plasma After Multiple-Dose Administration

Pharmacokinetic parameters	JTE-052					
	25 mg QD		50 mg QD		25 mg BID	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
N	6	6	6	6	6	6
t _{max} ^a (hr)	1.50 (1.00 - 3.00)	2.00 (0.50 - 3.00)	1.50 (0.50 - 2.00)	1.50 (1.50 - 3.00)	1.00 (0.50 - 2.00)	1.50 (0.50 - 3.00)
C _{max} (ng/mL)	251 ± 61.0	229 ± 79.8	581 ± 171	436 ± 112	247 ± 61.2	231 ± 56.2
t _{1/2} (hr)	NA	4.92 ± 2.27	NA	4.68 ± 1.36	NA	7.69 ± 4.23
AUC _{tau} (ng·hr/mL)	951 ± 154	959 ± 168	1817 ± 207	1756 ± 168	724 ± 63	779 ± 94
CL _F (L/hr)	NA	26.78 ± 5.03	NA	28.72 ± 3.04	NA	32.46 ± 3.67
V _z /F (L)	NA	188.5 ± 82.0	NA	190.1 ± 41.5	NA	357.0 ± 192.4

Mean ± standard deviation

Source: Table 12-5, Page 118 of 1474, clinical trial report NBX1-1
Abbreviations: AUC_{tau}, area under the concentration-time curve during the dosing interval; BID, twice daily; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; JTE-052, delgocitinib; N, number of subjects; NA, not available; QD, once daily; t_{1/2}, half-life; t_{max}, time to maximum concentration; V_z/F, apparent volume of distribution during terminal phase

In all the treatment groups, the administered oral dose of delgocitinib was mostly excreted into urine. Thus, the oral bioavailability of delgocitinib is expected to be high and delgocitinib was primarily eliminated as unchanged compound in the urine (approximately 75% of the total dose was found as unchanged compound in urine).

It was considered that there was no accumulation of delgocitinib following once-daily or twice-daily multiple-dose administration of delgocitinib for 14 days.

Mass Balance Trial

The Applicant did not conduct a mass balance trial in the current NDA for delgocitinib cream 20 mg/g and provided the following justification:

- The Applicant stated that the systemic exposure of delgocitinib after topical administration was consistently observed to be low across trials including the studies with subjects treated under maximal use conditions.
- The bioavailability of delgocitinib cream 20 mg/g under maximal use conditions in subjects with CHE was found to be low (approx. 0.5 to 0.6% versus oral).
 - The mean relative bioavailability of delgocitinib cream across all oral doses is 0.6%.
 - The calculated relative bioavailability for delgocitinib cream 20 mg/g (2285) compared to the different oral doses in Trial NBX1-1 and Trial 1409 is presented below ([Table 124](#)).
- The low bioavailability and topical administration regimen make it difficult to obtain reliable results from absorption, distribution, metabolism, and excretion studies (mass balance trial) due to high variability associated with recovery.
- Low metabolic turnover of delgocitinib (in vitro as well as clinical data from Trial NBX1-1), about approximately 75% of the total drug dose is excreted unchanged in urine and levels of four main metabolites were low (approximately 0.8%, 0.4%, 0.7%, and 1.7% of the average delgocitinib).

Table 124. Summary of Relative Bioavailability of Delgocitinib Cream Compared to Different Oral Doses, Trials NBX1-1 and 1409

Trial NBX1-1	Dose (mg) ^a			
	5	25	50	100
AUC _{0-inf} (ng×h/mL)	175	957	1815	3212
F _{rel} (%)	0.58	0.53	0.56	0.63
Trial 1409	Dose (mg)			
	1.5	3	6	12
AUC _{0-inf} (ng×h/mL)	39.6	66.6	211	408
F _{rel} (%)	0.77	0.92	0.58	0.60
Mean F _{rel} across all doses (%)	0.6			

Notes: For Trial 2285, the following data were used for the calculations; Dose_{cream}: the amount of delgocitinib cream 20 mg/g used in Trial 2285 at Day 8 was 0.91 g, corresponding to 18.2 mg delgocitinib; AUC_{cream}: the AUC at Day 8 was 3.7 h×ng/mL. ^a The 1 mg dose is not included for Trial NBX1-1 since the AUC_{0-inf} could not be calculated.

Source: Panel 28, Page 55 of 74, Module 2.7.2 Summary of Clinical Pharmacology 1

Abbreviations: AUC_{0-inf}, area under the concentration-time curve estimated to infinity; F_{rel}, relative bioavailability

Therefore, based on low systemic exposure, low metabolic turnover, and primary excretion route being unchanged drug in the urine, the Applicant concluded that mass balance trial is not warranted.

The Applicant's justifications for not conducting mass balance trial are reasonable.

Pharmacodynamic Assessments

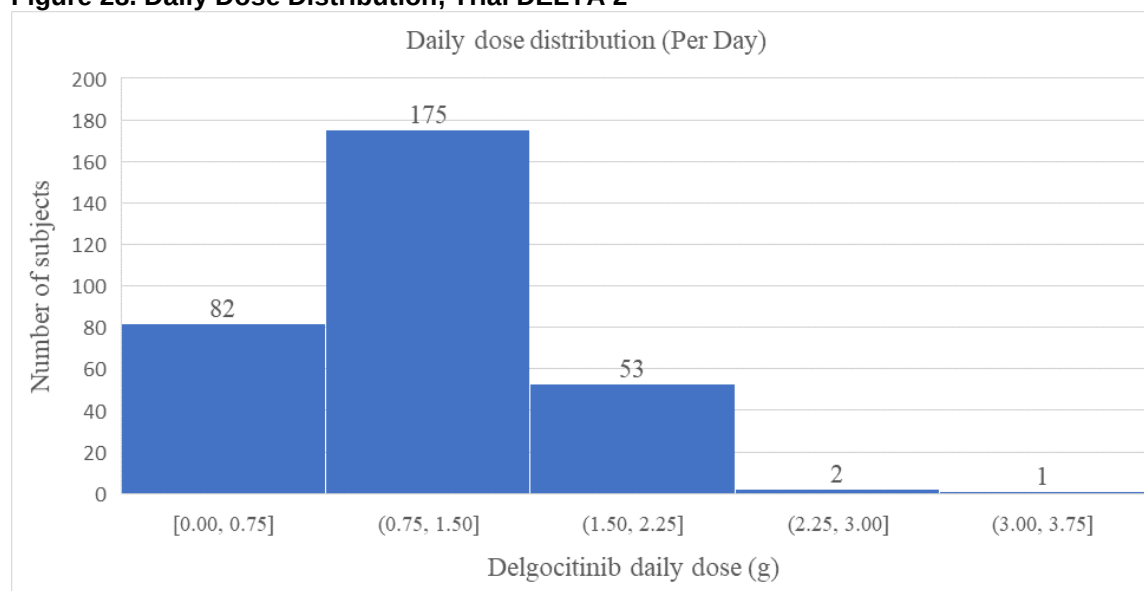
The Applicant assessed skin colonization with *S. aureus* in Study 1273. This pharmacodynamic assessment will not be described further as it is not relevant to the mode of the proposed treatment. Pharmacodynamic assessments also included assessment of gene expression that evaluated inflammatory and skin barrier integrity markers. This pharmacodynamic evaluation is considered as exploratory, and it will also not be included in this review.

Dosing Trend in the Phase 3 Trials

The daily dose of the cream used in the Phase 3 trials ((DELTA 1 and DELTA 2) is shown below.

For DELTA 2, there are 257 subjects used delgocitinib cream up to 1.5 g/day and 56 subjects used the cream dose of more than 1.5 g/ day. The box plot of the dose used for the DELTA 2 trial is shown below.

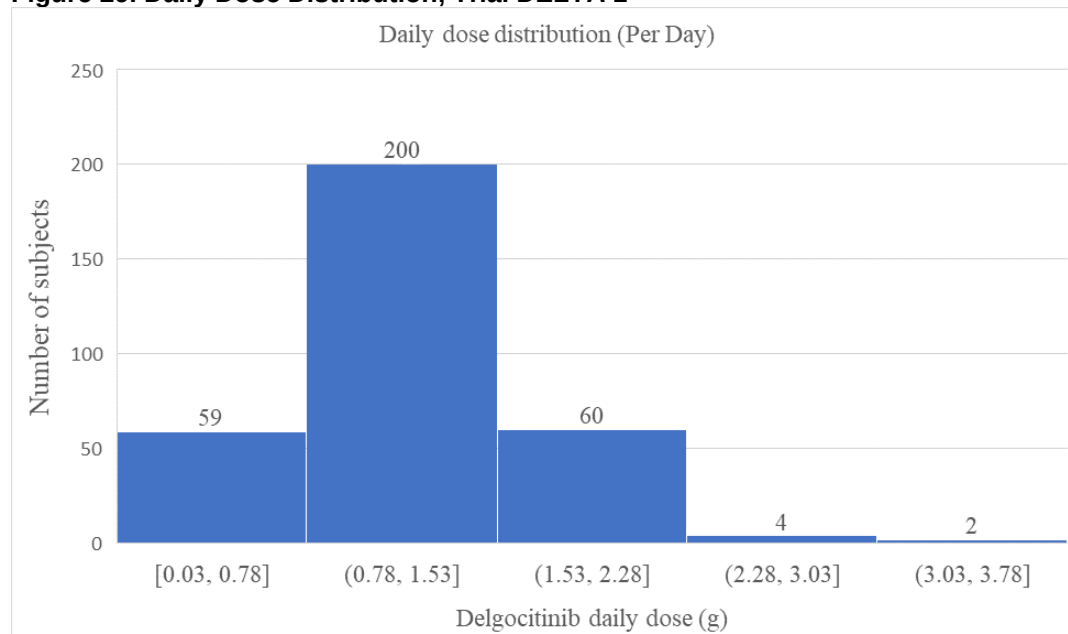
Figure 28. Daily Dose Distribution, Trial DELTA 2



Source: Reviewer generated figure

In the DELTA 1 trial, there are 256 subjects used delgocitinib cream up to 1.5 g/day and 69 subjects used the cream dose of more than 1.5 g/ day. The box plot of the dose used for the DELTA 1 trial is shown below.

Figure 29. Daily Dose Distribution, Trial DELTA 1



Source: Reviewer generated figure

14.3. Bioanalytical Method Validation and Performance

An HPLC-MS/MS method for the determination of delgocitinib in human plasma in clinical studies was developed and validated over a range of 5 to 5000 pg/mL with an LLOQ of 5 pg/mL. Summary of method validation is shown in [Table 125](#) below.

Table 125. Summary of Bioanalytical Method Validation Data

Information Requested	Analyte: Delgocitinib
Bioanalytical method validation report location	Module: 5.3.1.4 \\CDSESUB1\EVSPROD\nda219155\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\klm0254\study-klm0254-report-body.pdf
Study report number	Validation of a Bioanalytical Method for the Determination of delgocitinib (LEO124249) in Human Plasma (Sodium Heparin) using Liquid Chromatography with tandem mass spectrometric detection (LC-MS/MS) (Study No. KLM0254)
Analyte	Delgocitinib (LEO124249A)
Internal standard (IS)	LEO124249B
Method description	Solid phase extraction
Validated assay range	5 to 5000 pg/mL
Limit of quantitation	5.0 pg/mL
Anticoagulant used	Heparin sodium
Validation parameters	Validation Summary
Average recovery of drug (%)	62.3% (low concentration) (%CV =7.7) 74.8% (high concentration) (%CV =2.6)
Average recovery of IS (%)	57.4% (low concentration) (%CV =7.4) 74.1% (high concentration) (%CV =6.0)

Information Requested	Analyte: Delgocitinib
Standard curve concentrations (ng/ml)	5 to 5000 pg/mL
QC concentrations (ng/ml)	5 pg/mL, 15 pg/mL, 200 pg/mL and 3750 pg/mL
Intra-assay reproducibility (%RE)	2.3 to 16.1%
Intra-assay accuracy (% RE)	-16.8 to 11.3%
Inter assay reproducibility (%CV)	4.8 to 14.8%
Inter assay accuracy (%RE)	-8.6 to 8.7%
Bench-top stability (hrs.)	4 hours at room temperature
Processed stability	3 days at +4°C
Freeze-thaw stability (cycles)	3 cycles at -20°C and -70°C
Long-term storage stability (days)	482 days at -20°C
Dilution integrity	DQC: 37500 pg/mL (1/10 dilution) %RE: -0.3 %CV: 4.1 DQC: 375000 pg/mL (1/100 dilution) %RE: 1.1 %CV: 3.2
Selectivity	No interference was observed >20% of the LLOQ, or >5% of internal standard.
Carryover effects	No measured values were affected by carryover, results met with the acceptance criteria.
Matrix effect	No matrix effect affecting the quantification was observed.

Source: Reviewer compiled data from Table 1 to Table 12, Method Validation report (KLM0254)

Abbreviations: CV, coefficient of variation; DQC, LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantitation; RE, relative error

Table 126. Summary of Bioanalytical Method Within Study Analysis Data

Bioanalytical Method	Met Acceptance Criteria?
Study LP0133-1181	
Assay passing rate	25 successful analytical runs (including 04 ISR runs). Run 15 was rejected due to interference peaks in the chromatograms (Watson Run 23). The batch was then re-injected in Watson run 25 which was later rejected due to interference peaks. Yes
Standard curve performance	Cumulative RE range: -2.9 to 3.8% Cumulative precision: 3.1 to 7.6% (Standard curve range: 5 to 5000 pg/mL) Yes
QC performance	Cumulative RE range: -5.6 to 15.7% Cumulative precision: 2.1 to 10.9% Yes
Repeat analysis	105 samples were reanalyzed due to predose levels, above ULOQ and Anomalous/ questionable value, mis extraction /injection and repeated in error etc. Yes
Method reproducibility (incurred sample reanalysis)	Incurred sample reanalysis was performed in 73 study samples (out of 548; 13.3% of total sample size) and 94.5% of samples met the prespecified criteria (±20.0%). Yes

Bioanalytical Method		Met Acceptance Criteria?
Study sample analysis/stability	Samples were stored for a maximum of 450 days at -20°C between first sample collection is within the established long-term stability window of 482 days at -20°C.	
Study DELTA 2 (Study No. 8474247)		
Assay passing rate	accepted runs, including repeat analysis, 05 rejected runs reported in the study and 03 rejected runs from ISR.	Yes
Standard curve performance	Cumulative bias range: -2.2 to 2.8% Cumulative precision: 3.9 to 7.5%	Yes
QC performance	Cumulative bias range: -6.4 to 5.6% Cumulative precision: 3.8 to 9.3%	Yes
Repeat analysis	188 samples were reanalyzed	Yes
Method reproducibility (incurred sample reanalysis)	Incurred sample reanalysis was performed in 99 study samples and 99% of samples met the prespecified criteria ($\pm 20.0\%$).	Yes
Study sample analysis/stability	Samples were stored for a maximum of 159 days at -20°C between first sample collection is within the established long-term stability window of 482 days at -20°C.	Yes
Study LP0133-2285 (Study No. 8500500)		Met Acceptance Criteria?
Assay passing rate	09 accepted runs, including repeat analysis and ISR. 03 rejected runs reported in the study	Yes
Standard curve performance	Cumulative bias range: -4.5 to 2.8% Cumulative precision: 3.4 to 8.2% (Standard curve range: 5 to 5000 pg/mL)	Yes
QC performance	Cumulative bias range: -1.07 to 0.7% Cumulative precision: 4.0 to 10.5%	Yes
Repeat analysis	08 samples were reanalyzed	Yes
Method reproducibility (incurred sample reanalysis)	Incurred sample reanalysis was performed in 30 study samples and 70% of samples met the prespecified criteria ($\pm 20.0\%$).	Yes
Study sample analysis/stability	Samples were stored for a maximum of 66 days at -20°C between first sample collection is within the established long-term stability window of 482 days at -20°C.	Yes

Source: Reviewer compiled data from analytical reports for studies LP0133-1181 (BA1902), DELTA 2 (BA2102) and LP0133-2285
Abbreviations: ISR, incurred sample reanalysis; QC, quality control; RE, relative error ULOQ, upper limit of quantitation

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

Not applicable.

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

The protocol synopses were provided by the Applicant. Cross-references within the synopses are therefore not consistent with the remainder of the review.

15.1. Phase 3 Protocol Synopsis (DELTA 1)

Table 127. Phase 3 Protocol Synopsis (Version 4.0; August 20, 2021) for LP0133-1401 (NCT04871711)

Trial ID EudraCT no.	LP0133-1401 2020-002960-30		
Title of trial	A phase 3 clinical trial to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 1).		
Short title of trial	Efficacy and safety of delgocitinib cream in adults with moderate to severe chronic hand eczema.		
Main objectives, estimands, and endpoints	Objectives	Estimand type and strategy	Endpoints
	Primary objective: To confirm the efficacy of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adult subjects with moderate to severe CHE.	Primary. 'Composite' strategy. First supplementary. 'Pandemic modified composite' strategy. Second supplementary for endpoints at Week 16. 'Treatment policy' strategy.	Primary endpoint: • IGA-CHE ¹ TS at Week 16. Key secondary endpoints: • HECSI-75 at Week 16. • HECSI-75 at Week 8. • HECSI-90 at Week 16. • IGA-CHE TS at Week 8. • IGA-CHE TS at Week 4. • Percentage change in HECSI ² score from baseline to Week 16.

	Secondary objective: To confirm the health-related quality of life and efficacy of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adult subjects with moderate to severe CHE.	Primary. 'Composite' strategy. First supplementary. 'Pandemic modified composite' strategy. Second supplementary for endpoints at Week 16. 'Treatment policy' strategy.	Key secondary endpoints: • Reduction of HESD³ itch score (weekly average) of ≥ 4 points from baseline at Week 16.⁴ • Reduction of HESD itch score (weekly average) of ≥ 4 points from baseline at Week 8.⁴ • Reduction of HESD itch score (weekly average) of ≥ 4 points from baseline at Week 4.⁴ • Reduction of HESD itch score (weekly average) of ≥ 4 points from baseline at Week 2.⁴ • Reduction of HESD score (weekly average) of ≥ 4 points from baseline at Week 16.⁵ • Reduction of HESD score (weekly average) of ≥ 4 points from baseline at Week 8.⁵ • Reduction of HESD score (weekly average) of ≥ 4 points from baseline at Week 4.⁵ • Reduction of HESD pain score (weekly average) of ≥ 4 points from baseline at Week 16.⁶ • Reduction of HESD pain score (weekly average) of ≥ 4 points from baseline at Week 8.⁶ • Reduction of HESD pain score (weekly average) of ≥ 4 points from baseline at Week 4.⁶ • Reduction of DLQI score of ≥ 4 points from baseline at Week 16.⁷ • Change in HESD itch score (weekly average) from baseline to Week 16. • Change in HESD score (weekly average) from baseline to Week 16. • Change in HESD pain score (weekly average) from baseline to Week 16. • Change in HEIS⁸ score from baseline to Week 16. • Change in HEIS PDAL score from baseline to Week 16. • Change in DLQI score from baseline to Week 16.	
	Secondary objective: To evaluate the safety of twice-	Not applicable.	Secondary endpoint: • Number of treatment-emergent⁹ AEs from baseline up to Week 16 (Week 18 for subjects not	

	daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adult subjects with moderate to severe CHE.		participating in the LTE trial) per subject.
1) The IGA-CHE is an instrument used in clinical trials to rate the severity of the subject's global CHE and is based on a 5-point scale ranging from 0 (clear) to 4 (severe). 2) The HECSI is an instrument used in clinical trials to rate the severity of 6 clinical signs (erythema, infiltration/papulation, vesicles, fissures, scaling, and oedema) and the extent of the lesions in each of the 5 hand regions (fingertips, fingers [except fingertips], palm of hands, back of hands, and wrists) by use of standard scales. The HECSI score will range from 0 (lowest possible score) to 360 (highest possible score). 3) The HESD is an eDiary in which subjects will assess the worst severity of 6 individual signs and symptoms of CHE (itch, pain, cracking, redness, dryness, flaking) over the past 24 hours using an 11-point numeric rating scale throughout the trial on a daily basis. 4) Among subjects with a baseline HESD itch score (weekly average) ≥ 4 points. 5) Among subjects with a baseline HESD score (weekly average) ≥ 4 points. 6) Among subjects with a baseline HESD pain score (weekly average) ≥ 4 points. 7) Among subjects with a baseline DLQI score ≥ 4 points. 8) The HEIS addresses 9 items within the following domains: PDAL, embarrassment with the appearance of the hands, frustration with CHE, sleep, work, and physical functioning. Each item is scored on a 5-point scale ranging from 0 (not at all) to 4 (extremely). 9) An event will be considered treatment emergent if started after the first application of IMP or if started before the first application of IMP and worsened in severity after first dose of IMP. Abbreviations: CHE = chronic hand eczema; DLQI = Dermatology Life Quality Index; HECSI = Hand Eczema Severity Index; HECSI-75 = at least 75% improvement in HECSI score from baseline; HECSI-90 = at least 90% improvement in HECSI score from baseline; HEIS = Hand Eczema Impact Scale; HESD = Hand Eczema Symptom Diary; IGA-CHE = Investigator's Global Assessment for chronic hand eczema; IGA-CHE TS = IGA-CHE treatment success, i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥ 2 step improvement from baseline; IMP = investigational medicinal product; PDAL = Proximal Daily Activity Limitations.			
Final collection of data for the primary endpoint	Week 16.		
Trial design	The trial is a phase 3 randomised, double-blind, vehicle-controlled, parallel-group, multi-site trial in which adult subjects with moderate to severe CHE will be treated with delgocitinib cream 20 mg/g or cream vehicle for 16 weeks. The trial consists of a screening period, a treatment period, and a follow-up period. <u>Screening period</u> The screening period has a minimum duration of 1 week and a maximum duration of 4 weeks. At the screening visit, the subjects' eligibility to enter the trial will be checked, and wash-out of treatments listed as exclusion criteria will be initiated if applicable. In view of a 28-day wash out for some of these treatments, the screening period can be extended up to 31 days. The subjects will receive an eDiary device and training in completion of the eDiary. <u>Treatment period</u> At baseline (Day 1), the subjects' eligibility to enter the trial will be confirmed. If still eligible, the subjects will be randomised 2:1 to treatment with delgocitinib cream 20 mg/g or cream vehicle. The randomisation will be stratified by the baseline severity of CHE according to IGA-CHE (moderate and severe) and region (Europe and North America).		

	The first application of IMP will occur at the trial site at baseline (Day 1). The subsequent IMP applications will be performed by the subjects at home twice daily for 16 weeks. During the treatment period, the subjects will be required to return to the trial site for the visits scheduled at Weeks 1, 2, 4, 8, 12, and 16. The last IMP application will occur at the subject's home before the subject attends the visit scheduled at Week 16. <u>Follow-up period</u> The subjects will attend a follow-up visit (performed via phone but can be a site visit if needed) approximately 2 weeks after the last IMP application for assessment of safety. Eligible subjects who complete the treatment period (i.e. who do not permanently discontinue IMP prior to Week 16) will be invited to participate in an open-label LTE trial (LP0133-1403, conducted under a separate protocol). Subjects who continue in the LTE trial will not be required to complete the follow-up period, as collection of safety data and safety surveillance will continue in the LTE trial. * For subjects using treatments that are listed as exclusion criteria, the duration of the screening period will depend on the required wash-out period as defined in Section 8.3. In view of a 28-day wash-out for some of these treatments, the screening period can be extended up to 31 days. Abbreviations: d = day; IGA-CHE = Investigator's Global Assessment for chronic hand eczema; LTE = long term extension; N = number of subjects; w = week.
Main assessments	<u>Investigator assessments of efficacy:</u> - IGA-CHE for assessment of disease severity. - HECSI for assessment of the clinical signs of CHE. <u>Subject assessments of efficacy and health-related quality of life; PROs:</u> - Hand Eczema Symptom Diary (HESD). - Hand Eczema Impact Scale (HEIS). - Dermatology Life Quality Index (DLQI). <u>Safety assessments:</u> Vital signs, physical examination, ECG, laboratory testing, subject assessment of local tolerability, and AE reporting.
Main criteria for inclusion	Age 18 years or above at screening.

	• Diagnosis of CHE, defined as hand eczema that has persisted for more than 3 months or returned twice or more within the last 12 months. • Disease severity graded as moderate to severe at screening and baseline according to IGA-CHE (i.e. an IGA-CHE score of 3 or 4). • HESD itch score (weekly average) of ≥ 4 points at baseline. • Subjects who have a documented recent history of inadequate response to treatment with TCS (at any time within 1 year before the screening visit) or for whom TCS are documented to be otherwise medically inadvisable (e.g. due to important side effects or safety risks). • Subjects adherent to standard non-medicated skin care including avoidance of known and relevant irritants and allergens.
Main criteria for exclusion	• Concurrent skin diseases on the hands, e.g. tinea manuum. • Active AD requiring medical treatment in regions other than the hands and feet. • Active psoriasis on any part of the body. • Hyperkeratotic hand eczema in combination with a history of psoriasis on any part of the body. • Clinically significant infection (e.g. impetiginised hand eczema) on the hands. • Systemic treatment with immunosuppressive drugs (e.g. methotrexate, cyclosporine, azathioprine), immunomodulating drugs, retinoids (e.g. alitretinoin), or corticosteroids within 28 days prior to baseline (steroid eyedrops and inhaled or intranasal steroids corresponding to up to 1 mg prednisolone for allergic conjunctivitis, asthma, or rhinitis are allowed). • Use of tanning beds, phototherapy (e.g. UVB, UVA1, PUVA), or bleach baths on the hands within 28 days prior to baseline. • Previous or current treatment with JAK inhibitors (including delgocitinib/LEO 124249), systemic or topical. • Cutaneously applied treatment with immunomodulators (e.g. PDE-4 inhibitors, pimecrolimus, tacrolimus) or TCS on the hands within 14 days prior to baseline. • Use of systemic antibiotics or cutaneously applied antibiotics on the hands within 14 days prior to baseline. • Other transdermal or cutaneously applied therapy on the hands (except for the use of subject's own emollients) within 7 days prior to baseline. • Cutaneously applied treatments in regions other than the hands, which could interfere with clinical trial evaluations or pose a safety concern within 7 days prior to baseline. • Treatment with any marketed biological therapy or investigational biologic agents (including immunoglobulin, anti-IgE, and dupilumab): ○ Any cell-depleting agents including but not limited to rituximab: within 6 months prior to baseline, or until lymphocyte count returns to normal, whichever is longer. ○ Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to baseline. • Clinically significant infection within 28 days prior to baseline which, in the opinion of the investigator, may compromise the safety of the subject in the trial, interfere with evaluation of the IMP, or reduce the subject's ability to participate in the trial. Clinically significant infections are defined as: ○ A systemic infection. ○ A serious skin infection requiring parenteral (intravenous or intramuscular) antibiotics, antiviral, or antifungal medication.

	- History of any known primary immunodeficiency disorder including a positive HIV test at screening, or the subject taking antiretroviral medications as determined by medical history and/or subject's verbal report. - Any disorder which is not stable and could: - Affect the safety of the subject throughout the trial. - Impede the subject's ability to complete the trial. - Examples include but are not limited to cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, immunological, and psychiatric disorders, and major physical impairment. - Positive hepatitis B surface antigen or hepatitis C virus antibody serology at screening.
Investigational medicinal product	- Name of IMP: delgocitinib cream. - Active substance: delgocitinib. - Dosage form: cream. - Concentration: 20 mg/g and cream vehicle. - Dose and method of administration: topical application twice daily.
Duration of trial participation	The duration of trial participation will be up to 22 weeks, consisting of a screening period of up to 4 weeks, a treatment period of 16 weeks, and a safety follow-up period of 2 weeks (safety follow-up period not applicable for subjects participating in the LTE trial).
Number of subjects	A total of 470 eligible subjects will be randomised in a 2:1 ratio to delgocitinib cream 20 mg/g or cream vehicle.
Number and distribution of trial sites	Approximately 55 sites in Europe and Canada.
Statistical methods	For the primary and key secondary endpoints, confirmatory one-sided (superiority) hypotheses will be tested for delgocitinib cream 20 mg/g vs. cream vehicle based on the primary analysis for the primary estimand. A closed testing procedure with hierarchical tests, alpha splitting, and alpha recycling will be used to control the overall type I error at a nominal one-sided 2.5% level. The statistical testing strategy is built on the principle that the IGA-CHE TS superiority at Week 16 will have to be established before testing for additional benefits (key secondary endpoints) related to efficacy and health-related quality of life. The primary estimand for the primary and key secondary endpoints will use a 'composite' strategy where the occurrence of pre-defined IEs (initiation of rescue treatment and permanent discontinuation of IMP) is a component of the endpoint. A first supplementary estimand will use a 'pandemic modified composite' strategy which follows a 'composite' strategy for IEs independent of the COVID-19 pandemic, attempting to quantify the effect of the randomised treatment in a world without COVID-19 pandemic. A second supplementary estimand will use a 'treatment policy' strategy which attempts to quantify the effect of the randomised treatment regardless of whether an IE occurs. The second supplementary estimand will be used for endpoints related to Week 16 (primary endpoint visit). The primary analysis for the primary estimand for the binary endpoints will be CMH test stratified by region and baseline IGA-CHE score. The primary analysis for the primary estimand for the continuous endpoints will be ANCOVA with effects of treatment group, region, baseline IGA-CHE score, and baseline value (endpoint of interest).

Signatory investigator	Robert Bissonnette, MD, dermatologist Innovaderm Research Inc., Montreal (Quebec), Canada
Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark

Source: page 17-23 of the protocol (Version 4.0) for Trial LP0133-1401.

Abbreviations: ANCOVA, analysis of covariance; CHE, chronic hand eczema; CMH, Cochran-Mantel-Haenszel; DLQI, Dermatology Life Quality Index; HEIS, Hand Eczema Impact Scale; HESCI, Hand Eczema Severity Index; HESD, Hand Eczema Symptom Diary; IE, intercurrent event; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; IMP, investigational medicinal product; LTE, long-term extension; PDAL, proximal daily activity limitations; PDE, phosphodiesterase; PRO, patient-reported outcome; JAK, Janus kinase; PUVA, psoralen plus UVA therapy; IgE, immunoglobulin E; TCS, topical corticosteroids; TS, treatment success; UVA, ultraviolet A

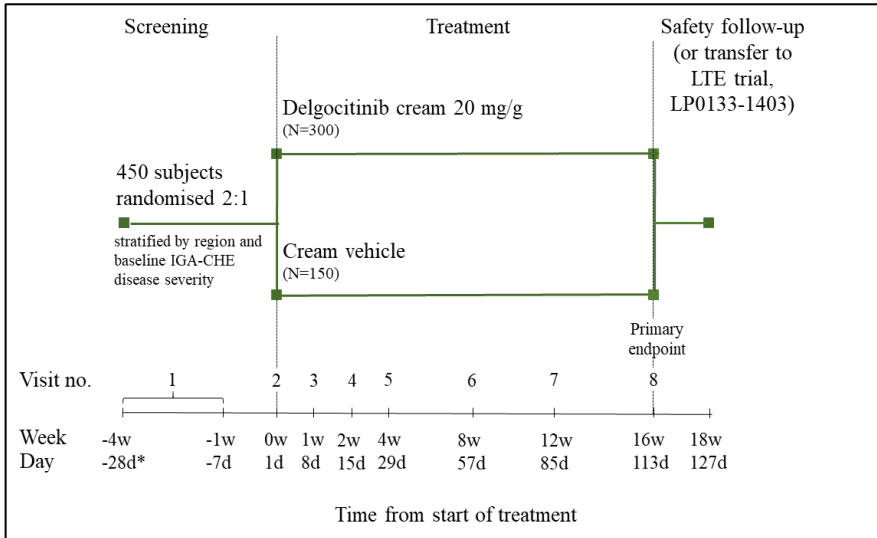
15.2. Phase 3 Protocol Synopsis (DELTA 2)

Table 128. Phase 3 Protocol Synopsis (Version 4.0; August 20, 2021) for LP0133-1402 (NCT04872101)

Trial ID EudraCT no.	LP0133-1402 2020-002961-32		
Title of trial	A phase 3 clinical trial to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 2).		
Short title of trial	Efficacy and safety of delgocitinib cream in adults with moderate to severe chronic hand eczema.		
Main objectives, estimands, and endpoints			
	Objectives	Estimand type and strategy	Endpoints
	Primary objective: To confirm the efficacy of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adult subjects with moderate to severe CHE.	Primary. 'Composite' strategy. First supplementary. 'Pandemic modified composite' strategy. Second supplementary for endpoints at Week 16. 'Treatment policy' strategy.	Primary endpoint: • IGA-CHE ¹ TS at Week 16. Key secondary endpoints: • HECSI-75 at Week 16. • HECSI-75 at Week 8. • HECSI-90 at Week 16. • IGA-CHE TS at Week 8. • IGA-CHE TS at Week 4. • Percentage change in HECSI ² score from baseline to Week 16.

	Secondary objective: To confirm the health-related quality of life and efficacy of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adult subjects with moderate to severe CHE.	Primary. ‘Composite’ strategy. First supplementary. ‘Pandemic modified composite’ strategy. Second supplementary for endpoints at Week 16. ‘Treatment policy’ strategy.	Key secondary endpoints: • Reduction of HESD³ itch score (weekly average) of ≥4 points from baseline at Week 16.⁴ • Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Week 8.⁴ • Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Week 4.⁴ • Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Week 2.⁴ • Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 16.⁵ • Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 8.⁵ • Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 4.⁵ • Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 16.⁶ • Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 8.⁶ • Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 4.⁶ • Reduction of DLQI score of ≥4 points from baseline at Week 16.⁷ • Change in HESD itch score (weekly average) from baseline to Week 16. • Change in HESD score (weekly average) from baseline to Week 16. • Change in HESD pain score (weekly average) from baseline to Week 16. • Change in HEIS⁸ score from baseline to Week 16. • Change in HEIS PDAL score from baseline to Week 16. • Change in DLQI score from baseline to Week 16.
	Secondary objective: To evaluate the safety of twice-daily applications	Not applicable.	Secondary endpoint: • Number of treatment-emergent⁹ AEs from baseline up to Week 16 (Week 18 for subjects not participating in the LTE trial) per subject.

	of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adult subjects with moderate to severe CHE. 1) The IGA-CHE is an instrument used in clinical trials to rate the severity of the subject's global CHE and is based on a 5-point scale ranging from 0 (clear) to 4 (severe). 2) The HECSI is an instrument used in clinical trials to rate the severity of 6 clinical signs (erythema, infiltration/papulation, vesicles, fissures, scaling, and oedema) and the extent of the lesions in each of the 5 hand regions (fingertips, fingers [except fingertips], palm of hands, back of hands, and wrists) by use of standard scales. The HECSI score will range from 0 (lowest possible score) to 360 (highest possible score). 3) The HESD is an eDiary in which subjects will assess the worst severity of 6 individual signs and symptoms of CHE (itch, pain, cracking, redness, dryness, flaking) over the past 24 hours using an 11point numeric rating scale throughout the trial on a daily basis. 4) Among subjects with a baseline HESD itch score (weekly average) ≥ 4 points. 5) Among subjects with a baseline HESD score (weekly average) ≥ 4 points. 6) Among subjects with a baseline HESD pain score (weekly average) ≥ 4 points. 7) Among subjects with a baseline DLQI score ≥ 4 points. 8) The HEIS addresses 9 items within the following domains: PDAL, embarrassment with the appearance of the hands, frustration with CHE, sleep, work, and physical functioning. Each item is scored on a 5-point scale ranging from 0 (not at all) to 4 (extremely). 9) An event will be considered treatment-emergent if started after the first application of IMP or if started before the first application of IMP and worsened in severity after first dose of IMP. Abbreviations: CHE = chronic hand eczema; DLQI = Dermatology Life Quality Index; HECSI-75 = at least 75% improvement in HECSI score from baseline; HECSI-90 = at least 90% improvement in HECSI score from baseline; HECSI = Hand Eczema Severity Index; HEIS = Hand Eczema Impact Scale; HESD = Hand Eczema Symptom Diary; IGA-CHE = Investigator's Global Assessment for chronic hand eczema; IGA-CHE TS = IGA-CHE treatment success, i.e., an IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥ 2 step improvement from baseline; IMP = investigational medicinal product;; PDAL = Proximal Daily Activity Limitations.		
Final collection of data for the primary endpoint	Week 16.		
Trial design	The trial is a phase 3 randomised, double-blind, vehicle-controlled, parallel-group, multisite trial in which adult subjects with moderate to severe CHE will be treated with delgocitinib cream 20 mg/g or cream vehicle for 16 weeks. The trial consists of a screening period, a treatment period, and a follow-up period. <u>Screening period</u> The screening period has a minimum duration of 1 week and a maximum duration of 4 weeks. At the screening visit, the subjects' eligibility to enter the trial will be checked, and wash-out of treatments listed as exclusion criteria will be initiated if applicable. In view of a 28-day wash out for some of these treatments, the screening period can be extended up to 31 days. The subjects will receive an eDiary device and training in completion of the eDiary. <u>Treatment period</u> At baseline (Day 1), the subjects' eligibility to enter the trial will be confirmed. If still eligible, the subjects will be randomised 2:1 to treatment with delgocitinib cream 20 mg/g or cream vehicle. The randomisation will be stratified by the baseline severity of CHE according to IGA-CHE (moderate and severe) and region (Europe and North America). The first application of IMP will occur at the trial site at baseline (Day 1). The subsequent IMP applications will be performed by the subjects at home twice		

	daily for 16 weeks. During the treatment period, the subjects will be required to return to the trial site for the visits scheduled at Weeks 1, 2, 4, 8, 12, and 16. The last IMP application will occur at the subject's home before the subject attends the visit scheduled at Week 16. <u>Follow-up period</u> The subjects will attend a follow-up visit (performed via phone, but can be a site visit if needed) approximately 2 weeks after the last IMP application for assessment of safety. Eligible subjects who complete the treatment period (i.e., who do not permanently discontinue IMP prior to Week 16) will be invited to participate in an open-label LTE trial (LP0133-1403, conducted under a separate protocol). Subjects who continue in the LTE trial will not be required to complete the follow-up period, as collection of safety data and safety surveillance will continue in the LTE trial.  * For subjects using treatments that are listed as exclusion criteria, the duration of the screening period will depend on the required wash-out period as defined in Section 8.3. In view of a 28-day wash-out for some of these treatments, the screening period can be extended up to 31 days. Abbreviations: d = day; IGA-CHE = Investigator's Global Assessment for chronic hand eczema; LTE = long-term extension; N = number of subjects; w = week.
Main assessments	<u>Investigator assessments of efficacy:</u> - IGA-CHE for assessment of disease severity. - HECSI for assessment of the clinical signs of CHE. <u>Subject assessments of efficacy and health-related quality of life; PROs:</u> - Hand Eczema Symptom Diary (HESD). - Hand Eczema Impact Scale (HEIS). - Dermatology Life Quality Index (DLQI). <u>Safety assessments:</u> Vital signs, physical examination, ECG, laboratory testing, subject assessment of local tolerability, and AE reporting.
Main criteria for inclusion	- Age 18 years or above at screening. - Diagnosis of CHE, defined as hand eczema that has persisted for more than 3 months or returned twice or more within the last 12 months. - Disease severity graded as moderate to severe at screening and baseline according to IGA-CHE (i.e., an IGA-CHE score of 3 or 4). - HESD itch score (weekly average) of ≥ 4 points at baseline.

	- Subjects who have a documented recent history of inadequate response to treatment with TCS (at any time within 1 year before the screening visit) or for whom TCS are documented to be otherwise medically inadvisable (e.g., due to important side effects or safety risks). - Subjects adherent to standard nonmedicated skin care including avoidance of known and relevant irritants and allergens.
Main criteria for exclusion	- Concurrent skin diseases on the hands, e.g., tinea manuum. - Active AD requiring medical treatment in regions other than the hands and feet. - Active psoriasis on any part of the body. - Hyperkeratotic hand eczema in combination with a history of psoriasis on any part of the body. - Clinically significant infection (e.g., impetiginised hand eczema) on the hands. - Systemic treatment with immunosuppressive drugs (e.g., methotrexate, cyclosporine, azathioprine), immunomodulating drugs, retinoids (e.g., alitretinoin), or corticosteroids within 28 days prior to baseline (steroid eyedrops and inhaled or intranasal steroids corresponding to up to 1 mg prednisolone for allergic conjunctivitis, asthma, or rhinitis are allowed). - Use of tanning beds, phototherapy (e.g., UVB, UVA1, PUVA), or bleach baths on the hands within 28 days prior to baseline. - Previous or current treatment with JAK inhibitors (including delgocitinib/LEO 124249), systemic or topical. - Cutaneously applied treatment with immunomodulators (e.g., PDE-4 inhibitors, pimecrolimus, tacrolimus) or TCS on the hands within 14 days prior to baseline. - Use of systemic antibiotics or cutaneously applied antibiotics on the hands within 14 days prior to baseline. - Other transdermal or cutaneously applied therapy on the hands (except for the use of subject's own emollients) within 7 days prior to baseline. - Cutaneously applied treatments in regions other than the hands, which could interfere with clinical trial evaluations or pose a safety concern within 7 days prior to baseline. - Treatment with any marketed biological therapy or investigational biologic agents (including immunoglobulin, anti-IgE, and dupilumab): - Any cell-depleting agents including but not limited to rituximab: within 6 months prior to baseline, or until lymphocyte count returns to normal, whichever is longer. - Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to baseline. - Clinically significant infection within 28 days prior to baseline which, in the opinion of the investigator, may compromise the safety of the subject in the trial, interfere with evaluation of the IMP, or reduce the subject's ability to participate in the trial. Clinically significant infections are defined as: - A systemic infection. - A serious skin infection requiring parenteral (intravenous or intramuscular) antibiotics, antiviral, or antifungal medication. - History of any known primary immunodeficiency disorder including a positive HIV test at screening, or the subject taking antiretroviral medications as determined by medical history and/or subject's verbal report. - Any disorder which is not stable and could: - Affect the safety of the subject throughout the trial.

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

	○ Impede the subject's ability to complete the trial. (1) Examples include but are not limited to cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, immunological, and psychiatric disorders, and major physical impairment. • Positive hepatitis B surface antigen or hepatitis C virus antibody serology at screening.
Investigational medicinal product	• Name of IMP: delgocitinib cream. • Active substance: delgocitinib. • Dosage form: cream. • Concentration: 20 mg/g and cream vehicle. • Dose and method of administration: topical application twice daily.
Duration of trial participation	The duration of trial participation will be up to 22 weeks, consisting of a screening period of up to 4 weeks, a treatment period of 16 weeks, and a safety follow-up period of 2 weeks (safety follow-up period not applicable for subjects participating in the LTE trial).
Number of subjects	A total of 450 eligible subjects will be randomised in a 2:1 ratio to delgocitinib cream 20 mg/g or cream vehicle.
Number and distribution of trial sites	Approximately 55 sites in Europe and Canada.
Statistical methods	For the primary and key secondary endpoints, confirmatory one-sided (superiority) hypotheses will be tested for delgocitinib cream 20 mg/g versus cream vehicle based on the primary analysis for the primary estimand. A closed testing procedure with hierarchical tests, alpha splitting, and alpha recycling will be used to control the overall type I error at a nominal one-sided 2.5% level. The statistical testing strategy is built on the principle that the IGA-CHE TS superiority at Week 16 will have to be established before testing for additional benefits (key secondary endpoints) related to efficacy and health-related quality of life. The primary estimand for the primary and key secondary endpoints will use a 'composite' strategy where the occurrence of pre-defined IEs (initiation of rescue treatment and permanent discontinuation of IMP) is a component of the endpoint. A first supplementary estimand will use a 'pandemic modified composite' strategy which follows a 'composite' strategy for IEs independent of the COVID-19 pandemic, attempting to quantify the effect of the randomised treatment in a world without COVID-19 pandemic. A second supplementary estimand will use a 'treatment policy' strategy which attempts to quantify the effect of the randomised treatment regardless of whether an IE occurs. The second supplementary estimand will be used for endpoints related to Week 16 (primary endpoint visit). The primary analysis for the primary estimand for the binary endpoints will be CMH test stratified by region and baseline IGA-CHE score. The primary analysis for the primary estimand for the continuous endpoints will be ANCOVA with effects of treatment group, region, baseline IGA-CHE score, and baseline value (endpoint of interest).
Signatory investigator	Sibylle Schliemann, PD Dr. med. Department of Dermatology, University Hospital Jena, Germany
Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark

Source: page 17-23 of the protocol (Version 4.0) for Trial LP0133-1402
Abbreviations: ANCOVA, analysis of covariance; CHE, chronic hand eczema; CMH, Cochran-Mantel-Haenszel; DLQI, Dermatology Life Quality Index; HEIS, Hand Eczema Impact Scale; HESCI, Hand Eczema Severity Index; HESD, Hand Eczema Symptom Diary; IE, intercurrent event; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; IMP, investigational medicinal product; LTE, long-term extension; PDAL, proximal daily activity limitations; PDE, phosphodiesterase; PRO, patient-reported outcome; JAK, Janus kinase; PUVA, psoralen plus UVA therapy, IgE, immunoglobulin E; TCS, topical corticosteroids; TS, treatment success; UVA, ultraviolet A

15.3. Phase 3 Protocol Synopsis (DELTA 3)

Table 129. Phase 3 Protocol Synopsis (Version 4.0; April 3, 2023) for LP0133-1403 (NCT04949841)

Trial ID EudraCT no.	LP0133-1403 2020-002962-15	
Title of trial	A phase 3 extension trial of DELTA 1 and DELTA 2 to evaluate the long-term safety of a twice-daily treatment with delgocitinib cream 20 mg/g as needed for up to 36 weeks in adult subjects with chronic hand eczema (DELTA 3)	
Short title of trial	An open-label multisite extension trial in subjects who completed the LP0133-1401 (DELTA 1) or LP0133-1402 (DELTA 2) trials	
Main objectives and endpoints	Objectives	Endpoints
	Primary objective: To evaluate the long-term safety of an as-needed treatment with twice-daily applications of delgocitinib cream 20 mg/g.	Primary endpoints: • Number of treatment-emergent AEs from baseline up to Week 38.
	Secondary objective: To evaluate the long-term efficacy of an as-needed treatment with twice-daily applications of delgocitinib cream 20 mg/g.	Secondary endpoints: • IGA-CHE¹ score at each scheduled visit from baseline up to Week 36. • IGA-CHE score of 0 (clear) or 1 (almost clear) at each scheduled visit from baseline up to Week 36. • HECSI² score at each scheduled visit from baseline up to Week 36. • HECSI-75 at each scheduled visit from baseline up to Week 36. • HECSI-90 at each scheduled visit from baseline up to Week 36.
	The IGA-CHE is an instrument used in clinical trials to rate the severity of the subject's global chronic hand eczema (CHE) and is based on a 5-point scale ranging from 0 (clear) to 4 (severe). The HECSI is an instrument used in clinical trials to rate the severity of 6 clinical signs (erythema, infiltration/papulation, vesicles, fissures, scaling, and oedema) and the extent of the lesions on each of the 5 hand areas (fingertips, fingers [except fingertips], palm of hands, back of hands, and wrists) by use of standard scales. Abbreviations: AE = adverse event; HECSI = Hand Eczema Severity Index; HECSI-75 = at least 75% improvement in HECSI score from baseline in parent trial; HECSI-90 = at least 90% improvement in HECSI score from baseline in parent trial; IGA-CHE = Investigator's Global Assessment for chronic hand eczema.	
Final collection of data for the primary endpoint	Week 38	
Trial design	Subjects who completed the treatment period in the parent trials (LP0133-1401 or LP0133-1402) will be offered the opportunity to participate in this extension trial.	

	In the parent trials, subjects were treated either with delgocitinib cream 20 mg/g or cream vehicle twice daily for 16 weeks. The trial will include a screening period of about 4 weeks (during participation in the parent trial). The baseline visit in this extension trial will coincide with the Week 16 visit (end-of-treatment visit) in the parent trial. From baseline to Week 36, subjects will be treated on an as-needed basis with delgocitinib cream 20 mg/g twice daily, i.e., at any time during the trial, if a subject has an IGA-CHE score ≥ 2, the investigator will dispense delgocitinib cream 20 mg/g and instruct the subject to start treatment with twice-daily applications. When the subject achieves IGA-CHE score of 0 (clear) or 1 (almost clear) the investigator will instruct the subject to stop treatment. Between baseline and Week 36, subjects will attend site visits every 4 weeks. If the subject experiences worsening of CHE signs and symptoms between scheduled visits, an unscheduled visit should be planned as soon as possible in order to decide if treatment with delgocitinib cream 20 mg/g should be started. Similarly, once symptoms resolve, the subject should visit the site as soon as possible (either at a planned visit or unscheduled visit) so that the investigator can assess if treatment should be stopped. A follow-up phone visit will be conducted approximately 2 weeks after the end-of-treatment/early termination visit. Abbreviations: IGA-CHE: Investigator's Global Assessment for chronic hand eczema. W: week.
Main assessments	Safety assessments: AE reporting, vital signs, physical examination, electrocardiogram (ECG), laboratory testing, subject and investigator assessment of local tolerability. Efficacy assessments: HECSI and IGA-CHE.
Criteria for inclusion	- Signed and dated informed consent has been obtained prior to any protocol-related procedures. - The baseline visit in this extension trial must coincide with the Week 16 (end-of-treatment) visit in the parent trial. - Subjects must have met eligibility criteria at screening and baseline in the parent trial. - Subjects must have completed the treatment period in the parent trial (to be assessed at baseline visit in this extension trial). - Subjects must have complied with the clinical trial protocol in the parent trial to the satisfaction of the investigator. - A woman of childbearing potential must use an acceptable method of birth control throughout the trial up until the end-of-treatment/early termination visit.

Criteria for exclusion	- Subjects who prematurely discontinued treatment with the investigational medicinal product (IMP) or initiated rescue treatment in the parent trial. - Subjects who experienced any AE during participation in the parent trial, which precludes further treatment with delgocitinib cream 20 mg/g in the judgement of the investigator. - Any medical or psychiatric condition that could put the subject at undue risk by participating in the trial, or which, by the investigator's judgment, makes the subject inappropriate for the trial. - Current participation in any other interventional clinical trial, except for parent trials.
Investigational medicinal product	- Name of IMP: delgocitinib cream. - Active substance: delgocitinib. - Dosage form: cream. - Concentration: 20 mg/g and cream vehicle (only used for patch test). - Dose and method of administration: topical application twice daily as needed.
Duration of trial participation	The duration of trial participation will be up to 42 weeks, consisting of a screening period of up to 4 weeks (coinciding with the last 4 weeks of treatment in the parent trial), a treatment period of 36 weeks, and a safety follow-up period of 2 weeks.
Number of subjects	All eligible subjects who completed the treatment period in the parent trial will be offered the opportunity to participate in this extension trial. It is assumed that approximately 600 eligible subjects will roll over from the parent trials.
Number and distribution of trial sites	Approximately 110 sites in Europe and North America.
Statistical methods	Primary endpoint: Treatment-emergent AEs (AEs emerging from baseline in this extension trial up to Week 38) will be summarised for all enrolled subjects and will be presented by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and primary system organ class (SOC). AEs will be summarised in terms of the number and percentage of subjects with AEs, the number of AEs, and the rate of AEs (number of AEs per 100 person years of observation time). Secondary endpoints: IGA-CHE and HECSI scores will be summarised at each scheduled visit from baseline up to Week 36. The proportion of subjects with IGA-CHE score of 0 (clear) or 1 (almost clear) will be summarised at each scheduled visit from baseline up to Week 36. HECSI-75 and HECSI-90 will be summarised at each scheduled visit from baseline up to Week 36. For the calculation of HECSI-75 and HECSI-90, the baseline score from the parent trial will be used. If nothing else is stated, an observed-cases approach will be used for tabulations of data by visit (that is, involving only those subjects who attended each specific visit). For binary response tabulations, subjects experiencing discontinuation of IMP, initiation of rescue treatment, or withdrawal from trial, will be imputed as nonresponders. Otherwise, missing values will not be imputed.
Signatory investigator	Tove Agner, Prof, MD, DMSc Department of Dermatology Bispebjerg Hospital, Copenhagen, Denmark

Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark.

Source: page 14-17 of the protocol (Version 4.0) for Trial LP0133-1403.
Abbreviations: CHE, chronic hand eczema; DLQI, Dermatology Life Quality Index; HEIS, Hand Eczema Impact Scale; HESCI, Hand Eczema Severity Index; HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; IMP, investigational medicinal product; LTE, long-term extension; PDAL, proximal daily activity limitations; PRO, patient-reported outcome, AE, adverse event; SOC, MedDRA Medical Dictionary for Regulatory Activities; TCS, topical corticosteroids; TS, treatment success

16. Efficacy

16.1. Clinical Outcome Assessments

16.1.1. CHE COA Conceptual Frameworks

The conceptual framework consists of the conceptual and measurement models, which explain the concept(s) of interests under evaluation and how the COA is intended to generate scores that measure the concept(s) of interest in the proposed context of use.

Hand Eczema Symptom Diary

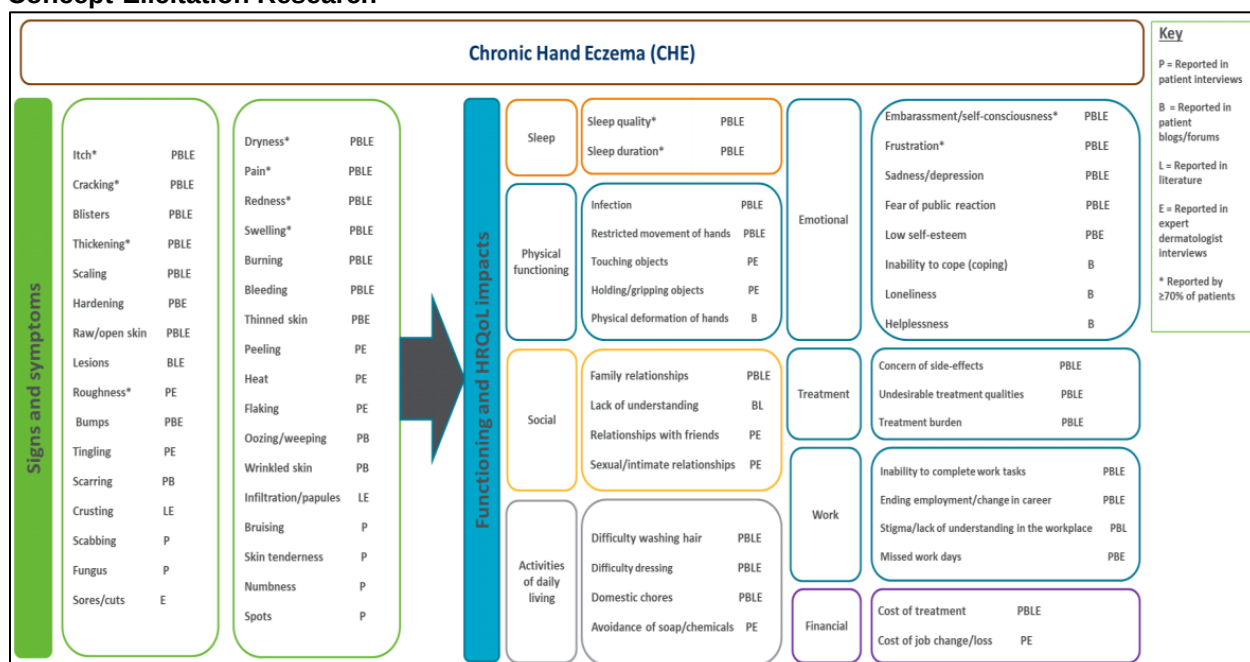
[Figure 30](#) below represents the conceptual framework for the HESD.

Figure 30. 6-Item HESD Conceptual Framework



Source: HESD COA Dossier, p. 22
Abbreviation: HESD, Hand Eczema Symptom Diary

Figure 31. Final HESD Conceptual Model, Developed Based on Literature Review and Qualitative Concept-Elicitation Research



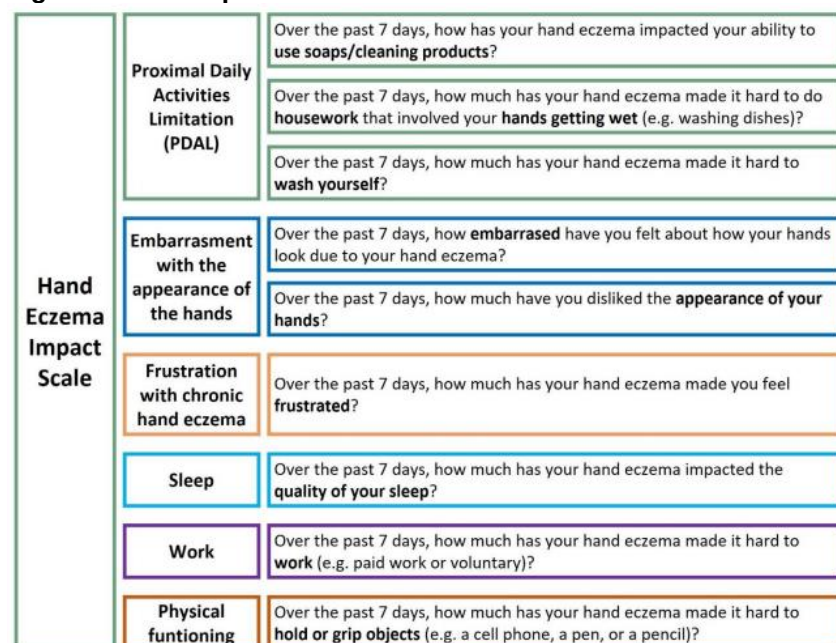
Source: HESD COA Dossier, p. 25

Abbreviations: HESD, Hand Eczema Symptom Diary, CHE, chronic hand eczema

Hand Eczema Impact Scale

Figure 32 below illustrates the conceptual model of the HEIS by domain.

Figure 32. Conceptual Model for the HEIS



Source: HEIS COA Dossier, p. 13

Abbreviation: HEIS, Hand Eczema Impact Scale

16.1.2. COA Content Validity

Investigator's Global Assessment for Chronic Hand Eczema and Hand Eczema Severity Index

The Applicant did not complete instrument development activities to evaluate the content validity of the IGA-CHE or the HECSI. The clinician interviews conducted provided some information related to the content of the instruments.

Hand Eczema Symptom Diary and Hand Eczema Impact Scale

The Applicant completed the following instrument development activities to evaluate the content validity of the HESD and HEIS:

- Literature review
- Expert input (concept elicitation interviews)
- Patient input (concept elicitation, cognitive interviews)

A high-level summary of the results for each activity is described below. Refer to the COA evidence dossier for full details regarding the methodology and results of each activity.

16.1.2.1. Expert Input

Transcripts of interviews with clinical experts were provided for review, along with a qualitative report analyzing the data. The Applicant conducted 60-minute qualitative concept-elicitation interviews with dermatologists (n=5) via telephone to understand the signs/symptoms and impacts of CHE from a clinical perspective, particularly the relative clinical importance of each sign/symptom and associated impact on the patient.

Dermatologists from the United States (n=2), Germany (n=2), and Denmark (n=1) were interviewed. Most of the clinicians were female (n=3/5, 60%) with a mean age of 57.8 years (range: 52 to 65 years). Four were academic professors/dermatologists (80%), while the other was a specialist in dermatological immunology (20%). The mean length of time in position was 21.6 years (range 9 to 35) and the mean length of time treating patients with hand eczema was 26 years (range: 15 to 35 years). The mean number of hand eczema patients seen in the last year was 230 (range: 50 to 500). The most frequently spontaneously reported signs by all clinicians (n=5/5, 100%) were itch, redness, cracking, dryness, and pain. Experts noted that signs/symptoms associated with encountering allergens or irritants and representing an inflammation of the skin on the hands occurred at the same time as CHE signs/symptoms, although this does not necessarily indicate that the symptoms are the same or that they had a direct impact or cause on the other (i.e., they may present simultaneously). For example, redness, pain, and swelling (all associated with inflammation) were most commonly reported to occur at the same time.

16.1.2.2. Patient Input

16.1.2.2.1. Concept Elicitation Interviews

The Applicant conducted two rounds of 60-minute qualitative, face-to-face, concept elicitation interviews with 20 patients (N=20) with CHE in the United States to 1) explore the signs/symptoms and impacts of CHE from the patient perspective and 2) use the findings to update the conceptual model to include any aspects of the patient experience of CHE not included based on the literature review.

A total of 30 distinct signs/symptoms associated with CHE were reported. Of those signs/symptoms, “itch” (n=20/20; 100%), “redness” (n=20/20; 100%), and “cracking” (n=20/20; 100%), were reported by all subjects and nearly all subjects (n=19/20, 95%), regardless of CHE subtype, reported that cracked skin was a relevant symptom of their CHE. Nearly all subjects reported thickening of the skin (n=17/20, 85%) and pain in their hands (n=18/20, 90%). Concept saturation across all five patient groups was demonstrated for the following in descending order (overall n, %) based on patients who spontaneously reported the concept: itch (n=19/20, 95%), redness/erythema (n=17/20, 85%), dryness (n=17/20, 85%), burning (n=13/20, 65%), roughened texture (n=12/20, 60%), cracking/fissuring (n=11/20, 55%), flaking (n=10/20, 50%), bleeding (n=9/20, 45%), and raw/broken skin (n=9/20, 45%). Patients reported that CHE signs/symptoms affect eight domains: sleep (n=16/20, 80%), physical functioning (n=12/20, 60%), daily activities (n=15/20, 75%), emotional well-being (n=16/20, 80%), social functioning (n=7/20, 35%), work (n=12/20, 60%), finances (n=6/20, 30%), and use of topical treatments to alleviate symptoms of CHE (20/20, 100%). They reported the following proximal daily limitations during the interview: avoiding certain soaps and chemicals (n=15/20, 75%); difficulty completing household chores, particularly those that involve getting hands wet (n=13/20, 65%); difficulty performing self-care activities (n=12/20, 60%); and an impact on leisure activities (n=8/20, 40%).

Of note, nearly all (n=19/20, 95%) patients reported at least one environmental factor that they perceived either triggered or exacerbated their CHE symptoms, including various allergens and/or chemicals (n=10/20, 50%), cold temperatures (particularly the winter) (n=9/20, 45%), excessive hand washing (n=3/20, 15%), warm temperatures (n=4/20, 20%), stress (n=2/20, 10%), sun exposure (n=1/20, 5%), and humidity (n=1/20, 5%). Fifteen patients (n=15/20, 75%) reported avoiding touching detergents, soaps, and chemicals or stated they always wear gloves when using detergents and cleaning products.

Based on the qualitative research, the concepts of itch, pain, cracking, redness, dryness, and flaking included in the HESD appear relevant to the target population. Patients were not asked which were the most important or most bothersome signs/symptoms.

The results of the literature review and the qualitative concept elicitation interviews informed the item generation and development of the HESD. Of the 30 distinct signs/symptoms that were reported in the patient concept elicitation interviews and reported by expert dermatologists, 13 concepts were drafted into PRO items. The remaining 17 signs/symptoms were excluded based on infrequent reports from patients during the interviews and least clinical relevance as reported by the expert dermatologists.

16.1.2.2.2. Cognitive Interviews

The Applicant conducted two rounds of 60-minute, face-to face, cognitive interviews with 20 patients in the United States (n=10 per round) with a clinician-confirmed diagnosis of CHE to evaluate the content relevance and comprehension of the HESD. A total of 15 items were debriefed across the interviews. In all, 13 items were debriefed in the first round of interviews, and the same 13 items, plus an additional 2 items were tested in the second round of interviews.

HESD items were well understood (e.g., N=20/20, 100%, understood items assessing dryness, roughness, flaking, bleeding, swelling, redness, cracking, pain, and burning) and all participants reported that items assessing itch, redness, roughness, and dryness were relevant, regardless of CHE subtype. Items assessing swelling, bleeding, heat, thickening, and blisters were the least relevant, but all were still experienced by 14 or more participants (>70%). Five participants (n=5/20, 25%) appeared to have difficulty understanding the item or recall period or did not believe the recall period was relevant for a given item. The greatest conceptual overlap was reported between flaking and cracking (n=6/7), heat and burning (n=5/7), hardness and rough skin (n=5/7), and hardness and thickened skin (n=5/7). Due to the conceptual overlap between items pertaining to hardness, thickness, and roughness of the skin, and because these signs were relatively less relevant to patients, hardness and roughness were removed. The item referring to blisters was also removed from the HESD.

HEIS items were understood by participants, although a few had difficulty understanding questions related to impacts to work (n=3), the use of soaps/cleaning products (n=1) and disliking the appearance of the hands (n=1). In terms of relevance, most patients found the questions to be pertinent (especially dislike of appearance, embarrassment, self-consciousness, and soap/cleaning products). However, touching objects, wearing gloves, and work were less relevant, based on CHE type and physician-rated CHE severity. In terms of relevance, items assessing feeling annoyed, frustration, and disliking the appearance of the hands were the most relevant items for patients irrespective of CHE subtype. Items assessing the impact to patient's ability to hold objects (n=9/19, 47%), touch objects (n=8/19, 42%), and get dressed (n=9/19, 47%) were reportedly the least relevant.

16.1.3. COA Scoring Algorithms

16.1.3.1. Investigator's Global Assessment for Chronic Hand Eczema

The IGA-CHE generates a single item score that ranges from 0 to 4, with higher scores indicating greater CHE severity.

16.1.3.2. Hand Eczema Symptom Diary

The HESD generates single item scores and a total score. The single item scores range from 0 to 10, with higher scores indicating greater symptom severity. The total score ranges from 0 to 80 with higher scores indicating a greater symptom severity.

The weekly HESD score was the average of the seven evening diary entries prior to each site visit by the patient. A weekly average was calculated as long as four or more of the seven diary entries were completed. The averages were calculated for the HESD total score.

16.1.3.3. Hand Eczema Severity Index

The HECSI generates a total score, ranging from 0 to 360, with higher scores indicating a greater severity of hand eczema.

The total score is calculated as follows:

- Clinical Signs: For each of the given five areas of the hand (i.e., fingertips, fingers, palms, back of hands and wrists), the severity of each sign is scored on a 0 to 3 scale (0=none, 1 slight, 2=moderate, 3=severe).
- Extent of Involvement: The extent of lesions in each area is assessed based on the percentage of surface area involved and given a value between 0 and 4 (0=0%, 1=1 to 25%, 2=26 to 50%, 3=51 to 75%, 4=76 to 100%).
- The total HECSI score is calculated by multiplying the extent score for each location by the total sum of the intensity of each clinical feature, and then summing these scores across all locations.

There was insufficient evidence supporting the validity and reliability of the scoring for the HECSI.

16.1.3.4. Hand Eczema Impact Scale

The HEIS PDAL generates a domain score that ranges from 0 to 4, with higher scores indicating a higher impact. The HEIS PDAL domain score is the average of the three items in that domain. Scores are calculated when $\geq 50\%$ of the items are present.

Given that multiple functional impacts for CHE co-occur with other dermatologic disease, the HEIS PDAL was not considered specific to CHE.

16.1.4. IGA-CHE Test-Retest Reliability

Assessing inter-rater and intrarater reliability of ClinROs helps ensure that scores are consistent within a given rater as well as across different raters. While the Applicant did not collect data to assess inter- or intrarater reliability of the IGA-CHE, the Applicant evaluated the test-retest reliability of IGA-CHE scores. Test-retest reliability measures the degree to which scores are similar at different time points in a subset of “stable” subjects. Using data from Trial DELTA 1, the Applicant calculated Cohen’s weighted Kappa with quadratic weights¹ across two time points: Week 2 to Week 4 and Week 4 to Week 8, using the PaGA, HESD PGI-S, and HECSI to

¹ The use of quadratic weights penalize larger differences more heavily and is generally preferred for ordinal scales such as the IGA-CHE.

define stable patients.² The Kappa coefficients reported in [Table 130](#) indicate adequate test-retest reliability for IGA-CHE scores at both timepoints, using all three COAs to define stable subjects.

Table 130. Test-Retest Reliability: IGA-CHE Score Weighted Kappa Coefficient Estimates and 95% Confidence Interval Between Week 2 and Week 4 and Between Week 4 and Week 8, Trial DELTA 1

Time Point	Stability Definition	N (%)	Kappa Coefficient	95% Confidence Interval	
				Lower	Upper
Week 2 to Week 4	PaGA	142 (50.7%)	0.625	0.525	0.725
	HESD PGI-S	154 (55.0%)	0.678	0.592	0.764
	HECSI	218 (77.9%)	0.690	0.615	0.766
Week 4 to Week 8	PaGA	144 (51.4%)	0.761	0.687	0.834
	HESD PGI-S	161 (57.5%)	0.760	0.692	0.827
	HECSI	227 (81.1%)	0.756	0.699	0.812

Source: Table 10 in LC7839J IGA-CHE report v1.0.

Note: Stable patients were defined as follows: The PaGA population consists of subjects who reported a change in PaGA=0 between the two time points, The HESD PGI-S population consists of subjects who reported a change in HESD PGI-S=0 between the two time points. The HECSI population consists of subjects who have HECSI change score <0.50 baseline SD between the two time points.

Abbreviations: HECSI: Hand Eczema Severity Index; HESD PGI-S, Chronic Hand Eczema Symptom Diary Patient Global Impression of Severity; N, sample size.; PaGA, Patient Global Assessment of Disease Severity

While the Kappa coefficient point estimates appear adequate, the lower bound of the 95% confidence intervals indicate lower reliability, especially between Week 2 and Week 4. Notably, these reliability estimates were calculated using data collected from subjects on treatment. As the test-retest reliability of scores should be assessed in the absence of any intervening effects other than time, the Agency sent the Applicant an information request on February 13, 2025, requesting additional test-retest reliability analyses looking at (1) all subjects (pooled across treatment arms) at Screening (i.e., Visit 1) and Baseline (i.e., Visit 2), and (2) vehicle subjects only at Baseline and Week 2 in each trial separately. The Applicant provided a response on February 27, 2025 (see [Table 131](#)). The results indicate moderate test-retest reliability between Screening and Baseline and poor test-retest reliability based on vehicle subjects only between Baseline and Week 2. The Applicant states lower Kappa coefficient estimates between Screening and Baseline as compared to between Week 2 and Week 4 and between Week 4 and Week 8 may be in part due to “the wash out period between screening and baseline, reflecting the dynamic and fluctuating nature of the disease coupled with effects of treatment withdrawal.” The Applicant states the poor test-retest reliability between Baseline and Week 2 for vehicle subjects may be due to “a known placebo effect in addition to the cream vehicle effect, in the first few weeks following randomization especially, leading to a lack of stability for control subjects.” The Applicant’s claims appear reasonable.

² Stable patients were defined as follows: The PaGA population consists of subjects that reported a change in PaGA=0 between the two time points, The HESD PGI-S population consists of subjects that reported a change in HESD PGI-S=0 between the two time points. The HECSI population consists of subjects who have HECSI change score <0.50 baseline SD between the two time points.

Table 131. Test-Retest Reliability: IGA-CHE Score Weighted Kappa Coefficient Estimates and 95% Confidence Interval Between Screening and Baseline (FAS) and Between Baseline and Week 2 (Vehicle Only), Trials DELTA 1 and DELTA 2

Sample	Time Point	Trial	N	Kappa Coefficient	95% Confidence Interval	
					Lower	Upper
FAS	Screening to Baseline	1401	487	0.610	0.533	0.686
		1402	472	0.564	0.473	0.655
Vehicle Subjects	Baseline to Week 2	1401	162	0.252	0.147	0.357
		1402	159	0.263	0.179	0.348

Source: Table 10 in LC7839J IGA-CHE report v1.0.

Abbreviations: FAS, full analysis set; HECSI, Hand Eczema Severity Index; HESD PGI-S, Chronic Hand Eczema Symptom Diary Patient Global Impression of Severity; N, sample size.; PaGA: Patient Global Assessment of Disease Severity

Taken together, these results suggest IGA-CHE scores may be sufficiently stable over time and consistently reflect subject's CHE symptoms.

Results showed a graduate decline in HESD total scores from Baseline (mean =7.0, SD =1.50) to Week 16 (mean =3.6, SD =2.84).

While there were high levels of missing data (74 datapoints) at Week 16, it is unlikely that any missing data with contrary results (i.e., no change or an increase in symptoms) would have affected the pattern of decreased scores across the treatment period.

Anchor scales – Patient Global Impression of Change for itch, pain, and HESD, IGA-CHE, and PaGA – showed comparable improvements over the treatment period.

[Table 132](#) below summarizes the median HESD item scores (weekly average) at baseline and Week 16 in Trials DELTA 1 and DELTA 2.

Table 132. Summary of Median HESD Item Scores (Weekly Average) at Baseline and Week 16, Trials DELTA 1 and DELTA 2

Item	DELTA 1						DELTA 2					
	Delgocitinib (20 mg/g) (N=325)			Vehicle (N=162)			Delgocitinib (20 mg/g) (N=325)			Vehicle (N=162)		
	Baseline	Week 16	CFB	Baseline	Week 16	CFB	Baseline	Week 16	CFB	Baseline	Week 16	CFB
HESD itch score	7.18	2.43	-4.43	7.57	4.86	-2.29	7.74	2.80	-4.07	7.14	4.29	-2.00
HESD pain score	7.14	2.15	-3.86	7.15	4.43	-2.17	6.71	2.00	-4.14	6.71	3.86	-1.79
HESD cracking score	7.57	3.00	-4.10	7.43	5.14	-2.14	7.14	2.43	-3.88	7.29	4.57	-2.29
HESD redness score	7.00	2.76	-3.80	7.17	5.00	-2.00	6.86	2.31	-3.71	7.00	4.71	-1.86
HESD dryness score	7.86	3.55	-3.86	7.93	5.86	-1.86	7.71	3.29	-3.71	7.71	5.71	-1.37
HESD flaking score	7.29	3.00	-3.64	7.17	5.00	-2.14	7.14	2.62	-3.79	7.00	4.57	-1.63
HESD total score	7.22	2.79	-4.06	7.30	4.93	-2.00	6.95	2.52	-3.83	7.07	4.37	-1.74

Source: DCOA Reviewer Analysis.

Abbreviations: CFB, change from baseline; HESD, Hand Eczema Symptom Diary; N, number of subjects in trial arm

There was a notable difference in the CFB scores between the treatment and placebo groups across Trials DELTA 1 and DELTA 2.

16.1.5. HESD Itch Score and HESD Pain Score

Test-retest reliability evaluation of the HESD Itch score (weekly average) and HESD Pain score (weekly average) showed acceptable reliability with intra-class correlation coefficients ranging from 0.93 to 0.98. Other validity evidence (i.e., convergent, known groups) clearly demonstrated that HESD Itch and Pain scores discriminated between groups expected to differ in symptom severity and were sensitive to change over time. Meaningful change thresholds were evaluated by the Applicant, supported by anchor-based analyses and empirical cumulative distribution function plots, with evidence supporting a 4-point threshold for improvement for HESD Itch and HESD Pain scores.

16.1.6. HECSI

The Applicant submitted psychometric analyses for the HECSI using data from their phase 2b study (Trial LP-0133-1273), which included *Change in HECSI score from Baseline to Week 16* as a secondary endpoint. As the assessment of meaningful change is specific to the endpoint being interpreted, and the HECSI-based endpoints being interpreted in Trial DELTA 1 and Trial DELTA 2 were based on a percent change from Baseline at Week 16 (see Section 6.2.3), the analyses reported in the Applicant’s original submission could not be used to aid in the interpretation of the Trial DELTA 1 or Trial DELTA 2 HECSI-based endpoint scores. Despite the limitations regarding the content validity of the HECSI (see Section 6.3.2), for completeness, the Agency sent an information request to the Applicant on February 13, 2025, to request additional anchor-based analyses using the PaGA as an anchor to aid in the interpretation of percent change from Baseline at Week 16 in HECSI-based endpoint scores, using the FAS in each trial separately. The Applicant provided the requested analyses on February 27, 2025.

The correlations between change from Baseline to Week 16 in PaGA score and percent change from baseline at Week 16 in HECSI scores were moderate (see Table 133). Notably, the Pearson correlation estimates are weaker than the corresponding Spearman correlation estimates. This can likely be attributed to the range restriction in PaGA scores at baseline due to the inclusion criteria of a score of moderate or severe on the IGA-CHE, which assesses a similar concept as the PaGA. Such a range restriction would suggest the Spearman correlation coefficient is more appropriate than the Pearson correlation coefficient to estimate the relationship between the change in PaGA and HECSI from Baseline to Week 16. These Spearman correlations suggest the PaGA may have utility in deriving the amount of change in HECSI-based endpoint scores that represents a meaningful benefit to patients.

Table 133. Correlations Between Change From Baseline to Week 16 in PaGA Score and Percent Change From Baseline at Week 16 in HECSI Score, Trials DELTA 1 and DELTA 2 (FAS)

Trial	Pearson Correlation	Spearman Correlation
DELTA 1	0.471	0.634
DELTA 2	0.434	0.606

Source: Panel 1 in Applicant’s IR Response dated February 27, 2025.
Abbreviations: FAS, full analysis set; HECSI, Hand Eczema Severity Index; PaGA, Patient Global Assessment of Disease Severity

As this analysis was not part of the Applicant’s original submission, there was no prespecified target anchor change category to indicate the amount of change on the PaGA that was

meaningful to subjects. [Table 134](#) and [Table 135](#) show cross-tabulations of PaGA responses at Baseline and Week 16 in both trials. Most subjects reported moderate or severe symptoms at baseline for Trial DELTA 1 and Trial DELTA 2, respectively. Across both trials, most subjects experienced either a 1-category improvement or no change from Baseline to Week 16 with the exception of subjects who reported severe symptoms at Baseline and were most likely to experience a 2-category improvement or 1-category improvement.

Table 134. Cross-Tabulation of PaGA at Baseline and Week 16, Trial DELTA 1 (FAS)

PaGA at Baseline	PaGA at Week 16						Total
	Clear n (%)	Almost clear n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Missing n (%)	
Clear	0	0	0	0	0	0	0
Almost clear	1 (33%)	1 (33%)	1 (33%)	0	0	0	3
Mild	5 (14%)	6 (17%)	12 (34%)	9 (26%)	1 (3%)	2 (6%)	35
Moderate	20 (8%)	57 (24%)	71 (30%)	60 (25%)	12 (5%)	17(7%)	237
Severe	18 (9%)	26 (13%)	47 (23%)	66 (32%)	26 (13%)	21 (10%)	204
Missing	0	0	4 (50%)	1 (13%)	1 (13%)	2 (25%)	8

Source: Table 3.4.1 in Applicant's IR Response dated February 21, 2025.

Abbreviations: FAS, full analysis set; n, number of subjects with disposition; PaGA, Patient Global Assessment of Disease Severity

Table 135. Cross-Tabulation of PaGA at Baseline and Week 16, Trial DELTA 2 (FAS)

PaGA at Baseline	PaGA at Week 16						Total
	Clear n (%)	Almost clear n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Missing n (%)	
Clear	0	0	0	0	0	0	0
Almost clear	2 (50%)	0	1 (25%)	0	0	1 (25%)	4
Mild	8 (13%)	18 (30%)	18 (30%)	5 (8%)	2 (3%)	10 (16%)	61
Moderate	21 (10%)	42 (19.1%)	68 (30.9%)	50 (23%)	6 (3%)	33 (15%)	220
Severe	10 (5%)	22 (12%)	57 (31%)	41 (22%)	38 (21%)	16 (9%)	184
Missing	0	1 (33%)	1 (33%)	1 (33%)	0	0	3

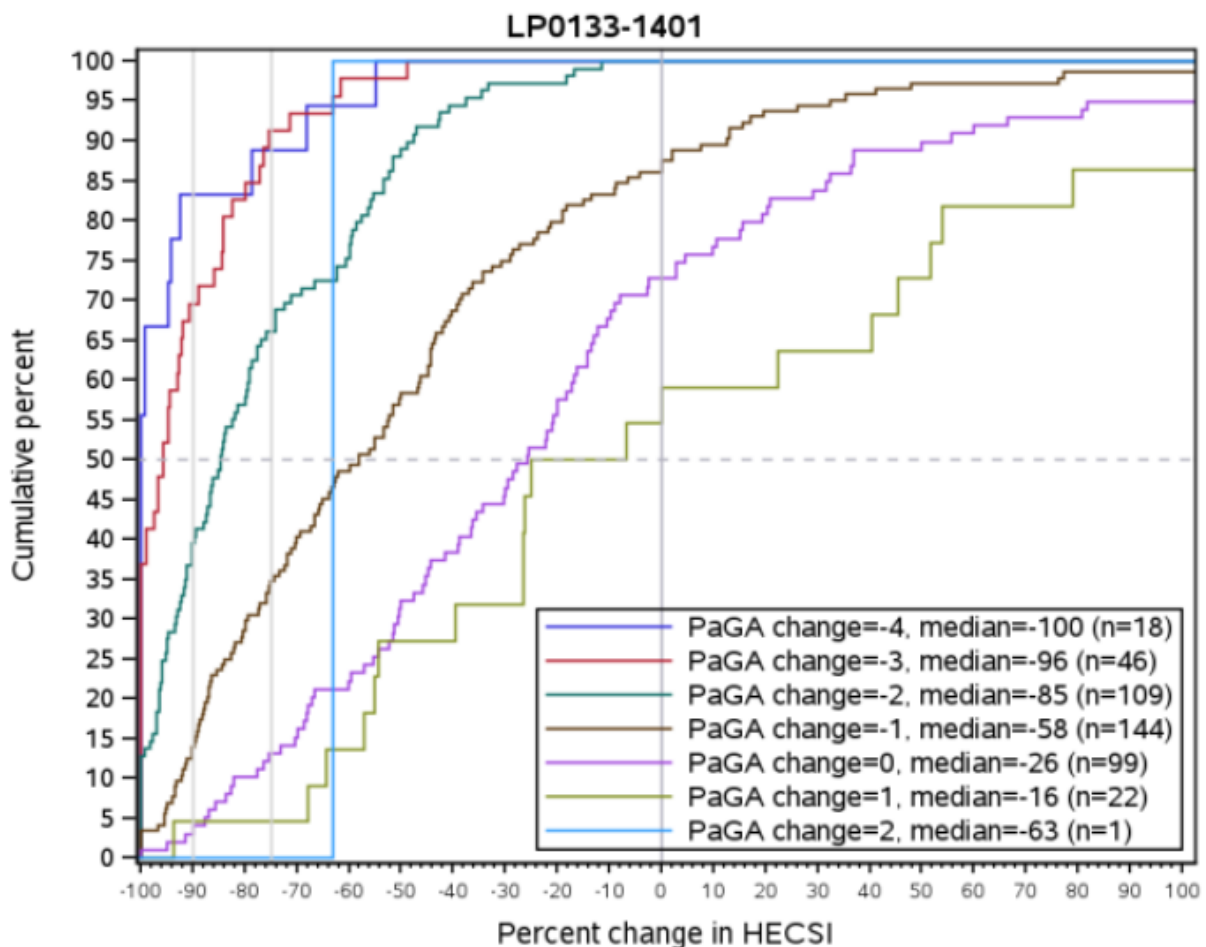
Source: Table 3.4.2 in Applicant's IR Response dated February 21, 2025.

Abbreviations: FAS, full analysis set; n, number of subjects with disposition; PaGA, Patient Global Assessment of Disease Severity

Given these observations in PaGA, the review team determined that it would be reasonable for the anchor-based analyses to focus on a 1-category improvement as the primary target anchor-change.

[Figure 33](#) and [Figure 34](#) show the empirical cumulative distribution function curves for the percent change in HECSI from Baseline to Week 16 by change in PaGA from Baseline to Week 16 for Trial DELTA 1 and Trial DELTA 2, respectively. In Trial DELTA 1, the median percent change in HECSI score for subjects who experienced a 1-category improvement in PaGA is 58%. However, at this value, more than 20% of subjects who reported no change or worsening on the PaGA would be misclassified as having improved on the HECSI. A percent change of at least 77% would be needed to minimize the number of subjects who would be misclassified as having meaningfully improved on the HECSI-based endpoint scores. In Trial DELTA 2, the median percent change in HECSI score for subjects who experienced a 1-category improvement in PaGA is 69%. However, at this value, more than 20% of subjects who reported no change or worsening on the PaGA would be misclassified as having improved on the HECSI. A percent change of at least 82% would be needed to minimize the number of subjects who would be misclassified as having meaningfully improved on the HECSI-based endpoint scores.

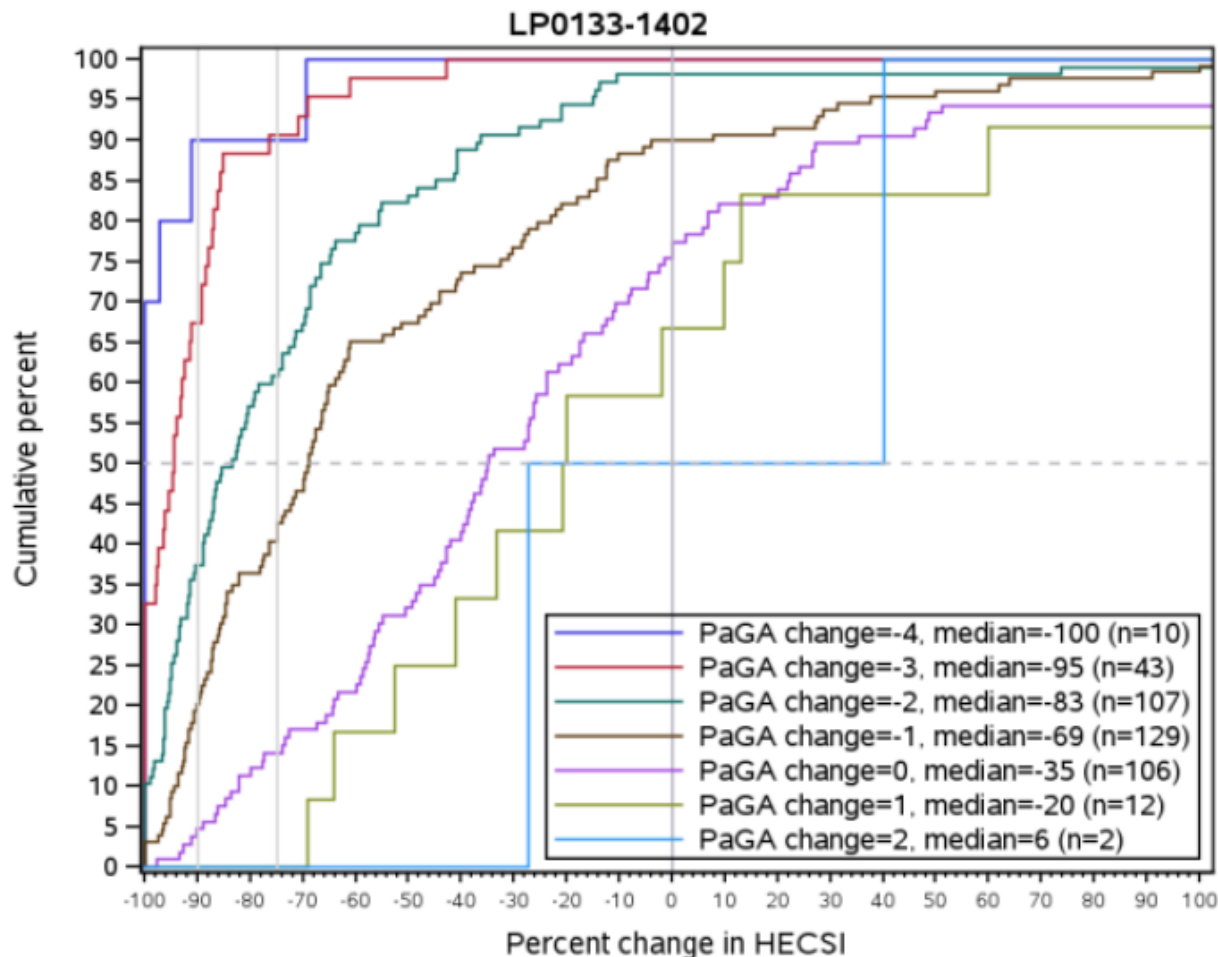
Figure 33. eCDF of Percent Change From Baseline in HECSI at Week 16 by PaGA Change From Baseline to Week 16, Trial DELTA 1 (FAS)



Source: Panel 2 in Applicant's IR Response dated February 27, 2025.

Abbreviations: eCDF, empirical cumulative function; FAS, full analysis set; HECSI, Hand Eczema Symptom Index; PaGA, Patient Global Assessment of Disease Severity, n, number of subjects with disposition

Figure 34. eCDF of Percent Change From Baseline in HECSI at Week 16 by PaGA Change From Baseline to Week 16, Trial DELTA 2 (FAS)



Source: Panel 2 in Applicant's IR Response dated February 27, 2025.

Abbreviations: eCDF, empirical cumulative function; FAS, full analysis set; HECSI, Hand Eczema Symptom Index; n, number of subjects with disposition; PaGA, Patient Global Assessment of Disease Severity

As the amount of change that subjects consider meaningful may depend on their baseline symptom severity, the review team requested the Applicant to provide the distribution of HECSI-based endpoint scores by baseline PaGA for subjects who experienced a 1-category improvement in HECSI from Baseline to Week 16. In Trial DELTA 1, a percent change of at least 72.5% would be needed so that 50% of subjects who reported moderate symptoms on the PaGA at Baseline would be classified as having experienced a meaningful improvement (see [Table 136](#)). For Trial DELTA 2, a percent change of at least 69% would be needed so that 50% of subjects who reported moderate symptoms on the PaGA at baseline would be classified as having experienced a meaningful improvement (see [Table 137](#)).

Table 136. Percentiles for Percent Change From Baseline in HECSI Score at Week 16 by PaGA at Baseline for Subjects With a 1-Category Improvement in PaGA From Baseline to Week 16, Trial DELTA 1 (FAS)

Percent Change in HECSI Score from Baseline to Week 16	PaGA at Baseline			
	Almost Clear (N=1)	Mild (N=6)	Moderate (N=71)	Severe (N=66)
10 th Percentile	-100	-100	-93.9	-82.1
25 th Percentile	-100	-100	-89.0	-63.3
Median	-100	-78.5	-72.5	-39.6
75 th Percentile	-100	-75.9	-46.7	0
90 th Percentile	-100	-43.5	-27.3	32.4

Source: Table 5.1.1 in Applicant's IR Response dated February 21, 2025.
Abbreviations: FAS, full analysis set, N, sample size; HECSI, Hand Eczema Symptom Index; PaGA: Patient Global Assessment of Disease Severity

Table 137. Percentiles for Percent Change From Baseline in HECSI Score at Week 16 by PaGA at Baseline for Subjects With a 1-Category Improvement in PaGA From Baseline to Week 16, Trial DELTA 2 (FAS)

Percent Change in HECSI Score from Baseline to Week 16	PaGA at Baseline			
	Almost Clear (N=1)	Mild (N=6)	Moderate (N=71)	Severe (N=66)
10 th Percentile	-100	-97.4	-95.0	-82.1
25 th Percentile	-100	-93.7	-87.5	-71.9
Median	-87.5	-92.1	-69.0	-48.2
75 th Percentile	-75.0	-85.2	-45.0	-10.3
90 th Percentile	-75.0	-12.2	-14.3	31.3

Source: Table 5.1.2 in Applicant's IR Response dated February 21, 2025.
Abbreviations: FAS, full analysis set, N, sample size; HECSI, Hand Eczema Symptom Index; PaGA, Patient Global Assessment of Disease Severity

While HECSI scores themselves have limited interpretability due to a lack of evidence to support the content validity of the scores (see Section 6.3.2), for completeness, the Agency requested the Applicant conduct anchor-based analyses using percent change in HECSI scores to aid in the interpretation of the multiplicity-controlled HECSI-based endpoints in Trial DELTA 1 and Trial DELTA 2. Based on the anchor-based analyses conducted using the PaGA as an anchor measure, taking into account the full distribution of HECSI percent change scores, subjects' baseline symptom severity, and the misclassification of subjects who reported no improvement or worsening on the PaGA, the Agency determined a plausible meaningful change range for percent change in HECSI scores from Baseline to Week 16 of between a 69- and 82-percentage point improvement. However, these meaningful change analyses have limited interpretability as it is unclear what the HECSI score represents (i.e., did not clinically characterize the severity and extent of hand eczema) and therefore what change (or percent change) in HECSI scores means.

16.1.7. Hand Eczema Impact Scale

Meaningful within-person change scores were not evaluated for the HEIS because it did not meet the requisite criteria for content validity.

16.2. Different Approaches for Handling Missing Data and Intercurrent Events

[Table 138](#) and [Table 139](#) present the number and percentage of subjects with missing data for the primary efficacy endpoint for Trials DELTA 1 and DELTA 2, respectively. The tables also present the results of the sensitivity analyses for handling missing data as well as the supplementary analyses for handling the ICEs. The sensitivity analyses for the primary estimand, including the tipping point analysis, supported the conclusion of the primary analysis. The results were similar across the various imputation methods in both trials. The Applicant's tipping point analysis did not tip (i.e., $p\text{-value} \geq 0.05$) for any of the iterations evaluated by the Applicant. Under the extreme case (i.e., subjects with missing data in the delgocitinib group are imputed as nonresponders and subjects with missing data in the vehicle group are imputed as responders), delgocitinib remained significantly superior to vehicle ($p\text{-values} < 0.05$) in both trials. The primary analysis of the first supplementary estimand (pandemic-modified composite) and the second supplementary estimand (treatment policy) also led to the same conclusion as the primary analysis of the primary estimand (composite).

Table 138. Results of Sensitivity Analysis and Supplementary Analyses for the Primary Efficacy Endpoint, Trial DELTA 1 (FAS)¹

Approach	Delgocitinib (N=325)	Vehicle (N=162)	Difference (95% CI) ⁵	p-Value ⁶
Subject with missing data	1 (0.3%)	0	-	-
NRI (primary) ²	19.7%	9.9%	9.8% (3.6%, 16.1%)	0.006
MI p=0.1 ³	19.7%	9.9%	9.9% (3.6%, 16.2%)	0.002
MI p=0.2 ⁴	19.7%	9.9%	9.9% (3.6%, 16.2%)	0.002
Tipping point analysis ⁷ : percentage of response imputed into the vehicle group				
0%	19.7%	9.9%	9.8% (3.6%, 16.1%)	0.006
10%	19.7%	9.9%	9.8% (3.6%, 16.1%)	0.006
50%	19.7%	9.9%	9.8% (3.6%, 16.1%)	0.006
100%	19.7%	9.9%	9.8% (3.6%, 16.1%)	0.006
First supplementary estimand ⁸ pandemic-modified composite	19.7%	9.9%	9.8% (3.6%, 16.1%)	0.006
Second supplementary estimand ⁸ treatment policy	21.2%	13.1%	8.1% (1.1%, 15.2%)	0.024

Source: Sensitivity analysis: page 55 and Statistical Reviewer's Analysis (same as Applicant's Analysis); adiga.xpt; Tipping Point Analysis and Supplementary analysis: page 55 and page 299 of clinical study report for Trial LP0133-DELTA 1

¹ FAS: all subjects randomized and dosed.

³ Missing data imputed from a Bernoulli distribution with parameter $p=0.1$ using multiple imputation (MI).

⁴ Missing data imputed from a Bernoulli distribution with parameter $p=0.2$ using multiple imputation (MI).

⁵ Mantel-Haenszel risk difference, stratified by region and baseline IGA-CHE score.

⁶ Cochran-Mantel-Haenszel test, stratified by region and baseline IGA-CHE score.

⁷ Tipping Point Analysis: see Section 6.2.6 for details.

⁸ Supplementary Analysis: see Section 6.2.6 for details.

Abbreviations: CI, confidence interval; FAS, full analysis set; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; MI, multiple imputation; N, number of subjects in treatment arm; NRI, nonresponder imputation

Table 139. Results of Sensitivity Analysis and Supplementary Analyses for the Primary Efficacy Endpoint, Trial DELTA 2 (FAS)¹

Approach	Delgocitinib (N=313)	Vehicle (N=159)	Difference (95% CI) ⁵	p-Value ⁶
Subject with missing data	0	1 (0.6%)	-	-
NRI (primary) ²	29.1%	6.9%	22.2% (15.8%, 28.5%)	<0.001
MI p=0.1 ³	29.1%	7.0%	22.1% (15.7%, 28.5%)	<0.001
MI p=0.2 ⁴	29.1%	7.0%	22.0% (15.6%, 28.4%)	<0.001
Tipping point analysis ⁷ : percentage of response imputed into the vehicle group				
0%	29.1%	6.9%	22.2% (15.8%, 28.5%)	<0.001
10%	29.1%	7.0%	22.1% (15.8%, 28.5%)	<0.001
50%	29.1%	7.2%	22.2% (15.8%, 28.5%)	<0.001
100%	29.1%	7.5%	22.2% (15.8%, 28.5%)	<0.001
First supplementary estimand ⁸ pandemic-modified composite	29.1%	7.5%	22.2% (15.8%, 28.5%)	<0.001
Second supplementary estimand ⁸ treatment policy	30.4%	8.8%	21.6% (14.5%, 28.7%)	<0.001

Source: Sensitivity analysis: page 55 and Statistical Reviewer's Analysis (same as Applicant's Analysis); adiga.xpt; Tipping Point Analysis and Supplementary analysis: page 55 and page 299 of clinical study report for Trial LP0133-1402.

¹ FAS: all subjects randomized and dosed.

³ Missing data imputed from a Bernoulli distribution with parameter p=0.1 using multiple imputation (MI).

⁴ Missing data imputed from a Bernoulli distribution with parameter p=0.2 using multiple imputation (MI).

⁵ Mantel-Haenszel risk difference, stratified by region and baseline IGA-CHE score.

⁶ Cochran-Mantel-Haenszel test, stratified by region and baseline IGA-CHE score.

⁷ Tipping Point Analysis: see Section 6.2.6 for details.

⁸ Supplementary Analysis: see Section 6.2.6 for details.

Abbreviations: CI, confidence interval; FAS, full analysis set; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; MI, multiple imputation; N, number of subjects in treatment arm; NRI, nonresponder imputation

16.3. Findings in Special/Subgroup Populations

Results for the subgroup analyses by age (<65 and ≥65 years), sex, race, ethnicity, region, and baseline IGA-CHE score are presented in [Table 140](#) and [Table 141](#) for Trials DELTA 1 and DELTA 2, respectively. For Trial DELTA 1, the treatment effect was higher in males and in the North America subgroup for region. However, for Trial DELTA 2, the treatment effect was generally consistent across all the subgroups for sex and region. For race and ethnicity, the sample sizes for some of the subgroups were relatively small; therefore, it would be difficult to detect any differences in efficacy between these subgroups and their complements.

Table 140. Results for IGA-CHE Treatment Success¹ at Week 16 by Age, Sex, Race, Ethnicity, Region, and Baseline IGA-CHE Score, Trial DELTA 1 (FAS)²

Demographic/Subgroup (N _d , N _v)	Delgocitinib (N=325)	Vehicle (N=162)	Difference (95% CI) ³
Age (years)			
<65 years (297, 154)	20.5%	10.4%	10.1% (3.5%, 16.8%)
≥65 years (28, 8)	10.7%	0	10.7% (-0.7%, 22.2%)
Sex			
Female (202, 104)	19.8%	14.4%	5.4% (-3.3%, 14.1%)
Male (123, 58)	19.5%	1.7%	17.8% (10.0%, 25.6%)

Demographic/Subgroup (N _d , N _v)	Delgocitinib (N=325)	Vehicle (N=162)	Difference (95% CI) ³
Race			
White (283, 144)	19.8%	11.1%	8.7% (1.8%, 15.6%)
Asian (14, 5)	28.6%	0%	28.6% (4.9%, 52.2%)
Black or African American (3,1)	0%	0%	Not estimable
Other (2, 0)	0%	-	Not estimable
American Indian or Alaska Native (1, 0)	0%	-	Not estimable
Ethnicity			
Hispanic or Latino (14, 4)	7.1%	0%	7.1% (-6.3%, 20.6%)
Non-Hispanic or Latino (292, 147)	20.5%	10.9%	9.7% (2.8%, 16.5%)
Region			
Europe (260, 130)	17.7%	11.5%	6.2% (-1.0%, 13.3%)
North America (65, 32)	27.7%	3.1%	24.6% (12.1%, 37.0%)
Baseline IGA-CHE			
Moderate (218, 109)	23.4%	12.8%	10.6% (2.1%, 19.0%)
Severe (107, 53)	12.1%	3.8%	8.4% (0.3%, 16.4%)

Source: Statistical Reviewer's Analysis; adiga.xpt

¹ IGA-CHE treatment success is defined as IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥2-step improvement from baseline.

² FAS: all subjects randomized and dosed. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered nonresponse.

³ Difference and 95% CI are from Cochran-Mantel-Haenszel test for general association.

Abbreviations: CI, confidence interval; FAS, full analysis set; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; N, number of subjects in treatment arm; N_d, number of subjects who received delgocitinib in the subgroup, N_v, number of subjects who received vehicle cream in the subgroup

Table 141. Results for IGA-CHE Treatment Success¹ at Week 16 by Age, Sex, Race, Ethnicity, Region, and Baseline IGA-CHE Score, Trial DELTA 2 (FAS)²

Demographic/Subgroup (N _d , N _v)	Delgocitinib (N=325)	Vehicle (N=162)	Difference (95% CI) ³
Age (years)			
<65 years (285, 150)	29.1%	6.7%	22.5% (15.8%, 29.1%)
≥65 years (28, 9)	28.6%	11.1%	17.5% (-9.0%, 43.9%)
Sex			
Female (203, 108)	31.5%	8.3%	23.2% (14.9%, 31.4%)
Male (110, 51)	24.5%	3.9%	20.6% (11.0%, 30.3%)
Race			
White (294, 146)	29.9%	7.5%	22.4% (15.6%, 29.2%)
Asian (8, 7)	0%	0%	Not estimable
Black or African American (2,1)	50.0%	0%	50.0% (-19.3%, 119.3%)
Native Hawaiian or Other Pacific Islander (1, 0)	0%	-	Not estimable
Other (5, 1)	20.0%	0%	20.0% (-15.1%, 55.1%)
Ethnicity			
Hispanic or Latino (2, 5)	0%	0%	Not estimable
Non-Hispanic or Latino (309, 152)	29.4%	7.2%	22.2% (15.7%, 28.8%)

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Demographic/Subgroup (N_d, N_v)	Delgocitinib (N=325)	Vehicle (N=162)	Difference (95% CI)³
Region			
Europe (249, 126)	29.7%	7.1%	22.6% (15.3%, 29.8%)
North America (64, 38)	26.6%	6.1%	20.5% (7.0%, 34.0%)
Baseline IGA-CHE			
Moderate (238, 121)	30.3%	9.1%	21.2% (13.4%, 28.9%)
Severe (75, 38)	25.3%	0%	25.3% (15.5%, 35.2%)

Source: Statistical Reviewer's Analysis; adiga.xpt

¹ IGA-CHE treatment success is defined as IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥2-step improvement from baseline.

² FAS: all subjects randomized and dosed. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered nonresponse.

³ Difference and 95% CI are from Cochran-Mantel-Haenszel test for general association.

Abbreviations: CI, confidence interval; FAS, full analysis set; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; N, number of subjects in treatment arm; N_d, number of subjects who received delgocitinib in the subgroup, N_v, number of subjects who received vehicle cream in the subgroup

17. Clinical Safety

17.1. Clinical Safety: Additional Information

Table 142. Subject Specific Information for Hemoglobin Shifts

Shift to worst post-baseline	Population	Subject ID	Worst post-baseline grade	Shift	Screening value	Baseline value	Worst post-baseline value	Lower limit of normal	Upper limit of normal	Day of worst post-baseline shift	Any PK samples (Y/N)	PK value Week 1	PK value Week 4	PK value Week 16	Subject rolled in 1403 (Y/N)	Returned to screening or BL value (Y/N)	If returned to screening or BL value, day of return	If returned to screening or BL value, total days of elevated values prior to return	If did not return to screening or BL value, value subject returned to	Any associated TEAE? (Y/N/Specify TEAE)	Day of TEAE	If TEAE occurred, considered related by investigator? (Y/N)
Shift 0->1	W1-16 exposure	(b) (6)	Grade 1	1 Grade worsening	117	121	108	115	160	113	NA	NA	NA	NA	Y	Y	169	57				
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	112	115	108	115	160	14	NA	NA	NA	NA	Y	Y	28	15				
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	118	121	106	115	160	55	NA	NA	NA	NA	Y	Y	113	59				
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	168	161	128	130	175	85	NA	NA	NA	NA	Y	Y	113	29		Y/Normocytic anaemia	85	N
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	118	115	112	115	160	122	NA	NA	NA	NA	Y	Y	186	65				
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening																Y/Red blood cell count decreased, Haemoglobin decreased	169, 169	N, N
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	132	140	108	115	160	86	NA	NA	NA	NA	Y	N			117			
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	130	130	120	130	175	30	NA	NA	NA	NA	Y	Y	86	57				
Shift 1->2	W1-16 exposure		Grade 2	1 Grade worsening	104	103	99	115	160	49	NA	NA	NA	NA	N	N						
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	115	117	111	115	160	112	NA	NA	NA	NA	Y	N			101			
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	144	142	128	130	175	55	Y	0.178	2.22		N	N						
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	133	134	126	130	175	54	Y	0.247	0.146	0.399	Y	Y	110	57				
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening		116	114	115	160	26	Y	0.21	0.384	0.09	Y	Y	56	31				
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	127	129	109	115	160	117	Y	0.112	0.281	0.205	Y	Y	257	141				
Shift 0->1	W1-16 exposure	Grade 1	1 Grade worsening	119	116	110	115	160	27	Y	0.335	0.188	0.109	Y	Y	85	59					

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Shift 0->1	W1-16 exposure	(b) (6)	Grade 1	1 Grade worsening	122	122	114	115	160	57	Y	0.0387	0.411	0.0025	Y	Y	175	119				
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	126	123	107	115	160	56	Y	0.0829	0.0193	0.0358	N	N			120			
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	159	159	127	130	175	114	Y		0.0025	0.0025	N	N						
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	136	122	106	115	160	21	Y		0.00948	0.0025	N	Y	29	9				
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	140	137	123	130	175	27	Y	0.0025	0.0025		N	N			134			
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	115	122	113	115	160	17	Y	0.62	0.252	0.0377	Y	Y	32	16				
Shift 1->2	W1-16 exposure		Grade 2	1 Grade worsening	109	106	95	115	160	111	Y	0.0149	0.0803	0.0447	Y	N			100			
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	120	120	108	115	160	97	Y	0.0719	0.0643	0.244	Y	N			109	Y/Microcytic anaemia	197	N
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	122	121	114	115	160	111	Y	0.356	0.542	0.0438	Y	N			120			
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	122	116	114	115	160	44	Y	0.017			N	N						
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	145	142	127	130	175	59	Y	1.19		0.282	Y	Y	113	55		Y/Anaemia	43	N
Shift 0->1	W1-16 exposure		Grade 1	1 Grade worsening	126	129	114	115	160	115	Y	0.1	0.046	0.0025	Y	Y	290	176				
Shift 0->1	52 weeks exposure		Grade 1	1 Grade worsening	118	121	106	115	160	55	NA	NA	NA	NA	Y	Y	113	59				
Shift 0->1	52 weeks exposure		Grade 1	1 Grade worsening	137	137	124	130	175	365	NA	NA	NA	NA	Y	N						
Shift 0->1	52 weeks exposure		Grade 1	1 Grade worsening	118	115	112	115	160	122	NA	NA	NA	NA	Y	Y	186	65				
Shift 0->2	52 weeks exposure		Grade 2	2 Grade worsening	115	117	96	115	160	224	NA	NA	NA	NA	Y	N			101			
Shift 0->1	52 weeks exposure		Grade 1	1 Grade worsening	130	131	122	130	175	365	NA	NA	NA	NA	Y	N						
Shift 0->1	52 weeks exposure		Grade 1	1 Grade worsening	137	140	124	130	175	288	NA	NA	NA	NA	Y	N			134			
Shift 0->1	52 weeks exposure		Grade 1	1 Grade worsening	119	116	108	115	160	286	NA	NA	NA	NA	Y	Y	372	87				
Shift 0->1	52 weeks exposure		Grade 1	1 Grade worsening	115	122	113	115	160	17	NA	NA	NA	NA	Y	Y	32	16				

Source: Applicant response to information requested June 12, 2025

Abbreviations: BL, baseline; N, no; NA, not available; PK, pharmacokinetic; TEAE, treatment emergent adverse event; W, week; Y, yes

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Table 143. Subject Specific Information for Neutrophil Shifts

Shift to worst post-baseline	Population	Subject ID	Worst post-baseline grade	Shift	Screening value	Baseline value	Worst post-baseline value	Lower limit of normal	Upper limit of normal	Day of worst post-baseline shift	Any PK samples (Y/N)	PK value Week 1	PK value Week 4	PK value Week 16	Subject rolled in 1403 (Y/N)	Returned to screening or BL value (Y/N)	If returned to screening or BL value, day of return	If returned to screening or BL value, total days of elevated values prior to return	If did not return to screening or BL value, value subject returned to	Any associated TEAE? (Y/N/Specify TEAE)	Day of TEAE	If TEAE occurred, considered related by investigator?
		(b) (6)																				
Shift 0→1	W1-16 exposure		Grade 1	1 Grade worsening	117	121	108	115	160	113	NA	NA	NA	NA	Y	Y	169	57				
Shift 0→1	W1-16 exposure		Grade 1	1 Grade worsening	112	115	108	115	160	14	NA	NA	NA	NA	Y	Y	28	15				
Shift 0→1	W1-16 exposure		Grade 1	1 Grade worsening	118	121	106	115	160	55	NA	NA	NA	NA	Y	Y	113	59				
Shift 0→1	W1-16 exposure		Grade 1	1 Grade worsening	168	161	128	130	175	85	NA	NA	NA	NA	Y	Y	113	29		Y/Normocytic anaemia	85	N
Shift 0→1	W1-16 exposure		Grade 1	1 Grade worsening	118	115	112	115	160	122	NA	NA	NA	NA	Y	Y	186	65				
Shift 0→1	W1-16 exposure		Grade 1	1 Grade worsening																Y/Red blood cell count decreased, Haemoglobin decreased	169, 169	N, N
Shift 0→1	W1-16 exposure		Grade 1	1 Grade worsening	132	140	108	115	160	86	NA	NA	NA	NA	Y	N			117			
Shift 0→1	W1-16 exposure		Grade 1	1 Grade worsening	130	130	120	130	175	30	NA	NA	NA	NA	Y	Y	86	57				
Shift 1→2	W1-16 exposure		Grade 2	1 Grade worsening	104	103	99	115	160	49	NA	NA	NA	NA	N	N						
Shift 0→1	W1-16 exposure		Grade 1	1 Grade worsening	115	117	111	115	160	112	NA	NA	NA	NA	Y	N			101			
Shift 0→1	W1-16 exposure		Grade 1	1 Grade worsening	144	142	128	130	175	55	Y	0.178	2.22		N	N						
Shift 0→1	W1-16 exposure		Grade 1	1 Grade worsening	133	134	126	130	175	54	Y	0.247	0.146	0.399	Y	Y	110	57				
Shift 0→1	W1-16 exposure		Grade 1	1 Grade worsening		116	114	115	160	26	Y	0.21	0.384	0.09	Y	Y	56	31				
Shift 0→1	W1-16 exposure		Grade 1	1 Grade worsening	127	129	109	115	160	117	Y	0.112	0.281	0.205	Y	Y	257	141				
Shift 0→1	W1-16 exposure		Grade 1	1 Grade worsening	119	116	110	115	160	27	Y	0.335	0.188	0.109	Y	Y	85	59				

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Shift 0-->1	W1-16 exposure	(b) (6)	Grade 1	1 Grade worsening	122	122	114	115	160	57	Y	0.0387	0.411	0.0025	Y	Y	175	119				
Shift 0-->1	W1-16 exposure		Grade 1	1 Grade worsening	126	123	107	115	160	56	Y	0.0829	0.0193	0.0358	N	N			120			
Shift 0-->1	W1-16 exposure		Grade 1	1 Grade worsening	159	159	127	130	175	114	Y		0.0025	0.0025	N	N						
Shift 0-->1	W1-16 exposure		Grade 1	1 Grade worsening	136	122	106	115	160	21	Y		0.00948	0.0025	N	Y	29	9				
Shift 0-->1	W1-16 exposure		Grade 1	1 Grade worsening	140	137	123	130	175	27	Y	0.0025	0.0025		N	N			134			
Shift 0-->1	W1-16 exposure		Grade 1	1 Grade worsening	115	122	113	115	160	17	Y	0.62	0.252	0.0377	Y	Y	32	16				
Shift 1-->2	W1-16 exposure		Grade 2	1 Grade worsening	109	106	95	115	160	111	Y	0.0149	0.0803	0.0447	Y	N			100			
Shift 0-->1	W1-16 exposure		Grade 1	1 Grade worsening	120	120	108	115	160	97	Y	0.0719	0.0643	0.244	Y	N			109	Y/Microcytic anaemia	197	N
Shift 0-->1	W1-16 exposure		Grade 1	1 Grade worsening	122	121	114	115	160	111	Y	0.356	0.542	0.0438	Y	N			120			
Shift 0-->1	W1-16 exposure		Grade 1	1 Grade worsening	122	116	114	115	160	44	Y	0.017			N	N						
Shift 0-->1	W1-16 exposure		Grade 1	1 Grade worsening	145	142	127	130	175	59	Y	1.19		0.282	Y	Y	113	55		Y/Anaemia	43	N
Shift 0-->1	W1-16 exposure		Grade 1	1 Grade worsening	126	129	114	115	160	115	Y	0.1	0.046	0.0025	Y	Y	290	176				
Shift 0-->1	52 weeks exposure		Grade 1	1 Grade worsening	118	121	106	115	160	55	NA	NA	NA	NA	Y	Y	113	59				
Shift 0-->1	52 weeks exposure		Grade 1	1 Grade worsening	137	137	124	130	175	365	NA	NA	NA	NA	Y	N						
Shift 0-->1	52 weeks exposure		Grade 1	1 Grade worsening	118	115	112	115	160	122	NA	NA	NA	NA	Y	Y	186	65				
Shift 0-->2	52 weeks exposure		Grade 2	2 Grade worsening	115	117	96	115	160	224	NA	NA	NA	NA	Y	N			101			
Shift 0-->1	52 weeks exposure		Grade 1	1 Grade worsening	130	131	122	130	175	365	NA	NA	NA	NA	Y	N						
Shift 0-->1	52 weeks exposure		Grade 1	1 Grade worsening	137	140	124	130	175	288	NA	NA	NA	NA	Y	N			134			
Shift 0-->1	52 weeks exposure		Grade 1	1 Grade worsening	119	116	108	115	160	286	NA	NA	NA	NA	Y	Y	372	87				
Shift 0-->1	52 weeks exposure		Grade 1	1 Grade worsening	115	122	113	115	160	17	NA	NA	NA	NA	Y	Y	32	16				

Source: Applicant response to information requested June 12, 2025

Abbreviations: BL, baseline; NA, not available; N, no; PK, pharmacokinetic; TEAE, treatment emergent adverse event; W, week; Y, yes

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Table 144. Subject Specific Information for Lymphocyte Shifts

Shift to worst post-baseline	Population	Subject ID	Worst post-baseline grade	Shift	Screening value	Baseline value	Worst post-baseline value	Lower limit of norm	Upper limit of norm	Day of worst post-baseline shift	Any PK samples? (Y/N)	PK value Week 1	PK value Week 4	PK value Week 16	Rolled in 1403? (Y/N)	Did subject return to screening or BL value? (Y/N)	If return to screening or BL value, day of return	If return to screening or BL value, total days of elevated values prior to return	Any associated TEAE? (Y/N/TEAE)	If TEAE occurred, considered related by investigator? (Y/N)
Shift 0-->2	W1-16 exposure	(b) (6)	2	2 Grade worsening	1.9	2	0.7	1	4.8	26	NA	NA	NA	NA	N	Y	54	29	N	
Shift 0-->1	W1-16 exposure		1	1 Grade worsening	1	1.1	0.9	1	4.8	81	NA	NA	NA	NA	Y	Y	113	33	N	
Shift 0-->2	W1-16 exposure		2	2 Grade worsening	1.8	1.9	0.7	1	4.8	85	NA	NA	NA	NA	Y	Y	113	29	N	
Shift 0-->1	W1-16 exposure		1	1 Grade worsening	1.8	1.8	0.8	1	4.8	31	NA	NA	NA	NA	Y	Y	59	29	N	
Shift 0-->1	W1-16 exposure		1	1 Grade worsening	0.8	1.1	0.9	1	4.8	58	NA	NA	NA	NA	Y	Y	86	29	N	
Shift 0-->2	W1-16 exposure		2	2 Grade worsening	1.1	1.1	0.7	1	4.8	15	NA	NA	NA	NA	Y	Y	28	14	N	
Shift 0-->1	W1-16 exposure		1	1 Grade worsening	1.1	1.4	0.9	1	4.8	17	NA	NA	NA	NA	Y	Y	90	74	N	
Shift 0-->2	W1-16 exposure		2	2 Grade worsening	1.3	1.3	0.6	1	4.8	86	NA	NA	NA	NA	Y	Y	113	28	N	
Shift 2-->3	W1-16 exposure		3	1 Grade worsening	0.5	0.6	0.4	1	4.8	113	Y	0.724	0.322	0.073	Y	Y	141	29	N	
Shift 0-->1	W1-16 exposure		1	1 Grade worsening	1.2	1.1	0.8	1	4.8	34	Y		0.485	0.231	Y	Y	57	24	N	
Shift 0-->1	W1-16 exposure		1	1 Grade worsening	1.5	1.8	0.9	1	4.8	114	Y	0.383	0.0646	0.152	Y	Y	191	78	N	
Shift 0-->1	W1-16 exposure		1	1 Grade worsening	1.6	1.1	0.9	1	4.8	29	Y	0.211	1.23	0.518	Y	Y	58	30	N	
Shift 0-->2	W1-16 exposure		2	2 Grade worsening	1.2	1.3	0.7	1	4.8	112	Y	0.39	0.489	1.42	Y	Y	169	58	N	
Shift 0-->1	W1-16 exposure		1	1 Grade worsening	1.4	1.4	0.9	1	4.8	15	Y	0.573	0.173		Y	Y	29	15	N	
Shift 0-->1	W1-16 exposure		1	1 Grade worsening	1.3	1.1	0.9	1	4.8	85	Y	0.107	0.225	0.375	Y	Y	113	29	N	
Shift 0-->2	W1-16 exposure		2	2 Grade worsening	1.4	2.2	0.5	1	4.8	115	Y	0.224	0.125	0.0459	Y	Y	171	57	N	
Shift 0-->1	Continuous 52 weeks exposure		Grade 1	1 Grade worsening	1.4	1.2	0.9	1	4.8	225	NA	NA	NA	NA	Y	Y	281	57	N	
Shift 0-->1	Continuous 52 weeks exposure		Grade 1	1 Grade worsening	1.1	1	0.9	1	4.8	288	NA	NA	NA	NA	Y	Y	364	77	N	
Shift 0-->1	Continuous 52 weeks exposure		Grade 1	1 Grade worsening	1.7	1.8	0.9	1	4.8	288	NA	NA	NA	NA	Y	Y	365	78	N	
Shift 0-->1	Continuous 52 weeks exposure		Grade 1	1 Grade worsening	1.1	1.4	0.9	1	4.8	17	NA	NA	NA	NA	Y	Y	90	74	N	
Shift 0-->2	Continuous 52 weeks exposure		Grade 2	2 Grade worsening	1.3	1.3	0.6	1	4.8	86	NA	NA	NA	NA	Y	Y	113	28	N	
Shift 2-->3	Continuous 52 weeks exposure		Grade 3	1 Grade worsening	0.5	0.6	0.4	1	4.8	113	NA	NA	NA	NA	Y	Y	141	29	N	
Shift 0-->1	Continuous 52 weeks exposure		Grade 1	1 Grade worsening	1.6	1.1	0.9	1	4.8	29	NA	NA	NA	NA	Y	Y	58	30	N	

Source: Applicant response to information requested June 12, 2025

Abbreviations: BL, baseline; N, no; NA, not available; PK, pharmacokinetic; TEAE, treatment emergent adverse event; W, week; Y, yes

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Table 145. Subject Specific Information for Platelet Shifts

Subject ID	Worst post-baseline grade	Shift	Screening value	Baseline value	Worst post-baseline value	Lower limit of normal	Upper limit of normal	Day of worst post-baseline shift	Did subject have any PK samples? (Y/N)	PK value Week 1	PK value Week 4	PK value Week 16	Subject rolled in 1403? (Y/N)	Did subject return to screening or baseline value? (Y/N)	If subject returned to screening or baseline value, day of return	If subject returned to screening or baseline value, total days of elevated values prior to return	If subject did not return to screening or baseline value, subject returned to	Any associated TEAE? (Y/N/Specify TEAE)
(b) (6)	Grade 2	1 Grade worsening	68	82	69	130	400	85	NA	NA	NA	NA	Y	Y	113	29		N
	Grade 1	1 Grade worsening	129	137	120	130	400	29	NA	NA	NA	NA	Y	Y	85	57		N
	Grade 1	1 Grade worsening	221	215	98	130	400	87	Y	0.0429	0.0201		Y	Y	92	6		N
	Grade 3	1 Grade worsening		60	38	130	400	111	Y	0.481	0.0949	0.112	N	N				N
	Grade 1	1 Grade worsening	153	147	128	130	400	85	Y		0.584		Y	Y	200	116		N
	Grade 2	1 Grade worsening	68	82	61	130	400	169	NA	NA	NA	NA	Y	Y	274	106		N
	Grade 1	1 Grade worsening	129	137	102	130	400	365	NA	NA	NA	NA	Y	N				

Source: Applicant response to information requested June 12, 2025

Abbreviations: BL, baseline; NA, not available; N, no; PK, pharmacokinetic; TEAE, treatment emergent adverse event; W, week; Y, yes

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Table 146. Subject Specific Information for Leukocyte Shifts

Shift to worst post-BL	Population	Subject ID	Worst post-baseline grade	Screening value	Baseline value	Worst post-baseline value	Lower limit of norm	Upper limit of norm	Day of worst post-baseline shift	Did subject have any PK samples? (Y/N)	PK value Week 1	PK value Week 4	PK value Week 16	Rolled in 1403? (Y/N)	Return to screening or BL value? (Y/N)	If return to screening or BL value, day of return	If return to screening or BL value, total days of elevated values prior to return	If did not return to screening or BL value, value returned to	Any associated TEAE? (Y/N/Specify TEAE)	Day of TEAE	If TEAE occurred, considered related by investigator (Y/N)
Shift 0-->1	Week 1 to 16	(b) (6)	1	4.1	4.7	3.5	4.5	11	21	NA	NA	NA	NA	Y	Y	32	12				
Shift 0-->1	Week 1 to 16		1	5.2	5	4.4	4.5	11	113	NA	NA	NA	NA	Y	Y	226	114				
Shift 0-->1	Week 1 to 16		1	4.6	5.9	3.6	4.5	11	57	NA	NA	NA	NA	Y	Y	113	57				
Shift 0-->1	Week 1 to 16		1	4.8	4.7	4	4.5	11	57	NA	NA	NA	NA	Y	Y	282	226				
Shift 0-->1	Week 1 to 16		1	4.7	4.9	3.1	4.5	11	108	NA	NA	NA	NA	Y	Y	365	258				
Shift 0-->1	Week 1 to 16		1	4.2	5	4.3	4.5	11	15	NA	NA	NA	NA	Y	Y	64	50				
Shift 0-->1	Week 1 to 16		1	5.6	4.9	3.8	4.5	11	30	NA	NA	NA	NA	Y	Y	59	30				
Shift 0-->1	Week 1 to 16		1	5.6	5.4	4.4	4.5	11	58	NA	NA	NA	NA	Y	Y	84	27				
Shift 0-->1	Week 1 to 16		1	5.1	4.6	4	4.5	11	92	NA	NA	NA	NA	Y	Y	142	51				
Shift 0-->1	Week 1 to 16		1	5.3	4.8	3.7	4.5	11	84	NA	NA	NA	NA	Y	N			4.3			
Shift 0-->1	Week 1 to 16		1	6.6	6.3	4.3	4.5	11	108	NA	NA	NA	NA	N	N						
Shift 0-->1	Week 1 to 16		1	5.4	4.8	4.4	4.5	11	88	NA	NA	NA	NA	Y	Y	169	82				
Shift 0-->1	Week 1 to 16		1	5	5.8	3.9	4.5	11	59	NA	NA	NA	NA	N	N			4.8			
Shift 0-->1	Week 1 to 16		1	3.9	6	4.1	4.5	11	114	NA	NA	NA	NA	Y	Y	227	114				

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Shift 0-->1	Week 1 to 16	(b) (6)	1	4.7	7.3	4.2	4.5	11	84	NA	NA	NA	NA	Y	Y	224	141					
Shift 0-->1	Week 1 to 16		1	5.1	10	4.4	4.5	11	111	NA	NA	NA	NA	Y	Y	363	253					
Shift 0-->1	Week 1 to 16		1	4.3	6.2	4.1	4.5	11	29	NA	NA	NA	NA	Y	Y	57	29					
Shift 0-->1	Week 1 to 16		1	4.6	4.8	3.4	4.5	11	58	NA	NA	NA	NA	Y	Y	169	112					
Shift 0-->1	Week 1 to 16		1	4.6	5.5	4.1	4.5	11	113	NA	NA	NA	NA	N	N							
Shift 0-->1	Week 1 to 16		1	4.6	6.2	4.1	4.5	11	113	NA	NA	NA	NA	Y	Y	225	113					
Shift 0-->1	Week 1 to 16		1	5.6	6.2	4.2	4.5	11	16	NA	NA	NA	NA	Y	Y	55	40					
Shift 0-->1	Week 1 to 16		1	5.7	6.1	4.1	4.5	11	113	NA	NA	NA	NA	Y	Y	225	113					
Shift 0-->1	Week 1 to 16		1	5.4	6	4	4.5	11	29	NA	NA	NA	NA	Y	Y	57	29					
Shift 0-->1	Week 1 to 16		1	5	5.2	3.9	4.5	11	53	NA	NA	NA	NA	Y	Y	119	67					
Shift 0-->1	Week 1 to 16		1	4.9	6.8	4	4.5	11	86	NA	NA	NA	NA	Y	Y	119	34					
Shift 0-->1	Week 1 to 16		1	5.3	5.3	4.4	4.5	11	85	NA	NA	NA	NA	Y	Y	239	155					
Shift 0-->1	Week 1 to 16		1	5	5.4	3.9	4.5	11	29	NA	NA	NA	NA	Y	Y	84	56					
Shift 0-->1	Week 1 to 16		1	4.6	4.8	3.9	4.5	11	34	NA	NA	NA	NA	Y	Y	90	57					
Shift 0-->1	Week 1 to 16		1	5.1	4.8	4.3	4.5	11	85	NA	NA	NA	NA	Y	Y	281	197					
Shift 0-->1	Week 1 to 16		1	8.5	8.1	4.4	4.5	11	57	NA	NA	NA	NA	Y	N			7.2				
Shift 0-->1	Week 1 to 16		1	5.7	5.2	4.1	4.5	11	29	NA	NA	NA	NA	Y	N			5.1				
Shift 0-->1	Week 1 to 16		1	7.9	5.3	3.6	4.5	11	54	NA	NA	NA	NA	Y	Y	281	228					
Shift 0-->1	Week 1 to 16		1	5.5	6.1	4.1	4.5	11	86	NA	NA	NA	NA	Y	Y	169	84					
Shift 0-->1	Week 1 to 16		1	6.2	6.6	4.4	4.5	11	112	NA	NA	NA	NA	Y	Y	162	51					
Shift 0-->1	Week 1 to 16		1	6.3	7	4.4	4.5	11	56	NA	NA	NA	NA	Y	Y	86	31					
Shift 0-->1	Week 1 to 16		1	7.6	6.1	3.8	4.5	11	90	NA	NA	NA	NA	Y	Y	168	79					
Shift 0-->1	Week 1 to 16		1	8.4	5.1	3.6	4.5	11	59	NA	NA	NA	NA	Y	Y	87	29					
Shift 0-->1	Week 1 to 16		1	5.9	5.8	3.3	4.5	11	120	NA	NA	NA	NA	Y	N			4.9				
Shift 1-->2	Week 1 to 16		Grade	2	3.5	3.4	2.5	4.5	11	113	Y	0.724	0.322	0.073	Y	Y	141	29		Y/Leukopenia	113	Possibly related
Shift 0-->1	Week 1 to 16		1	4.4	4.8	4.3	4.5	11	15	Y	0.666	0.698	2.26	Y	Y	29	15					
Shift 0-->1	Week 1 to 16		1	4.7	6.3	4.4	4.5	11	87	Y		0.194	0.44	Y	Y	171	85					
Shift 0-->1	Week 1 to 16		1	7.6	6.2	4	4.5	11	15	Y	0.112	0.134	0.062	Y	Y	58	44					
Shift 0-->1	Week 1 to 16		1		4.7	4.3	4.5	11	88	Y	0.21	0.384	0.09	Y	Y	166	79					
Shift 0-->1	Week 1 to 16		1	4.8	5.9	3.5	4.5	11	114	Y	0.383	0.0646	0.152	Y	Y	191	78					
Shift 0-->1	Week 1 to 16		1	5	5.2	4.3	4.5	11	13	Y	0.154	0.0501	0.0215	Y	Y	87	75					
Shift 0-->1	Week 1 to 16		1	4.7	5.4	4.3	4.5	11	27	Y	0.47	0.123	0.0516	N	Y	57	31					
Shift 0-->1	Week 1 to 16	1		6.6	4.4	4.5	11	22	Y	0.481	0.0949	0.112	N	N			6.5					
Shift 0-->2	Week 1 to 16	2	4.3	6.7	2.8	4.5	11	117	Y	0.112	0.281	0.205	Y	Y	257	141						
Shift 0-->1	Week 1 to 16	1	4.7	4.7	3.6	4.5	11	16	Y	0.0862	0.0933	0.205	Y	Y	30	15						
Shift 0-->1	Week 1 to 16	1	4.1	4.6	3.9	4.5	11	113	Y	0.0926	0.021	0.107	Y	Y	225	113						
Shift 0-->1	Week 1 to 16	1	6	4.8	4.4	4.5	11	57	Y	0.195	0.143	1.04	Y	Y	114	58						
Shift 0-->1	Week 1 to 16	1	3.5	5.2	4.2	4.5	11	15	Y	1.52	1.46		Y	Y	29	15						
Shift 0-->1	Week 1 to 16	1	5.3	5.3	4.4	4.5	11	85	N				Y	Y	169	85						
Shift 0-->1	Week 1 to 16	1	5.6	4.9	4.3	4.5	11	113	Y	0.176	1.35	0.152	Y	Y	227	115						
Shift 0-->1	Week 1 to 16	1	6.5	7.3	4.1	4.5	11	111	Y	0.234	0.17	0.262	Y	Y	279	169						
Shift 0-->1	Week 1 to 16	1	6.6	5.7	4.3	4.5	11	29	Y	0.211	1.23	0.518	Y	Y	58	30						
Shift 0-->1	Week 1 to 16	1	7.3	4.9	4.2	4.5	11	30	Y	0.418	0.369	0.577	Y	Y	60	31						
Shift 0-->1	Week 1 to 16	1	4.7	4.7	4	4.5	11	84	Y	0.0025	0.0594	0.0228	Y	N			4.6					

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Shift 0-->1	Week 1 to 16	(b) (6)	1	4.6	4.8	4.1	4.5	11	16	Y	1.81	1.12	1.07	Y	Y	29	14				
Shift 0-->1	Week 1 to 16		1	4.8	4.6	4.3	4.5	11	38	Y	0.466	0.309	0.179	N	Y	84	47				
Shift 0-->1	Week 1 to 16		1	5	5.5	3.3	4.5	11	25	Y		0.584		Y	Y	368	344		Y/Leukopenia	200	N
Shift 0-->1	Week 1 to 16		1	8.4	5.2	4.2	4.5	11	18	Y	0.0548	0.119	0.015	Y	Y	88	71				
Shift 0-->1	Week 1 to 16		1		5.7	3.9	4.5	11	116	Y	0.0937	0.247	0.0094	N	N						
Shift 0-->1	Week 1 to 16		1	4.7	5.4	4.2	4.5	11	84	Y	0.0829	0.0193	0.0358	N	N			4.4			
Shift 0-->1	Week 1 to 16		1	5.4	5.2	3.8	4.5	11	112	Y	0.39	0.489	1.42	Y	Y	169	58				
Shift 0-->1	Week 1 to 16		1	6.4	5.9	4.3	4.5	11	15	Y	0.124	0.455	0.0862	Y	Y	29	15				
Shift 0-->1	Week 1 to 16		1	8.2	6.8	4.4	4.5	11	15	Y	0.573	0.173		Y	Y	29	15				
Shift 0-->1	Week 1 to 16		1	6.9	5	4.3	4.5	11	15	Y	0.0025	0.0025	0.0025	Y	Y	57	43				
Shift 0-->1	Week 1 to 16		1	5.8	5.9	4.4	4.5	11	30	Y	0.0265	0.0536	0.0476	Y	Y	169	140				
Shift 0-->1	Week 1 to 16		1	5	5	4.3	4.5	11	29	Y	0.871	0.304	0.37	Y	Y	84	56				
Shift 0-->1	Week 1 to 16		1	6.8	5.4	4	4.5	11	86	Y	0.612	0.499	0.197	Y	Y	170	85				
Shift 0-->1	Week 1 to 16		1	4.6	4.8	4.2	4.5	11	29	Y	0.0286	0.238	0.0705	Y	Y	57	29				
Shift 0-->1	Week 1 to 16		1	4.5	5.7	3.6	4.5	11	113	Y	0.107	0.225	0.375	Y	N			3.7			
Shift 0-->1	Week 1 to 16		1	6	5.2	4	4.5	11	85	Y	0.49	0.802		Y	Y	113	29				
Shift 0-->1	Week 1 to 16		1	5.4	5.3	4	4.5	11	30	Y	0.14	0.17	0.117	Y	Y	113	84				
Shift 0-->1	Week 1 to 16		1	7.2	10.8	4.1	4.5	11	86	Y	0.0804	0.0469	0.273	Y	N			6.8			
Shift 0-->1	Week 1 to 16		1	5	5.7	4.3	4.5	11	29	Y		0.185		Y	Y	58	30				
Shift 0-->1	Week 1 to 16		1	5.5	4.9	4.4	4.5	11	85	Y	0.171	0.415	0.0927	Y	Y	115	31				
Shift 0-->1	Week 1 to 16		1	5.7	5.4	4.3	4.5	11	86	Y	1.7	0.166	0.225	Y	Y	114	29				
Shift 0-->1	Week 1 to 16		1	4.4	4.5	4.2	4.5	11	15	Y	0.139	0.304	0.0268	Y	Y	29	15				
Shift 0-->1	Week 1 to 16		1	3.7	5.6	3.9	4.5	11	53	Y	0.757	0.906	0.282	Y	Y	85	33				
Shift 0-->1	Week 1 to 16		1	6.3	7.1	4.4	4.5	11	29	Y	0.315	0.167	0.139	Y	Y	169	141				
Shift 0-->1	Week 1 to 16		1	4.9	5.5	4.2	4.5	11	26	Y	0.138	0.0564	0.0398	Y	Y	57	32				
Shift 0-->1	Week 1 to 16		1	5.3	5.5	4.3	4.5	11	113	Y	0.126	0.0843	0.184	Y	Y	227	115				
Shift 0-->1	Week 1 to 16		1	8	4.7	3.9	4.5	11	85	Y	0.18		0.0025	Y	Y	120	36				
Shift 0-->1	Week 1 to 16		1	5.1	6.2	3.8	4.5	11	31	Y	0.167			N	N						
Shift 0-->1	Week 1 to 16		1	3.4	4.7	3.4	4.5	11	87	Y	0.1	0.046	0.0025	Y	Y	115	29				
Grade																					
Shift 0-->1	Cont 52 weeks		1	5.8	5.5	4.4	4.5	11	369	NA	NA	NA	NA	Y	N						
Shift 0-->1	Cont 52 weeks		1	3.8	4.8	4.1	4.5	11	288	NA	NA	NA	NA	Y	Y	372	85				
Shift 0-->1	Cont 52 weeks		1	5.6	4.9	3.5	4.5	11	166	NA	NA	NA	NA	Y	Y	227	62				
Shift 0-->1	Cont 52 weeks		1	4.9	5.1	4.1	4.5	11	229	NA	NA	NA	NA	Y	N			4.8			
Shift 0-->1	Cont 52 weeks		1	5.3	4.8	3.7	4.5	11	84	NA	NA	NA	NA	Y	N			4.3			
Grade																					
Shift 1-->2	Cont 52 weeks		2	3.9	3.5	2.6	4.5	11	288	NA	NA	NA	NA	Y	Y	364	77				
Shift 0-->1	Cont 52 weeks		1	4.6	6.1	4.3	4.5	11	366	NA	NA	NA	NA	Y	N						
Shift 0-->1	Cont 52 weeks		1	5.1	10	4.4	4.5	11	111	NA	NA	NA	NA	Y	Y	363	253				
Shift 0-->1	Cont 52 weeks		1	6	5	4.3	4.5	11	225	NA	NA	NA	NA	Y	Y	365	141				
Shift 0-->1	Cont 52 weeks		1	4.3	6.2	4.1	4.5	11	29	NA	NA	NA	NA	Y	Y	57	29				
Shift 0-->1	Cont 52 weeks		1	4.6	6.2	4.1	4.5	11	113	NA	NA	NA	NA	Y	Y	225	113				

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

Shift 0-->1	Cont 52 weeks	(b) (6)	1	5	5.2	3.9	4.5	11	53	NA	NA	NA	NA	Y	Y	119	67				
Shift 0-->1	Cont 52 weeks		1	5	5.4	3.7	4.5	11	251	NA	NA	NA	NA	Y	Y	365	115				
Shift 0-->1	Cont 52 weeks		1	4.6	4.8	3.9	4.5	11	34	NA	NA	NA	NA	Y	Y	90	57				
Shift 0-->1	Cont 52 weeks		1	6.5	5.5	4.2	4.5	11	362	NA	NA	NA	NA	Y	N						
Shift 0-->1	Cont 52 weeks		1	8.5	8.1	4.4	4.5	11	57	NA	NA	NA	NA	Y	N			7.2			
Shift 0-->1	Cont 52 weeks		Grade																		
Shift 0-->1	Cont 52 weeks		1	4.7	5.1	4.1	4.5	11	362	NA	NA	NA	NA	Y	N						
Shift 0-->1	Cont 52 weeks		1	4.5	6.9	4.4	4.5	11	282	NA	NA	NA	NA	Y	Y	364	83				
Shift 0-->1	Cont 52 weeks		1	5.5	6.1	4.1	4.5	11	86	NA	NA	NA	NA	Y	Y	169	84				
Shift 0-->1	Cont 52 weeks		1	5.5	5.9	3.7	4.5	11	225	NA	NA	NA	NA	Y	Y	281	57				
Shift 1-->2	Cont 52 weeks		2	4.7	3.9	2.9	4.5	11	372	NA	NA	NA	NA	Y	N			3			
Shift 1-->2	Cont 52 weeks		Grade																		
Shift 1-->2	Cont 52 weeks		2	3.5	3.4	2.5	4.5	11	113	NA	NA	NA	NA	Y	Y	141	29		Y/Leukopenia	113	Possibly related
Shift 0-->1	Cont 52 weeks		1	4.7	6.3	4.4	4.5	11	87	NA	NA	NA	NA	Y	Y	171	85				
Shift 0-->1	Cont 52 weeks		1	6.7	6.3	3.3	4.5	11	226	NA	NA	NA	NA	Y	Y	282	57				
Shift 0-->1	Cont 52 weeks		1	9.4	9.4	4.2	4.5	11	224	NA	NA	NA	NA	Y	Y	274	51				
Shift 0-->1	Cont 52 weeks		1	5.6	4.9	4.3	4.5	11	113	NA	NA	NA	NA	Y	Y	227	115				
Shift 0-->1	Cont 52 weeks		1	6.6	5.7	4.3	4.5	11	29	NA	NA	NA	NA	Y	Y	58	30				
Shift 0-->1	Cont 52 weeks		1	5.1	4.5	4.2	4.5	11	172	NA	NA	NA	NA	Y	Y	222	51				
Shift 0-->1	Cont 52 weeks		1	4.6	4.8	4.2	4.5	11	29	NA	NA	NA	NA	Y	Y	57	29				
Shift 0-->1	Cont 52 weeks		1	6.3	7.1	4.4	4.5	11	29	NA	NA	NA	NA	Y	Y	169	141				

Source: Applicant response to information requested June 12, 2025

Abbreviations: BL, baseline; N, no; NA, not available; PK, pharmacokinetic; TEAE, treatment emergent adverse event; W, week; Y, yes

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

One phase 2 clinical trial (Trial 1273) was conducted which had the exploratory objectives of evaluating the effect of delgocitinib on *Staphylococcus aureus* colonization of the skin, skin microbiome, skin barrier function, and skin inflammation. The trial design and results are described in Section [3.2](#) of this review. To test the exploratory endpoints of evaluating the change in *S. aureus* colonization from Baseline to Week 16, swabs were collected from lesion and nonlesion areas at the Baseline visit and Week-16 visit. The skin swabs were used to determine *S. aureus* colonization levels using quantitative polymerase chain reaction (qPCR).

For *S. aureus* colonization, DNA using a QIAGEN robot and extraction kit was extracted from the skin swabs. The extracted DNA was used in a qPCR analysis using probes targeting the *femA* gene, a universal 16S rDNA probe, and a 18S rDNA probe. The signal from the *femA* probes was compared to a standard curve created using DNA from *S. aureus* ATCC 7000699DQ and the genome copy number was calculated. No information was provided in either trial study report or the bioanalytical report regarding quality control for the DNA extraction or qPCR method. Additionally, no data were provided to show correlation between genome copy number and colony forming units (CFUs).

Approximately half of the samples did not have detectable levels of *S. aureus* (limit of detection was reported as approximately 2 CFUs/cm²). The lack of detectable *S. aureus* results in a limited number of subjects available for analysis who had a successful clinical outcome ([Table 147](#)). A reduction in colonization levels of *S. aureus* was observed for most of the subjects receiving delgocitinib irrespective of the clinical outcome of treatment. Increases in bacterial load were seen in samples from nonlesional areas in subjects with clinical failure who received 3 mg/g of delgocitinib or vehicle control ([Figure 35](#)). Samples from either lesion or nonlesional areas of subjects with clinical success who received vehicle control showed at least a 2-fold increase in *S. aureus* burden.

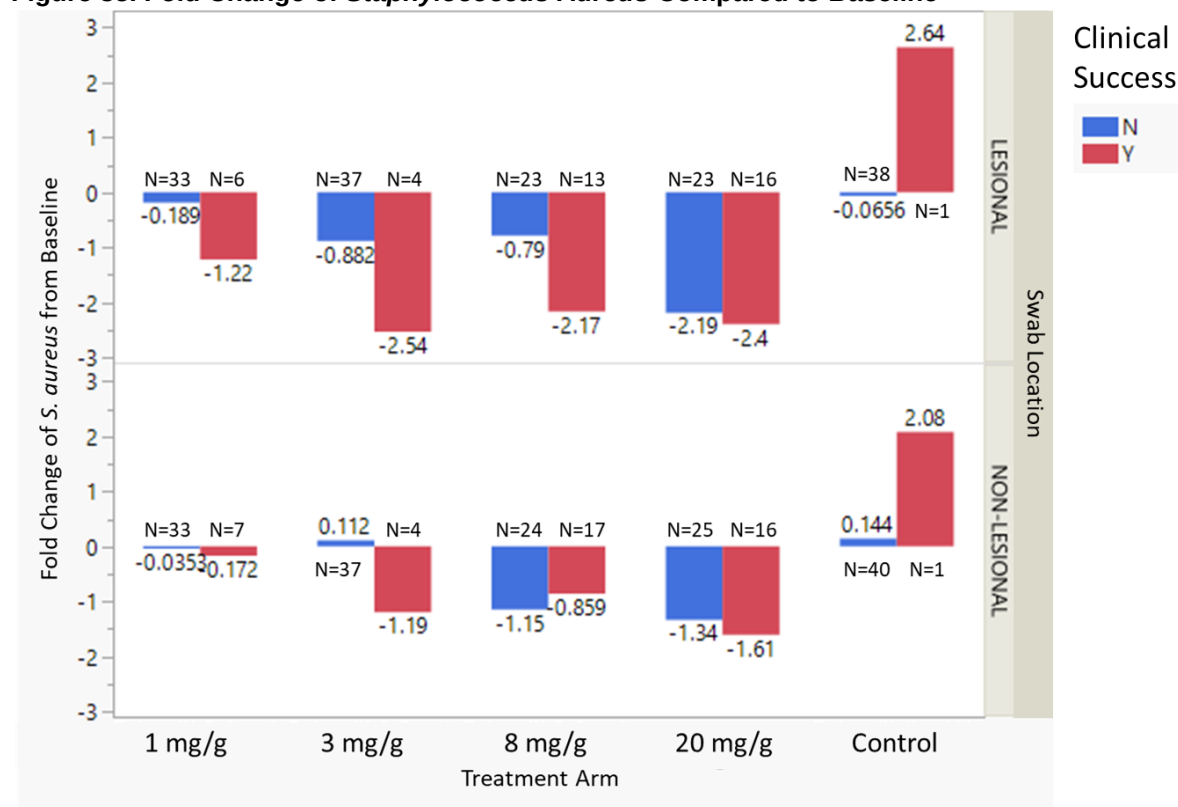
Despite the difference in bacterial burden observed in subjects who received vehicle control compared to those who received higher doses (8 mg/g or 20 mg/g) of delgocitinib, it is not possible to determine the effect of delgocitinib on *S. aureus* colonization due to the lack of quality control data regarding the enumeration method, the lack of comparison between the method used (qPCR) compared to the standard colony counts, and the small population of subjects in each arm with detectable microbiological data.

Table 147. Primary Response in Subjects With Available Microbiological Data

Treatment Arm	Primary Efficacy Response at Week 16 All Subjects		Primary Efficacy Response at Week 16 Subjects With Microbiological Data	
	Failure	Success	Failure	Success
Vehicle control	46	4	41	1
1 mg/g	41	11	34	7
3 mg/g	47	4	40	4
8 mg/g	33	19	24	17
20 mg/g	33	20	27	17

Source: Reviewer made table from data presented in Study 1273

Figure 35. Fold Change of *Staphylococcus Aureus* Compared to Baseline



Source: Reviewer made table from data presented in Study 1273.

Abbreviations: N, no; Y, yes; *S. aureus*; *Staphylococcus aureus*, N, number of subjects with clinical outcome

20. Mechanism of Action/Drug Resistance

Not applicable.

21. Other Drug Development Considerations

Not applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Not applicable.

23. Labeling: Key Changes

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant’s draft PI ([Table 148](#)). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

In addition, the Applicant submitted draft (b) (4) The review team revised (b) (4) medication guide due to the addition of subsection 5.4 in the Warnings and Precautions section of labeling (potential risk related to JAK inhibitors. Changing this document (b) (4) will ensure distribution to patients per CFR 208.24 Distributing and Dispensing a Medication Guide (refer to Patient Labeling Review by Division of Medical Policy Programs and Office of Prescription Drug Promotion dated April 23, 2025).

Table 148. Key Labeling Changes and Considerations

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant’s Draft PI
1 INDICATIONS AND USAGE	Limitations of Use statement was added Language was added to the administration instructions to emphasize that ANZUPGO is to be applied “only” to the hands and wrists. This dosage- and administration-related information is particularly critical to the safe and effective use of the drug. Nonadherence to this recommendation may result in increased systemic exposure to this JAK inhibitor.
2 DOSAGE AND ADMINISTRATION	Language was added stating “Do not use more than one 30 gram tube per 2 weeks or one 60 gram tube per month.” Refer to Clinical Pharmacology section of this review for rationale. Removed the statement (b) (4) (b) (4) i (b) (4). This information is related to the (b) (4) is not recommended for inclusion in labeling.
4 CONTRAINDICATIONS	No changes
5 WARNINGS AND PRECAUTIONS	The Applicant did not propose any W+P. The following subsections are added: 5.1 Serious Infections 5.2 Non-melanoma Skin Cancers 5.3 Immunizations

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
	5.4 Potential Risks Related to JAK Inhibition The Applicant proposed inclusion of application site reactions.
6 ADVERSE REACTIONS	The review team added adverse reactions that were reported in DELTA 1 and DELTA 2 in <1% of subjects in the ANZUPGO group (application site pain, paresthesia, pruritus, erythema, and bacterial skin infections including finger cellulitis, paronychia, other skin infections, leukopenia and neutropenia).
7 DRUG INTERACTIONS	No clinically significant drug interactions have been observed or are predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods. This Section has been omitted from labeling.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Contraception recommendations were not included by the review team because the safety margins observed in nonclinical studies, along with animal reproduction data, do not suggest an increased risk of adverse developmental outcomes and no appreciable risks to human fertility are expected following topical delgocitinib. In Section 8.2 the Applicant proposed the statement: After oral administration, delgocitinib was present in the milk of lactating rats (b) (4). The review team added the language "When a drug is present in animal milk, it is likely that the drug will be present in human milk." In addition, the Applicant proposed (b) (4) The review team removed this statement since (b) (4) (b) (4) Refer to the nonclinical section of the review and the Maternal Health Team review in DARRTS (Reference ID: 5554590) for additional information. The language under subsection 8.4 Pediatric Use and 8.5 Geriatric Use was modified to be consistent with the recommendations in the guidances for industry <i>Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling</i> (March 2019) and <i>Geriatric Information in Human Prescription Drug and Biological Product Labeling</i> (September 2020) (when final, this guidance will represent FDA's current thinking on this topic).
9 DRUG ABUSE AND DEPENDENCE	ANZUPGO is not scheduled under the Controlled Substances Act and this Section has been omitted from labeling.
10 OVERDOSAGE	No specific human overdosage data are available that would be useful to the healthcare provider. This section has been omitted from labeling.
12 CLINICAL PHARMACOLOGY	In Section 12.2 the Applicant proposed a claim (b) (4) (b) (4) (b) (4) The review team determined the data provided did not support this claim, therefore it was deleted (Refer to Section 19 Clinical Microbiology of this review).

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
	In Section 12.3 the Applicant proposed the statement "The systemic exposure (AUC and C _{max}) between Day 1 and Day 8 (b) (4) similar." However, the systemic exposure from max-use PK data were measurable, not subnanomolar, and the relationship between the level, extent, and duration of systemic exposure and the potential for adverse events is not well defined for this class. (b) (4)
13 NONCLINICAL TOXICOLOGY	The finding of benign thymoma was added to the description of the 2-year oral rat carcinogenicity study. (b) (4) (b) (4) removed from the proposed label as it is (b) (4)
14 CLINICAL STUDIES	Additional information was added concerning the study population (demographic characteristics and inclusion criteria) and the IGA-CHE and HESD were defined per the recommendation in the guidance for industry <i>Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format</i> (January 2006). Refer to the Biostatistics Section of the review for additional information concerning the presentation of the efficacy results in labeling.
17 PATIENT COUNSELING INFORMATION	The Applicant did not propose any W+P. The review team added the following W+P: 5.1 Serious Infections 5.2 Non-melanoma Skin Cancers 5.3 Immunizations 5.4 Potential Risks Related to JAK Inhibition
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	Section 3: Included packaging information that facilitates prescribing. Section 11: No major changes Section 16: Per 21 CFR 201.57(c)(17), included the strength or potency/potencies of the dosage form in metric system. Refer to the Integrated Quality Assessment in DARRTS (Reference ID: 5552271) for additional information.

Source: Reviewer's Summary

¹ Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.

² For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviation(s): PI, Prescribing Information; JAL, Janus Kinase; JAKi, Janus kinase inhibitor; DARRTS, Document Archiving, Reporting, and Regulatory Tracking System; MACE, major adverse cardiovascular event; W+P, weight and placebo; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; Hand Eczema Symptom Diary; AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; GLP, good laboratory practice; PK, pharmacokinetic

23.1. Approved Labeling Types

Upon approval of this original NDA 219155, the following labeling documents will be FDA-approved:

- Prescribing Information
- Medication Guide
- Carton Label
- Container Label

24. Postmarketing Requirements and Commitments

Clinical postmarketing requirements are intended to characterize the risks of delgocitinib use in special populations (lactating women and pediatrics) and address the safety of this product with long-term use in the target population with CHE.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to less than 11 years because the studies are impossible or highly impractical.

We are deferring submission of your pediatric study for ages 12 years to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

PMR 4877-1

Conduct an assessment of the efficacy, safety, and pharmacokinetics of delgocitinib cream in adolescent subjects ages 12 to 17 years with moderate to severe chronic hand eczema.

Final Report Submission: 10/2025

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

NDA 219155
ANZUPGO (delgocitinib) cream, 2%

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the Federal Food, Drug, and Cosmetic Act will not be sufficient to identify the unexpected serious risks of the drug (or its active metabolites) being present in breast milk, and the effects on milk production in lactating women, and the effects on the breastfed infant.

Furthermore, the active postmarket risk identification and analysis system as available under Section 505(k)(3) of the Federal Food, Drug, and Cosmetic Act will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that the Applicant is required to conduct the following:

PMR 4877-2

Conduct a milk-only lactation study in lactating women who have received delgocitinib to measure concentrations of delgocitinib in breast milk using a validated assay. Assess the effects on the breastfed infant, if available, based on the study population.

Draft Protocol Submission: 01/2026
Final Protocol Submission: 07/2026
Study Completion: 07/2028
Final Report Submission: 01/2029

PMR 4877-3

Conduct a randomized, active-controlled clinical trial to evaluate the long-term safety of delgocitinib in patients with moderate to severe chronic hand eczema. The trial should be of sufficient size and duration to characterize safety events of interest (e.g., effects on bone marrow and viral reactivation).

Draft Protocol Submission: 01/ 2026
Final Protocol Submission: 07/ 2026
Trial Completion: 07/ 2029
Final Report Submission: 01/ 2030

25. Financial Disclosure

Table 149. Covered Clinical Studies, Trial DELTA 1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: Enter text here.200		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): Enter text here.0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: Enter text here.0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
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): 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

Table 150. Covered Clinical Studies, Trial DELTA 2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 189		
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): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
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): 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

Journal Articles

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NDA 219155

ANZUPGO (delgocitinib) cream, 2%

Kawakami, Y, T Ando, JR Lee, G Kim, Y Kawakami, T Nakasaki, M Nakasaki, K Matsumoto, YS Choi, and T Kawakami, 2017, Defective natural killer cell activity in a mouse model of eczema herpeticum, *J Allergy Clin Immunol*, 139(3):997-1006 e1010.

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Zalewski, A and JC Szepietowski, 2023, Topical and systemic JAK inhibitors in hand eczema - a narrative review, *Expert Rev Clin Immunol*, 19(4):365-373.

Guidances

ICH harmonised guideline *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk M7(R2)* (April 2023)

NDA 219155

ANZUPGO (delgocitinib) cream, 2%

FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)

FDA guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products - Content and Format* (January 2006)

FDA guidance for industry *Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling* (March 2019)

FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)

FDA guidance for industry *Geriatric Information in Human Prescription Drug and Biological Product Labeling* (September 2020)

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Websites

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HECSI, 2025, Hand Eczema Severity Index, Yasemin Topal Yüksel and Tove Agner, accessed, 2025, <https://hecsiscore.com/>.

27. Review Team

Table 151. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	K. Searcy
Nonclinical reviewer	K. Ebert
Nonclinical team leader	J. Wang
OCP reviewer(s)	P. Bhagav
OCP team leader(s)	C. Shukla
Clinical reviewers	J. Nguyen, K. Dev Verma
Clinical team leader	M. McCord
Biometrics reviewer	M. Xiang
Biometrics concurring reviewer	M. Guerra
Cross-discipline team leader	M. McCord
Division director (pharm/tox)	J. Chen
Division director (OCP)	S. Chandrahas
Division director (clinical)	G. Diglisic
Office director (or designated signatory authority)	N. Nikolov

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 152. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	B. Ma, R. Ranga, S. Bain, L. Perez, G. Hamad, J. Patel, S. Thumma, M. Koppenol-Raab, Y. Zheng
Microbiology	U. Waack, A. Goodwin
OPDP	R. Mayrosh
OSI	M. Fedowitz, S. Coquia
OSE/DEPI	B. Booth, S. Peprah
OSE/DMEPA	J. Kogan, M. Patel, W. Manitspitkul
OSE/DRM	J. Sheppard, C. Darling, A. Tavakoli
OSE/DPV	J. Klucken, M. Reyes, J. Bailey
DCOA	K. Khurshid, N. Knoble
PFSS	L. Garrard, M. Morell
DPMH	K. Shaab, T. Johnson
Associate director for labeling	M. White

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

27.1. Reviewer Signatures

Table 27-153 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Andrew Goodwin OII DPTII	Sections: 5.1, 7.1, 8.4, 13.1, 13.2, 13.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Andrew Goodwin Digitally signed by Andrew Goodwin Date: 7/22/2025 3:05 PM EDT GUID: 202572219535				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Microbiology Discipline Primary Reviewer	Ursula Waack OID DAI	Sections: 19	Based on my assessment of the application: ✓ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Ursula Waack Digitally signed by Ursula Waack Date: 7/22/2025 3:06 PM EDT GUID: 202572219620				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Other Discipline Primary Reviewer	Monica Morell OB DBIII	Sections: 6.3.2.1, 16.1.4, 16.1.6	Based on my assessment of the application: ✓ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Monica Morell Digitally signed by Monica Morell Date: 7/22/2025 3:06 PM EDT GUID: 202572219655				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Kevin Ebert OII DPTII	Sections: 5.1, 7.1, 8.4, 13.1, 13.2, 13.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Kevin Ebert Digitally signed by Kevin Ebert Date: 7/22/2025 3:06 PM EDT GUID: 202572219659				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Reviewer	Kapil Verma OII DDD	Sections: 1.1, 1.2, 2.1, 2.2, 3.1.2, 3.2, 4, 7, 17, 23, 24, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Kapil Verma Digitally signed by Kapil Verma Date: 7/22/2025 3:15 PM EDT GUID: 2025722191536				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Melinda Mccord OII DDD	Sections: Module 1,2,3,4,7,8,9,10,11,12 ,13,15,17,22,23,24,25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Melinda Mccord Digitally signed by Melinda Mccord Date: 7/22/2025 3:15 PM EDT GUID: 2025722191542				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Kimberle Searcy ORO DROII	Sections: Summary of Regulatory History	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Kimberle Searcy Digitally signed by Kimberle Searcy Date: 7/22/2025 3:21 PM EDT GUID: 202572219216				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Associate Director	Jianmeng Chen OCP DIIP	Sections: 1, 5.2, 7.7, 8, 14,	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jianmeng Chen Digitally signed by Jianmeng Chen Date: 7/22/2025 3:21 PM EDT GUID: 2025722192120				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Meiruo Xiang OB DBIII	Sections: Sections: 6, 15, 16 and 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Meiruo Xiang Digitally signed by Meiruo Xiang Date: 7/22/2025 3:22 PM EDT GUID: 2025722192257				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Matthew Guerra OB DBIII	Sections: 6, 15, 16, and 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Matthew Guerra Digitally signed by Matthew Guerra Date: 7/22/2025 3:23 PM EDT GUID: 202572219236				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Susan Rhee ORO DROII	Sections: Summary of Regulatory History	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Susan Rhee Digitally signed by Susan Rhee Date: 7/22/2025 3:28 PM EDT GUID: 202572219280				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Other Discipline Secondary Reviewer	Lili Garrard OB DBIII	Sections: 6.3.2.1, 16.1.4, 16.1.6	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Lili Garrard		Digitally signed by Lili Garrard Date: 7/22/2025 3:32 PM EDT GUID: 2025722193227		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Secondary Reviewer	Baoqing Ma OPQAII DPQAVII	Sections: 9. Product Quality	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Baoqing Ma		Digitally signed by Baoqing Ma Date: 7/22/2025 3:36 PM EDT GUID: 2025722193641		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Chinmay Shukla OCP DIIP	Sections: 5.2, 8.1, 8.2, and 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Chinmay Shukla		Digitally signed by Chinmay Shukla Date: 7/22/2025 3:37 PM EDT GUID: 2025722193731		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Supervisor / Team Lead	Baoqing Ma OPQAII DPQAVII	Sections: 9. Product Quality	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Baoqing Ma		Digitally signed by Baoqing Ma Date: 7/22/2025 3:37 PM EDT GUID: 2025722193751		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Prakash Bhagav OCP DIIP	Sections: 5.2, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Prakash Bhagav Digitally signed by Prakash Bhagav Date: 7/22/2025 3:40 PM EDT GUID: 2025722194024				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Jessica Nguyen OII DDD	Sections: 2.1; 2.2; 3.1.1.1; 3.1.2.2; 3.2; 4; 7.3; 7.4; 7.5; 7.6, 7.7; 23; 24; 25; 26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jessica Nguyen Digitally signed by Jessica Nguyen Date: 7/22/2025 3:53 PM EDT GUID: 2025722195343				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Non-Clinical Reviewer Discipline Secondary Reviewer	Jianyong Wang OII DPTII	Sections: 5.1, 7.1, 8.4, and 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jianyong Wang Digitally signed by Jianyong Wang Date: 7/22/2025 3:54 PM EDT GUID: 2025722195441				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Outcomes Assessment Reviewer Discipline Primary Reviewer	Kiran Khurshid ODES DCOA	Sections: 4, 6.2, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Kiran Khurshid Digitally signed by Kiran Khurshid Date: 7/22/2025 4:14 PM EDT GUID: 2025722201440				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Matthew White OII DDD	Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Matthew White Digitally signed by Matthew White Date: 7/22/2025 4:22 PM EDT GUID: 2025722202243				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Outcomes Assessment Reviewer Discipline Secondary Reviewer	Naomi Knoble ODES DCOA	Sections: 4, 6.2, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Naomi Knoble Digitally signed by Naomi Knoble Date: 7/22/2025 4:38 PM EDT GUID: 202572220387				

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Outcomes Assessment Reviewer Discipline Tertiary Reviewer	David Reasner ODES DCOA	Sections: 4, 6.2, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: David Reasner Digitally signed by David Reasner Date: 7/22/2025 4:50 PM EDT GUID: 202572220507				

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MELINDA L MCCORD
07/22/2025 05:18:59 PM

GORDANA DIGLISIC
07/22/2025 05:22:08 PM

NIKOLAY P NIKOLOV
07/22/2025 06:06:05 PM