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RESEARCH**

APPLICATION NUMBER:

214958Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	214958
Priority or Standard	Standard
Submit Date(s)	September 10, 2021
Received Date(s)	September 10, 2021
PDUFA Goal Date	September 10, 2022
Division/Office	Division of Dermatology and Dentistry, Office of Immunology and Inflammation
Review Completion Date	September 9, 2022
Established/Proper Name	deucravacitinib
(Proposed) Trade Name	Sotyktu
Pharmacologic Class	Tyrosine kinase 2 inhibitor
Code name	BMS-986165
Applicant	Bristol-Myers Squibb Company
Dosage form	tablet
Applicant proposed Dosing Regimen	6 mg orally once daily, with or without food.
Applicant Proposed Indication(s)/Population(s)	Treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Psoriasis (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Psoriasis (disorder)
Recommended Dosing Regimen	6 mg orally once daily, with or without food

Table of Contents

Table of Tables.....	6
Table of Figures	11
Reviewers of Multi-Disciplinary Review and Evaluation.....	14
Glossary	18
1. Executive Summary	20
1.1. Product Introduction	20
1.2. Conclusions on the Substantial Evidence of Effectiveness	20
1.3. Benefit-Risk Assessment.....	22
1.4. Patient Experience Data	37
2. Therapeutic Context	38
2.1. Analysis of Condition	38
2.2. Analysis of Current Treatment Options	38
3. Regulatory Background	49
3.1. U.S. Regulatory Actions and Marketing History	49
3.2. Summary of Presubmission/Submission Regulatory Activity	49
4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety	53
4.1. Office of Scientific Investigations (OSI).....	53
4.2. Product Quality.....	54
4.3. Clinical Microbiology	54
4.4. Devices and Companion Diagnostic Issues	54
5. Nonclinical Pharmacology/Toxicology.....	55
5.1. Executive Summary	55
5.2. Referenced NDAs, BLAs, DMFs	57
5.3. Pharmacology	57
5.3.1. Safety Pharmacology.....	58
5.4. ADME/PK.....	59
5.5. Toxicology	61
5.5.1. General Toxicology.....	61
5.5.2. Genetic Toxicology.....	66
5.5.3. Carcinogenicity.....	67
5.5.4. Reproductive and Developmental Toxicology	68
5.5.5. Other Toxicology Studies	75
6. Clinical Pharmacology.....	78
6.1. Executive Summary	78
6.1.1. Recommendations.....	79

Multi-disciplinary Review and Evaluation

NDA 214958 Sotykto (deucravacitinib) tablets, 6 mg

6.1.2. Post-Marketing Requirement	79
6.2. Summary of Clinical Pharmacology Assessment	79
6.2.1. Pharmacology and Clinical Pharmacokinetics.....	79
6.2.2. General Dosing and Therapeutic Individualization	81
6.3. Comprehensive Clinical Pharmacology Review	82
6.3.1. General Pharmacology and Pharmacokinetic Characteristics	82
6.3.2. Clinical Pharmacology Questions.....	94
7. Sources of Clinical Data and Review Strategy.....	103
7.1. Table of Clinical Studies	103
7.2. Review Strategy	109
8. Statistical and Clinical and Evaluation	110
8.1. Review of Relevant Individual Trials Used to Support Efficacy.....	110
8.1.1. Trial Design	110
8.1.2. Objectives and Endpoints	113
8.1.3. Statistical Methodologies	115
8.1.4. Subject Disposition, Demographics, and Baseline Disease Characteristics	120
8.1.5. Results for the Co-Primary Efficacy Endpoints.....	123
8.1.6. Results for Secondary Efficacy Endpoints	125
8.1.7. Results for Secondary Efficacy Endpoints Against Placebo.....	125
8.1.8. Results for the Secondary Efficacy Endpoints Against Apremilast.....	126
8.1.9. Patient Reported Outcomes (PROs).....	129
8.1.10. Efficacy Over Time	132
8.1.11. Maintenance Period or Randomized Withdrawal Period	134
8.1.12. Findings in Special/Subgroup Populations.....	136
8.1.13. Sex, Race, Age, Weight, Baseline Disease Severity and Prior Use of Systemic Therapy	136
8.1.14. Geographic Location (Country).....	140
8.2. Review of Safety	143
8.2.1. Safety Review Approach	143
8.2.2. Review of the Safety Database	144
8.2.3. Adequacy of Applicant’s Clinical Safety Assessments.....	145
8.2.4. Safety Results.....	148
8.2.5. Analysis of Submission-Specific Safety Issues	170
8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability.....	255
8.2.7. Safety Analyses by Demographic Subgroups	255
8.2.8. Specific Safety Studies/Clinical Trials	257
8.2.9. Additional Safety Explorations.....	257

Multi-disciplinary Review and Evaluation	
NDA 214958 Sotykto (deucravacitinib) tablets, 6 mg	
8.2.10. Safety in the Postmarket Setting	263
8.2.11. Integrated Assessment of Safety	263
8.3. Summary and Conclusions.....	267
8.3.1. Statistical Issues	267
8.3.2. Conclusions and Recommendations	268
9. Advisory Committee Meeting and Other External Consultations	270
10. Pediatrics	271
11. Labeling Recommendations	272
11.1. Prescription Drug Labeling.....	272
11.2. Patient Labeling	273
12. Risk Evaluation and Mitigation Strategies (REMS).....	274
13. Postmarketing Requirements and Commitment.....	275
13.1. Postmarketing Requirements Under 505(o).....	275
13.1.1. Long Term Safety PMR.....	275
13.1.2. Pregnancy PMR 1	276
13.1.3. Pregnancy PMR 2	276
13.1.4. Lactation PMR.....	276
13.2. Required Pediatric Assessments: Pediatric Research Equity Act (PREA) (21 U.S.C. 355c)	
.....	277
13.2.1. Pediatric PMR	277
13.2.2. Pediatric PMR	278
14. Division Director (DPT-II) Comments.....	279
15. Division Director (OCP) Comments.....	280
16. Division Director (OB) Comments.....	280
17. Division Director (Clinical)/Division Associate Director for Therapeutics Review (DDD)	
Comments	280
18. Office Director Comments.....	282
19. Appendices	285
19.1. References	285
19.2. Financial Disclosure	287
19.3. Nonclinical Pharmacology/Toxicology.....	292
19.3.1. Calculations for Multiples of Exposure	292
19.3.2. Review of Carcinogenicity Studies Conducted With Deucravacitinib	292
19.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)	301
19.4.1. Population PK Analysis.....	301
19.4.2. Exposure-Response Analysis.....	311
19.4.3. Summary of Bioanalytical Method Validation and Performance.....	323

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

19.5. Clinical/Biostatistics.....	336
19.5.1. Scales Assessing Efficacy.....	336
19.5.2. Sensitivity Analysis for Site 0092 in Trial IM011046	340
19.5.3. Endpoints at Week 24 - Sensitivity Analysis for Missing Data Due to COVID-19	340

Table of Tables

Table 1. Summary of Treatment Armamentarium for Moderate to Severe Psoriasis	39
Table 2. Multiples of exposure of BMT-153261 and BMT-158170 in Nonclinical Toxicity Studies	75
Table 3. Summary of Clinical Pharmacology Review	78
Table 4. Absolute Bioavailability of Deucravacitinib From Study IM011067	83
Table 5. PK Parameters of Deucravacitinib Following a Single Oral Dose and IV Dose in Healthy Subjects From Study IM011067	83
Table 6. Summary of PK Parameters for Deucravacitinib From a Mass Balance, Study IM011016.....	84
Table 7. Summary of PK Parameters for Total Radioactivity in Plasma and Whole Blood From Study IM011016	84
Table 8. Total Recovery of Radioactive Dose in Urine, Feces and All Excreta.....	85
Table 9. Distribution of Drug-related Components in Plasma	86
Table 10. Distribution of Drug-related Components in Urine and Feces.....	87
Table 11. Contribution of Biotransformation Pathways to Deucravacitinib Elimination..	87
Table 12. PPK Model Predicted Deucravacitinib Exposures at Steady-state at 6 mg QD	87
Table 13. PPK Model Predicted Time to Steady-state C_{max} , C_{avg} , and C_{min} of Deucravacitinib at a 6 mg QD	88
Table 14. PPK Model Predicted BMT-153261 Exposures at Steady-state at 6 mg QD.....	88
Table 15. Estimated Ratio of BMT-153261 to Deucravacitinib Exposure at Steady-state	89
Table 16. Changes in Psoriasis-Related Differentially Expressed Genes (DEGs) in Lesional Skin Biopsies Among 3004 DEGs.....	89
Table 17. Relative Bioavailability Between Capsule and Solution Formulations of Deucravacitinib	93
Table 18. Relative Bioavailability Between Capsule and Tablet Formulations of Deucravacitinib	93
Table 19. Number of Subjects Who Completed the Study by Renal Function Group.....	95
Table 20. Effect of Renal Impairment on PK of Deucravacitinib	95
Table 21. Effect of Renal Impairment on PK of BMT-153261	95
Table 22. Summary of Deucravacitinib Extraction Through Dialysis in ESRDH Group	96
Table 23. Effect of Hepatic Impairment on PK of Deucravacitinib.....	97
Table 24. Effect of Hepatic Impairment on PK of BMT-153261	97
Table 25. The Effect of Food on PK Parameters of Deucravacitinib	98
Table 26. The Effect of Food on PK Parameters of BMT-153261	98

Multi-disciplinary Review and Evaluation

NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Table 27. Listing of Clinical Trials Relevant to this BLA	104
Table 28. Clinical Pharmacology Studies Pertinent to the Review of Efficacy or Safety .	107
Table 29. Key Secondary Objectives and Endpoints for Trials 046/047	113
Table 30. Testing Order of Key Secondary Endpoints for Trial IM011046 (U.S. Submission).....	117
Table 31. Testing Order of Key Secondary Endpoints for Trial IM011047 (U.S. Submission).....	117
Table 32. Subject Disposition through Week 16 – Trials IM011046/47 (FAS*)	121
Table 33. Disposition of Subjects for Weeks 16-24 – Trials IM011046/47 (FAS*)	121
Table 34. Demographics and Baseline Disease Characteristics – Trials IM011046/47 (FAS*)	122
Table 35. Results for the Co-Primary Endpoints at Week 16 – Trials IM011046/47 (FAS; NRI ¹)	123
Table 36. Missing Data for the Co-Primary Endpoints by Week up to Week 16 – Trials IM011046/47 (FAS*).....	123
Table 37. Results for the Co-Primary Endpoints at Week 16 With Different Approaches of Handling the Missing Data at Week 16 – Trial IM011046 (FAS ¹)	124
Table 38. Results for the Co-Primary Endpoints at Week 16 With Different Approaches of Handling the Missing Data at Week 16 – Trial IM011047 (FAS ¹)	124
Table 39. Results for the Investigator-Reported Secondary Endpoints at Week 16 Against Placebo – Trials IM011046/47 (FAS; NRI ¹)	126
Table 40. Results for the Investigator-Reported Secondary Endpoints at Week 16 Against Apremilast – Trials IM011046/47 (FAS; NRI ¹)	126
Table 41. Results for the Investigator-Reported Secondary Endpoints at Week 24 Against Apremilast – Trials IM011046/47 (FAS; NRI ¹)	128
Table 42. Results for the Investigator-Reported Secondary Endpoints at Weeks 24 and 52 Against Apremilast – Trials IM011046/47 (FAS; NRI ¹).....	128
Table 43. Absolute Change From Baseline in PSSD Symptom Domain Score at Week 16 – Trials IM011046/47 (FAS; mBOCF ¹).....	129
Table 44. Proportion of Subjects With a PSSD Symptom Domain Score of 0 at Week 16 – Trials IM011046/47 (FAS; NRI ¹).....	130
Table 45. Summary of PSSD Symptom Domain Meaningful Change Thresholds for Improvement Estimates.....	132
Table 46. Disposition of Subjects for Weeks 16-52 – Trials IM011046/ IM011047 (FAS*).....	134
Table 47. Missing Data Due to COVID-19 for the Co-Primary Endpoints by Week Between Week 24 and Week 52/56 – Trials IM011046/47 (FAS*)	135
Table 48. Response at Week 52 Among Week 24 Responders – Trial IM011047 (FAS; NRI ¹)	135

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotykto (deucravacitinib) tablets, 6 mg

Table 49. sPGA 0/1 at Week 16 by Age, Sex, Race, Weight, Baseline sPGA Score and Prior Use of Systemic Therapy – Trial IM011046 (FAS; NRI ¹)	138
Table 50. PASI-75 Response at Week 16 by Age, Sex, Race, Weight, Baseline sPGA Score and Prior Use of Systemic Therapy – Trial IM011046 (FAS; NRI ¹)	138
Table 51. sPGA 0/1 at Week 16 by Age, Sex, Race, Weight, Baseline sPGA Score and Prior Use of Systemic Therapy - Trial IM011047 (FAS; NRI ¹)	139
Table 52. PASI-75 Response at Week 16 by Age, Sex, Race, Weight, Baseline sPGA Score and Prior Use of Systemic Therapy - Trial IM011047 (FAS; NRI ¹)	139
Table 53. Response Rates at Week 16 in Subgroup Who Had Treatment Failure or Intolerance to Prior Systemic Therapy for Psoriasis/Psoriatic Arthritis - Trials IM011046/047 (FAS; NRI ¹)	140
Table 54. sPGA 0/1 and PASI-75 Response at Week 16 by Country - Trial IM011046 (FAS; NRI ¹)	140
Table 55. sPGA 0/1 and PASI-75 Response at Week 16 by Country - Trial IM011047 (FAS; NRI ¹)	141
Table 56. AEs Leading to Discontinuation of Study Treatment for Subjects in IM011046 Who Were Randomized to and Continued on the Same Active Treatment Controlled Safety Pool Excluding IM011046 Site 0092 – As-Treated Population Week 0 Through Week 52 - Exposure Adjusted Incidence Rate	154
Table 57. Adverse Events Leading to Treatment Discontinuation ≥ 2 Subjects – Phase 3 Safety Pool – As-Treated Population	155
Table 58. Skin Adverse Events of Interest - Controlled Safety Pool (Week 0-16) – As-Treated Population	157
Table 59. Mouth Ulceration Reported Summary (Week 0 through Week 16) Treatment Based on Actual Treatment Regimens Without Switching	159
Table 60. Mouth Ulceration Reported Summary (Week 0 through Week 24) Treatment Based on Actual Treatment Regimens Without Switching	159
Table 61. Mouth Ulceration Reported Summary (Week 0 through Week 52) Treatment Based on Actual Treatment Regimens Without Switching	160
Table 62. Pooled Preferred Terms	164
Table 63. Most Frequent Adverse Events Reported in ≥ 1% of Subjects, by Frequency of PT in 16 Weeks (Controlled Safety Pool)	166
Table 64. Most Frequent Adverse Events Reported in ≥ 1% of Subjects, by Frequency of PT in 52 Weeks, As-Treated Population, Trial IM011046	166
Table 65. Infection Serious Adverse Events, Controlled Safety Pool (Week 0-52) and Phase 3 Safety Pool - All Treated Subjects	176
Table 66. Adverse Events of Herpes Zoster - Phase 3 Psoriasis Trials	179
Table 67. Tuberculosis-Related Adverse Events	184
Table 68. Malignant Tumor and Nonmelanoma Skin Cancer AEs in Deucravacitinib-Treated Subjects - Phase 3 Safety Pool	188

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Table 69. Hemoglobin, Hematocrit, and Platelet Lab Results of Subject With Serious Gastrointestinal Hemorrhage	212
Table 70. Hematology Laboratory Test Results	215
Table 71. Subjects With Total Bilirubin >2x ULN With ALT or AST >3x ULN, ALT or AST > 5x ULN, ALP> 2x ULN, or Liver-related Serious Adverse Event - Phase 3 Safety Pool (Through 15-Jun-2021)	236
Table 72. ISS Liver Biochemistry Results	237
Table 73. Subject IM011046-141-0582 Liver Test Results	241
Table 74. High Level Summary of Significant Labeling Changes	272
Table 75. List of Investigators and Sub investigators With Information to Disclose.....	290
Table 76. List of Investigators and Sub-investigators Due Diligence.....	291
Table 77. Multiples of Exposure	292
Table 78. Toxicokinetics Analysis in the 6-Month Carcinogenicity Study in rasH2 Transgenic Mice	296
Table 79. Summary of Mortality Ratios With % Survival	298
Table 80. Toxicokinetics Analysis of Deucravacitinib and Metabolites in Rats.....	300
Table 81. PPK Review Summary.....	301
Table 82. Summary of Baseline Characteristics and Laboratory Values in the PPK Dataset.....	303
Table 83. Parameter Estimates and SE From Final Population PK Model: Deucravacitinib Parent Drug.....	305
Table 84. Parameter Estimates and SE From Final Population PK Model Deucravacitinib Active Metabolite BMT-153261	306
Table 85. Exposure-Response Review Summary	311
Table 86. Parameter Estimates and SE From Final Efficacy E-R Model: PASI.....	314
Table 87. Parameter Estimates and SE From Final Efficacy E-R Model: sPGA	315
Table 88. Summary of LC-MS/MS Bioanalytical Method Validation for Determination of Deucravacitinib in Plasma.....	324
Table 89. Summary of Method BAS RPT 1566 Cross Validation and Partial Validation..	324
Table 90. Summary of LC-MS/MS Bioanalytical Method Validation for Determination of Deucravacitinib and BMT-153261 in Plasma	326
Table 91. Cross Validation Summary of Method 171731VRM_BPN	327
Table 92. Summary of LC-MS/MS Bioanalytical Method Validation for Determination of BMT-158170 in Plasma	327
Table 93. Cross Validation Summary of Method 171775VWBA_BPN	328
Table 94. Summary of LC-MS/MS Bioanalytical Method Validation for Determination of BMT-334616 in Plasma	328

Multi-disciplinary Review and Evaluation

NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Table 95. Summary of LC-MS/MS Bioanalytical Method Validation for Determination of Deucravacitinib and BMT-409408-02 in Plasma	329
Table 96. Summary of LC-MS/MS Bioanalytical Method Validation for Determination of Deucravacitinib in Urine	330
Table 97. Cross Validation Summary of Method BAS RPT 1567	330
Table 98. Summary of LC-MS/MS Bioanalytical Method Validation for Determination of BMT-153261 and BMT-158170 in Urine	331
Table 99. Summary of LC-MS/MS Bioanalytical Method Validation for Determination of BMT-334616 in Urine.....	332
Table 100. Results for the Co-Primary Endpoints at Week 16 in Trial IM011046 With and Without Site 0092 (FAS; NRI1)	340
Table 101. Results for the Investigator-Reported Secondary Endpoints at Weeks 24 Against Apremilast – Trial IM011047 (FAS; NRI1)	340

Table of Figures

Figure 1. Primary Efficacy Analysis (PASI75 Response Rates at Day 85) From IM011011	82
Figure 2. Proposed In Vivo Biotransformation Pathways of [14C]Deucravacitinib in Humans	86
Figure 3. Fold Changes in IL17A Over Non-lesional Baseline With Deucravacitinib Treatment Over 85 Days in Skin Biopsies	90
Figure 4. Percent Change From Baseline of Biomarkers (IL-17A, IL-19, and β -defensin) in Phase 3 Trials	91
Figure 5. Correlations Between Biomarkers (IL-17A, IL-19, and β -defensin) and PASI Score in Phase 3 Trials.....	92
Figure 6. Effect of Coadministered Drugs on Deucravacitinib and BMT-153261.....	99
Figure 7. Effect of Deucravacitinib on the PK of Coadministered Drugs.....	102
Figure 8. Trial Design Schematic for Trial IM011046	112
Figure 9. Trial Design Schematic for Trial IM011047	112
Figure 10. Results for sPGA 0/1 and PASI 75 Through Week 24 – Trials IM011046/47 (FAS; NRI ¹).....	133
Figure 11. sPGA 0/1 and PASI-75 Response Rates During the Randomized-Withdrawal Period - Trial IM011047 (FAS; NRI ¹)	136
Figure 12. Proposed Edits to the Label, Pharmacodynamics	170
Figure 13. Kaplan-Meier Plot for Cumulative Incidence of Subjects With MACE Event, Week 0 Through Week 52, As-Treated Population in Trial IM011046	201
Figure 14. Kaplan-Meier Plot for Cumulative Incidence of Subjects With MACE Event, Week 0 Through Week 52, As-Treated Population in Trial IM011047	201
Figure 15. Mean Lymphocytes ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 16, As-Treated Population.....	214
Figure 16. Mean Change From Baseline in Lymphocytes ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 24, Subjects Who Were Randomized to and Remained on the Same Treatment.....	217
Figure 17. Mean Change From Baseline in Lymphocytes ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 52, Subjects Who Were Continuously Treated in IM011046	218
Figure 18. Mean Neutrophils ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 16, As-Treated Population.....	220
Figure 19. Mean Change From Baseline in Neutrophils ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 24, Subjects Who Were Randomized to and Remained on the Same Treatment.....	222

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Figure 20. Mean Change From Baseline in Neutrophils ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 52, Subjects Who Were Continuously Treated in IM011046 224

Figure 21. Mean Platelets ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 16, As-Treated Population.....226

Figure 22. Mean Change From Baseline in Platelets ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 24, Subjects Who Were Randomized to and Remained on the Same Treatment.....227

Figure 23. Mean Change From Baseline in Platelets ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 52, Subjects Who Were Continuously Treated in IM011046 228

Figure 24. Mean Hemoglobin ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 16, As-Treated Population.....230

Figure 25. Mean Change From Baseline in Hemoglobin (g/L) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 24, Subjects Who Were Randomized to and Remained on the Same Treatment.....231

Figure 26. Mean Change From Baseline in Hemoglobin (g/L) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 52, Subjects Who Were Continuously Treated in IM011046 232

Figure 27. ISS eDISH Plot, Weeks 0-16 238

Figure 28. ISS eDISH Plot, Weeks 0-24 (No Placebo Arm).....238

Figure 29. Liver Enzymes by Multiples of ULN Study Day for Subject IM011046-005-00272 240

Figure 30. Mean Creatinine ($\mu\text{mol/L}$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 16, As-Treated Population.....245

Figure 31. Mean Creatine Kinase (U/L) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 16, As-Treated Population.....248

Figure 32. Goodness-of-Fit Plots for the Final Population PK Models: Deucravacitinib Parent Drug.....307

Figure 33. Goodness-of-Fit Plots for the Final Population PK Models: Deucravacitinib Active Metabolite BMT-153261 308

Figure 34. VPC for Deucravacitinib PPK Model 309

Figure 35. Influence of Covariates in the Final Model on Steady-State $AUC_{0-\tau}$ and C_{max} of the Parent Drug 310

Figure 36. VPC of Final PASI E-R Model.....316

Figure 37. VPC of Final sPGA E-R Model 317

Figure 38. Predicted Probability of PASI 75 Response vs $C_{\text{avg,ss}}$ at Weeks 16 and 24 318

Figure 39. Predicted Probability of sPGA0/1 Response vs $C_{\text{avg,ss}}$ at Weeks 16 and 24 ...318

Figure 40. VPC of Final Infections/Infestations E-R Model 319

Multi-disciplinary Review and Evaluation

NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Figure 41. Infections/Infestations Event Rate vs $C_{min,ss}$ of the Parent Drug	320
Figure 42. CK Gr3+ Event Rate vs $C_{max,ss}$ of the Parent Drug.....	321
Figure 43. Age Distribution of Subjects With or Without CK Event.	321
Figure 44. Maximal/Minimal Laboratory Values or Change From Baseline vs $C_{max,ss}$ of the Parent Drug up to Week 16	323
Figure 45. Static Physician's Global Assessment (sPGA)	336
Figure 46. Psoriasis Symptoms and Signs Diary (PSSD).....	339

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Multi-disciplinary Review and Evaluation
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Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Clinical Reviewer	Maryjoy Mejia, MD	OII/DDD	Sections: 1 , 2 , 3 , 4 , 7 , 8.2 , 8.3.2 , 9 , 10 , 11 , 12 , 13 , 19.2	Select one: ☒ Authored ☐ Approved
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Multi-disciplinary Review and Evaluation
 NDA 214958 Sotykto (deucravacitinib) tablets, 6 mg

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Mary Kim, MD	OII/DDD	Sections: 8.2.5.6 , 8.2.5.10	Select one: ☒ Authored ☐ Approved
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Clinical Team Leader	Amy Woitach, DO, MS	OII/DDD	Sections: 1 , 2 , 3 , 4 , 7 , 8.2 , 8.3.2 , 9 , 10 , 11 , 12 , 13 , 19.2	Select one: ☐ Authored ☒ Approved
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Statistical Reviewer	Marilena Flouri, PhD	OTS/OB/DBIII	Sections: 8.1, 8.3	Select one: ☐ Authored ☐ Approved
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Statistical Team Leader	Mohamed Alish, PhD	OTS/OB/DBIII	Sections: 8.1, 8.3	Select one: ☐ Authored ☒ Approved
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Office Director (Clinical)	Julie Beitz, MD	OND/OII	Section: 18	Select one: ☐ Authored ☒ Approved
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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSA	body surface area
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
COVID-19	coronavirus disease 2019
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EOP	end-of-phase
ETASU	elements to assure safe use
FAS	full analysis set
FCS	fully conditional specification
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
JAK	Janus kinase
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mBOCF	modified baseline observation carried forward

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

MI	multiple imputation
MTP	multiplicity testing procedure
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NRI	non-responder imputation
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PASI	Psoriasis Area and Severity Index
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PGA-F	Physician's Global Assessment-Fingernails
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert (also known as Patient Information)
PPS	per protocol set
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSSD	Psoriasis Symptoms and Signs Diary
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
sPGA	static Physician's Global Assessment
ss-PGA	scalp specific Physician's Global Assessment
TEAE	treatment emergent adverse event
TYK	tyrosine kinase

1. Executive Summary

1.1. Product Introduction

SOTYKTU (deucravacitinib) tablets, for oral use is a small molecule that inhibits the tyrosine kinase 2 (TYK2) enzyme. TYK2 is a member of the Janus Kinase (JAK) family. Janus kinases are intracellular enzymes that mediate signals arising from cytokine or growth factor receptor interactions on the cell membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression.

Based on in vitro data, deucravacitinib binds to the pseudokinase domain of TYK2 and uniquely stabilizes an autoinhibitory interaction between the pseudokinase domain and the catalytic domain of the enzyme thereby inhibiting its kinase activity. In vitro, deucravacitinib displayed selectivity for TYK2/JAK1 and TYK2/JAK2-mediated over JAK1/JAK3 and JAK2/JAK2-mediated cellular responses in cell-based assays. TYK2 is thought to pair with JAK1 or JAK2 to regulate downstream signaling of type I interferons, as well as Interleukins 10, 6, 12, and 23, which are naturally occurring cytokines involved in inflammatory and immune responses. The established pharmacologic class for deucravacitinib is "tyrosine kinase 2 inhibitor".

The NDA 214958 is an original NDA for deucravacitinib and was submitted on September 10, 2021. The proposed indication is for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The proposed dosing regimen is 6mg orally, with or without food.

The Agency concluded that the proposed proprietary name, SOTYKTU, was conditionally acceptable from both a promotional and safety perspective [Proprietary Name Review by Madhuri R. Patel, PharmD, Division of Medication Error Prevention and Analysis (DMEPA) dated April 25, 2022].

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from two adequate and well controlled Phase 3 clinical trials, IM011046 and IM011047, which provide evidence of the effectiveness of deucravacitinib for the treatment of moderate to severe plaque psoriasis (Ps) in adult patients who are candidates for systemic therapy or phototherapy.

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

In the clinical trials, efficacy of deucravacitinib for the treatment of patients with moderate to severe Ps who are candidates for systemic therapy or phototherapy was evaluated compared to placebo for the following co-primary endpoints at Week 16:

- The proportion of subjects who achieved a Static Physician's Global Assessment (sPGA) of 0 (clear) or 1 (minimal) and at least a 2-grade improvement from baseline
- The proportion of subjects who achieved Psoriasis Area and Severity Index (PASI) 75 (i.e., at least 75% reduction from baseline in PASI score).

In both trials, deucravacitinib was superior to placebo (p-values < 0.001) for sPGA (Trial IM011046: 54% vs 7% and Trial IM011047: 50% vs 9%) and PASI 75 (Trial IM011046: 58% vs 13% and Trial IM011047: 53% vs 9%) at Week 16.

In addition, efficacy of deucravacitinib was evaluated compared to apremilast for the treatment of patients with moderate to severe Ps who are candidates for systemic therapy or phototherapy. In both trials (IM011046 and IM011047) deucravacitinib was superior to apremilast (p-values < 0.001) for sPGA (Trial IM011046: 54% vs 32% and Trial IM011047: 50% vs 34%) and PASI 75 (Trial IM011046: 58% vs 35% and Trial IM011047: 53% vs 40%) at Week 16.

The Applicant has demonstrated that deucravacitinib 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.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Psoriasis is a chronic, inflammatory disease that primarily manifests with skin pathology characterized by erythematous and scaly plaques and is associated with a substantial impairment of quality of life.

Deucravacitinib tablets for oral use is proposed for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Deucravacitinib is an inhibitor of tyrosine kinase 2 (TYK2) enzyme. TYK2 is a member of the Janus Kinase (JAK) family. Janus kinases are intracellular enzymes that mediate signals arising from cytokine or growth factor receptor interactions on the cell membrane to influence cellular processes of hematopoiesis and immune cell function. TYK2 pairs with JAK1 or JAK2 to regulate downstream signaling of type I interferons, as well as Interleukins 10, 6, 12, and 23, which are naturally occurring cytokines involved in inflammatory and immune responses.

Current therapeutic options for the treatment of adults with moderate to severe plaque psoriasis include phototherapy and photochemotherapy with methoxsalen, systemic small molecule drugs (acitretin, cyclosporine, methotrexate, apremilast), and biologic immune modifying products. The injectable biologic products are comprised of anti-tumor necrosis factor (TNF) agents (adalimumab, etanercept, infliximab, certolizumab), interleukin (IL) 17A blockers (secukinumab, ixekizumab), an IL-17 Receptor A antagonist (brodalumab), an IL 12/23 blocker (ustekinumab), and IL 23 inhibitors (guselkumab, tildrakizumab, and risankizumab). Treatment effect varies among these drug products and no product produces a response in all patients or provides a permanent cure.

Currently available therapies have limitations affecting their use. Phototherapy and photochemotherapy may be impractical due to office based administration requirements. Acitretin is teratogenic. Methotrexate and cyclosporine have restricted indications because of safety concerns for hepatic, pulmonary, and renal toxicities and are approved for the treatment of patients with severe, recalcitrant, disabling disease that is not adequately responsive to other forms of therapy. Apremilast has a more benign safety profile, however, the treatment effect is only 16-18% for physician's global assessment (PGA) clear or almost clear, the Agency's preferred endpoint. The anti-IL17, -IL 12/23, and -IL 23 products demonstrate a treatment effect of 55-88% for PGA of clear or almost clear and carry risks for serious and sometimes fatal infections. Brodalumab, which is the only product that targets the IL-17 receptor, carries an additional boxed warning for suicidal ideation and behavior. Ustekinumab, an IL 12/23 blocker, is

labeled for malignancy, as well as posterior leukoencephalopathy syndrome. TNF inhibitors have been marketed longest and the safety for this drug class is well characterized. They carry a BW for serious infections, lymphomas, and other malignancies. Due to these limitations, there is a need for additional therapeutic options despite the number of available therapies.

Substantial evidence of effectiveness of deucravacitinib for the treatment of adult patients with moderate to severe plaque psoriasis was provided from two 52-week, multicenter, randomized, double-blind, placebo- and active comparator-controlled trials with apremilast as the comparator, IM011046 and IM011047. During these trials, 1684 adult subjects with moderate to severe plaque psoriasis who were eligible for systemic therapy or phototherapy were treated with deucravacitinib 6 mg daily (N = 841), placebo (N = 421), or apremilast 30 mg twice daily (N = 422) for 16 weeks. Enrolled subjects had a Static Physician's Global Assessment (sPGA) score ≥ 3 ("moderate") on a 5-point scale of overall disease severity, Psoriasis Area and Severity Index (PASI) score ≥ 12 , and $\geq 10\%$ of body surface area (BSA) involvement at baseline.

The co-primary endpoints were assessed at Week 16 and included i) the proportion of subjects who achieved an sPGA of 0 (clear) or 1 (minimal) and at least a 2-grade improvement from baseline and ii) the proportion of subjects who achieved PASI 75 (i.e., at least 75% reduction from baseline in PASI score). In both trials, deucravacitinib was superior to placebo (p-values < 0.001) for sPGA (Trial IM011046: 54% vs 7% and Trial IM011047: 50% vs 9%) and PASI 75 (Trial IM011046: 58% vs 13% and Trial IM011047: 53% vs 9%) at Week 16.

Secondary endpoints for both trials included the proportion of subjects at Week 16 who achieved an sPGA of 0, PASI 90, PASI 100 (only for comparison to placebo), Scalp specific Physician's Global Assessment (ss-PGA) 0/1 on a 5-point scale for subjects with baseline ss-PGA ≥ 3 ("moderate"), and patient-reported outcomes based on the Psoriasis Symptoms and Signs Diary (PSSD). Evidence submitted by the Applicant demonstrated that the PSSD Symptom domain and its corresponding endpoint that assesses complete resolution of symptoms adequately support labeling claims. In both trials, deucravacitinib was statistically superior to placebo and apremilast (p-values < 0.001) for pre-specified secondary endpoints based on sPGA, PASI, and ss-PGA at Week 16. For the proportion of subjects who had a PSSD Symptom Score ≥ 1 at baseline and achieved a PSSD symptom score of 0 at Week 16, deucravacitinib was statistically superior to placebo (p-values < 0.002) but not to apremilast (p-values > 0.09) in both trials. While a greater proportion of subjects treated with deucravacitinib compared to placebo achieved a PSSD symptom score of 0 at Week 16, the treatment effect was small (7%) in both trials. Nonetheless, complete absence of itch, pain, burning, stinging, and skin tightness is clinically meaningful as these symptoms (individually as well as collectively) directly impact how patients feel and function. It is recommended that sPGA of 0, PASI 90, PASI 100 (only for comparison to placebo), ss-PGA 0/1, and the PSSD be included in labeling.

To evaluate maintenance and durability of response, subjects in both trials were followed to Week 52 and a subset of subjects were withdrawn from treatment. In Trial IM011046, for subjects who achieved an sPGA 0/1, PASI-75 and PASI-90 response at Week 24 while receiving deucravacitinib, their response rates at Week 52 were 78% (151/194) for sPGA 0/1, 82% (187/228) for PASI-75 and 74% (103/140) for PASI-90. In Trial IM011047, subjects originally randomized to deucravacitinib at baseline and who were PASI 75 responders at Week 24 were re-randomized to either continue deucravacitinib or withdraw therapy (i.e., receive placebo). For subjects who were clear or almost clear (sPGA 0/1) at Week 24, 70% re-randomized to continue treatment with deucravacitinib had an sPGA response of 0 or 1 at Week 52 compared to 24% who were re-randomized to withdrawal. For those who achieved PASI 75 at Week 24, 80% were PASI 75 responders at Week 52 compared to 31% who were re-randomized to withdrawal. For responders at Week 24 who were re-randomized to treatment withdrawal, the median time to loss of sPGA 0/1 response was approximately 8 weeks and the median time to loss of PASI-75 response was approximately 12 weeks.

The safety of deucravacitinib for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy was assessed primarily using data from two Phase 3 trials (IM011046 and IM011047) and an ongoing open-label long-term extension trial (IM011075) in which all subjects who completed IM011046 and IM011047 could enroll to receive deucravacitinib.

The size of the overall safety database, consistent with ICH E1, included 1519 subjects exposed to at least 1 dose of deucravacitinib and a total of 1179 subjects who received deucravacitinib without switching treatment for at least 1 year. Although the clinical trial experience has been sufficiently extensive to assess short-term safety in the general adult psoriasis patient population, the size of the database and duration of treatment do not sufficiently reflect expected use in the patient population where there is concern, based on clinical information from the Janus Kinase (JAK) inhibitor pharmacologic class, that deucravacitinib may cause late developing adverse reactions (ARs) or ARs that increase in severity or frequency over time. In particular, the 52-week duration of treatment may not be sufficient to identify an unexpected serious risk for major adverse cardiovascular events (MACE), overall malignancy, and opportunistic infections that may manifest after prolonged deucravacitinib exposure. To further characterize the risk of MACE and thrombosis, as well as opportunistic infections and malignancy that may arise from long-term TYK2 inhibition with deucravacitinib, the Applicant will be required to conduct a long-term randomized clinical trial comparing deucravacitinib to an active comparator; this post-approval requirement is consistent with the advice provided by the Medical Policy and Program Review Council (MPPRC).

The safety database is also considered insufficient to assess the risks of deucravacitinib use in specific populations (pregnant and

lactating females, as well as pediatrics). Pregnant and lactating females were excluded from clinical trials with deucravacitinib. There were limited reported cases (13) of inadvertent exposure to deucravacitinib during pregnancy and no reported cases relevant to lactation during clinical trials. Also, published literature is lacking with regards to deucravacitinib use during pregnancy, presence of deucravacitinib in human milk, the effects on the breastfed infant, and the effects of the drug on milk production. Further, an evaluation of the safety of deucravacitinib in the pediatric population has not been conducted. Therefore, to evaluate for drug-associated risks of major maternal or fetal outcomes, assess impact on lactation, and determine benefit-risk in the pediatric population, postmarketing assessments will be required for the specific pregnancy and pediatric populations.

Analysis of adverse reactions was based on deucravacitinib's immunomodulatory mechanism of action and potential for JAK inhibition, including serious infections, viral reactivation, and lymphoma. Treatment with deucravacitinib was associated with an increase in creatine phosphokinase (CPK) and triglycerides, as well as a reduction in glomerular filtration rate (GFR).

While these identified and potential risks would not preclude approval, their relevance to the known safety issues described in labeling for JAK inhibitors (tofacitinib, baricitinib, upadacitinib, and abrocitinib) that are approved for the treatment of chronic inflammatory conditions, was important to consider for the purposes of labeling. Tofacitinib, baricitinib, upadacitinib, and abrocitinib are labeled with a Boxed Warning for risk of serious infections, all-cause mortality, malignancies, MACE, and thrombosis, as well as risks described in the Warnings and Precautions section for neutropenia, lymphopenia, anemia, lipid elevation, serum creatinine elevation, increased CPK, liver enzyme elevations, gastrointestinal (GI) perforation, and hypersensitivity. The risks comprised within the Boxed Warning are in part informed by data from a post-marketing trial (A3921133) in subjects with rheumatoid arthritis (RA) and elevated cardiovascular (CV) risk who received tofacitinib. This trial identified a new safety signal of Major Adverse Cardiac Events (MACE, including cardiovascular death), confirmed the safety signal of malignancy noted in the original tofacitinib program, and confirmed the safety signals of all-cause mortality and thrombosis. Because it is unclear which JAK pathway(s) might be responsible for the various adverse drug reactions, and given the lack of an animal model to show that inhibition of particular JAKs leads to specific outcomes, the risks associated with tofacitinib were considered reasonably expected to apply to all approved JAK inhibitors.

Although deucravacitinib targets the JAK/STAT (Signal Transducers and Activators of Transcription) pathway like the approved JAK inhibitors, in vitro data demonstrate that deucravacitinib has a different binding domain and stabilizes an autoinhibitory interaction between the pseudokinase domain and the catalytic domain of the enzyme thereby inhibiting its kinase activity. While JAK inhibitors exhibit a spectrum of pharmacodynamic and selectivity profiles, deucravacitinib induces a set of cytokines that are different from those mediated by other JAK inhibitors. Based on this evaluation, the pharmacology toxicology review team

ascertained that the appropriate pharmacologic class designation for deucravacitinib is a tyrosine kinase 2 (TYK2) inhibitor.

Determining whether these in vitro and nonclinical differences translate to a different clinical safety profile was key to the safety review.

Deucravacitinib-induced immunosuppression was not associated with an increased incidence of serious infections; however, the most common serious infections associated with deucravacitinib use included pneumonia and COVID-19 infection, which necessitated acute inpatient care and interventions such as mechanical ventilation, continuous assessments in the Intensive Care Unit (ICU) setting, and frequent intravenous antimicrobial infusions. Evaluation of opportunistic infections identified a subject who did not have latent tuberculosis (TB) and developed active TB while receiving deucravacitinib. Viral reactivation assessments showed that the frequency of herpes simplex infections in deucravacitinib-treated subjects was higher than in placebo-treated subjects and also identified a case of herpes zoster affecting multiple dermatomes. Further, while relatively rare in young adults, the submitted data also showed that during Trials IM011046, IM011047 and IM011075, 10 of the 15 subjects who reported AEs of herpes zoster were under 50 years of age.

The serious and opportunistic infections described in labeling for JAK inhibitors approved for chronic inflammatory conditions include esophageal candidiasis, cryptococcus, acute histoplasmosis, pneumocystis jirovecii pneumonia and BK virus encephalitis. It is not clear, if after more prolonged use, the risk for deucravacitinib-related infections in the psoriasis population will be similar to these invasive fungal infections.

Also of concern is the lymphoma finding observed with deucravacitinib treatment. The exposure-adjusted incidence rate (EAIR) of lymphoma observed in deucravacitinib-treated subjects with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy during the Phase 3 clinical trials (0.1/100 PY) is higher than the rate observed in patients with psoriasis (0.04-0.06/100 PY) (Gelfand et al. 2006) and comparable to the rate described in labeling for rheumatoid arthritis subjects treated with tofacitinib 10 mg twice a day during clinical trials (Pfizer 2021).

Another concern is the association of deucravacitinib treatment with several laboratory abnormalities. A higher incidence of overall CPK elevation and Grade 4 CPK elevations ($>10 \times$ ULN) was seen with deucravacitinib treatment. An increase in triglycerides was observed which is concerning with regards to the potential for cardiovascular risk especially with long-term deucravacitinib treatment in the psoriasis population wherein literature suggests a strong relationship with cardiovascular disease. A reduction in GFR (< 45 mL/min) that led to discontinued treatment was reported in more deucravacitinib-treated subjects compared to the other treatment groups and worsening proteinuria was observed in those with already reduced GFRs.

Considering that the clinical safety outcomes in deucravacitinib-treated subjects with moderate to severe psoriasis are different than those described in labeling for JAK inhibitors approved for inflammatory conditions, and the in vitro as well as nonclinical information are different, a discussion with the Medical Policy and Program Review Council (MPPRC) regarding whether the labeling for deucravacitinib should carry the same labeling as JAK inhibitors for the treatment of chronic inflammatory conditions, took place on July 6, 2022.

The MPPRC advised that labeling communicate the scientific information from the deucravacitinib program and also inform prescribers and patients of the potential risks related to JAK inhibition. The Council also supported not restricting deucravacitinib's indication and agreed that a randomized postmarketing safety trial be conducted to further address residual uncertainties regarding the long-term safety of deucravacitinib. The review team is aligned with this advice.

Based on the available safety and efficacy data, the overall risk-benefit profile is favorable and supports the approval of deucravacitinib 6 mg for oral administration for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Deucravacitinib is a new molecular entity that is not approved for any indication. It would be the first TYK2 inhibitor for the treatment of patients with moderate to severe plaque psoriasis. As an oral agent, deucravacitinib would provide potential advantages over existing injectable biologic products.

Given that the established treatment effect compared to placebo reflects a strong efficacy profile and the safety information for deucravacitinib reflects potential rather than established risks, the indication will not be restricted. Limitations of Use specifying that deucravacitinib is not recommended in combination with (b) (4) other potent immunosuppressants will be described in labeling.

Product labeling will also describe adverse reactions observed during the deucravacitinib program along with the potential risks related to JAK inhibition. In particular, adverse reactions considered serious and life-threatening [i.e., all-cause mortality, including sudden cardiovascular death, major adverse cardiovascular events, overall thrombosis, deep venous thrombosis, pulmonary embolism, and malignancies (excluding non-melanoma skin cancer)] that were observed in a large randomized postmarketing safety trial of a JAK inhibitor in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor will be specified in the Warnings and Precautions section.

To address residual uncertainties regarding these potential risks associated with use of JAK inhibitors indicated for the treatment of chronic inflammatory conditions and capture the full extent of safety concerns that may arise from long-term deucravacitinib

use, a long-term randomized clinical trial with an active comparator in patients with moderate to severe psoriasis will be required.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Psoriasis is a common, chronic, inflammatory multi-system disorder which primarily affects the skin and joints and is associated with substantial impairment of quality of life. The prevalence of psoriasis in the U.S. is approximately 2-3 % (Armstrong et al. 2021), of which an estimated 20% have moderate to severe disease. One third of patients have concomitant arthritis. Comorbidities that have been reported to be potentially associated with psoriasis include depression/suicide, autoimmune disease, cardiovascular disease, and metabolic syndrome.	Moderate to severe plaque psoriasis is a serious disease because of its chronicity, impact on quality of life, and potential for associated comorbidities.
Current Treatment Options	- FDA approved drugs for the treatment of moderate to severe psoriasis include anti-metabolites (methotrexate), tumor necrosis factor (TNF) inhibitors (etanercept, adalimumab, infliximab, certolizumab), IL-12/23 blockers (ustekinumab), IL-17A blockers (secukinumab and ixekizumab), an IL-17A receptor antagonist (brodalumab), IL-23 blockers (guselkumab, tildrakizumab, and risankizumab), a T cell inhibitor (cyclosporine), retinoids (acitretin) and phosphodiesterase 4 inhibitors (apremilast). Other treatment options include phototherapy with either PUVA (UVA light combined with methoxsalen) or UVB light (narrow or broadband). - All approved therapeutic options may be associated with the risk of serious adverse reactions or administration challenges. The use of phototherapy and photochemotherapy are limited by the need for office administration and additional photoprotection. Teratogenicity and hyperlipidemia are labeled risks with acitretin. Depression and weight loss are safety concerns with apremilast. The primary risks of cyclosporine use are nephrotoxicity and hypertension. Methotrexate has teratogenic,	There are several FDA-approved products with an acceptable benefit-risk profile for the treatment of moderate-to-severe plaque psoriasis in adults. None of these treatments provides a permanent cure or ubiquitous response, and all these products are associated with one or more serious risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional therapeutic options. Additionally, deucravacitinib provides an option with a

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	hepatotoxic, and nephrotoxic effects and may cause bone marrow toxicity and pulmonary fibrosis. Other systemic products may cause immunosuppression, serious infections and malignancy. All biologic products may be associated with loss of effect and serious hypersensitivity reactions. Refer to the Summary of Treatment Armamentarium for Moderate to Severe Psoriasis for the specific labeled safety issues for each product.	novel target (TYK2).
<u>Benefit</u>	- Data from two Phase 3 randomized trials, IM011046 and IM011047, provided evidence of the effectiveness of deucravacitinib in adults with moderate to severe plaque psoriasis, defined as a Static Physician's Global Assessment (sPGA) score ≥ 3 ("moderate") on a 5-point scale of overall disease severity, Psoriasis Area and Severity Index (PASI) score ≥ 12, and $\geq 10\%$ of body surface area (BSA) involvement. During these trials, 1684 adult subjects with moderate to severe plaque psoriasis who were eligible for systemic therapy or phototherapy were treated with deucravacitinib 6 mg daily (N = 841), placebo (N = 421), or apremilast 30 mg twice daily (N = 422). These numbers reflect exclusion of 2 subjects enrolled in Trial IM011046/Site 0092 based on findings of non-compliance with ICH Guidelines for Good Clinical Practice E6 R2 and FDA 21 CFR 312.60-69. - The co-primary endpoints were assessed at Week 16: i) the proportion of subjects who achieved an sPGA of 0 (clear) or 1 (minimal) and at least a 2-grade improvement from baseline and ii) the proportion of subjects who achieved PASI 75 (i.e., at least 75% reduction from baseline in PASI score). In both trials, deucravacitinib was superior to placebo (p-values < 0.001) for sPGA (Trial IM011046: 54% vs 7% and Trial IM011047: 50% vs 9%) and PASI 75 (Trial IM011046: 58% vs 13% and Trial IM011047: 53% vs 9%) at Week 16.	The data submitted by the Applicant met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. The trials were adequate and well-controlled. The quality and strength of the evidence was satisfactory. Achievement of clear or almost clear skin is an inherently meaningful outcome for psoriasis, a chronic, inflammatory disorder that affects multiple organ systems but primarily manifests with cutaneous signs and symptoms. The data support that a patient with moderate to severe plaque psoriasis treated with deucravacitinib 6 mg daily is likely to achieve clear or almost clear skin by Week 16 and to maintain this effect with continued treatment to Week 52. Although the treatment effect was small (7%) in both trials, the complete absence of itch,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Secondary endpoints for both trials included the proportion of subjects at Week 16 who achieved an sPGA of 0, PASI 90, PASI 100 (only for comparison to placebo), Scalp specific Physician’s Global Assessment (ss-PGA) 0/1 on a 5-point scale for subjects with baseline ss-PGA ≥ 3 (“moderate”), and patient-reported outcomes based on Psoriasis Symptoms and Signs Diary (PSSD). In both trials, deucravacitinib was statistically superior to placebo (p-values < 0.001) for pre-specified secondary endpoints based on sPGA, PASI, and ss-PGA at Week 16. - For the proportion of subjects who had a PSSD Symptom Score ≥ 1 at baseline and achieved a PSSD symptom score of 0 at Week 16, deucravacitinib was statistically superior to placebo (p-values <0.002). - Head-to-head active comparison of benefit demonstrated that in both trials, deucravacitinib was superior to apremilast for sPGA (Trial IM011046: 54% vs 32% and Trial IM011047: 50% vs 34%) and PASI 75 (Trial IM011046: 58% vs 35% and Trial IM011047: 53% vs 40%) at Week 16. In both trials, deucravacitinib was statistically superior to apremilast (p-values < 0.001) for pre-specified secondary endpoints based on sPGA, PASI, and ss-PGA at Week 16. For the proportion of subjects who had PSSD Symptom Score ≥ 1 at baseline and achieved a PSSD symptom score of 0 at Week 16, deucravacitinib was not statistically superior to apremilast (p-values >0.09). - To evaluate maintenance and durability of response, subjects in both trials were followed to Week 52 and a subset of subjects were withdrawn from treatment. In Trial IM011046, for subjects who achieved an sPGA 0/1, PASI-75 and PASI-90 response at Week 24 while receiving deucravacitinib, the response rates at Week 52 were 78% (151/194) for sPGA 0/1, 82% (187/228) for PASI-75 and 74% (103/140) for PASI-90. In Trial IM011047, subjects originally randomized to deucravacitinib at baseline and who	pain, burning, stinging, and skin tightness by Week 16 as measured by the Psoriasis Symptoms and Signs Diary is clinically meaningful as these symptoms (individually as well as collectively) directly impact how patients feel and function. The addition of deucravacitinib to the psoriasis armamentarium will address the needs of patients who don’t achieve an adequate response, as was demonstrated via the direct comparison of benefit to apremilast during trials IM011046 and IM011047, or don’t maintain response over time with existing therapies. The oral route of administration of deucravacitinib as opposed to the parenteral route of systemic biologics may be preferable to some patients. Further, although most of the injectable biologics with differing targets have demonstrated high levels of efficacy and are relatively well tolerated, they all carry the risk of immunogenicity, which might limit use.

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	were PASI 75 responders at Week 24 were re-randomized to either continue deucravacitinib or withdraw therapy (i.e., receive placebo). For subjects who were clear or almost clear (sPGA 0/1) at Week 24, 70% re-randomized to continue treatment with deucravacitinib had an sPGA response of 0 or 1 at Week 52 compared to 24% who were re-randomized to withdrawal. For those who achieved PASI 75 at Week 24, 80% were PASI 75 responders at Week 52 compared to 31% who were re-randomized to withdrawal. For responders at Week 24 who were re-randomized to treatment withdrawal, the median time to loss of sPGA 0/1 response was approximately 8 weeks and the median time to loss of PASI-75 response was approximately 12 weeks. The results in the subpopulation who used prior systemic therapy and received deucravacitinib showed similar superiority over placebo compared to the overall results on sPGA response (Trial IM011046: 54% vs 8%; Trial IM011047: 50% vs 9%) and PASI 75 (Trial IM011046: 59% vs 8%; Trial IM011047: 50% vs 6%) at Week 16.	

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	- The safety of deucravacitinib for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy was assessed primarily using data from two Phase 3 trials (IM011046 and IM011047) and an ongoing open-label long-term extension trial (IM011075) in which all subjects who completed IM011046 and IM011047 could enroll to receive deucravacitinib. - A Phase 2 dose-ranging trial (IM01101) provided additional supportive data. - The size of the overall safety database, consistent with ICH E1, included 1519 subjects exposed to at least 1 dose of deucravacitinib and a total of 1179 subjects who received deucravacitinib without switching treatment for at least 1 year. - Although, the clinical trial experience has been sufficiently extensive to assess short-term safety in the general adult psoriasis population, the size of the database and duration of treatment do not sufficiently reflect expected use in the patient population where there is concern, based on clinical information from the Janus Kinase (JAK) inhibitor pharmacologic class, that deucravacitinib may cause late developing adverse reactions (ARs) or ARs that increase in severity or frequency over time. In particular, the 52-week duration of treatment may not be sufficient to identify a potential risk for major adverse cardiovascular events (MACE), overall malignancy, and opportunistic infections that may manifest after prolonged deucravacitinib exposure. - The safety database is also considered insufficient to assess the risks of deucravacitinib use in specific populations (pregnant and lactating females, as well as pediatrics). Pregnant and lactating females were excluded from clinical trials with deucravacitinib. There were limited	- The size of the database and duration of treatment do not sufficiently reflect expected use in the patient population where there is concern, based on clinical information from the Janus Kinase (JAK) inhibitor pharmacologic class, that deucravacitinib may cause late developing adverse reactions (ARs) or ARs that increase in severity or frequency over time. - The safety database is also considered insufficient to assess the risks of deucravacitinib use in specific populations (pregnant and lactating females, as well as pediatrics). - Based on in vitro data and an overall nonclinical toxicity profile that appears different, the pharmacology toxicology review team ascertained that the appropriate pharmacologic class designation for deucravacitinib is a tyrosine kinase 2 (TYK2) inhibitor. - Considering that in vitro data, nonclinical information, and clinical safety outcomes in deucravacitinib-treated subjects with moderate to severe psoriasis are different

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	reported cases (13) of inadvertent exposure to deucravacitinib during pregnancy and no reported cases relevant to lactation during clinical trials. - Published literature is lacking with regards to deucravacitinib use during pregnancy, presence of deucravacitinib in human milk, the effects on the breastfed infant, and the effects of the drug on milk production. - Further, an evaluation of the safety of deucravacitinib in the pediatric population has not been conducted. - Therefore, to evaluate for drug-associated risks of major maternal or fetal outcomes, assess impact on lactation, and determine benefit-risk in the pediatric population, postmarketing assessments will be required for the specific pregnancy and pediatric populations. - Analysis of adverse reactions was based on deucravacitinib's immunomodulatory mechanism of action and potential for JAK inhibition, including serious infections, viral reactivation, and lymphoma. - Treatment with deucravacitinib was associated with an increase in creatine phosphokinase (CPK) and triglycerides, as well as a reduction in glomerular filtration rate (GFR). - While these identified and potential risks would not preclude approval, their relevance to the known safety issues described in labeling for JAK inhibitors (tofacitinib, baricitinib, upadacitinib, and abrocitinib) that are approved for the treatment of chronic inflammatory conditions, was important to consider for the purposes of labeling. - Although deucravacitinib targets the JAK/STAT (Signal Transducers and Activators of Transcription) pathway like the approved JAK inhibitors, in vitro data demonstrate that deucravacitinib has a different binding domain and stabilizes an autoinhibitory interaction between the	than those described in labeling for JAK inhibitors approved for inflammatory conditions, product labeling will describe adverse reactions observed during the deucravacitinib program along with the potential risks related to JAK inhibition. In particular, adverse reactions considered serious and life-threatening [i.e., all-cause mortality, including sudden cardiovascular death, major adverse cardiovascular events, overall thrombosis, deep venous thrombosis, pulmonary embolism, and malignancies (excluding non-melanoma skin cancer)] that were observed in a large randomized postmarketing safety trial of a JAK inhibitor in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor will be specified in the Warnings and Precautions section. To further characterize the risk of MACE, thrombosis, as well as opportunistic infections, and malignancy that may arise from long-term TYK2 inhibition with deucravacitinib, the review team will require the Applicant to conduct a long-term randomized clinical trial comparing deucravacitinib to an active comparator;

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	pseudokinase domain and the catalytic domain of the enzyme thereby inhibiting its kinase activity. • While JAK inhibitors exhibit a spectrum of pharmacodynamic and selectivity profiles, deucravacitinib induces a set of cytokines that are different from those mediated by other JAK inhibitors. • Based on this evaluation, the pharmacology toxicology review team ascertained that the appropriate pharmacologic class designation for deucravacitinib is a tyrosine kinase 2 (TYK2) inhibitor. Whether these differences translate to a different clinical safety profile is unknown. • Common adverse reactions include upper respiratory infections, blood creatine phosphokinase increased, herpes simplex, mouth ulcers, folliculitis, and acne and will be included labeling. • Treatment with deucravacitinib did not appear to increase the risk of mortality. • The most common serious infections associated with deucravacitinib use included pneumonia and COVID-19 infection. • Evaluation of opportunistic infections identified a subject who did not have latent tuberculosis (TB) and developed active TB while receiving deucravacitinib. • Viral reactivation assessments showed that the frequency of herpes simplex infections in deucravacitinib-treated subjects was higher than in placebo-treated subjects and also identified a case of herpes zoster affecting multiple dermatomes. • While relatively rare in young adults, 10 of the 15 subjects who reported AEs of herpes zoster were under 50 years of age, 6 of whom were between the ages of 27 and 39 years.	this post-approval requirement is consistent with the advice provided by the Medical Policy and Program Review Council (MPPRC). • To ascertain the benefit and risk profile in the pediatric population with moderate to severe Ps, the Applicant will be required to conduct two separate trials: • A randomized, controlled trial to evaluate the safety, efficacy, and pharmacokinetics of deucravacitinib in the adolescent population (12 years to less than 18 years) with moderate to severe psoriasis who are candidates for systemic therapy and phototherapy. The Applicant will be required to evaluate at least 300 subjects exposed to deucravacitinib for a minimum of 52 weeks. • A trial to evaluate the safety, efficacy, and pharmacokinetics of deucravacitinib in the pediatric population (4 years to less than 12 years) with moderate to severe psoriasis who are candidates for systemic therapy and phototherapy. The Applicant will be required to evaluate at least 150 subjects exposed to deucravacitinib (the highest proposed dosage) for a minimum of 52

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Serious and opportunistic infections described in labeling for JAK inhibitors approved for chronic inflammatory conditions include esophageal candidiasis, cryptococcus, acute histoplasmosis, pneumocystis jirovecii pneumonia and BK virus encephalitis. It is not clear if the risk for deucravacitinib-related infections after more prolonged use in the psoriasis population will be similar to these invasive fungal infections. • Also of concern is the lymphoma finding observed with deucravacitinib treatment. The exposure-adjusted incidence rate of lymphoma observed in deucravacitinib-treated subjects with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy during the Phase 3 clinical trials (0.1/100 PY) is higher than the rate observed in patients with psoriasis (0.04-0.06/100 PY), comparable to the rate described in labeling for rheumatoid arthritis subjects treated with tofacitinib 10 mg twice a day during clinical trials, and 5-fold higher than the rate of lymphoma expected in the general U.S. population based on the 5-Year Age-Adjusted Incidence Rates, 2015-2019 Surveillance, Epidemiology, and End Results (SEER) Database. • Another concern is the association of deucravacitinib treatment with several laboratory abnormalities. A higher incidence of overall CPK elevation and Grade 4 CPK elevations (>10 x ULN) was seen with deucravacitinib treatment. An increase in triglycerides was observed which is concerning with regards to the potential for cardiovascular risk especially with long-term deucravacitinib treatment in the psoriasis population wherein literature supports a strong relationship with cardiovascular disease. A reduction in GFR (< 45 mL/min) that led to discontinued treatment was reported in more deucravacitinib-treated subjects compared to the other treatment groups and worsening proteinuria was observed in 2 subjects with already reduced GFRs.	weeks. The trial should not be initiated until results from PMR 1 for pediatric subjects 12 to less than 18 years of age are reviewed by the Agency. Based on the review, the Agency will determine the type of data that would be required to evaluate the pediatric population age 4 years to less than 12 years. • Because the uptake of the drug is expected to be substantial, the Applicant will be required to evaluate pregnancy outcomes in two studies. The first study will be a prospective, registry based observational exposure cohort study comparing women exposed to deucravacitinib during pregnancy and an unexposed control population. The second study will use a different design (e.g., a retrospective cohort study using claims or electronic medical record data or a case control study). Both studies will record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. • Based on the lack of available clinical data and the anticipated use of deucravacitinib

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		in females of reproductive potential, a clinical lactation study (milk only) to assess the concentration of deucravacitinib in human milk using a validated assay will be required. • These six postmarketing requirements in conjunction with routine pharmacovigilance and communication of adverse reactions via prescription and patient labeling are adequate to manage the risks of the product. A REMS is not recommended for this application.

1.4. Patient Experience Data

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

☒	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	Section 8.1.2 , Appendix 19.5.1
☒	Patient reported outcome (PRO)	Section 8.1.2 , 8.1.9 Appendix 19.5.1
☐	Observer reported outcome (ObsRO)	
☒	Clinician reported outcome (ClinRO)	Section 8.1.2 Appendix 19.5.1
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify):	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify):	
☐	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Psoriasis is a common, chronic, immune-mediated, inflammatory skin disorder with a strong hereditary component. The pathogenesis of psoriasis is complex and the etiology is not completely understood. Inflammatory cytokines appear to play a role in the pathogenesis and a number of cytokines have been targeted and have demonstrated therapeutic benefit.

The prevalence of psoriasis in the US is approximately 2-3%, of which an estimated 20% have moderate to- severe disease. Psoriasis can first appear at any age, but more commonly appears in adulthood. Two peaks in age of onset have been reported: one at 20–30 years of age and a second peak at 50–60 years.

The most common form of the disease is chronic plaque psoriasis (psoriasis vulgaris). The characteristic lesion is a sharply demarcated scaly, erythematous plaque with scale, and the plaques may be localized or widespread in distribution and symmetrically distributed. These plaques are the result of increased keratinocyte proliferation and commonly involve the extensor surfaces of the extremities, but may present anywhere from the scalp to the soles of the feet. The natural history of psoriasis is chronic with intermittent remissions. A diagnosis of psoriasis can typically be made by history and physical examination, though skin biopsy can provide confirmation if needed.

The extent of body surface area affected may vary from limited to extensive, and the extent of involvement is one consideration in the approach to patient management. Disease of limited extent may be effectively managed with topical treatment. Moderate to severe psoriasis is often treated with phototherapy or systemic therapy.

Psoriasis is considered part of a multisystem inflammatory disorder that is associated with several comorbid diseases including metabolic syndrome, cardiovascular disease (atherosclerosis, myocardial infarction), psoriatic arthritis, inflammatory bowel disease, as well as psychological and psychiatric disorders (depression, anxiety, suicidal ideation, poor self-esteem and body image, social isolation). The pathogenesis of comorbid disease in patients with psoriasis remains unknown.

Due to the variability in effectiveness and tolerability, access to treatment and uncertainty regarding long-term effects of available treatments, the development of additional safe and effective therapies for the treatment of psoriasis continues to be an important goal.

2.2. Analysis of Current Treatment Options

There are several FDA-approved products for the treatment of moderate-to-severe plaque psoriasis in adults which are described in [Table 1](#).

Table 1. Summary of Treatment Armamentarium for Moderate to Severe Psoriasis

Product(s) Name/Year Approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments					
Antimetabolite/Immunosuppressant					
Methotrexate 1972	Severe, recalcitrant, disabling, psoriasis not adequately responsive to other forms of therapy; <i>but only when diagnosis established, by biopsy and/or dermatologic consultation.</i> Must rule out undiagnosed concomitant disease affecting immune responses.	Starting Dose Schedules 1. Weekly single oral, intramuscular (IM) or intravenous (IV) dose schedule: 10 to 25 mg per week until adequate response is achieved. 2. Divided oral dose schedule: 2.5 mg at 12-hour intervals for three doses. 30 mg/wk should not ordinarily be exceeded.	No efficacy information for psoriasis in the label.	Boxed Warning (BW): Potentially fatal toxic reactions including bone marrow suppression, aplastic anemia, and gastrointestinal toxicity with concomitant NSAID Tx; hepatotoxicity, pulmonary toxicity, kidney toxicity, opportunistic infections, malignant lymphoma, tumor lysis syndrome, severe skin toxicity, fetal death and anomalies “should not be used in pregnant women with psoriasis”	Hepatic, lung, and renal toxicity; cytopenias; lymphoma; teratogen Recommend Periodic liver biopsy if tx long-term Pregnancy: contraindicated for treatment of non-malignant disease

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Product(s) Name/Year Approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Tumor Necrosis Factor Inhibitors					
Infliximab (Remicade) 2006	Chronic severe (extensive or disabling) plaque psoriasis, candidates for phototherapy or systemic therapy and when other systemic therapies are medically less appropriate.	5 mg/kg IV at 0, 2 and 6 weeks, then every 8 weeks	From the label: <u>3 R, DB, PC trials</u> PASI75 at week 10 1. Inflix (5mg/kg)- 80% vs 3% placebo 2. Inflix (5mg/kg)- 75% vs 2% placebo 3. Inflix (5mg/kg)- 88% vs Inflix (3mg/kg) 72% vs 6% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), malignancies including Hepatosplenic T-cell lymphomas (adolescents and young adults) Warnings: Hep B reactivation, heart failure, hepatotoxicity, cytopenias, hypersensitivity events, malignancy	
Adalimumab (Humira) 2008	Moderate to severe chronic plaque psoriasis, candidates for phototherapy or systemic therapy	80 mg via subcutaneous injection (SC) initial dose, followed by 40 mg SC every other week starting one week after initial dose	From the label: <u>2 R, DB, PC trials</u> PASI75 at week 16 1. Ada-71% vs 7% placebo 2. Ada-78% vs 19% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), malignancy including hepatosplenic T-cell lymphoma Warnings: hypersensitivity reactions, Hep B reactivation, demyelinating disease, cytopenias, heart failure, Lupus-like syndrome.	
Etanercept (Enbrel) 2004; 2016	Chronic moderate to severe psoriasis, candidates for phototherapy or systemic therapy; 11/2016-	50 mg SC twice weekly for 3 months, followed by 50 mg once weekly; <63 kg (138 lb)- 0.8 mg/kg SC weekly	From the label: <u>2 R, DB, PC5 trials</u> PASI75 at 3 months 1. Etan-47% vs 4% placebo 2. Etan-46% vs 3% placebo	BW: Risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), lymphomas, other malignancies Warnings: demyelinating disease, worsen CHF, pancytopenia,	

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Product(s) Name/Year Approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
	approved for patients 4 years of age and older			malignancy, Hep B reactivation	
IL-12 and IL-23 Blocker					
Ustekinumab (Stelara) 2009	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	For patients weighing <100 kg 45 mg SC initially and 4 weeks later, followed by 45 mg SC every 12 weeks For patients weighing >100 kg: 90 mg SC initially and 4 weeks later, followed by 90 mg SC every 12 weeks	From the label: <u>2 R, DB, PC trials</u> PASI75 at week 12 1. uste (90mg)-66% vs uste(45mg)-67% vs 3% placebo 2. uste (90mg)-76% vs uste(45mg)-67% vs 4% placebo	Warnings and Precautions (W&Ps): Infections (serious bacterial, fungal and viral), theoretical risk for serious infections, malignancy, reversible posterior leukoencephalopathy syndrome, pretreatment eval for TB.	

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Product(s) Name/Year Approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
IL-17A Blocker					
Secukinumab (Cosentyx) 2015	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	300 mg SC at Weeks 0, 1, 2, 3 and 4 followed by 300 mg SC every 4 weeks. For some patients, a dose of 150 mg may be acceptable	From the label: <u>4 R, DB, PC trials</u> PASI75 at week 12 1. sec (300mg)- 82% vs sec (150mg)- 71% vs 4% placebo 2. sec (300mg)- 76% vs sec (150mg)- 67% vs 5% placebo 3. sec (300mg)- 75% vs sec (150mg)- 69% vs 0% placebo 4. sec (300mg)- 87% vs sec (150mg)- 70% vs 3% placebo	W&Ps: Infections (serious bacterial, fungal and viral), theoretical risk for serious infections, Crohn's disease, hypersensitivity reactions, pretreatment eval for TB.	
Ixekizumab (Taltz) 2016	moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or photo-therapy	160 mg (two 80 mg injections) SC at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks	From the label: <u>3 R, DB, PC trials</u> PASI75 at Week 12 1. Ixe (80 mg q2wk) 89% vs 4% placebo 2. Ixe (80 mg q2wk) 90% vs 2% placebo 3. Ixe (160 mg x 1, then 80 mg q2wk) 87% vs 7% placebo	W&Ps: Infections (Upper respiratory tract, oral candidiasis, conjunctivitis and tinea infections; Inflammatory Bowel Disease (Crohn's disease and ulcerative colitis); hypersensitivity reactions; pretreatment eval for TB.	

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Product(s) Name/Year Approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
IL-17 Receptor A Antagonist					
Brodalumab (Siliq) 2017	moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies	210 mg by subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks	From the Label: <u>3 R, DB, PC trials</u> PASI 75 and sPGA of 0 (“clear”) or 1 (“almost clear”) at Week 12 1. Bro (210 mg q2wk) PASI 75 83% vs 3% placebo; sPGA 0 or 1 Bro 76% vs 1% placebo 2. Bro (210 mg q2wk) PASI 75 86% vs 8% placebo; sPGA 0 or 1 Bro 79% vs 4% placebo; PASI 100 Bro 44% vs Uste 22% 3. Bro (210 mg q2wk) PASI 75 85% vs 6% placebo; sPGA 0 or 1 Bro 80% vs 4% placebo; PASI 100 Bro 37% vs Uste 19%	Box warning for Suicidal Ideation and Behavior W&Ps: Suicidal ideation and behavior; Infections (serious infections and fungal infections); Crohn’s disease; pretreatment eval for TB; avoid live vaccines.	REMS requires prescribers and pharmacies to be certified; patients must sign a Patient- Prescriber agreement form
IL-23 blocker					
Guselkumab (Tremfya) 2017	Moderate-to-severe plaque psoriasis in adults who are candidates for	100 mg by subcutaneous injection at Week 0, Week 4, and every 8 weeks	From the Label: <u>3 R, DB, PC, AC trials</u> 1 & 2: PASI 90 and sPGA of 0 (“cleared”) or 1 (“minimal”) at Week 16	W&Ps: Infections (upper respiratory tract infections, gastroenteritis,	

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Product(s) Name/Year Approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
	systemic therapy or phototherapy	thereafter.	1. Gus (100 mg wk 0 & 4 then q8wk) PASI 90 73% vs 3% placebo; IGA 0 or 1, 85% vs 7% placebo 2. Gus (100 mg wk 0 & 4 then q8wk) PASI 90 70% vs 2% placebo; IGA 0 or 1, 84% vs 8% placebo 3. Subjects began tx with Uste; at wk16 Subjects with IGA 2 R to Gus or continued Uste; endpoint at wk 28 IGA 0 or 1 with 2 grade improvement; Gus 31% vs 14% Uste	tinea infections, and herpes simplex infections); pretreatment eval for TB; avoid live vaccines.	
Tildrakizumab (Ilumya) 2018	Moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	100 mg administered by subcutaneous injection at Weeks 0, 4, and every twelve weeks thereafter	3 R, DB, PC, AC trials The co- primary endpoints were assessed at Week 12: 1. The proportion of subjects who achieved an PGA score of 0 (“cleared”) or 1 (“minimal”), and 2. The proportion of subjects who achieved at least a PASI 75. Tildrakizumab was superior to placebo on both PGA (Trial P010: 58% vs 7% and Trial P011: 55%	W&Ps: Hypersensitivity, Infections (upper respiratory tract infections); pretreatment eval for TB; avoid live vaccines.	

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Product(s) Name/Year Approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
			vs 4%) and PASI 75 (Trial P010: 64% vs 6% and Trial P011: 61% vs 6%) at Week Applicant did not establish an adequate scientific bridge between U.S.-licensed Enbrel and EU-approved etanercept for labeling AC.		
Risankizumab (Skyrizi) 2019	Moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	150 mg administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter.	From the label: <u>2 R, DB, PC, AC</u> Co-primary endpoints at Week 16 were sPGA 0/1 and PASI 90: 1. ris 150mg sPGA 88% vs 8% PBO; ris 150mg PASI 90 75% vs 5% PBO 2. ris 150 mg sPGA 84% vs 5% PBO; ris 150mg 75% vs 2% PBO <u>1 R, DB, PC</u> At Week 16, ris was superior to PBO on the co-primary endpoints of sPGA 0 or 1 (84% ris and 7% PBO) and PASI 90 (73% ris and 2% PBO).	W&Ps: Infections; pretreatment eval for TB; avoid live vaccines.	

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Product(s) Name/Year Approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
T-Cell Inhibitor/Immunosuppressant					
Cyclosporine 1997	Adult, nonimmuno-compromised patients with severe recalcitrant disabling psoriasis who have failed at least one systemic therapy	Starting dose: 2.5 mg/kg/day, taken twice daily, dosage increases by 0.5 mg/kg/day at 2-week intervals, to a maximum of 4.0 mg/kg/day.	From the label: PASI75 - 51% at 8 weeks, 79% at 16 weeks	BW: Should only be used by MDs experienced in management of systemic immunosuppressive Rx, i susceptibility to infections and development of neoplasia including lymphoma, also hypertension, nephrotoxicity which t with t doses. In psoriasis patients with history of PUVA, UVB, coal tar or radiation Rx- t risk of skin malignancies Warnings: Hepatotoxicity, hyperkalemia, thrombotic microangiopathy, progressive multifocal leukoencephalopathy (PML), malignancies, serious infection, neurotoxicity	
Retinoid					
Acitretin (Soriatane) 1996	Severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of	Starting dose: 25 to 50 mg orally (PO) per day, Maintenance doses of 25 to 50 mg per day may be given dependent upon an individual patient's	From the label: <u>2 DB, PC trials</u> Mean change in PGA at 8 weeks 1. Acitretin(50mg)-2 vs -0.29 on placebo 2. Acitretin (50mg)- 1.57 vs Acitretin (25 mg)- 1.06 vs -0.06 on placebo (no	BW: Pregnancy must be prevented during Rx and for 3 years following due to teratogenicity, no ethanol ingestion by females of childbearing potential (FOCBP) due to metabolism to etretinate and t 1/2life, REMS (Do Your P.A.R.T.)	W&P: hepatotoxicity, skeletal abnormalities, lipids, Cardiovascular risk, Ophthalmologic effects, Pancreatitis,

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Product(s) Name/Year Approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
	other treatments	response to initial Rx	multiplicity adjustment for trial B)	participation required for FOCBP-see Drugs @ FDA for details. Patients cannot donate blood for 3 years post Rx, See label for data on pregnancies in partners of male patients on acitretin	capillary leak syndrome, pseudotumor cerebri, exfoliative dermatitis, depression
Phosphodiesterase 4 (PDE4) Inhibitor					
Apremilast (Otezla) 2014	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	To reduce risk of gastrointestinal symptoms, titrate to recommended dose of 30 mg PO twice daily	From the label: <u>2 R, DB, PC trials</u> PASI75 at 16 weeks 1. aprem 33% vs 5% in placebo 2. aprem 28.8% vs 5.8% in placebo	W&P: Depression, weight decrease, drug interactions with strong P450 enzyme inducers (rifampin, phenobarbital, carbamazepine, phenytoin)	Diarrhea, nausea, URI, headache
Phototherapy					
PUVA-8-MOP (methoxsalen) + UVA therapy	Severe, recalcitrant, disabling psoriasis not responsive to other forms of therapy	20 -70 mg PO (based on weight), taken 2-4 hours before exposure to UVA light	No efficacy information for psoriasis in the label.	BW: Should only be used by MDs who have special competence in psoriasis management Warnings: serious skin burning, ocular damage, aging of the skin, skin cancer (including melanoma)	Nausea, erythema, pruritus, must avoid all exposure to sunlight (even through windows) to eyes and skin for 24 hours after ingestion;

Abbreviations: AC, active comparator; Aprem, Apremilast; Bro, Brodalumab; DB, double blind; Etan, Etanercept; Gus, Guselkumab; Inflix, Infliximab; Ixe, Ixekizumab; NSAID, non-steroidal anti-inflammatory drug; PBO, placebo; PC, placebo-controlled; R, randomized; ris, Risankizumab; Sec, Secukinumab; Uste, ustekinumab

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Because deucravacitinib is an original NDA and is not currently marketed in the United States, this section is not applicable.

3.2. Summary of Presubmission/Submission Regulatory Activity

On October 7, 2016, IND 131993 opened with Protocol IM011011, a dose-ranging, Phase 2 trial to evaluate the efficacy and safety of deucravacitinib in adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. A Study May Proceed letter was sent to the Sponsor on December 08, 2016 conveying the following comments:

- As the objective of Phase 2 trial is to select the appropriate dose for future Phase 3 trials and not to establish efficacy claims, formal statistical testing, and consequently powering, is not required. To ensure that your future Phase 3 trials are not underpowered, we recommend that your Phase 2 trial assess the treatment effect for the same patient population and the same “success” criterion that will be used in Phase 3 trials. In addition, we recommend you use a scientifically sound method for handling missing data.
- For a Phase 2 trial, you may investigate various endpoints to assess efficacy and dose-response of your product. However, for future Phase 3 trials, we recommend the following co-primary endpoints for the psoriasis indication:
 - Proportion of the subjects achieving a sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from the baseline at the selected primary timepoint (e.g. Week 12)
 - Proportion of subjects achieving PASI-75 at the selected primary timepoint (e.g., Week 12)

Therefore, we recommend your Phase 2 trial assess these endpoints to be used for powering Phase 3 trials.

- In the absence of more specific subject stopping criteria, consider use of a more global stopping criterion such as, “Subjects who experience CTCAE of grade 2 or higher should be discontinued from the trial”.

In July 2017, two Special Protocol Assessments (SPAs), a 2-year rat carcinogenicity study protocol and a 6-month transgenic mouse carcinogenicity study protocol, were submitted to evaluate the carcinogenic potential of deucravacitinib. On July 26, 2017 the Center for Drug Evaluation and Research (CDER) Carcinogenicity Assessment Committee (CAC) issued a final report: i) conveying concurrence with the proposed oral gavage doses for both studies, ii) recommending addition of a positive control group in the transgenic mouse study to ensure the validity of the study and to reduce the risk of false negative results, and iii) communicating that use of toxicokinetic dose groups was not needed.

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

On March 7, 2018, an End-of-Phase 2 (EOP2) was held during which comments were provided regarding secondary endpoints, stratification factors at randomization, criteria for re-randomization, definition of relapse, power of the Phase 3 trials, and the comparison against apremilast (NDA 205437, approved for the treatment of adult patients with plaque psoriasis who are candidates for phototherapy or systemic therapy). Specifically, meeting minutes issued on June 21, 2018 communicated the following regarding the proposed Phase 3 studies and prioritization of sPGA for judging efficacy:

- Although the division considered the co-primary endpoints [the proportion of subjects who achieve a 75% improvement in Psoriasis Area and Severity Index from baseline (PASI 75) to Week 16 and the proportion of subjects who achieve a static Physician's Global Assessment (sPGA) score of 0 (clear) or 1 (minimal) at Week 16] acceptable, priority is given to success based on the sPGA for judging efficacy. Therefore, testing for such endpoint should be given priority.
- In the randomized withdrawal trial (IM011047), re-randomization of subjects at Week 24 who originally received deucravacitinib 6 mg QD was based on PASI 75 response. The division recommend that re-randomization be based on the sPGA responders instead of PASI 75 responders. The Agency noted that the preference for maintenance is to be based on success of the PGA, as such an endpoint is the recommended endpoint for establishing efficacy. The Agency added that while randomization can be carried out for subjects with success on the PGA, the Applicant can randomize subjects who achieve success on PASI 75 but are not successful on PGA if they desire to meet the regulatory requirements of other Agencies.
- Additionally, in Trial IM011047, relapse was defined as a $\geq 50\%$ increase in the PASI score compared with that at Week 24. The division recommends the definition of relapse to be based on the sPGA instead of PASI.
- Many key secondary endpoints, (b) (4)) may not be clinically meaningful and therefore may not be included in the label. The division recommend that the number of key secondary endpoints be intended for labeling be limited to those that are clinically meaningful.
- For the key secondary endpoints based on patient reported outcomes (PROs), the instruments need to be validated and a clinically meaningful threshold level for treatment response be identified for each endpoint, along with justification for such level, as mere change from baseline may not translate to clinically meaningful treatment effect.
- The division confirmed that superiority of deucravacitinib over apremilast based on the endpoints used to establish efficacy of apremilast (i.e., sPGA score 0/1 and PASI 75 at Week 16) was reasonable and comparative efficacy information for systemic psoriasis products could be a useful addition to product labeling although replication of findings would be required.

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

On May 29, 2018, the Applicant submitted protocols for the Phase 3 trials. These Phase 3 protocols underwent several modifications. During the review of the multiple versions, the Agency repeatedly relayed the above mentioned comments conveyed during the EOP2 meeting.

Following submission of the Statistical Analysis Plans (SAPs) for trials IM011046/IM011047 (corresponding with version 5 of the protocols), an advice letter was issued on December 6, 2019, reiterating the comments provided during the EOP2 meeting pertaining to key secondary endpoints, patient-reported outcome (PRO) endpoints, re-randomization at Week 24, stratification for the efficacy analysis, power of the Phase 3 trials, and comparative efficacy.

With regards to pediatric assessments, correspondence was issued on December 3, 2018 communicating the Agency's agreement with the Agreed Initial Pediatric Study Plan (iPSP). The plan detailed a request for a partial waiver in patients aged from birth to < 4 years as studies in this age group are impossible or highly impractical. A request for deferral for development of an age-appropriate formulation(s) for children and a deferral for studies in pediatric patients aged 4-17 years until the benefit-risk in adults with psoriasis is determined to be favorable.

On April 14, 2020 the Applicant provided an official Dear Investigator Letter (DIL) describing the Applicant's plans for changes in their ongoing clinical trials because of the COVID-19 pandemic. The letter contained information regarding the Sponsor's intended actions related to new participant enrollment, site monitoring, site activation, subject site visits and ongoing participant treatment during the pandemic for many of their ongoing clinical trials in several INDs.

On November 13, 2020, preliminary Pre-NDA meeting minutes were communicated to the Sponsor regarding content, structure, and technical components of the NDA.

On May 12, 2021, another Pre-NDA meeting was held to discuss the clinical Phase 3 data in support of filing and review of the NDA. Meeting minutes were issued on June 10, 2021 including the following discussion points:

- The Agency recommended that the Applicant explore alternative methods for handling the missing data due to COVID-19, other than their current approach of [REDACTED] (b) (4). The Agency agreed with the Applicant's proposal to conduct sensitivity analyses using NRI and multiple imputation to assess the impact of missed visits due to COVID-19 will be included in the submission for key secondary endpoints at Weeks 24 and 52. The Agency further recommended the use of a model based imputation when conducting multiple imputations to account for subject responses at the visits prior to missing visits due to COVID-19.
- Comments reiterating that the key secondary endpoint for change in PSSD score may not be clinically meaningful to appear in labeling and that establishing efficacy claims against apremilast based on endpoints and/or timepoints other than the ones used to establish efficacy of apremilast.

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

- The Agency advised the Sponsor to submit a safety database that includes 1100 subjects exposed to deucravacitinib for at least one year with the original NDA submission.
- Provide details regarding the serious data breach related to study treatment assignment during the Randomized Withdrawal and Maintenance period in the clinical trial IM011047. The incident concerns an integrated response technology (IRT) error causing subjects to not be changed back to active treatment (deucravacitinib) after experiencing a protocol defined relapse [at least a 50% loss of the Week 24 Psoriasis Area and Severity Index (PASI) percent improvement from baseline].

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

4.1. Office of Scientific Investigations (OSI)

The Division requested and collaborated with the Office of Scientific Investigations (OSI) to select sites for clinical inspections. Two domestic sites (Trial IM011046: Naranjo Lopez/ Site 62 and Trial IM011047: Sofen/Site 160) were selected based on high enrollment of subjects and significant primary efficacy results pertinent to decision-making. A single international site (Trial IM011046: Szepietowski/Site 105) was chosen due to the higher than average efficacy numbers and lower than average safety numbers. Additionally, because this would be the first action taken on this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the OSI inspections to verify the quality of conduct of the trial.

Due to non-compliance issues, the review team decided to exclude data from Trial IM011046/Site 0092 based on findings of non-compliance with ICH Guidelines for Good Clinical Practice E6 R2 and FDA 21 CFR 312.60-69. Site 0092 in Trial IM011046 was initially put on a screening hold November 13, 2018 following non-compliance issues raised during the first interim monitoring visit. Without sufficient improvement over the next 2 interim monitoring visits, a for-cause audit was conducted in February 2019. Following insufficient Corrective and Preventive Action Plan (CAPA) implementation and despite continued re-training, the site did not improve to an acceptable level and was closed on September 17, 2019. The Applicant notified the Agency on August 13, 2019 that they were discontinuing clinical investigations conducted by this investigator based on findings of non-compliance with ICH Guidelines for Good Clinical Practice E6 R2 and FDA 21 CFR 312.60-69. The 2 subjects enrolled at this site were discontinued, despite the option to transfer the subjects to another local site. Both subjects were randomized to deucravacitinib and completed thru the Week 36 visit. The review team excluded data from these 2 subjects for the review of efficacy and safety.

Further, an inspection of the Applicant, Bristol Myers Squibb, was requested for verification of reported Good Clinical Practice (GCP) and protocol violations related to system vendor's database errors that affected 106 (10.4%) subjects under Protocol IM011047, whereby subjects were not switched to deucravacitinib per protocol after experiencing a relapse.

Based on the results of these inspections, Elena Boley, MD, MBA, OSI reviewer considered that despite some protocol deviations, the trials overall appear to have been conducted adequately, and the data generated by the sites appear to be acceptable in support of NDA 214958 (Review dated August 4, 2022).

4.2. Product Quality

Based on the evaluation of the available information by the Office of Pharmaceutical Quality, the Applicant provided sufficient information to support an approval recommendation from the product quality perspective. The Applicant provided adequate Chemistry, Manufacturing, and Controls (CMC) information to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

Thus, the Office of Pharmaceutical Quality (OPQ) recommends APPROVAL of NDA 214958 for commercialization of SOTYKTU (deucravacitinib) tablets, 6 mg.

The complete Integrated Quality Assessment (IQA) review, dated 08/01/2022, is archived in the CDER Informatics Platform.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Deucravacitinib is a new-molecular-entity tyrosine kinase 2 (TYK2) inhibitor. TYK2 belongs to the Janus kinase (JAK) family and plays a role in cytokine signaling. Currently, there is no TYK2 inhibitor approved in the US. The drug product under NDA 214958, i.e., deucravacitinib film-coated tablet, 6 mg, has been proposed to treat moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Deucravacitinib was evaluated in a battery of nonclinical studies that included evaluation of ADME, pharmacology, safety pharmacology, repeat-dose toxicity, genetic toxicology, carcinogenicity, and reproductive and developmental toxicology.

Deucravacitinib was evaluated in safety pharmacology studies, which included an in vitro assessment of the effects on hERG potassium channel current, in vivo assessments for neurobehavioral effects in rats and monkeys, in vivo assessments for respiratory effects in rats and monkeys, and an in vivo assessment for cardiovascular effects in monkeys. Deucravacitinib is not expected to inhibit hERG potassium channel current at clinically relevant concentrations. During the neurobehavioral and respiratory safety assessments, oral administration of deucravacitinib in rats at doses up to 75 mg/kg/day and in monkeys at doses up to 5 mg/kg/day did not cause neurological or respiratory effects. During the cardiovascular safety assessment, oral administration of deucravacitinib in monkeys at doses up to 5 mg/kg/day did not cause cardiovascular effects.

Deucravacitinib was evaluated in two pivotal repeat-dose general toxicity studies, one in rats and the other in monkeys. In the 6-month rat toxicity study, deucravacitinib was orally administered at the doses of 0, 5, 15, and 50 mg/kg, once daily. At ≥ 5 mg/kg/day, deucravacitinib caused immunosuppression which was an expected pharmacological effect, and the immunosuppression was largely resolved after recovery. At 50 mg/kg/day in males and females, reduced body weights were noted at the end of treatment and reduced body weights were noted at 15 and 50 mg/kg/day during the recovery phase. At 50 mg/kg/day, deucravacitinib was associated with a higher number of unexplained deaths compared to other groups. At 50 mg/kg/day, deucravacitinib increased the incidences of alveolar macrophage aggregation in the lungs. The increased incidences were still observed after recovery. The NOAEL for the 6-month oral toxicity study in rats was 5 mg/kg/day due to the sustained body weight reduction at 15 and 50 mg/kg/day.

In the 9-month monkey toxicity study, deucravacitinib was orally administered at the doses of 0, 1, 3, and 10 $\rightarrow$ 5 mg/kg, once daily. Deucravacitinib dose-dependently increased severity and/or incidences of skin abnormalities, including erosion, hyperkeratosis, and crust in the epidermis, and mixed cell infiltration in the superficial to mid-level dermis. A partial recovery occurred after termination of dosing. The NOAEL for the 9-month oral toxicity study in

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

monkeys was 1 mg/kg/day since the findings in skin at this dose were only slightly above the vehicle control group. In summary, at clinically relevant doses, deucravacitinib-related toxicological effects were mostly related to immunosuppression, which was reversible after dosing termination.

Deucravacitinib and its two major metabolites, BMT-158170 and BMT-153261, tested negative in a battery of genotoxicity studies, i.e., Ames tests (deucravacitinib and metabolites), an in vitro mammalian chromosome aberration test (deucravacitinib), in vitro micronucleus tests (metabolites), and an in vivo mammalian (rat) erythrocyte micronucleus test.

Deucravacitinib did not cause increases of tumor incidences in a 6-month oral carcinogenicity study in transgenic rasH2 mice and a 2-year oral carcinogenicity study in rats. In the mouse carcinogenicity study, deucravacitinib (0 [water], 0 [vehicle], 10, 30, and 60 mg/kg/day in both males and females) was orally administered once daily to transgenic rasH2 mice for six months. N-Nitrosomethylurea (NMU) as a positive control was administered at a single dose of 75 mg/kg (intraperitoneal injection on Day 1). The positive control produced expected results. Deucravacitinib treatment did not result in a significantly increased incidence of tumors in either male or female mice. In the rat carcinogenicity study, deucravacitinib [0 [water], 0 [vehicle], 3, 8, and 15 mg/kg/day in both males and females] was orally administered once daily to Sprague-Dawley rats for two years. All rats survived ≥ 90 weeks of treatment. Deucravacitinib treatment for a lifetime did not result in a significantly increased incidence of tumors in either male or female rats.

In rat fertility and early embryonic development studies, deucravacitinib (0, 5, 15, and 50 mg/kg/day) had no adverse effects on fertility or early embryonic development. The NOAEL for mating and fertility in males and the NOAEL for fertility and early embryonic development in females were both 50 mg/kg/day.

In a rat oral embryofetal study, deucravacitinib (0, 5, 15, and 75 mg/kg/day) had no adverse effects on maternal health or embryofetal development when administered from gestation day (GD) 6 to GD 17. The NOAEL for both maternal and embryofetal development toxicity was 75 mg/kg/day.

In a rabbit oral embryofetal study, deucravacitinib (0, 1, 3, and 10 mg/kg/day) had no adverse effects on maternal health or embryofetal development when administered from GD 7 to GD 19. The NOAEL for both maternal and embryofetal developmental toxicity was 10 mg/kg/day.

In a rat oral pre- and postnatal development study, deucravacitinib (0, 5, 15, and 50 mg/kg/day) had no adverse effects on maternal reproductive function or effects on survival, sexual maturation, neurobehavioral, and reproductive function of the offspring, when administered from GD 6 to lactation day (LD) 20. However, at 50 mg/kg/day, F1 offspring (both sexes) had lower body weight gains from postnatal day (PND) 10 to PND 21. Body weights of the affected F1 offspring gradually normalized to control levels after weaning. The maternal NOAEL was 50

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

mg/kg/day. The developmental NOAEL was 15 mg/kg/day due to pre-weaning decreases in body weight gains in F1 offspring at the dose of 50 mg/kg/day.

In a juvenile rat toxicity study, deucravacitinib (0, 5, 15, and 50 mg/kg) was orally administered from PND 21 to PND 90 (equivalent to human age of 2 to >18 years). At ≥ 5 mg/kg/day, deucravacitinib decreased spleen weights at all doses in both sexes with correlated lymphoid depletion in the spleen. The decreases in spleen weights persisted in females at ≥ 15 mg/kg/day after recovery. At ≥ 15 mg/kg/day, deucravacitinib caused immunosuppression, an expected pharmacological effect that was fully reversed after recovery. The NOAEL for the 10-week juvenile rat toxicity study was 5 mg/kg/day due to the persistent decrease of spleen weights in females at ≥ 15 mg/kg/day.

Deucravacitinib impurities in the drug substance are specified at or below the ICH Q3A qualification threshold, except (b) (4)

(b) (4) there is no need for further qualification. (b) (4)

(b) (4) were adequately qualified in a 1-month oral toxicity study in the rat. Mutagenic impurity (b) (4) is controlled at not more than (b) (4) $\mu\text{g/day}$ (b) (4) ppm). One Ames positive process impurity, (b) (4) tested negative in follow-up rat in vivo genotoxicity assays (a Pig-a gene mutation assay, an erythrocyte micronucleus assay, and a Comet assay in liver cells), and therefore is not expected to be genotoxic in vivo. Overall, the control strategies of deucravacitinib impurities are acceptable from a nonclinical perspective.

Deucravacitinib tablet does not contain novel excipients. All excipients are present at the same or lower levels when compared to levels in previously-approved oral drug products.

This NDA is approvable from a nonclinical perspective. There are no recommended nonclinical postmarketing commitments or postmarketing requirements for this NDA.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

Deucravacitinib is a first-in-class new molecular entity TYK2 inhibitor. TYK2 belongs to the JAK kinases family and plays a role in cytokine signaling. Deucravacitinib binds to the pseudokinase domain of TYK2 and stabilizes an autoinhibitory interaction between the pseudokinase domain and the catalytic domain of the enzyme and thereby inhibits its kinase activity. In competitive cell-free binding assays, deucravacitinib bound to the pseudokinase domain of TYK2 with an IC_{50} of 0.2 nM, and pseudokinase domain of JAK1 with an IC_{50} of 0.95 nM. In vitro, deucravacitinib displayed selectivity for TYK2/JAK1 and TYK2/JAK2-mediated over JAK1/JAK3 and JAK2/JAK2-mediated cellular responses in cell-based assays. In vivo, deucravacitinib inhibited interleukin (IL)-12, IL-23, and Type I interferon (IFN) mediated inflammatory responses in mice. Further,

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

deucravacitinib and two major human metabolites, BMT-153261 (pharmacologically active) and BMT-158170 (pharmacologically inactive) showed weak or no activity against a panel of kinases and pseudokinases, a panel of G-protein coupled receptors (GPCRs), transporters, ion channels, nuclear hormone receptors, and enzymes at clinically-relevant concentrations. The established pharmacologic class for deucravacitinib is “tyrosine kinase 2 inhibitor”.

5.3.1. Safety Pharmacology

Neurological Effects

Studies on neurobehavioral effects of deucravacitinib were embedded in 1-month oral toxicity studies in the rat and the monkey.

Crl:CD(SD) rats (15/sex/group) received deucravacitinib via oral gavage once daily for one month [doses: 0 (vehicle), 5, 15, and 75 mg/kg/day]. During Week 4, all available rats were evaluated on functions of the central nervous system (CNS) and the peripheral nervous system (PNS) before and 1-3 hours after a daily dose. There were no notable deucravacitinib-related neurological effects observed at any dose.

Cynomolgus monkeys (5/sex/group) received deucravacitinib orally once daily for one month [doses: 0 (vehicle), 0.5, 1.5, and 5 mg/kg/day]. During Week 4, all monkeys were evaluated on neurological functions before and 3-5 hours after a daily dose. There were no notable deucravacitinib-related neurological effects observed at any dose.

Respiratory Effects

Studies on respiratory effects of deucravacitinib were embedded in the same 1-month oral toxicity studies in the rat and the monkey. There were no notable deucravacitinib-related respiratory effects observed at any dose in either the rat or the monkey.

Cardiovascular Effects

Deucravacitinib caused 16%, 35%, and 44% inhibition of hERG potassium channel current in vitro at 1, 3, and 10 μM , respectively. However, at clinically relevant concentrations ($\leq 0.1 \mu\text{M}$), deucravacitinib is not expected to inhibit hERG potassium channel current.

Studies on cardiovascular effects of deucravacitinib were embedded in the 9-month oral toxicity study in the monkey. Cynomolgus monkeys (4/sex/group) received deucravacitinib at the doses of 0, 1, 3, and 10→5 mg/kg/day. Electrocardiography (ECG) was recorded pre-study, during Weeks 13 and 39, and at the end of the recovery period. ECG was recorded at the approximate T_{max} (2-3 hours after dosing) and evaluated for heart rate, RR, PR, QT, and QTc intervals, and QRS duration. There were no notable deucravacitinib-related cardiovascular effects observed at any dose.

5.4. ADME/PK

Type of Study	Major Findings
Distribution	
In vitro protein binding of deucravacitinib in the mouse, rat, dog, rabbit, monkey, and human serum/ NCPK156	In vitro, protein binding of deucravacitinib at 10 µM was 85.4%, 88.1%, 75.4%, 97.1%, 87.8%, and 86.6% in mouse, rat, dog, rabbit, monkey, and human serum, respectively.
Tissue distribution of total radioactivity after a single oral dose of ¹⁴C-deucravacitinib in male and female (non-pregnant and pregnant) SD rats/ NCPK580	Male and female (non-pregnant and pregnant) SD rats received a single oral dose (5 mg/kg) of ¹⁴C-deucravacitinib. Maximum concentration in most tissues was reached within 4 hours. The tissues showing the highest concentrations were liver, urinary bladder, kidney, adrenal gland, intervertebral ligaments, arterial wall, and most gastrointestinal tract organs (cecum, large and small intestine, esophagus). Radioactivity distribution was similar between non-pregnant and pregnant rats. Radioactivity was measurable in the placenta and amniotic sac through 12 hours post dose, but not detectable in fetal tissues or fetal blood at any time point.
Tissue distribution of total radioactivity after repeated oral dose of ¹⁴C-deucravacitinib in male SD rats/ NCPK580	Male SD rats received repeated oral doses (5 mg/kg/day) of ¹⁴C-deucravacitinib for 14 days. Tissue distribution was generally similar to that in the single dose study, and no overt accumulation of radioactivity was observed in any of the tissues.
Brain distribution of total radioactivity after a single oral dose of deucravacitinib in male SD rats/ NCPK213	Male SD rats received a single oral dose (10 mg/kg) of deucravacitinib. At 1 and 3 hours post dosing, deucravacitinib had minimal brain penetration, with a brain-to-plasma concentration ratio of 0.03-0.04.
Metabolism	
In vivo biotransformation of ¹⁴C-deucravacitinib in the mouse/ NCPK439	Male hybrid CByB6F1 mice received a single oral dose of ¹⁴C-deucravacitinib (10 mg/kg). Approximately 72.5% of deucravacitinib was not metabolized and recovered in urine and feces. In plasma, deucravacitinib was the predominant radioactive component. Based on AUC_{0-24h}, deucravacitinib and four prominent metabolites, BMT-158170, BMT-153261, M11, and M5 accounted for 87.7%, 2.94%, 2.60%, 0.80%, and 0.62%, respectively, of the total radioactivity in plasma.
In vivo biotransformation of ¹⁴C-deucravacitinib in the rat/ NCPK279	Male SD rats (intact and bile duct-cannulated) received a single oral dose of ¹⁴C-deucravacitinib (20 mg/kg). In intact rats, approximately 53.5% of the dose was eliminated as metabolites in urine (16.1%) and feces (37.4%). Deucravacitinib and three prominent metabolites, BMT-158170, BMT-153261, and M11, accounted for 73.3%, 19.2%, 3.2%, and 0.4%, respectively, of the total radioactivity in plasma at 7 hours post dosing. In bile duct-cannulated rats, approximately 73.1% of the dose was eliminated as metabolites (27.9% in urine, 14.9% in bile, and 30.3% in feces). The metabolic profile in the rat is similar to that in human.

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Type of Study	Major Findings
In vivo biotransformation of ¹⁴ C-deucravacitinib in bile duct-cannulated monkeys/ NCPK370	Male bile duct-cannulated monkeys received a single oral dose of ¹⁴ C-deucravacitinib (5 mg/kg). Approximately 38.5% of the dose was eliminated as metabolites (11.2% in urine, 25.4% in bile, and 1.9% in feces). In plasma, at 1, 2, 4, and 8 hours after dosing, deucravacitinib was the predominant component, accounting for 89% to 94% of the plasma total radioactivity. BMT-334616, M11, and BMT-153261 were minor circulating metabolites, each accounting for ≤ 2.5% of the total plasma radioactivity. The metabolic profile in the monkey is similar to that in human.
Excretion	
Excretion of radioactivity in urine and feces following a single oral dose of ¹⁴ C-deucravacitinib in the mouse/ NCPK394	Male hybrid CByB6F1 mice received a single oral dose of ¹⁴ C-deucravacitinib (100 mg/kg). The 168-hour recovery of radioactivity was 95.2% of the dose, including 7.95% in urine and 86.2% in feces.
Excretion of radioactivity in urine and feces following a single oral dose of ¹⁴ C-deucravacitinib in the rat/ NCPK279	Male SD rats received a single oral dose of ¹⁴ C-deucravacitinib (20 mg/kg). The 72-hour recovery of radioactivity was 92.2% of the dose, including 19.7% in urine and 72.5% in feces.
Excretion of radioactivity in bile, urine and feces following a single oral dose of ¹⁴ C-deucravacitinib in the monkey/ NCPK344	Male bile duct-cannulated monkeys received a single oral dose of ¹⁴ C-deucravacitinib (5 mg/kg). The 120-hour recovery of radioactivity was 97.5% of the dose, including 59.8% in bile, 14.4% in urine, and 15.6% in feces.
Lacteal excretion of deucravacitinib following a single oral dose in nursing rats/ NCPK580	Nursing SD rats received a single oral dose of ¹⁴ C-deucravacitinib (5 mg/kg). Radioactivity was detected in rat milk from 0.5 through 48 hours post dose, with milk to plasma concentration ratio ranging from 2.7 (0.5 hour post dose) to 30.9 (12 hours post dose).
TK data from general toxicology studies A 6-month repeated dose oral toxicity study of deucravacitinib in rats followed by a 2-month recovery period/ DN16020	<u>Rat at the NOAEL of 5 mg/kg/day (LD) during Week 26</u> T_{max} : 2-4 hours AUC_{0-24h} : 4.6 and 3.9 $\mu\text{g}\cdot\text{hr}/\text{mL}$ in M and F, respectively C_{max} : 0.51 and 0.48 $\mu\text{g}/\text{mL}$ in M and F, respectively Accumulation: No Dose proportionality: Exposure increased more than dose proportionally across all doses during Weeks 1, 13, and 26.
A 9-month repeated dose oral toxicity study of deucravacitinib in cynomolgus monkeys with a 2-month recovery period/ DN16021	<u>Monkey at the NOAEL of 1 mg/kg/day (LD) during Week 39</u> T_{max} : 3.7-4.3 hr AUC_{0-24h} : 3.3 and 3.4 $\mu\text{g}\cdot\text{hr}/\text{mL}$ in M and F, respectively C_{max} : 0.23 and 0.22 $\mu\text{g}/\text{mL}$ in M and F, respectively. Accumulation: slight accumulation at HD from Week 19 to 39 Dose proportionality: Exposure increased slightly more than dose proportionally across all doses during Weeks 1, 12, 19, and 39.
TK data from reproductive toxicology studies	

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Type of Study	Major Findings
Effect of oral deucravacitinib on fertility and early embryonic development to implantation in male and female rats/ DN16020	<u>Rat at the NOAEL of 50 mg/kg/day for mating and fertility in males and mating, fertility, and early embryonic development in females</u> AUC _{0-24h} : 106 and 87.8 µg·hr/mL in M and F, respectively C _{max} : 10 and 11.2 µg/mL in M and F, respectively
Effect of oral deucravacitinib on fertility and early embryonic development to implantation in female rats/ DN16234	<u>Rat at the NOAEL of 50 mg/kg/day for mating, fertility, and early embryonic development in females</u> AUC _{0-24h} : 81.1 µg·hr/mL C _{max} : 7.51 µg/mL
Effect of oral deucravacitinib on embryo-fetal development in rats/ DN16073	<u>Rat at the maternal and developmental NOAEL of 75 mg/kg/day on GD 15</u> AUC _{0-24h} : 126 µg·hr/mL C _{max} : 11.2 µg/mL
Effect of oral deucravacitinib on embryo-fetal development in rabbits/ DN16057	<u>Rabbit at the maternal and developmental NOAEL of 10 mg/kg/day on GD 19</u> AUC _{0-24h} : 43.2 µg·hr/mL C _{max} : 9.45 µg/mL
Effect of oral deucravacitinib on pre- and postnatal development in rats/ DN18002	<u>Rat at the maternal NOAEL of 50 mg/kg/day and developmental NOAEL of 15 mg/kg/day on LD 4</u> 50 mg/kg/day: AUC _{0-24h} : 51.9 µg·hr/mL C _{max} : 7.60 µg/mL 15 mg/kg/day: AUC _{0-24h} : 9.16 µg·hr/mL C _{max} : 1.58 µg/mL
TK data from Carcinogenicity studies A 26-week oral carcinogenicity study in Tg.rasH2 hemizygous mice/ DN18025	<u>Tg.rasH2 mouse at the NOAEL of 60 mg/kg/day on Day 180</u> AUC _{0-24h} : 74.1 (M) and 101 (F) µg·hr/mL C _{max} : 10.3 (M) and 11.6 (F) µg/mL
A 2-year oral carcinogenicity study in rats/ DN17062	<u>Rat at the NOAEL of 15 mg/kg/day in Week 26</u> AUC _{0-24h} : 24.6 (M) and 23.5 (F) µg·hr/mL C _{max} : 2.58 (M) and 3.02 (F) µg/mL

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: BMS-986165: Six-Month Oral Toxicity Study in Rats with a Two-Month Post-Dose Recovery/ DN16020

Key Study Findings

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

- At 50 mg/kg/day, there was a higher number of unexplained deaths compared to other groups.
- At 50 mg/kg/day in males and females, reduced body weights were noted at the end of treatment and reduced body weights were noted at 15 and 50 mg/kg/day during the recovery phase.
- Deucravacitinib caused immunosuppression at ≥ 5 mg/kg/day, which were largely resolved after recovery. This was an expected pharmacological effect.
- At 50 mg/kg/day, deucravacitinib increased the incidences of minimal to mild alveolar macrophage aggregation in the lungs of both sexes, and the increased incidences were still observed after recovery.
- The NOAEL for the 6-month oral toxicity study in rats is 5 mg/kg/day due to the sustained body weight reduction at 15 and 50 mg/kg/day. The AUC_{0-24h} at this dose is 4.6 and 4.0 $\mu\text{g}\cdot\text{hr}/\text{mL}$ in males and females, respectively.

Conducting laboratory and location: [REDACTED] (b) (4)
 [REDACTED] (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 5, 15, and 50 mg/kg, once daily
 Route of administration: Oral
 Formulation/Vehicle: [REDACTED] (b) (4)
 Species/Strain: Sprague Dawley rat
 Number/Sex/Group: 15/sex/group in the main phase and 10/sex/group in the recovery phase
 Age: Approximately 8 weeks old at the initiation of dosing
 Satellite groups/ unique design: 10/sex/group in recovery groups (all four doses); no separate TK groups
 Deviation from study protocol affecting result interpretation: No

Observations and Results: changes from control

Parameters	Major Findings
Mortality	There were 1, 1, 1, and 2 unexplained deaths in the control, LD, MD, and HD groups., respectively. The relationship of these deaths to deucravacitinib treatment is not clear. Other deaths are not considered deucravacitinib-related, which included 4 at HD due to dosing errors, 1 at HD due to obstructive uropathy, and 1 at LD due to malignant lymphoma which is considered spontaneous based on the absence of treatment-related lymphoid proliferative findings at higher doses.
Clinical Signs	Salivation was observed in HD males (24/25) and females (20/25). Resolved during the recovery phase.

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Parameters	Major Findings
Body Weights	M: body weights decreased at ≥ 5 mg/kg/day (LD: $\downarrow 5.8\%$; MD: $\downarrow 3.4\%$; HD: $\downarrow 9.9\%$, on Day 182). Separation from the control became evident on approximately Day 35. F: body weights decreased at ≥ 15 mg/kg/day (MD: $\downarrow 6.0\%$; HD: $\downarrow 11.3\%$, on Day 182). Separation from the control became evident on approximately Day 84. Statistically significant body weight decrease was noted at high dose, in both males and females, at the end of the treatment phase. During recovery, animals had similar body weight gains across all doses. At MD and HD, in both males and females, the mean body weights were still lower than in controls, but the differences were not statistically significant at the end of the recovery phase.
Ophthalmoscopy	No deucravacitinib-related adverse effects.
Hematology	Deucravacitinib dose-dependently decreased white blood cells [total WBC, monocytes, lymphocytes (T cells, B cells, NK cells), basophils, and eosinophils] in both males and females, measured in both Weeks 13 and 26. This is an expected pharmacological effect. Platelets were also decreased. The Week 26 representative results were: • Total WBC: $\downarrow 18\%$, 21%, and 37% in LD, MD, and HD, in males; and $\downarrow 29\%$, 47%, and 48% in LD, MD, and HD, in females. • Lymphocytes: $\downarrow 10\%$, 21%, and 44% in LD, MD, and HD, in males; and $\downarrow 31\%$, 53%, and 57% in LD, MD, and HD, in females. • Total T cells: $\downarrow 5\%$, 27%, and 54% in LD, MD, and HD, in males; and $\downarrow 32\%$, 51%, and 53% in LD, MD, and HD, in females. • B cells: $\downarrow 16\%$, 17%, and 37% in LD, MD, and HD, in males; and $\downarrow 27\%$, 57%, and 60% in LD, MD, and HD, in females. • Platelets: $\downarrow 12\%$ and 20% in MD and HD, in males; and $\downarrow 11\%$ and 20% in MD and HD, in females. The decreases in platelets did not have adverse effects on coagulation parameters. After recovery, the differences in white blood cells and platelets were largely resolved.
Clinical Chemistry	Deucravacitinib caused an increase in total bilirubin in HD males (Week 13: $\uparrow 75\%$; Week 26: $\uparrow 156\%$), with no clear evidence of marked decreases in RBC counts. The differences in total bilirubin were resolved after recovery.
Urinalysis	No deucravacitinib-related adverse effects.
Gross Pathology	At ≥ 15 mg/kg/day, deucravacitinib caused small spleen (MD: 1M and 1F; HD: 2M and 2F). At 50 mg/kg/day, deucravacitinib caused raised and/or pale focus in the lung (2M and 2F). After recovery, the macroscopic findings in the spleen were not observed; however, pale focus in the lung was present in one female at HD, which was histologically correlated with macrophage aggregation.
Organ Weights	At ≥ 5 mg/kg/day, deucravacitinib decreased spleen weights at all doses in both males ($\downarrow 31\%$, 31%, and 47% at LD, MD, and HD) and females ($\downarrow 16\%$, 24%, and 36% at LD, MD, and HD). After recovery, spleen weights in females completely recovered; however, in males, the recovery was partial ($\downarrow 25\%$, 21%, and 28% at LD, MD, and HD).
Histopathology Adequate battery: Yes/No	At ≥ 5 mg/kg/day, deucravacitinib caused minimal to mild decreases in hematopoietic cellularity in the bone marrow of both sexes (M: 2/14, 9/14, and 12/14 at LD, MD, and HD; F: 10/14, 11/14, and 12/13 at LD, MD, and HD).

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Parameters	Major Findings
	At ≥ 15 mg/kg/day, deucravacitinib increased the incidences of lymphoid cellularity reduction (minimal to mild) in the mandibular and/or mesenteric lymph nodes of both sexes. At ≥ 15 mg/kg/day, in male liver, deucravacitinib increased the incidences of minimal cystic degeneration (0/14, 0/8, 2/8, and 2/14 at vehicle, LD, MD, and HD), and the incidences of focus of cellular alteration (0/14, 0/8, 1/8, and 3/14 at vehicle, LD, MD, and HD). At 50 mg/kg/day, deucravacitinib caused minimal lymphoid depletion in the white pulp of the spleen of both sexes (M: 8/14; F: 9/13), which was correlated with small size and decreased weights of the spleen. At 50 mg/kg/day, deucravacitinib increased the incidences of minimal to mild alveolar macrophage aggregation in the lungs of both sexes (M: 3/14, 2/14, 4/14, and 8/14 at vehicle, LD, MD, and HD; F: 7/15, 2/14, 5/15, and 11/13 at vehicle, LD, MD, and HD). After recovery, the increased incidence and/or severity of macrophage aggregation in the lungs sustained at HD. The differences seen in the bone marrow, mandibular and mesenteric lymph nodes, liver, and spleen were all resolved.
T-cell Dependent Antibody Response (TDAR)	Deucravacitinib dose-dependently decreased KLH-specific IgM and IgG production in both sexes.

Abbreviations: LD: low dose; MD: mid dose; HD: high dose; M: male; F: female

Study title/ number: BMS-986165: Nine-Month Oral Toxicity Study in Monkeys with a Two-Month Post-Dose Recovery/ DN16021

Key Study Findings

- Deucravacitinib dose-dependently increased severity and/or incidences of skin abnormalities such as swelling, dryness, flaking, and scabs, which were correlated microscopically with evidence of erosion, hyperkeratosis, and crust in the epidermis, and mixed cell infiltration in the superficial to mid-level dermis. A partial recovery occurred after termination of dosing.
- The NOAEL for the 9-month oral toxicity study in monkeys is 1 mg/kg/day since the findings in skin at this dose were only slightly above the vehicle control group. The AUC_{0-24h} at this dose is 3.3 and 3.4 $\mu\text{g}\cdot\text{hr}/\text{mL}$ in males and females, respectively.

Conducting Laboratory and Location: (b) (4)

GMP Compliance: Yes

Methods

Dose and frequency of dosing: 0, 1, 3, and 10→5 mg/kg, once daily
 Route of administration: Oral
 Formulation/Vehicle: (b) (4)

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Methods

Species/Strain: Cynomolgus monkey
 Number/Sex/Group: 4/sex/group
 Age: 2-3 years
 Satellite groups/ unique design: 2/sex/group recovery groups. The high dose was lowered from 10 to 5 mg/kg/day starting on Day 57 due to deteriorating clinical condition of animals.
 Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major Findings
Mortality	No deucravacitinib-related findings.
Clinical Signs	At ≥ 3 mg/kg/day, deucravacitinib dose-dependently increased severity and/or incidences of skin abnormalities, including swollen, dry, lesion, flaking, papule, red, white and/or scab skin on the face (mouth, buccal mucosa, lips and gums), dorsum, fore- and hindlimbs, fore- and hindpaws, interscapular area, genitals and/or tail. The skin changes improved clinically with antibiotic treatment, suggesting the worsening skin conditions were likely due to bacterial infection secondary to immunosuppression caused by deucravacitinib. The severity of the skin findings at 1 mg/kg/day were only slightly above the vehicle control group and not considered adverse at this dose. After recovery, the skin findings were partially reversed.
Body Weights	No deucravacitinib-related findings.
Ophthalmoscopy	No deucravacitinib-related findings.
ECG	No deucravacitinib-related findings.
Hematology	No deucravacitinib-related suppression of immune cell populations. Red blood cell parameters (RBCs, hemoglobin, hematocrit) decreased in a generally dose-dependent fashion in both sexes, and reached lowest (RBC: up to $\downarrow 23\%$; hemoglobin: up to $\downarrow 20\%$; hematocrit: up to $\downarrow 23\%$) in Week 8 right before the switching of HD from 10 to 5 mg/kg/day. The decrease in RBCs was associated with an apparent increase in reticulocytes (up to $\uparrow 107\%$) with no clear dose-dependence. Platelets decreased at all doses in males (up to $\downarrow 44\%$) and in MD and HD females (up to $\downarrow 32\%$); however, coagulation parameters were not affected. Mean eosinophil counts were increased (up to 13-fold) at all doses in both sexes with no clear dose-dependence. After recovery, all hematological parameters were back to control levels.
Clinical Chemistry	Deucravacitinib increased total bilirubin values in males at HD (up to $\uparrow 53\%$) and in females at MD and HD (up to $\uparrow 153\%$), without correlated microscopic changes. The differences in total bilirubin values were resolved after recovery.
Urinalysis	No deucravacitinib-related findings.
Gross Pathology	No deucravacitinib-related findings, except the skin findings described in Clinical Signs.
Organ Weights	No deucravacitinib-related findings.
Histopathology Adequate battery: Yes/No	Yes. Deucravacitinib-related microscopic findings were limited to the skin at ≥ 3 mg/kg/day. Findings included evidence of erosion, hyperkeratosis, and crust in the epidermis, and mixed cell infiltration in the superficial to mid-level dermis in the skin areas described in Clinical Signs. Also, three animals at ≥ 3 mg/kg/day had increased

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Parameters	Major Findings
	myelopoiesis in the bone marrow, which was likely secondary to the skin inflammation. The severity of the microscopic skin findings at 1 mg/kg/day were only slightly above the vehicle control group and not considered adverse at this dose. After the recovery, there were decreased incidences and/or severity of the skin findings, indicating a partial recovery. The bone marrow findings disappeared after recovery.
T-cell Dependent Antibody Response (TDAR)	Deucravacitinib decreased KLH-specific IgM (↓17-73%, dose-dependently) and IgG (↓45-71%, dose-independently) production in both sexes.

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

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: BMS-986165: Ames Reverse-Mutation Study in Salmonella Typhimurium and Escherichia Coli/ DN15012

Study title/ number: BMT-158170: Ames Reverse-Mutation Study in Salmonella Typhimurium and Escherichia Coli/ DN17084

Study title/ number: BMT-153261: Ames Reverse-Mutation Study in Salmonella Typhimurium and Escherichia Coli/ DN17086

Key Study Findings:

- Deucravacitinib and two major metabolites BMT-158170 and BMT-153261 exhibited no mutagenic effects under the conditions of the Ames tests at concentrations up to 5000 µg/plate for each.

GLP compliance: Yes

Test system: *S. typhimurium* TA98, TA100, TA1535, TA1537, and *E. coli* WP2 uvrA; ±S9

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: BMS-986165: Cytogenetics Study in Chinese Hamster Ovary Cells/ DN15016

Study title/ number: BMT-158170: In Vitro Micronucleus Study in Chinese Hamster Ovary Cells/ DN17087

Study title/ number: BMT-153261: In Vitro Micronucleus Study in Chinese Hamster Ovary Cells/ DN17088

Key Study Findings:

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

- Deucravacitinib exhibited no in vitro clastogenic effects (chromosome aberration) at concentrations up to 298 µg/mL under the conditions of this assay.
- Major metabolite BMT-158170 exhibited no in vitro clastogenic effects at concentrations up to 357 µg/mL under the conditions of this assay.
- Major metabolite BMT-153261 exhibited no in vitro clastogenic effects at concentrations up to 98.7 µg/mL under the conditions of this assay.

GLP compliance: Yes

Test system: Chinese hamster ovary (CHO) cells, up to 298 µg/mL, 357 µg/mL, and 98.7 µg/mL for deucravacitinib, BMT-158170, and BMT-153261, respectively (-S9: 3-hour and 20-hour incubation; +S9: 3-hour incubation).

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: BMS-986165: One-Month Oral Toxicity Study in Rats with a 2-Week Recovery/ DN15002

Key Study Findings:

- Deucravacitinib exhibited no in vivo clastogenic effects in the rat erythrocyte micronucleus test when administered orally at doses up to 75 mg/kg/day.

GLP compliance: Yes

Test system: Rat, peripheral blood reticulocyte micronuclei; repeated oral dose of 0 (vehicle), 5, 15, or 75 mg/kg/day; assessments on Day 14 of the dosing period.

Study is valid: Yes

5.5.3. Carcinogenicity

In a 6-month carcinogenicity study in transgenic rasH2 mice, deucravacitinib was administered by oral gavage once daily at the doses of 0 (vehicle: [REDACTED] (b) (4)), 0 (water control), 10, 30, and 60 mg/kg/day. Deucravacitinib did not increase mortality at any dose. There were no deucravacitinib-related clinical signs observed at any dose. Deucravacitinib had no effects on body weights or food consumption at any dose. Deucravacitinib did not cause non-neoplastic changes. No deucravacitinib-related tumor findings were noted.

In a 2-year carcinogenicity study in Sprague-Dawley rats, deucravacitinib was administered by oral gavage once daily at the doses of 0 (vehicle: [REDACTED] (b) (4)), 0 (water control), 3, 8, and 15 mg/kg/day. There were no deucravacitinib-related effects on survival in males. For female rats, there was a statistically significant dose response relationship in mortality across the vehicle/water control groups and treated groups.

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

The pairwise comparisons showed a statistically significant increase in mortality between the vehicle control group and the high dose group, and between the water control group and each of the treated groups. There were no deucravacitinib-related clinical signs observed at any dose. Deucravacitinib had no effects on body weights or food consumption at any dose. Deucravacitinib increased the incidence of minimal to mild brown pigment accumulation in Kupffer cells in the liver in both sexes, which was not associated with any other microscopic findings such as hepatocellular degeneration/necrosis and/or inflammation. In male rats, there were no deucravacitinib-related tumor findings noted. In female rats, there was a statistically significant dose-dependent increase in the incidence of hepatocellular adenoma in the liver. However, none of the incidences reached statistical significance during pairwise analysis when compared to the vehicle/water control groups. Therefore, deucravacitinib was not carcinogenic in the 2-year carcinogenicity study in rats.

Refer to Appendix [19.3.2](#) for full carcinogenicity study reviews.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ number: BMS-986165: Six-Month Oral Toxicity Study in Rats With a Two-Month Postdose Recovery/DN16020

Key Study Findings

- Deucravacitinib had no effects on male reproductive parameters (mating, fertility, and sperm morphology), or early embryonic development of the litters when the males were treated at doses up to 50 mg/kg/day.
- The NOAEL for mating and fertility in males was 50 mg/kg/day, corresponding to AUC_{0-24h} of 106 µg·hr/mL.

Conducting Laboratory and Location: (b) (4)

GLP Compliance: Yes

Methods

Dose and frequency of dosing: 0, 5, 15, and 50 mg/kg, once daily

Route of administration: Oral

Formulation/Vehicle: (b) (4)

Species/Strain: Sprague Dawley rats

Number/Sex/Group: 25/sex/group

Satellite groups: N/A

Study design: Following 57 daily doses of deucravacitinib, deucravacitinib-treated male rats were assigned to cohabitation with treatment-naive female rats for a

maximum of 14 days. Fertility of male rats was determined by observation of pregnancy of the treatment-naive females at necropsy.

Deviation from study protocol affecting interpretation of results: No

Observations and Results

The male fertility study was part of the 6-month repeat dose rat oral toxicity study reviewed in Section 5.5.1. Observations and results not related to male fertility are therefore summarized in the study review in Section 5.5.1. For male fertility, deucravacitinib had no effects on male reproductive parameters (mating, fertility, and sperm morphology), or early embryonic development of the litters when only the males were treated at doses up to 50 mg/kg/day, corresponding to AUC_{0-24h} of 106 µg·hr/mL (Week 13 male TK data).

Study title/ number: BMS-986165: Oral Study of Fertility and Early Embryonic Development in Female Rats/ DN16234

Key Study Findings

- There were no deucravacitinib-related effects on maternal body weight, food consumption, and gross pathology.
- Deucravacitinib had no effects on estrous cyclicity, mating, or fertility in females at doses up to 50 mg/kg/day.
- At 50 mg/kg/day, there was an increase in the number of nonviable embryos (2.0 vs. 0.7 in controls), percent postimplantation loss (13% vs. 5% in controls), and number of dams with any nonviable embryos (19 [90.5%] vs. 8 [36.4%] in controls). However, the numbers were within the testing facility's historical control range. Further, the number of viable embryos per dam was comparable across all groups.
- The NOAEL for maternal toxicity and mating, fertility, and early embryonic development in females was 50 mg/kg/day, corresponding to AUC_{0-24h} of 81.1 µg·hr/mL.

Conducting Laboratory and Location: (b) (4)
(b) (4)

GLP Compliance: Yes

Methods

Dose and frequency of dosing: 0, 5, 15, and 50 mg/kg, once daily

Route of administration: Oral

Formulation/Vehicle: (b) (4)

Species/Strain: Sprague Dawley rats

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Methods

Number/Sex/Group: 24/sex/group
Satellite groups: N/A
Study design: Female rats were given the test article for two weeks and then assigned to cohabitation with treatment-naive male rats for a maximum of 14 days. The treatment continued daily through gestation day 7 (GD 7).

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major Findings
Mortality	No deucravacitinib-related effects.
Clinical Signs	No deucravacitinib-related effects.
Body Weights	No deucravacitinib-related effects.
Necropsy findings	Deucravacitinib had no effects on estrous cyclicity, mating, or fertility in females. At 50 mg/kg/day, there was an increase in the number of nonviable embryos (2.0 vs. 0.7 in controls), percent postimplantation loss (13% vs. 5% in controls), and number of dams with any nonviable embryos (19 [90.5%] vs. 8 [36.4%] in controls). However, the numbers were within the testing facility's historical control range. Further, the number of viable embryos per dam was comparable across all groups.

Embryo-Fetal Development

Study title/ number: Oral Study of Embryo-Fetal Development in Rats/DN16073

Key Study Findings:

- There were no deucravacitinib-related effects on maternal body weight, food consumption, and gross pathology.
- There were no deucravacitinib-related effects on reproductive assessment such as mean numbers of implantations, resorptions, live fetuses, sex ratio, or pre- and post-implantation loss. There were no deucravacitinib-related effects on fetal, placental, or litter weight. There was a slight dose-related decrease (< 4%) in mean fetal body weights, which was inversely related to mean litter size.
- There were no deucravacitinib-related fetal malformations at any dose.
- The NOAEL for both maternal and embryo-fetal development toxicity was 75 mg/kg/day, corresponding to the GD 15 AUC_{0-24h} of 126 µg•hr/mL.

Conducting Laboratory and Location: Bristol-Myers Squibb Company, Drug Safety Evaluation, One Squibb Drive, New Brunswick, NJ

GLP Compliance: Yes

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Methods

Dose and frequency of dosing: 0, 5, 15, and 75 mg/kg/day, once daily

Route of administration: Oral

Formulation/Vehicle:

(b) (4)

Species/Strain: Crl:CD(SD) rats

Number/Sex/Group: 24 pregnant females/group

Satellite groups: N/A

Study design: Deucravacitinib was dosed to mated females on GD 6 through GD 17 and the animals were euthanized on GD 21.

Deviation from study protocol affecting results interpretation: No

Observations and Results

Parameters	Major Findings
Mortality	No deucravacitinib-related effects.
Clinical Signs	No deucravacitinib-related effects.
Body Weights	No deucravacitinib-related effects.
Necropsy findings Cesarean Section Data	No deucravacitinib-related effects on reproductive assessment such as mean numbers of implantations, resorptions, live fetus, sex ratio, or pre- and post-implantation loss. No deucravacitinib-related effects on fetal, placental, or litter weight. There was a slight dose-related decrease (< 4%) in mean fetal body weights, which was inversely related to mean litter size.
Necropsy findings Offspring	There were no deucravacitinib-related fetal malformations at any dose.

Study title/ number: BMS-986165, Oral Study of Embryo-Fetal Development in Rabbits/DN16057

Key Study Findings:

- There were no deucravacitinib-related effects on maternal body weight, food consumption, and gross pathology.
- There were no deucravacitinib-related effects on reproductive assessment such as mean numbers of implantations, resorptions, live fetuses, sex ratio, or pre- and post-implantation loss. There were no deucravacitinib-related effects on fetal, placental, or litter weight.
- There were no deucravacitinib-related fetal malformations at any dose.
- The NOAEL for both maternal and embryo-fetal development toxicity was 10 mg/kg/day, corresponding to the GD 19 AUC_{0-24h} of 43.2 µg•hr/mL.

Multi-disciplinary Review and Evaluation
NDA 214958 Sotykto (deucravacitinib) tablets, 6 mg

Conducting Laboratory and Location: (b) (4)
(b) (4)

GLP Compliance: Yes

Methods

Dose and frequency of dosing: 0 (vehicle control), 1, 3 and 10 mg/kg/day, once daily

Route of administration: Oral

Formulation/Vehicle: (b) (4)

Species/Strain: New Zealand White rabbits

Number/Sex/Group: 22/group

Satellite groups: 4/group for toxicokinetic analysis

Study design: Animals were dosed between GD 7 and GD 19 and euthanized on GD 29

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings
Mortality	No deucravacitinib-related effects.
Clinical Signs	No deucravacitinib-related effects.
Body Weights	No deucravacitinib-related effects.
Necropsy findings Cesarean Section Data	No deucravacitinib-related effects.
Necropsy findings Offspring	There were no deucravacitinib-related fetal malformations at any dose.

Prenatal and Postnatal Development

Study title/ number: BMS-986165, Oral Study of Pre- and Postnatal Development in Rats/DN18002

Key Study Findings:

- Deucravacitinib had no effects on F0 maternal body weight, food consumption, or gross pathology during both gestation and lactation periods.
- Deucravacitinib had no effects on F0 maternal reproductive function.
- Deucravacitinib had no effects on F1 survival, sexual maturation, neurobehavioral (including learning and memory), or reproductive function.
- At 50 mg/kg/day, F1 offspring (both sexes) had lower body weight gains from PND 10 to PND 21. Body weights of F1 offspring at 50 mg/kg/day gradually normalized to control levels after weaning.
- The maternal reproductive NOAEL was the highest dose 50 mg/kg/day, corresponding to LD 4 AUC_{0-24h} of 51.9 µg•hr/mL. The developmental NOAEL was 15 mg/kg/day due to pre-

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

weaning decreases in body weight gains in F1 offspring at the dose of 50 mg/kg/day. The developmental NOAEL of 15 mg/kg/day corresponded to the LD 4 AUC_{0-24h} of 9.2 µg•hr/mL.

Conducting Laboratory and Location: (b) (4)

GLP Compliance: Yes

Methods

Dose and frequency of dosing: 0, 5, 15 and 50 mg/kg, once daily
Route of administration: Oral gavage
Formulation/Vehicle: (b) (4)
Species/Strain: Crl:CD(SD) rats
Number/Sex/Group: 24 pregnant females/group
Satellite groups: N/A
Study design: Animals were dosed from GD 6 to LD 20.
Deviation from study protocol affecting interpretation of results: None

Observations and Results

Generation	Major Findings
F0 Dams	No deucravacitinib-related effects on F0 maternal body weight, food consumption, and gross pathology during gestation and lactation periods. No deucravacitinib-related effects on F0 maternal reproductive function. F0 females at LD, MD, and HD had increased incidences of cool extremities at 2 hours postdose. This finding was transient and did not persist to the following day.
F1 Generation	No deucravacitinib-related effects on F1 survival, sexual maturation, neurobehavioral (including learning and memory), or reproductive function. HD males and females had lower body weight gains from PND 10 to PND 21 (males: 26 vs. 33 g in controls; female: 25 vs. 31 g in controls). Body weights of F1 offspring at HD gradually normalized to control levels after weaning.
F2 Generation	Not tested.

Abbreviations: LD: low dose; MD: mid dose; HD: high dose; PND: Postnatal day

Juvenile Animal Toxicity

BMS-986165, Ten-Week Oral Developmental Toxicity Study in Juvenile Rats with a Ten-Week Post-Dose Recovery Period/ DN18003

Key Study Findings:

- At ≥ 5 mg/kg/day, deucravacitinib decreased spleen weights at all doses in both sexes, which was correlated with minimal to moderate lymphoid depletion in the white pulp of the spleen. After recovery, the decreases in spleen weights persisted in females at MD and HD.
- At ≥ 15 mg/kg/day, deucravacitinib caused immunosuppression, which was fully reversed after recovery. This was an expected pharmacological effect.

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

- The NOAEL for the 10-week juvenile rat toxicity study was 5 mg/kg/day due to the persistent decrease of spleen weights in females at MD and HD. The NOAEL of 5 mg/kg/day corresponded to PND 21 AUC_{0-24h} of 2.86 and 1.99 mg·hr/mL in males and females, respectively; and PND 83 AUC_{0-24h} of 3.90 and 2.73 mg·hr/mL in males and females, respectively.

Conducting Laboratory and Location: (b) (4)
 (b) (4)

GLP Compliance: Yes

Methods

Dose and frequency of dosing: 0, 5, 15, and 50 mg/kg, once daily from PND 21 to PND 90

Route of administration: Oral

Formulation/Vehicle: (b) (4)

Species/Strain: Juvenile CrI:CD(SD) rat pups

Number/Sex/Group: 22/sex/group

Age: 21 days of age at initiation of dosing

Satellite groups/ unique design: TK blood samples were collected from 4 pups/sex/group on PND 21 and 5 pups/sex/group on PND 83 at 1, 2, 4, 8, and 24 hours post-dose.

Deviation from study protocol affecting result interpretation: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	There were no deucravacitinib-related mortalities.
Clinical Signs	There were no deucravacitinib-related clinical signs observed.
Body Weights	At 50 mg/kg/day, deucravacitinib caused a decrease in mean body-weight gain in males in the dosing phase, resulting in a 6.1% reduction of absolute body weight on PND 90. The body weight difference was resolved after recovery. There were no deucravacitinib-related effects on body weights at ≤15 mg/kg/day.
Ophthalmoscopy	Data not submitted.
Hematology	On PND 91, at 50 mg/kg/day, deucravacitinib caused slight increases (↑6-7%) of mean cell volume (MCV), mean corpuscular hemoglobin (MCH), and red cell distribution width (RDW), and decreases of white blood cell (WBC), lymphocytes, and eosinophils (↓65%, 58%, and 27%, respectively, sex combined). The differences were resolved after recovery. There were no other deucravacitinib-related effects on hematology or coagulation at any dose.
Clinical Chemistry	Deucravacitinib caused a dose-dependent decrease of urea nitrogen level in the blood at MD and HD (↓19% and 28%) in females. The differences in urea nitrogen were resolved after recovery. There were no other deucravacitinib-related effects on clinical chemistry at any dose.
Urinalysis	No deucravacitinib-related adverse effects.
Gross Pathology	No deucravacitinib-related adverse effects.

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Parameters	Major findings
Organ Weights	At $\geq$ 5 mg/kg/day, deucravacitinib decreased spleen weights at all doses in both males ($\downarrow$ 27%, 27%, and 40% at LD, MD, and HD) and females ($\downarrow$ 16%, 18%, and 36% at LD, MD, and HD). After recovery, the decreases in spleen weights persisted in females at MD and HD ($\downarrow$ 14% for each dose). There were no other deucravacitinib-related organ weight effects at any dose.
Histopathology Adequate battery: Yes/No	Yes. At $\geq$ 5 mg/kg/day, deucravacitinib caused minimal to moderate lymphoid depletion in the white pulp of the spleen of both sexes (M: 4/9, 6/10, and 9/10 at LD, MD, and HD; F: 7/10, 8/10, and 9/10 at LD, MD, and HD), which was correlated with lower spleen weights. The microscopic changes in the spleen were reversed after recovery.
Immunophenotyping	At $\geq$ 15 mg/kg/day in males and 50 mg/kg/day in females, deucravacitinib decreased absolute counts of total T, helper T, cytotoxic T, B, and NK lymphocytes. M: up to $\downarrow$ 41%, 37%, 52%, 43%, and 58% for total T, helper T, cytotoxic T, B, and NK cells, respectively. F: up to $\downarrow$ 46%, 42%, 57%, 36%, and 29 for total T, helper T, cytotoxic T, B, and NK cells, respectively. The decreases were fully reversed after recovery.
T-cell Dependent Antibody Response (TDAR)	At $\geq$ 15 mg/kg/day, deucravacitinib dose-dependently decreased KLH-specific IgM (up to $\downarrow$ 80%) and IgG (up to $\downarrow$ 73%) production in both sexes. The immunosuppression was fully reversed after recovery.
Sex Maturation	No deucravacitinib-related adverse effects.
Reproductive Functions	No deucravacitinib-related adverse effects.
Observation on F1 Litters	No deucravacitinib-related adverse effects on the number of pups born, percentage of males at birth, live litter size, or postnatal survival at any dose.

Abbreviations: LD: low dose; MD: mid dose; HD: high dose; M: male; F: female

5.5.5. Other Toxicology Studies

Major Metabolite Qualification

Deucravacitinib has three metabolites that are abundant in human circulation, BMT-158170, BMT-153261, and BMT-334616, which account for approximately 20%, 20%, and 9% of measured drug-related components (the steady-state AUCs), while deucravacitinib accounted for 49%. All three metabolites were detectable in rat and monkey plasma following oral administration of deucravacitinib. The following tables summarize the multiples of exposure of the two major metabolites, i.e., BMT-158170 and BMT-153261, based on AUC comparisons. AUC value of BMT-153261 at MRHD was 0.094 $\mu\text{g}\cdot\text{h}/\text{mL}$, based on a population PK study. The same AUC value can be applied to BMT-158170, given that two metabolites had similar steady-state AUCs of approximately 20%.

Table 2. Multiples of exposure of BMT-153261 and BMT-158170 in Nonclinical Toxicity Studies

Study Type	Deucravacitinib Dose (mg/kg/day)		BMT-153261*		BMT-158170*	
	NOAEL	Maximum Tested	Mean AUC ($\mu\text{g}\cdot\text{h}/\text{mL}$)	AUC Multiple	Mean AUC ($\mu\text{g}\cdot\text{h}/\text{mL}$)	AUC Multiple
Six-month rat oral toxicity study**		50	M: 5.0 F: 0.67	M: 53 F: 7.1	M: 13.8 F: 5.7	M: 147 F: 61

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Study Type	Deucravacitinib Dose (mg/kg/day)		BMT-153261*		BMT-158170*	
	NOAEL	Maximum Tested	Mean AUC (µg•h/mL)	AUC Multiple	Mean AUC (µg•h/mL)	AUC Multiple
Nine-month monkey oral toxicity study**		10→5	0.78	8.3	0.074	0.79
Fertility study in rats	50		M: 5.0 F: 0.36	M: 53 F: 3.8	4.80	51
EFD study in rats	75		0.42	4.5	6.39	68
EFD study in rabbits	10		3.26	35	0.04	0.43
PPND study in rats	Maternal effects: 50 F1 Generational effects: 15		Maternal: 0.31 F1: 0.035	Maternal: 3.3 F1: 0.37	Maternal: 6.84 F1: 1.20	Maternal: 73 F1: 13
Juvenile rat toxicity study***	5		0.10	1.1	0.17	1.8
Two-year rat carcinogenicity study	15		M: 0.53 F: 0.15	M: 5.6 F: 1.6	1.49	16

*: Exposures in male (M) and female (F) animals were generally similar and presented as sex-combined values except as noted.

** : TK data were not collected at the NOAEL doses. Multiples were calculated based on metabolite AUCs at the maximum tested doses.

***: values are averages from data collected on PNDs 21 and 83.

Impurity Qualification

The Applicant conducted a 1-month oral toxicity study in the rat to qualify impurities. A clean (unspiked) batch and an impurity-spiked batch of deucravacitinib were used as test articles. Three impurities were spiked in: (b) (4). In the spiked batch, the levels of the three impurities were (b) (4)%, respectively. The test articles were administered at a dose of 5 mg/kg/day. There were no notable impurities-related findings (including genotoxicity assessment in an embedded in vivo micronucleus assay) in the study. At the NOAEL of 5 mg/kg/day, the dose levels of the three impurities were (b) (4) µg/kg/day, which are equivalent to human doses of (b) (4) µg/day, respectively, based on a 60-kg body weight. (b) (4) are specified in the drug substance (DS) at not more than (NMT) (b) (4)% with the total daily intake (TDI) of (b) (4) µg/day, at the recommended dose of 6 mg/day. The 1-month rat toxicity study would provide a safety margin of (b) (4) respectively, for the three impurities.

Deucravacitinib is indicated for chronic use. Further, the NOAELs of the 3- and 6- month rat oral toxicity studies were 15 (highest dose in the 3-month study) and 5 mg/kg/day (sustained body weight reduction at 15 and 50 mg/kg/day in the 6-month study), respectively, suggesting further manifestation of toxicity of the DS during the longer duration of treatment. Therefore, a 3-month oral toxicity study in the rat may be more appropriate for qualification of the tested impurities. However, a 3-month rat study will most likely not give us additional information concerning the potential toxicities of the tested impurities. In the 1-month impurity qualification study, the findings were restricted to white blood cells and spleen, which were readily observed in longer duration general toxicity studies. Further, in the 3-month general

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

toxicity studies in rats and monkeys, other toxicity end points, such as changes in the liver and skin were largely reversible after dosing termination. Combined with the fact that the impurities have low TDIs ($\leq 30 \mu\text{g}/\text{day}$), a 3-month qualification study is not necessarily warranted. Therefore, there is no safety concern for general toxicity of the three impurities.

The Applicant conducted Ames tests for the following potential impurities: (b) (4)

(b) (4)
All of these impurities tested negative in the Ames tests, except (b) (4)

(b) (4) tested positive for mutagenicity in TA98 (313-5000 $\mu\text{g}/\text{plate}$) and TA100 (104-5000 $\mu\text{g}/\text{plate}$) strains in the presence of S9 metabolic activation. The Applicant has proposed to control this impurity at NMT (b) (4) ppm, which translates to the total daily intake (TDI) of (b) (4) $\mu\text{g}/\text{day}$ at the MDD of (b) (4) mg/day .

(b) (4) was positive for mutagenicity in the WP2 *uvrA* strain in the absence of S9 metabolic activation. In a follow-up assay, (b) (4) was orally administered to male rats for 30 days. Mutation of the Pig-a gene in erythrocytes (Pig-a gene mutation assay), micronucleus induction in peripheral blood reticulocytes (micronucleus test), and DNA damage in cells from liver tissue (Comet assay) were evaluated. (b) (4) did not appear to be genotoxic in the rat at the maximum tolerated dose of 300 $\text{mg}/\text{kg}/\text{day}$. Therefore, (b) (4) is not expected to pose a genotoxic risk.

Overall, the control strategies of the impurities evaluated above appear to be reasonable and acceptable from a nonclinical perspective.

Excipient Qualification

Deucravacitinib tablet does not contain novel excipients. All excipients are present at the same or lower levels when compared to levels in previously-approved oral tablet drug products.

6. Clinical Pharmacology

6.1. Executive Summary

The Applicant evaluated the pharmacokinetics (PK) of deucravacitinib and its major active metabolite BMT-153261 in the target patient population following the proposed dosing regimen in the two Phase 3 trials. Additional studies conducted to obtain clinical information include a thorough QT study, a dose-ranging study, a mass-balance study, a renal impairment study, a hepatic impairment study, nine clinical drug-drug interaction studies, and five bioavailability studies. Population PK analyses and the exposure-response (E-R) analyses were also performed.

The key review findings with specific recommendations and comments are summarized below in [Table 3](#).

Table 3. Summary of Clinical Pharmacology Review

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Efficacy of the proposed dosing regimen is established in two Phase 3 trials (IM011046 and IM011047). See Section 8.1 for efficacy data. The exposure-response analyses for efficacy (PASI and sPGA) from a Phase 2 trial and two Phase 3 trials provide supportive evidence of efficacy. See Section 19.4.2 for details.
Pharmacokinetics (PK)	The PK of deucravacitinib and its major active metabolite at the proposed dosing regimen of 6 mg once daily were characterized in two Phase 3 trials (IM011046 and IM011047).
Pharmacodynamics (PD)	Biomarkers related to efficacy and deucravacitinib's proposed mechanism of action as a selective tyrosine kinase 2 inhibitor were explored and evaluated from skin biopsy samples and serum samples.
General dosing instruction	The proposed dosing regimen of deucravacitinib 6 mg once daily administered orally is supported by the E-R analysis from a Phase 2 dose-ranging trial (IM011011) and efficacy and safety data from two Phase 3 trials (IM011046 and IM011047). The food effect study (IM011119) supports the dosing instruction without regards to meal.
Dosing in specific populations (intrinsic and extrinsic factors)	Deucravacitinib is not recommended in patients with severe hepatic impairment (Child-Pugh C).

Review Issues	Recommendations and Comments
Bridge between the to-be-marketed and clinical trial formulations	Three oral formulations were used to support the clinical development program (oral solution, capsule, and film-coated tablet). Two studies (IM011002 and IM011031) were conducted to evaluate the relative bioavailability of the capsule compared to solution and the tablet to capsule, respectively. The Phase 3 tablet formulation is similar to the proposed to-be-marketed formulation except the coating and printing, and these differences are supported by dissolution data per the Biopharmaceutics review team.
QTc prolongation potential	A thorough QT study (IM011048) was conducted. The QT-IRT determined that at a dose 6 times the proposed dose of the 6 mg once daily, deucravacitinib does not prolong the QTc interval to any clinically relevant extent.
Bioanalysis	Deucravacitinib and its metabolites in human plasma and urine were quantified using LC/MS/MS methods. The bioanalytical methods were adequately validated. See Section 19.4.3 for additional details.

Abbreviations: TQT = thorough QT/QTc, CDER = Center for Drug Evaluation and Research, IRT = interdisciplinary review team

6.1.1. Recommendations

From a Clinical Pharmacology standpoint, this NDA is acceptable to support the approval of deucravacitinib 6 mg once daily for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

6.1.2. Post-Marketing Requirement

A Pediatric Research Equity Act (PREA)-PMR will be issued to evaluate safety, efficacy and PK of deucravacitinib in pediatric subjects 4 to less than 18 years of age. See Section [13](#) for details.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

Deucravacitinib is a tyrosine kinase 2 (TYK2) inhibitor, which belongs to the Janus kinase family. The exact mechanism of action of deucravacitinib for the treatment of plaque psoriasis is unknown.

Pharmacokinetics

Deucravacitinib showed a rapid and complete absorption (oral bioavailability of 99%) and dose-proportional increase in exposures over a range from 3 mg to 36 mg in healthy subjects. The mean terminal half-life of deucravacitinib following a single 6 mg dose in healthy subject was

Multi-disciplinary Review and Evaluation NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

9.9 hr. The accumulation of deucravacitinib was <1.4-fold following once daily dosing. The PK of deucravacitinib and its active metabolite, BMT-153261, were comparable between healthy subjects and subjects with psoriasis. The population pharmacokinetics (PPK) model predicted geometric mean steady-state C_{max} , C_{min} and AUC_{24} of deucravacitinib following administration of 6 mg once daily are 45.1 ng/mL, 7.33 ng/mL and 472.8 ng·hr/mL, respectively. The PPK model predicted geometric mean steady-state C_{max} , C_{min} and AUC_{24} of the active deucravacitinib metabolite, BMT-153261, following administration of 6 mg once daily are 5.40 ng/mL, 2.49 ng/mL and 94.6 ng·hr/mL, respectively. The predicted median (range) to reach maximum concentration (T_{max}) and steady-state for deucravacitinib at steady-state was 74.0 (25.0-314) and 60.5 (12.0-301) hr, respectively. The predicted geometric mean (CV%) terminal half-life for deucravacitinib is 16.2 (22.8%) hr.

Deucravacitinib was metabolized by four primary biotransformation pathways. The active metabolite BMT-153261 is formed via N-demethylation at the triazole moiety by CYP1A2, the pharmacologically inactive metabolite BMT-158170 is formed via carboxylesterase (CES) 2, the weakly active metabolite BMT-334616 is formed via N-glucuronidation by UGT 1A9, and M11 is formed via mono-oxidation at the deuterated methyl group by CYP2B6 and 2D6. At steady-state, deucravacitinib was the major circulating species in plasma (49% of measured drug-related components), followed by BMT-158170, BMT-153261, and BMT-334616 accounting for approximately 20%, 20% and 9%, respectively. BMT-153261 has comparable potency to deucravacitinib.

Following an oral administration, deucravacitinib was eliminated via multiple pathways, including Phase I and II metabolisms, along with direct renal and fecal elimination. After a single dose of radiolabeled deucravacitinib, approximately 13% and 26% of the dose was recovered as unchanged in urine and feces, respectively. Approximately 6% and 12% of the dose was detected as BMS-153261 in urine and feces, respectively.

Pharmacodynamics

Deucravacitinib is a TYK2 inhibitor and it exerts its activity by TYK2/JAK2 and TYK2/JAK 1 pairing. Deucravacitinib showed dose-dependent reduction in pharmacodynamic (PD) markers associated with the interleukin-23/IL-17 axis such as IL-17A, IL-19, IL-36A, β -defensin and S100A9, Type I IFN-regulated genes such as *MX1* and *OASL*, and keratinocyte dysregulation markers such as *KRT16* and *CCL20* in skin biopsy samples from subjects with psoriasis. Deucravacitinib reduced IL-17A, IL-19 and beta-defensin in serum by 47 to 50%, 72%, and 81 to 84%, respectively following 16 weeks of once daily treatment.

Clinical Drug Interaction Studies

- No clinically significant differences in the PK of deucravacitinib were observed when coadministered with the following drugs: cyclosporine (dual P-gp/BCRP inhibitor), fluvoxamine (CYP1A2 inhibitor), ritonavir (CYP1A2 inducer), diflunisal (UGT 1A9 inhibitor), pyrimethamine (OCT1 inhibitor), famotidine (H2 receptor antagonist), or rabeprazole (proton pump inhibitor). The maximal change was observed when deucravacitinib was

Multi-disciplinary Review and Evaluation NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

coadministered with fluvoxamine, in which the AUC of deucravacitinib was increased by 57%. Any dosing adjustments of deucravacitinib are not deemed necessary.

- No clinically significant differences in the PK of the following drugs were observed when coadministered with deucravacitinib: rosuvastatin (BCRP/OATP substrate), methotrexate (MTX), mycophenolate mofetil (MMF) and oral contraceptives (norethindrone acetate and ethinyl estradiol). The most change observed was with rosuvastatin, in which C_{max} and AUC increased by 14%.

Food Effect

The effect of a high fat/high-calorie meal on the PK of 6 mg deucravacitinib was evaluated in healthy subjects. Under fed conditions, C_{max} and AUC of deucravacitinib decreased by 24% and 11%, respectively. Deucravacitinib is recommended to be taken without regards to meals.

QT Prolongation

At a dose of 36 mg which is 6 times the recommended dose, deucravacitinib did not show significant QTcF prolongation effect. See QT-IRT Review by Dr. Girish K Bende in DARRTS dated 03/21/2022 for details.

6.2.2. General Dosing and Therapeutic Individualization

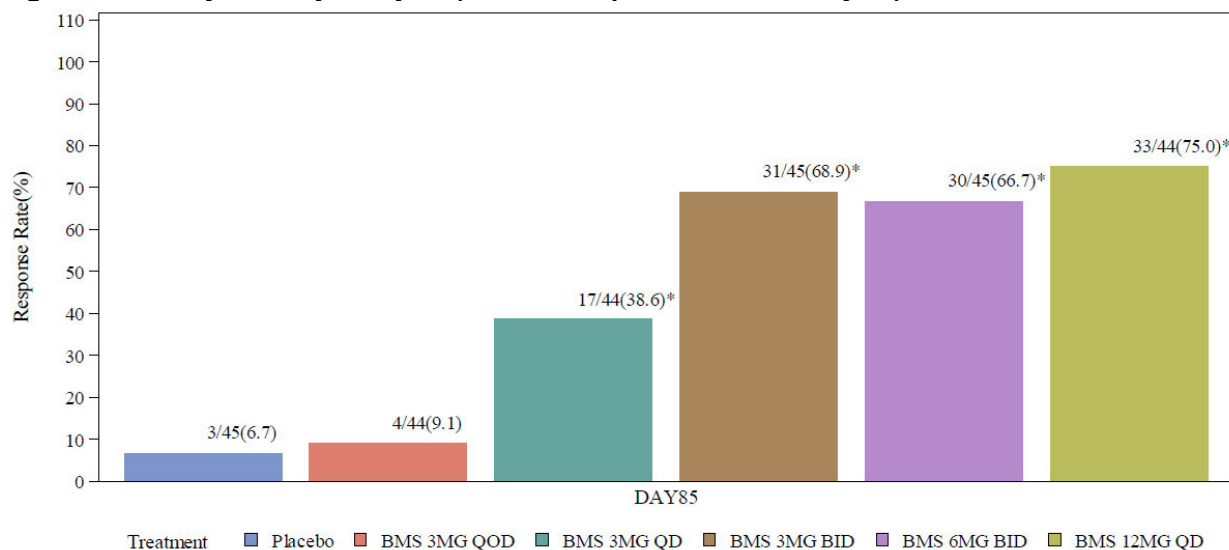
General Dosing

The proposed dosing regimen is 6 mg of deucravacitinib tablet administered orally once daily (QD), with or without food. This dosing regimen is supported by the efficacy and safety data from Phase 3 trials (IM011046 and IM011047).

The food effect study (IM011119) supports dosing instruction without regards to meal.

The 6 mg QD dose was selected based on modeling and simulation for the Phase 2 dose-ranging trial (IM011011) which clearly showed dose-response ([Figure 1](#)). Although doses higher than 3 mg BID showed better efficacy, they were not evaluated as there was a dose-dependent increase in the incidence of creatinine phosphokinase (CPK) observed in the Phase 2 study and doses lower than 3 mg BID were not very efficacious. Hence only 6 mg QD dose was selected for Phase 3 trials.

Figure 1. Primary Efficacy Analysis (PASI75 Response Rates at Day 85) From IM011011



Source: Figure S5.1.1, CSR for IM011011

Therapeutic Individualization

No dose adjustment is recommended in patients with mild or moderate hepatic impairment. Deucravacitinib is not recommended in patients with severe hepatic impairment (Child Pugh C) due to safety concerns with liver enzyme elevations.

Outstanding Issues

There are no outstanding issues from the Clinical Pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

6.3.1.1. Mechanism of Action

Deucravacitinib is a tyrosine kinase 2 (TYK2) inhibitor, which belongs to the Janus kinase family of enzymes. Deucravacitinib binds to the regulatory domain of TYK2, stabilizing an inhibitory interaction between the regulatory and the catalytic domains of the enzyme, and thereby inhibits receptor-mediated activation of TYK2 and its downstream activation of Signal Transducers and Activators of Transcription (STATs). The exact mechanism of action of deucravacitinib for the treatment of plaque psoriasis is unknown.

6.3.1.2. Pharmacokinetics

Absolute Bioavailability, Study IM011067

An open-label, single-period study was conducted to assess the absolute oral bioavailability of deucravacitinib. A single oral 12 mg dose of deucravacitinib tablet and a single IV 0.1 mg of [¹³C₂, ¹⁵N₃]-deucravacitinib solution was administered to healthy male subjects. The absolute

bioavailability and PK parameters obtained from this study are summarized in [Table 4](#) and [Table 5](#), respectively.

Table 4. Absolute Bioavailability of Deucravacitinib From Study IM011067

Statistic	1 mg ^a	1 mg eq ^b	F (%)
	Oral Deucravacitinib AUC _{inf} (ng.h/mL)	IV [¹³ C ₂ , ¹⁵ N ₃]-Deucravacitinib AUC _{inf} (ng.h/mL)	
n	8	8	8
Geo Mean	778	6.556	98.9
Geo CV (%)	29.6	27.4	4.7
Median	802	6.605	98.5

Source: Table 12, CSR for IM011067

^a AUC_{inf} normalized to 1 mg: (AUC_{inf}/12)

^b AUC_{inf} normalized to 1 mg eq deucravacitinib: ((AUC_{inf}*10)*[mass deucravacitinib/mass [¹³C₂, ¹⁵N₃]-deucravacitinib])

Table 5. PK Parameters of Deucravacitinib Following a Single Oral Dose and IV Dose in Healthy Subjects From Study IM011067

Statistic	AUC(0-T)	AUC(INF)	C _{max}	T _{max} ^a	t _{1/2}	CL	CL/F	V _{ss}
	(ng.h/mL)	(ng.h/mL)	(ng/mL)	(h)	(h)	(mL/h)	(mL/h)	(mL)
Oral Deucravacitinib								
n	8	8	8	8	8	8	8	8
Geo Mean	768	778	98.2	1.50	13.2	NC	15,415	NC
Geo CV%	28.9	29.6	17.8	1.00-2.50	43.0	NC	29.6	NC
[¹³ C ₂ , ¹⁵ N ₃]-Deucravacitinib								
n	8	8	8	8	8	8	8	8
Geo Mean	6,435	6,556	1,187	0.25	13.5	15,253	NC	139,877
Geo CV%	26.6	27.4	23.3	0.08-0.33	50.3	27.4	NC	14.9

Source: Table 11, CSR for IM011067

^a For T_{max}, the median, min and max are presented

Mass Balance, Study IM011016

An open-label study in healthy male subjects was conducted to assess the PK, metabolism and routes and extent of elimination of a single oral dose of 24 mg [¹⁴C] deucravacitinib containing approximately 100 µCi of total radioactivity (TRA). In addition, collected plasma, urine, and fecal samples were used to evaluate biotransformation profiles.

Metabolism was the major route of elimination for deucravacitinib, with 59.3% of the dose being eliminated as metabolites. The urinary excretion of deucravacitinib dose as unchanged was 11.7%. The mean percent AUC ratio of deucravacitinib to TRA in plasma was 38%. The association of TRA with red blood cells were minimum as the percent AUC ratio of TRA in plasma to whole blood was 101%. The elimination of TRA was similar between urinary and fecal excretion, at 52.5% and 51.9%, respectively. The PK parameters for deucravacitinib and TRA are summarized in [Table 6](#) and [Table 7](#), respectively. The cumulative total percent of dose recovered in urine, feces and combined excreta matrices is summarized in [Table 8](#).

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Table 6. Summary of PK Parameters for Deucravacitinib From a Mass Balance, Study IM011016

Parameter	Statistic	Value
C_{max} (ng/mL)	Geo Mean (n)	184 (6)
	%CV	14
T_{max} (hr)	Median (n)	2.00 (6)
	Min - Max	1.00 – 2.03
AUC_{0-t} (hr*ng/mL)	Geo Mean (n)	1485 (6)
	%CV	21
AUC_{inf} (hr*ng/mL)	Geo Mean (n)	1495 (6)
	%CV	20
$T_{1/2}$ (hr)	Mean (n)	7.58 (6)
	SD	0.930
CL/F (L/hr)	Geo Mean (n)	16.1 (6)
	%CV	18
V_z/F (L)	Geo Mean (n)	175 (6)
	%CV	10
% Urinary Recovery (%)	Geo Mean (n)	11.7 (6)
	%CV	33
Renal Clearance (L/hr)	Geo Mean (n)	1.87 (6)
	%CV	41

Source: Table 4, CSR for IM011016

Table 7. Summary of PK Parameters for Total Radioactivity in Plasma and Whole Blood From Study IM011016

Parameter	Statistic	TRA in Plasma	TRA in Whole Blood
C_{max} (ng/mL)	Geo Mean (n)	343 (6)	332 (6)
	%CV	11	14
T_{max} (hr)	Median (n)	2.00 (6)	2.00 (6)
	Min - Max	1.00 – 2.03	0.550 – 2.03
AUC_{0-t} (hr*ng/mL)	Geo Mean (n)	3655 (6)	3675 (6)
	%CV	16	12
AUC_{inf} (hr*ng/mL)	Geo Mean (n)	3932 (6)	3900 (6)
	%CV	14	13
$T_{1/2}$ (hr)	Mean (n)	9.06 (6)	9.01 (6)
	SD	1.075	1.110

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Parameter	Statistic	TRA in Plasma	TRA in Whole Blood
AUC (deucravacitinib)/AUC (TRA)			
	Geo Mean (n)	0.380 (6)	-
	%CV	9	
Plasma AUC (TRA)/ Blood AUC (TRA)			
	Geo Mean (n)	-	1.01 (6)
	%CV		5

Source: Table 5, CSR for IM011016.

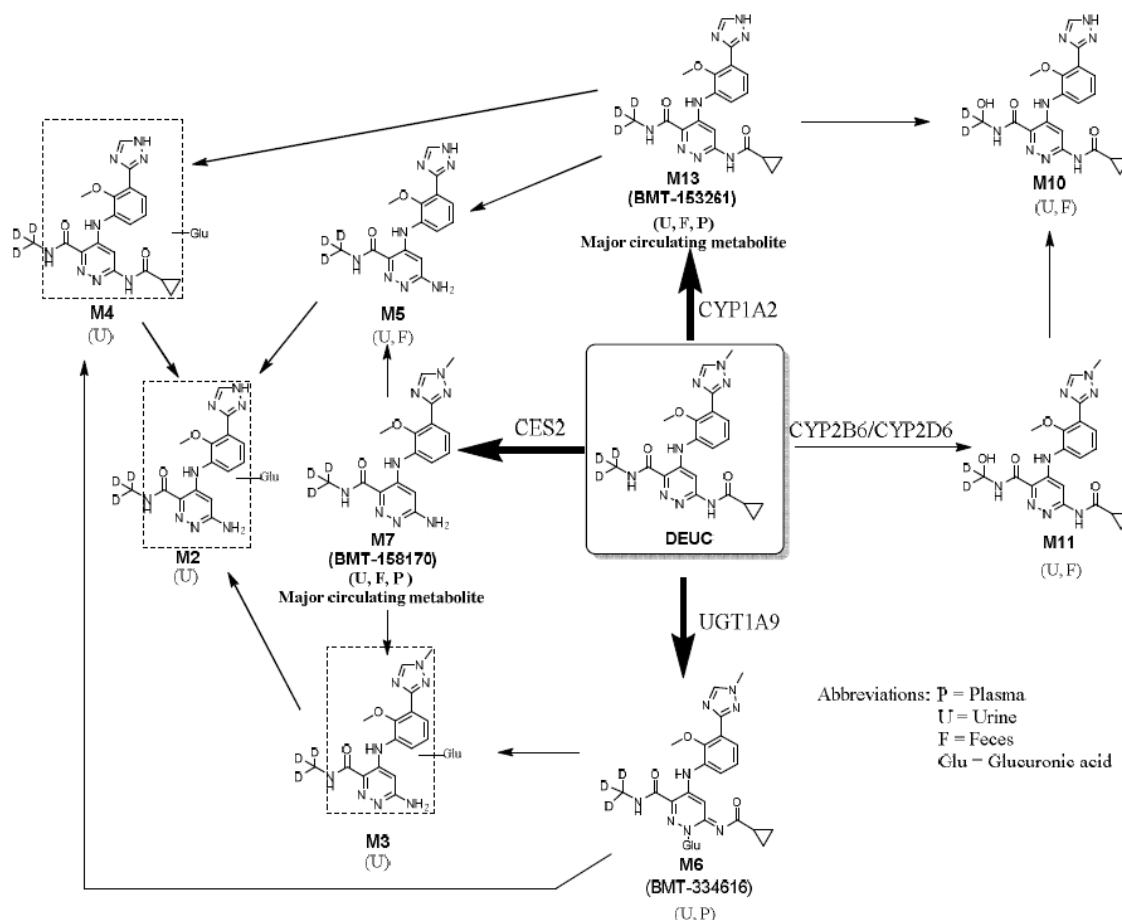
Table 8. Total Recovery of Radioactive Dose in Urine, Feces and All Excreta

Statistic	% Urinary Excretion	% Fecal Excretion	% Total
Mean (n)	52.5 (6)	51.9 (6)	104 (6)
SD	5.58	5.97	0.9

Source: Table 6, CSR for IM011016

The proposed in vivo biotransformation pathways of [¹⁴C]Deucravacitinib in human is shown in [Figure 2](#). The major biotransformation pathways include: 1) N-demethylation at the triazole moiety to form BMT-153261 (an active metabolite with comparable potency to the parent compound), 2) Cyclopropyl carboxamide hydrolysis to form BMT-158170 (375x less active than the parent compound), and 3) Direct glucuronidation of deucravacitinib to form BMT-334616 (biologically inactive metabolite).

Figure 2. Proposed In Vivo Biotransformation Pathways of [14C]Deucravacitinib in Humans



Source: Figure 3.1.3-1, Module 2.7.2.

In plasma, deucravacitinib was the most prominent drug-related component (43%), followed by BMT-158170 (24%), BMT-153261 (11%), and BMT-334616 (7%). Deucravacitinib represented 12.9% and 25.9% of the dose in urine and feces, respectively. The distribution of drug-related components in plasma and in urine and feces are summarized in [Table 9](#) and [Table 10](#), respectively. The contribution of biotransformation pathways to deucravacitinib elimination in humans is summarized in [Table 11](#).

Table 9. Distribution of Drug-related Components in Plasma

Parameter	BMT-334616	BMT-158170	BMT-153261	Parent (Deucravacitinib)	Others ^a	Subtotal (parent + 3 metabolites)	Total
AUC ₀₋₂₄ (ng*eq/mL)	211	747	335	1320	452	2613	3065
% Total	7	24	11	43	15	85	100

Source: Table 1.1-3, Report NCPK431.

^a Others are sum of all the unidentified small peaks that were 2 times higher than background; these were excluded from the subtotal (Parent+3 metabolites). The percentage of others was estimated based on the theoretical total percentage (100%) minus the subtotal.

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Table 10. Distribution of Drug-related Components in Urine and Feces

Parent Compound and Metabolites	Percent of Dose Recovered		
	Urine (0-120 h)	Feces (0-120 h)	Total
Deucravacitinib Parent	12.9	25.9	38.9
M2	0.39	ND	0.39
M3	3.14	ND	3.14
M4	1.36	ND	1.36
M5	1.43	1.29	2.72
BMT-334616 (M6)	18.6	ND	18.6
BMT-158170 (M7)	4.10	4.93	9.02
M10	0.59	0.91	1.50
M11	1.47	2.65	4.11
BMT-153261 (M13)	6.19	12.3	18.5
Sum of Metabolites	37.3	22.0	59.3
Total	50.2	48.0	98.2

Source: Table 1.1-4, Report NCPK431.

Abbreviations: ND: not detected by radioactivity detection

Table 11. Contribution of Biotransformation Pathways to Deucravacitinib Elimination

Enzymes Involved in the Pathway	Primary Metabolite	Recovery as the Primary Metabolite (% dose)	Downstream Metabolite formed via the Pathway	Sum of the Metabolites (%dose)	Contribution to Deucravacitinib Elimination
CYP1A2	BMT-153261	18.5%	M2, M4, M5, M10	24.5%	18.5%-24.5%
UGT1A9	BMT-334616	18.6%	M2, M3, M4	23.5%	18.6%-23.5%
CES2	BMT-158170	9.0%	M2, M3, M5	15.3%	9.0%-15.3%
CYP2B6 and CYP2D6	M11	4.1%	M10	5.6%	4.1%-5.6%

Source: Table 2.2.3.3-1, Module 2.7.2.

PK of Deucravacitinib and BMT-153261 at the Proposed Dosing Regimen

Based on the population PK (PPK) model developed using data from Phase 1, 2 and 3 trials, the systemic exposures of deucravacitinib and BMT-153261 in subjects with psoriasis were predicted at a 6 mg QD dosing regimen. The details of the PPK model can be found in Section 19.4.1 and the model validation is shown in Figure 34. The summaries of deucravacitinib exposures at steady-state and time to steady-state C_{max} , C_{avg} , and C_{min} are listed in Table 12 and Table 13, respectively. The summaries of BMT-153261 exposures at steady-state and the ratio of BMT-153261 to deucravacitinib exposure at steady-state are listed in Table 14 and Table 15, respectively.

Table 12. PPK Model Predicted Deucravacitinib Exposures at Steady-state at 6 mg QD

Deucravacitinib	After First Dose (N = 838)	Steady-state (N = 838)
C_{max} (ng/mL)		
Median [Min, Max]	36.6 [2.90, 140]	44.8 [3.70, 152]
Geo. Mean (Geo. CV%)	37.1 (34.1%)	45.1 (35.3%)
5th Percentile	23.4	27.4
95th Percentile	61.5	77.7

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Deucravacitinib	After First Dose (N = 838)	Steady-state (N = 838)
C_{min} (ng/mL)		
Median [Min, Max]	4.81 [0.610, 19.9]	6.77 [0.770, 45.4]
Geo. Mean (Geo. CV%)	4.99 (66.6%)	7.33 (82.2%)
5th Percentile	1.88	2.43
95th Percentile	14.0	26.2
C_{avg} (ng/mL)		
Median [Min, Max]	15.5 [1.60, 46.1]	18.8 [2.20, 62.0]
Geo. Mean (Geo. CV%)	15.9 (32.9%)	19.7 (44.0%)
5th Percentile	9.89	10.7
95th Percentile	27.3	43.3

Source: Table 5.1.3.2-1, PPK Report.

Table 13. PPK Model Predicted Time to Steady-state C_{max}, C_{avg}, and C_{min} of Deucravacitinib at a 6 mg QD

Parameter	Time to C _{max} SS (hr) (N=838)	Time to C _{avg} SS (hr) (N=838)
Mean (SD)	83.0 (43.3)	83.0 (45.7)
Median [Min, Max]	74.0 [25.0, 314]	60.5 [12.0, 301]
Geo. mean (Geo. CV%)	73.3 (53.4%)	70.5 (68.1%)

Source: Table 5.1.3.4-1, PPK Report.

Table 14. PPK Model Predicted BMT-153261 Exposures at Steady-state at 6 mg QD

BMT-153261	After First Dose (N = 834)	Steady-state (N = 834)
C_{max} (ng/mL)		
Median [Min, Max]	3.40 [0.600, 17.6]	5.40 [1.50, 25.2]
Geo. Mean (Geo. CV%)	3.32 (43.6%)	5.40 (40.5%)
5th Percentile	1.70	2.80
95th Percentile	6.40	10.3
C_{min} (ng/mL)		
Median [Min, Max]	1.68 [0.400, 7.06]	2.46 [0.500, 15.1]
Geo. Mean (Geo. CV%)	1.66 (45.7%)	2.49 (53.7%)
5th Percentile	0.800	1.11
95th Percentile	3.29	6.09
C_{avg} (ng/mL)		
Median [Min, Max]	2.50 [0.500, 12.7]	3.90 [1.20, 17.0]
Geo. Mean (Geo. CV%)	2.48 (41.6%)	3.94 (42.9%)
5th Percentile	1.30	2.10
95th Percentile	4.54	7.70

Source: Table 5.2.3.2-1, PPK Report.

Table 15. Estimated Ratio of BMT-153261 to Deucravacitinib Exposure at Steady-state

The Ratio of the BMT-153261 to Deucravacitinib Exposure	
Metrics	Overall (N = 834)
C_{max}SS Ratio	
Geo. Mean (Geo. CV%)	0.120 (38.8%)
Median [Min, Max]	0.123 [0.0261, 0.595]
C_{avg}SS Ratio	
Geo. Mean (Geo. CV%)	0.200 (49.1%)
Median [Min, Max]	0.212 [0.0288, 0.909]

Source: Table 5.2.3.3-1, PPK Report.

6.3.1.3. Pharmacodynamics

Biomarkers in Skin Biopsy Samples

In a Phase 2, dose-ranging trial (IM011011) in subjects with psoriasis, biomarkers from skin biopsies were obtained from a small subset of subjects (n=37). Biopsies were taken from non-lesional skin on Day 1 and from lesional skin on Days 1, 15 and 85. A total of 3004 psoriasis-related differentially expressed genes (DEGs) were identified in lesional versus non-lesional biopsies taken on Day 1. Changes in these 3004 DEGs following treatment with deucravacitinib were evaluated and are shown in [Table 16](#). In addition, changes in gene expression of several biomarkers related to the IL-23, IL-12, Type I IFN pathways and keratinocyte regulation genes were evaluated; and IL17A, IL19, IL36A, β -defensin 4A, S100A9, MX1, OASL, KRT16 and CCL20 all showed dose-dependent reduction with deucravacitinib treatment, with most of them showing noticeable changes at dose levels 3 mg BID and higher. The changes of IL17A are shown in [Figure 3](#) as an example. The changes for other biomarkers are not included in this review, but they showed similar trends. Data for the aforementioned biomarkers are also published by Catlett et al (Catlett et al. 2022).

Table 16. Changes in Psoriasis-Related Differentially Expressed Genes (DEGs) in Lesional Skin Biopsies Among 3004 DEGs

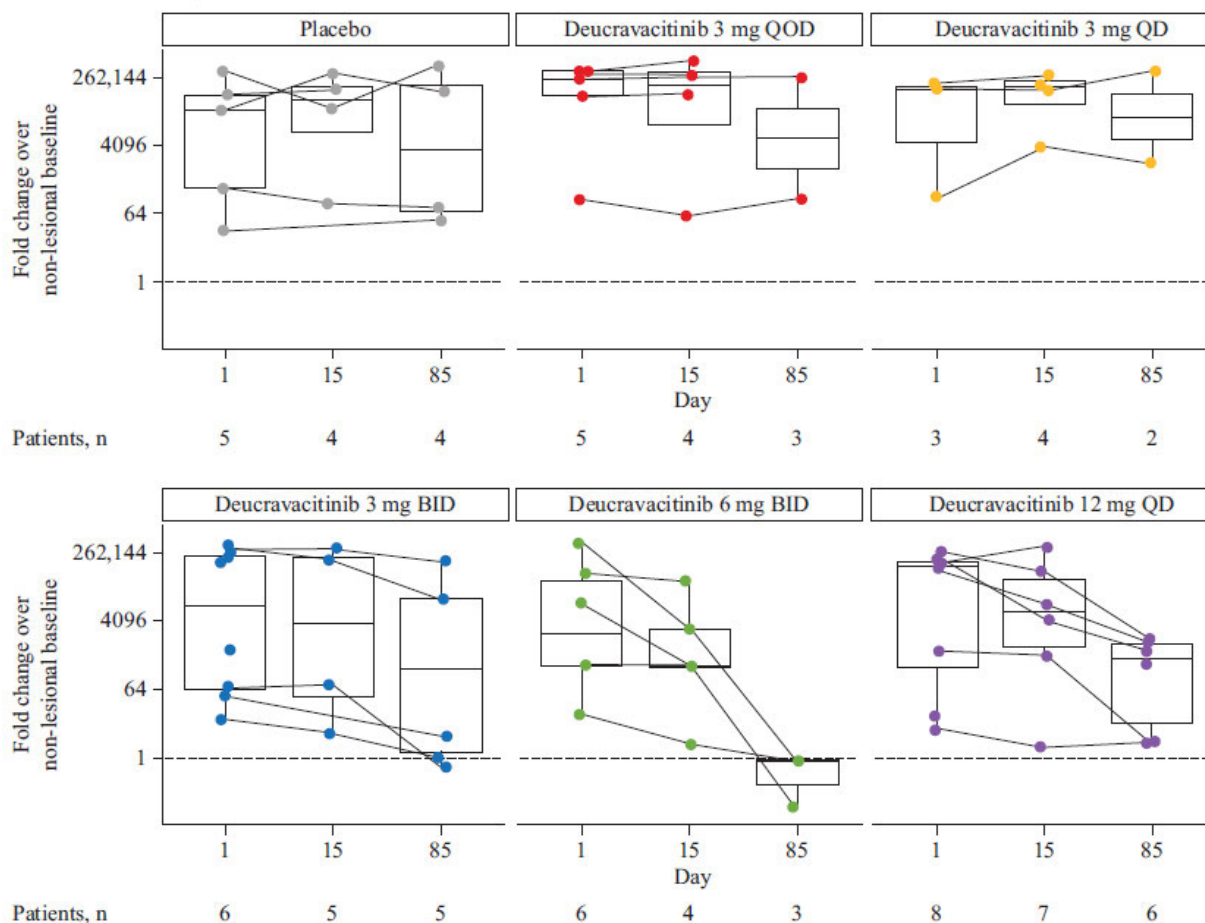
Dosage group	Number of Differentially Expressed Genes	
	Day 85 Versus Day 1	Day 85 Deucravacitinib Versus Placebo
Placebo	0	-
Deucravacitinib 3 mg QOD	0	2
Deucravacitinib 3 mg QD	NA	NA
Deucravacitinib 3 mg BID	1472	1065
Deucravacitinib 6 mg BID	1723	1470
Deucravacitinib 12 mg QD	1836	1532

Source: Table 4, Addendum to CRS for IM011011.

Abbreviations: NA, not available due to limited sample size

Significant changes (up- or down-regulated) in psoriasis-related DEGs were observed on Day 85 versus Day 1 and deucravacitinib versus placebo at dose levels 3 mg BID and higher, suggesting the efficacy dose levels of deucravacitinib in treatment of psoriasis. Note that the Applicant's simulations based on the Phase 2 trial exposure-response model indicated comparable systemic exposure (C_{avg}SS) and PASI75 response rate following 3 mg BID dosing and the proposed 6 mg QD dosing, as shown in [Figure 38](#).

Figure 3. Fold Changes in IL17A Over Non-lesional Baseline With Deucravacitinib Treatment Over 85 Days in Skin Biopsies



Source: Figure 6, Addendum to CRS for IM011011

Note: box represent the median and interquartile range (IQR). Whiskers extend to the nearest data point to 1.5x the IQR.

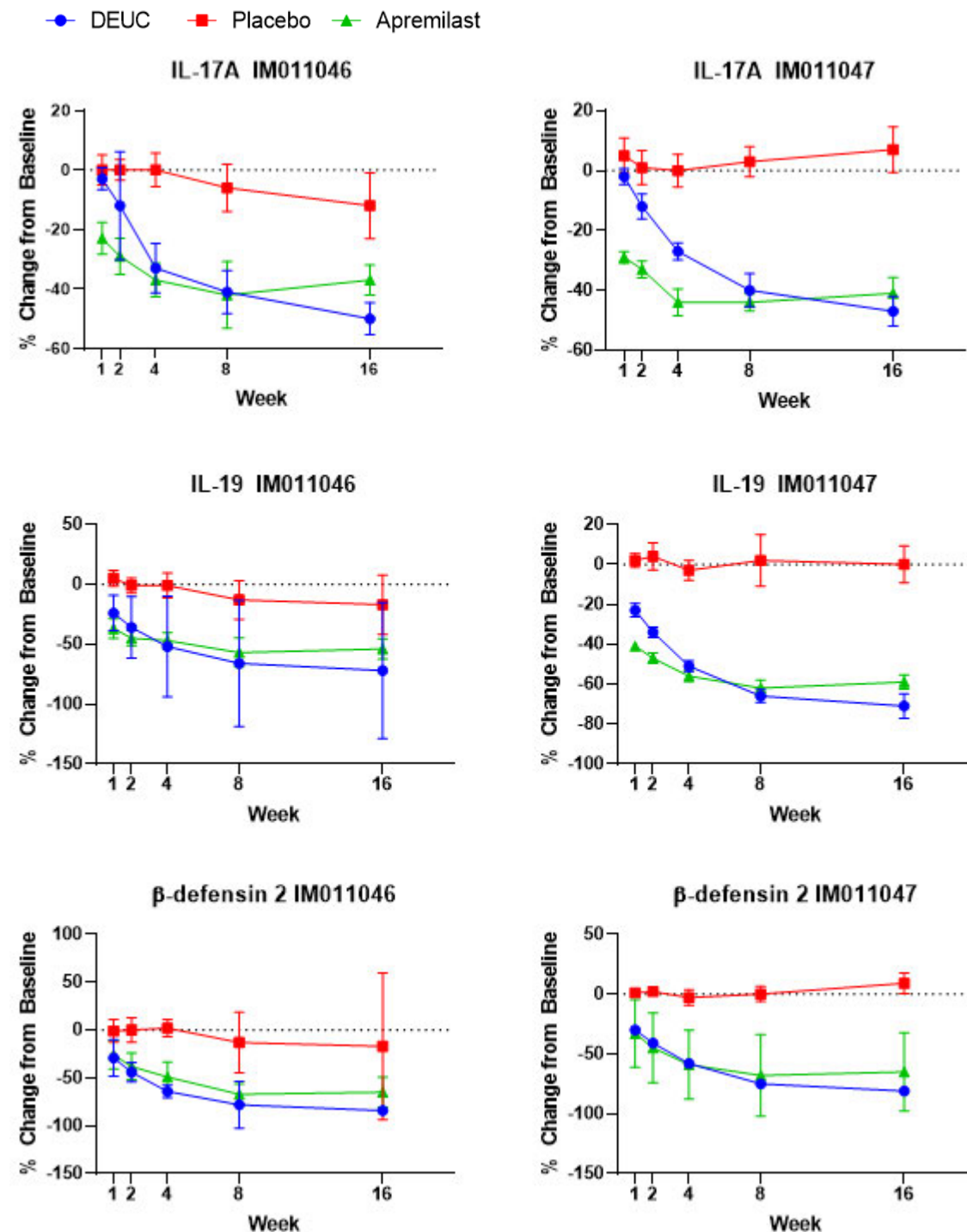
Similar to the changes in DEGs ([Table 16](#)), the changes in 17A which is regulated by the IL-23 pathway and is involved regulation of keratinocyte genes were noticeable at dose levels 3 mg BID and higher. In addition, the changes were more pronounced on Day 85, compared to Day 15. Similar trends were observed with other biomarkers evaluated in this study (figures not included in this review).

Biomarkers in Serum Samples

In two Phase 3 pivotal trials (IM011046 and IM011047), several biomarkers in serum were evaluated, such as IL-17A, IL-19, IL-22, IL-23, lipocalin and TNF. Among these biomarkers, IL-17A, IL-19 and β -defensin showed meaningful changes that were correlated with the efficacy results (PASI response). The changes of these three biomarkers over 16 weeks of 6 mg once daily treatment with deucravacitinib, placebo, or apremilast (active comparator) are shown in [Figure 4](#). The reduction of the three biomarkers in serum were observed in the deucravacitinib and apremilast treatment groups but not in the placebo group. The median % changes in IL-17A, IL-19 and beta-defensin were 47 to 50%, 72%, and 81 to 84%, respectively following 16

weeks of once daily treatment. The correlations between these three biomarkers and PASI score at baseline and over time are shown in [Figure 5](#).

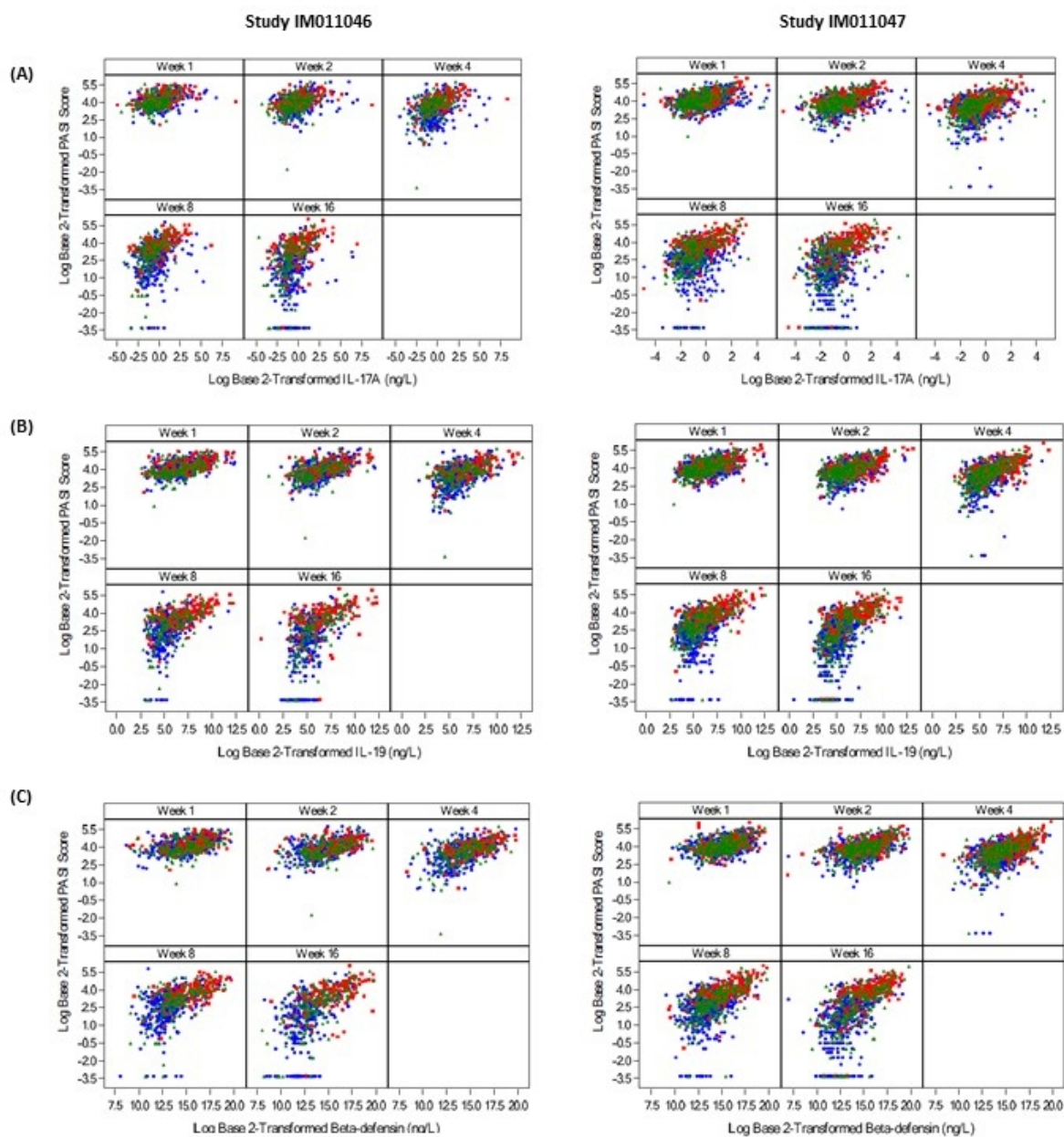
Figure 4. Percent Change From Baseline of Biomarkers (IL-17A, IL-19, and β -defensin) in Phase 3 Trials



Source: Reviewer's graph; Median $\pm$ SEM

Figure 5. Correlations Between Biomarkers (IL-17A, IL-19, and β -defensin) and PASI Score in Phase 3 Trials

● DEUC ■ Placebo ▲ Apremilast



Source: Figure S.9.4.1, Figure S.9.4.2, Figure S.9.4.3, CRS for IM011046 and Figure S.9.4.1, Figure S.9.4.2, Figure S.9.4.3, CRS for IM011047.
 Note: (A) IL-17A, (B) IL-19 and (C) β -defensin.

6.3.1.4. Formulation Bridge

Three oral formulations (oral solution, capsule, and film-coated tablet) were utilized in the clinical development program of deucravacitinib.

Two studies (IM011002 and IM011031) were conducted to evaluate the relative bioavailability of the capsule compared to solution and the tablet compared to the capsule, respectively. The to-be-marketed formulation is a film-coated tablet.

Relative Bioavailability Between Capsule and Solution: IM011002, Part D

The Part D of Study IM011002 evaluated the relative bioavailability of deucravacitinib oral capsule compared with the oral solution formulation under fasted conditions in healthy subjects. The results are shown in [Table 17](#).

Table 17. Relative Bioavailability Between Capsule and Solution Formulations of Deucravacitinib

Parameter	Geometric LS Mean Ratio (90% CI)	
	C_{max}	AUC_{inf}
Capsule vs. Solution (fasted)	0.900 (0.792, 1.021)	0.937 (0.881, 0.997)

Source: Data extracted from Table 2.2.5.1-1, Module 2.7.2.

The systemic exposures of capsule formulation were slightly lower than those of solution formulation; C_{max} was 10% lower and AUC_{inf} was 6% lower. The 90% CI for C_{max} was slightly outside the no effect boundary of 80 to 125% but the 90% CI for AUC_{inf} were within the no effect boundary. The small differences observed between capsule and solution formulations are not considered significant.

Relative Bioavailability Between Capsule and Tablet, IM011031

Study IM011031 evaluated the relative bioavailability of deucravacitinib oral capsule compared with the oral tablet in healthy subjects. Two dose strengths (3 mg and 12 mg) per formulation type were evaluated. The results are shown in [Table 18](#).

Table 18. Relative Bioavailability Between Capsule and Tablet Formulations of Deucravacitinib

Parameter	Geometric LS Mean Ratio (90% CI)	
	C_{max}	AUC_{inf}
Tablet vs. Capsule (3 mg)	0.939 (0.859, 1.025)	1.003 (0.960, 1.047)
Tablet vs. Capsule (12 mg)	1.034 (0.947, 1.129)	1.068 (1.023, 1.115)

Source: Data extracted from Table 2.2.5.1-1, Module 2.7.2.

The systemic exposures of capsule and tablet formulations were comparable for both strengths evaluated. The 90% CI for all comparisons using C_{max} and AUC_{inf} were within the no effect boundary of 80 to 125%. Although the strengths of capsules and tablets evaluated in this study are different (i.e., 3 mg and 12 mg) from the strength of the to-be-marketed tablet formulation (i.e., 6 mg), the tablets are compositionally proportional per the CMC review team and thus using different strengths in this study compared to the proposed to-be-marketed strength is acceptable and the findings from this study are deemed applicable to the 6 mg tablet formulation.

It was also noted that the to-be-marketed tablet formulation is similar to the tablet formulation used in the Phase 3 trials, but with different coating and printing. Per the Applicant, these changes are considered minimal, and their comparability are supported by dissolution data. The CMC review team concurred with the Applicant's position. Based on the data from the two relative bioavailability studies in addition to the food effect/pH effect study (IM011119) conducted with the to-be-marketed tablet formulation, there are no concerns with utilizing clinical pharmacology information obtained from different formulations to support the deucravacitinib development program.

6.3.2. Clinical Pharmacology Questions

Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

Yes. The efficacy of deucravacitinib for the treatment of moderate to severe plaque psoriasis was demonstrated in the two Phase 3 trials. See Section [8.1](#) for details of efficacy data. The clinical pharmacology data such as dose-response relationships for efficacy which is described in Section [19.4.1.2](#) and results of pharmacodynamic biomarkers in Section [6.3.1.3](#) provide supportive evidence of effectiveness.

Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

Yes. The proposed dosing regimen, 6 mg once daily, is appropriate for the general patient population for the treatment of moderate to severe plaque psoriasis in adults. The dosing regimen is supported by the dose-response results from a Phase 2 dose-ranging trial (IM011011) and the exposure-response analyses from the Phase 2 trial and two Phase 3 trials (IM011046 and IM011047) which are described in Section [19.4.1.2](#). In addition, population PK (PPK) model which indicated no clinically meaningful differences on deucravacitinib exposures based on various intrinsic/extrinsic factors (race, baseline PASI, smoking status, age, body weight, eGFR and sex), supports the proposed dosing regimen for the general patient population (Section [19.4.1](#)).

Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

Use of deucravacitinib is not recommended in patients with severe hepatic impairment (Child Pugh C), due to safety concerns with liver enzyme elevations. See Section [8.2](#) for details.

The Applicant conducted dedicated renal impairment and hepatic impairment studies in order to evaluate the effect of renal and hepatic functions on the PK of deucravacitinib. The changes in the exposures of deucravacitinib and BMT-153261 were not significant to warrant dose modifications based on the PK study results. These studies are described below.

Renal Impairment Study, IM011061

A dedicated, open-label, single-dose (12 mg), renal impairment study was conducted to evaluate the effect of mild, moderate, severe renal impairment, and end-stage renal disease subjects requiring hemodialysis (ESRDH) on PK of deucravacitinib and BMT-153261. The renal

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

function groups and the number of subjects who completed the study in each group are described in [Table 19](#).

Table 19. Number of Subjects Who Completed the Study by Renal Function Group

Group	Population	eGFR (mL/min/1.73m ²)	Number of Subjects
A	Normal renal function ^a	≥90	12
B	Mild renal function impairment	≥60 to <90	8
C	Moderate renal function impairment	≥30 to <60	8
D	Severe renal function impairment ^b	<30	8
E	Participants with ESRDH	<15	8

Source: Table 2, CRS for IM011061.

^a Control group

^b Severe renal function impairment subjects not requiring hemodialysis

The summaries of the effect of renal impairment on exposures of deucravacitinib and BMT-153261 are shown in [Table 20](#) and [Table 21](#), respectively. The summary of deucravacitinib extraction data from subjects in the ESRDH group is in [Table 22](#).

Table 20. Effect of Renal Impairment on PK of Deucravacitinib

Comparison (Test/Reference)	PK Parameter Deucravacitinib	Test n	Test Geo LS Mean	Reference n	Reference Geo LS Mean	Geo LS Mean Ratio (Test/Reference)	
						Estimate	90% CI
Mild vs. Normal	C _{max} (ng/mL)	8	97.5	12	113	0.862	0.724, 1.030
	AUC(0-T) (h•ng/mL)	8	1004	12	972	1.030	0.765, 1.400
	AUC(INF) (h•ng/mL)	8	1023	12	997	1.030	0.760, 1.380
Moderate vs. Normal	C _{max} (ng/mL)	8	120	12	113	1.060	0.892, 1.270
	AUC(0-T) (h•ng/mL)	8	1363	12	972	1.400	1.040, 1.900
	AUC(INF) (h•ng/mL)	8	1389	12	997	1.390	1.030, 1.880
Severe vs. Normal	C _{max} (ng/mL)	8	113	12	113	0.995	0.836, 1.190
	AUC(0-T) (h•ng/mL)	8	1253	12	972	1.290	0.954, 1.740
	AUC(INF) (h•ng/mL)	8	1273	12	997	1.280	0.946, 1.720
ESRDH vs. Normal	C _{max} (ng/mL)	8	113	12	113	0.995	0.836, 1.180
	AUC(0-T) (h•ng/mL)	8	1310	12	972	1.350	0.998, 1.820
	AUC(INF) (h•ng/mL)	8	1333	12	997	1.340	0.991, 1.800

Source: Table 7, CRS for IM011061

ANOVA = analysis of variance; CI = confidence interval; ESRDH = end-stage renal disease requiring hemodialysis; LS= least square

Note: The C_{max} and AUC analyses were performed on ln-transformed parameters using an ANOVA model.

Note: The ANOVA includes the records from the renal function groups Normal, Mild, Moderate, Severe, and ESRDH in the period when a dose of BMS-986165 is administered after end of dialysis.

Table 21. Effect of Renal Impairment on PK of BMT-153261

Comparison (Test/Reference)	PK Parameter BMT-153261	Test n	Test Geo LS Mean	Reference n	Reference Geo LS Mean	Geo LS Mean Ratio (Test/Reference)	
						Estimate	90% CI
Mild vs. Normal	C _{max} (ng/mL)	8	8.02	12	9.01	0.89	0.629, 1.260
	AUC(0-T) (h•ng/mL)	8	210	12	211	0.993	0.696, 1.420
	AUC(INF) (h•ng/mL)	8	231	12	236	0.982	0.703, 1.370
Moderate vs. Normal	C _{max} (ng/mL)	8	8.31	12	9.01	0.923	0.652, 1.310
	AUC(0-T) (h•ng/mL)	8	269	12	211	1.27	0.893, 1.820
	AUC(INF) (h•ng/mL)	8	293	12	236	1.24	0.891, 1.740

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Comparison (Test/Reference)	PK Parameter BMT-153261	n	Test Geo LS Mean	Reference n	Reference Geo LS Mean	Geo LS Mean Ratio (Test/Reference)	
						Estimate	90% CI
Severe vs. Normal	C_{max} (ng/mL)	8	11.6	12	9.01	1.28	0.906, 1.820
	AUC(O-T) (h•ng/mL)	8	396	12	211	1.87	1.310, 2.670
	AUC(INF) (h•ng/mL)	8	426	12	236	1.81	1.290, 2.520
ESRDH vs. Normal	C_{max} (ng/mL)	8	9.78	12	9.01	1.09	0.767, 1.540
	AUC(O-T) (h•ng/mL)	8	275	12	211	1.3	0.913, 1.860
	AUC(INF) (h•ng/mL)	8	300	12	236	1.27	0.911, 1.780

Source: Table 9, CRS for IM011061.

ANOVA = analysis of variance; CI = confidence interval; ESRDH = end-stage renal disease requiring hemodialysis; LS= least square

Note: The C_{max} and AUC analyses were performed on ln-transformed parameters using an ANOVA model.

Note: The ANOVA includes the records from the renal function groups Normal, Mild, Moderate, Severe, and ESRDH in the period when a dose of BMS-986165 is administered after end of dialysis.

Table 22. Summary of Deucravacitinib Extraction Through Dialysis in ESRDH Group

PK (unit)	Statistics	BMS- 986165
CLD(mL/h)	n	8
	Mean	2345
	SD	322
	%CV	13.7
	Median	2297
	Min, Max	1864, 2857
	Geometric Mean	2325
DRt(mg)	n	8
	Mean	0.697
	SD	0.288
	%CV	41.4
	Median	0.617
	Min, Max	0.369, 1.21
%DRt	n	8
	Mean	5.83
	SD	2.44
	%CV	41.9
	Median	5.15
	Min, Max	3.10, 10.2
	Geometric Mean	5.40

Source: Table 9.2.3-1, CRS for IM011061.

Abbreviations: CLD = dialysate clearance; DRt = cumulative amount of deucravacitinib excreted unchanged into dialysate; %DRt = DRt in the percentage of administered dose.

There were no clinically meaningful differences in the PK of deucravacitinib and BMT-153261 across varying degrees of renal impairment (mild, moderate, severe, and ESRD). The maximal changes on the PK of deucravacitinib were 13.8% decrease in C_{max} and 39% increase in AUC_{inf} . The maximal changes on the PK of BMT-153261 were 28% increase in C_{max} and 81% increase in AUC_{inf} . In ESRDH subjects, 5.4% of the administered dose of deucravacitinib was excreted unchanged into dialysate, indicating the minimal extraction of deucravacitinib through dialysis. Based on the results from this study, in addition to the PPK analyses which included renal function as a covariate, no dose adjustment is recommended in mild, moderate, severe renal impairment, or in subjects with ESRD requiring hemodialysis.

Hepatic Impairment Study, IM011062

A dedicated, open-label, single-dose (12 mg), hepatic impairment study was conducted to evaluate the effect of mild, moderate, and severe hepatic impairment on PK of deucravacitinib and BMT-153261. A total of 32 subjects completed the study; eight (8) subjects each in Child Pugh class A (mild), B (moderate) and C (severe) and normal hepatic function. The summaries of the effect of hepatic impairment on exposures of deucravacitinib and BMT-153261 are shown in [Table 23](#) and [Table 24](#), respectively.

Table 23. Effect of Hepatic Impairment on PK of Deucravacitinib

Hepatic Impairment	Geometric LS Mean Ratio (90% CI)	
	C_{max}	AUC_{inf}
Mild HI (n=8)/ Normal (n=8)	1.04 (0.797, 1.36)	1.1 (0.854, 1.42)
Moderate HI (n=8)/ Normal (n=8)	1.1 (0.846, 1.44)	1.4 (1.09, 1.81)
Severe HI (n=8)/ Normal (n=8)	1.01 (0.771, 1.31)	1.43 (1.11, 1.85)

Data extracted from: Table 9.2.1.3-1, CRS for IM011062.

Table 24. Effect of Hepatic Impairment on PK of BMT-153261

Hepatic Impairment	Geometric LS Mean Ratio (90% CI)	
	C_{max}	AUC_{inf}
Mild HI (n=8)/ Normal (n=8)	0.755 (0.442, 1.29)	0.972 (0.679, 1.39)
Moderate HI (n=8)/ Normal (n=8)	0.407 (0.238, 0.696)	0.803 (0.561, 1.15)
Severe HI (n=8)/ Normal (n=8)	0.213 (0.119, 0.38)	0.499 (0.247, 1.01)

Data extracted from: Table 9.3.1.3-1, CRS for IM011062.

The varying degrees of hepatic functions did not have significant effect on C_{max} of deucravacitinib. The AUC_{inf} of deucravacitinib increased by 40% and 43% in subjects with moderate and severe hepatic impairment, respectively, compared to those with normal hepatic function. The C_{max} of BMT-153261 were decreased by 25%, 59%, and 79% in subjects with mild, moderate and severe hepatic impairment, respectively, compared to those with normal hepatic function. The AUC_{inf} of BMT-153261 were decreased by 3%, 20%, and 50% in subjects with mild, moderate and severe hepatic impairment, respectively, compared to those with normal hepatic function. While the effect of hepatic impairment, especially the severe hepatic impairment, on the PK of BMT-153261 is significant, BMT-153261 accounts for only approximately 20% of circulating drug-related components in plasma at steady-state ([Table 15](#)). In addition, since deucravacitinib is the major circulating species in plasma, the potential effect of reduced efficacy due to the decreased exposure of BMT-153261 in hepatic impairment could be offset by the modest increase in exposure of deucravacitinib in hepatic impairment. Based on the results of this study, no dose adjustment in mild and moderate hepatic impairment is

recommended; however, deucravacitinib is not recommended in severe hepatic impairment due to safety concerns with liver enzyme elevations as stated above.

Are There Clinically Relevant Food-drug or Drug-drug Interactions, and What is the Appropriate Management Strategy?

No. Deucravacitinib is recommended to be taken without regards to meal, as the effect of high-fat/high-calorie meal on the PK of deucravacitinib was not clinically significant. See the summary of study results below. In addition, a series of clinical drug-drug interaction studies indicated no clinically significant interactions with the studied drugs as described below.

Effect of Food on Deucravacitinib

The effect of high-fat/high-calorie meal on the PK of deucravacitinib as a commercial-image 6 mg tablet in healthy subjects was evaluated in Study IM011119. The effect of food on PK parameters of deucravacitinib and BMT-153261 is shown in [Table 25](#) and [Table 26](#), respectively.

Table 25. The Effect of Food on PK Parameters of Deucravacitinib

Deucravacitinib Parameter	Fed (Test)		Fasted (Ref)		Geo LS Mean Ratio (Test/Ref)	
	n	Result	n	Result	Estimate	90% CI
C_{max} (ng/mL)	18	27.5	18	36.2	0.761	(0.694, 0.833)
AUC(0-T) (h*ng/mL)	18	316.5	18	354.8	0.892	(0.848, 0.938)
AUC(INF) (h*ng/mL)	18	329.1	18	368.7	0.893	(0.851, 0.936)

Source: Table S6, CRS for IM011119.

Abbreviations: CI = confidence interval; LS = least-squares; Ref = reference.

Table 26. The Effect of Food on PK Parameters of BMT-153261

BMT-153261 Parameter	Fed (Test)		Fasted (Ref)		Geo LS Mean Ratio (Test/Ref)	
	n	Result	n	Result	Estimate	90% CI
C_{max} (ng/mL)	18	3.8	18	4.9	0.769	(0.705, 0.838)
AUC(0-T) (h*ng/mL)	18	84.6	18	99.0	0.855	(0.798, 0.915)
AUC(INF) (h*ng/mL)	17	100.4	16	111.7	0.898	(0.850, 0.950)

Source: Table S9, CRS for IM011119.

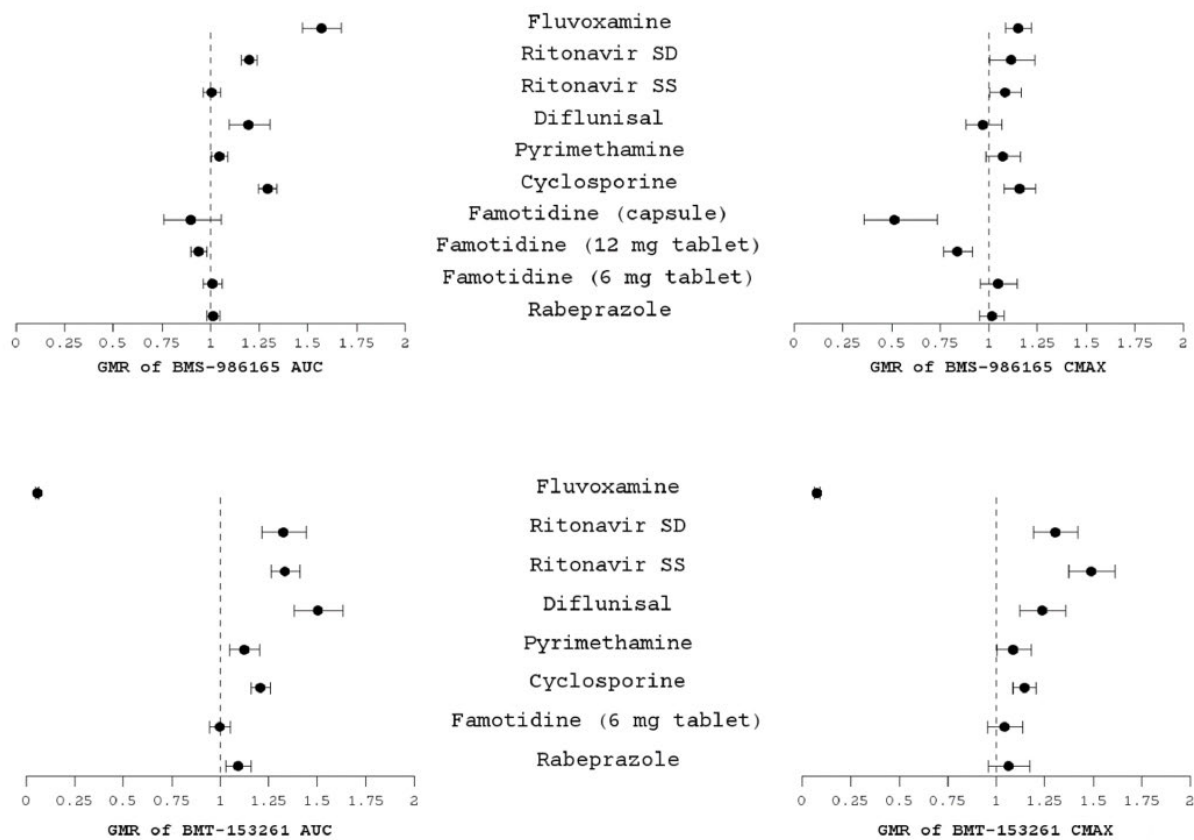
Abbreviations: CI = confidence interval; LS = least-squares; Ref = reference.

A modest decrease in systemic exposures of deucravacitinib and BMT-153261 were observed when deucravacitinib was taken under fed conditions with a high-fat/high-calorie meal, compared to when taken under fasted conditions. C_{max} was decreased by 24% and 23% for deucravacitinib and BMT-153261, respectively. AUC_{inf} was decreased by 11% and 10% for deucravacitinib and BMT-153261, respectively. The magnitudes of these reductions are not considered clinically meaningful and thus the study results support the dosing instruction for deucravacitinib to be taken without regards to meal.

Effect of Other Drugs on Deucravacitinib

The effect of coadministered drugs on deucravacitinib and BMT-153261 is summarized in [Figure 6](#) and described below.

Figure 6. Effect of Coadministered Drugs on Deucravacitinib and BMT-153261



Source: Figure 3.5.2.2-1, Module 2.7.2.
Abbreviations: BMS-986165 = deucravacitinib

- Fluvoxamine (a strong inhibitor of CYP1A2 and CYP2C19, a moderate inhibitor of CYP3A): Concomitant administration of deucravacitinib (a single 12 mg dose on Days 1 and 8) with fluvoxamine (100 mg QD on Days 5 through 10) to healthy subjects resulted in 15% increase in C_{max} and 57% increase in AUC of deucravacitinib. The concomitant administration resulted in 93% decrease in C_{max} and 94% decrease in AUC of BMT-153261. No dose adjustment is recommended.
- Ritonavir (a weak inducer of CYP1A2^a, CYP2B6, CYP2C9 and CYP2C19, an inhibitor of P-gp and OATP1B1): Concomitant administration of deucravacitinib (a single 12 mg dose on Days 1, 5 and 15) and ritonavir (100 mg QD on Days 5 through 17) to healthy subjects resulted in no significant changes in C_{max} and AUC of deucravacitinib (8% and <1% increase,

respectively). The concomitant administration resulted in 49% increase in C_{max} and 33% increase in AUC of BMT-153261. No dose adjustment is recommended.

- The Applicant conducted a clinical drug interaction study with ritonavir to investigate the effects of CYP1A2 induction by ritonavir on the PK of deucravacitinib. Currently, the Agency recommends 800 mg dose of ritonavir to be used when utilizing ritonavir as a moderate CYP1A2 inducer and states that “the effect on CYP1A2 at lower doses of ritonavir is unknown” (FDA 2022). The 100 mg dose of ritonavir that the Applicant used in the study is in line with the Agency’s recommendation when ritonavir is used as a weak inducer of CYP2B6, CYP2C9 and CYP2C19.
- Based on the metabolism and excretion data and the biotransformation pathways of deucravacitinib, contribution of CYP1A2 for elimination of deucravacitinib is estimated between 18.5-24.5% (see [Table 11](#)). Per the FDA Guidance for Industry – In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Medicated Drug Interactions, when an enzyme is responsible for $\geq 25\%$ of the drug’s elimination, the contribution is considered significant and recommends conducting clinical drug interaction studies (January 2020). In addition, smoking which is a moderate CYP1A2 inducer, was not identified as a significant covariate on deucravacitinib PK parameters and deucravacitinib and BMT-153261 exposures were comparable ($\leq 20\%$) between heavy smokers and nonsmokers/past smokers (Section [19.4.1.3](#)). Based on the totality of evidence, CYP1A2 inducers are not likely to have clinically meaningful effect on PK of deucravacitinib.
- Diflunisal (an inhibitor of UGT1A9): Concomitant administration of deucravacitinib (a single 6 mg dose on Days 1 and 10) and diflunisal (500 mg BID on Days 5 through 13) to healthy subjects resulted in 3% decrease in C_{max} and 19% increase in AUC of deucravacitinib. The concomitant administration resulted in 24% increase in C_{max} and 50% increase in AUC of BMT-153261. No dose adjustment is recommended.
- Pyrimethamine (an inhibitor of OCT1, OCT2, MATE1, MATE2-K): Concomitant administration of deucravacitinib (a single 6 mg dose on Days 1 and 5) and pyrimethamine (50 mg on Day 5) to healthy subjects resulted in no significant changes in C_{max} and AUC of deucravacitinib (7% and 5% increase, respectively) and BMT-153261 (9% and 12% increase, respectively). No dose adjustment is recommended.
- Cyclosporine (an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OCT1): Concomitant administration of a single dose cyclosporine (500 mg on Day 6) with deucravacitinib (6 mg QD on Days 1 through 6) at steady-state to healthy subjects resulted in 16% increase in C_{max} and 29% increase in AUC of deucravacitinib. The concomitant administration resulted in 15% increase in C_{max} and 21% decrease in AUC of BMT-153261. No dose adjustment is recommended.
- Famotidine (gastric pH modulator; H2 receptor antagonist): Pretreatment with famotidine (a single dose of 40 mg, administered 2 hours before administration of a single dose of 6 mg deucravacitinib) to healthy subjects under fasting conditions resulted in no significant changes in C_{max} and AUC of deucravacitinib (5% and 1% increase, respectively) and BMT-

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

153261 (4% increase and <1% decrease, respectively). No dose adjustment is recommended.

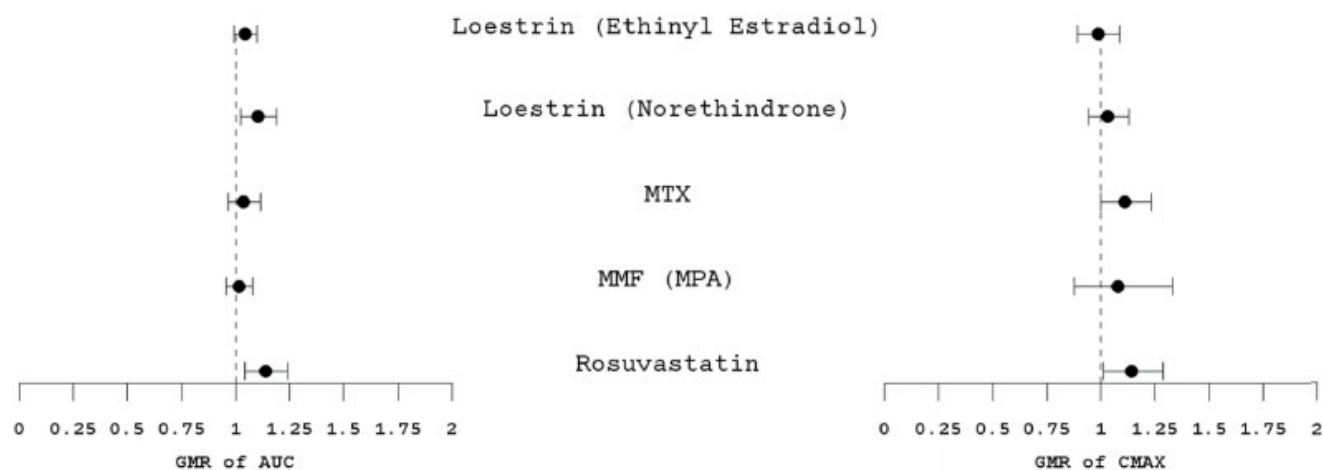
- Rabeprazole (gastric pH modulator; proton pump inhibitor): Concomitant administration of deucravacitinib (a single 12 mg dose on Days 1 and 9) with rabeprazole (20 mg QD on Days 5 through 11) to healthy subjects resulted in no significant changes in C_{max} and AUC of deucravacitinib (1% increase in both parameters) and BMT-153261 (6% and 9% increase, respectively). No dose adjustment is recommended.

In the drug interaction studies summarized above in which deucravacitinib was evaluated as a substrate, the most pronounced changes in the exposures of deucravacitinib and BMT-153261 were observed when deucravacitinib was coadministered with fluvoxamine, a strong CYP1A2 inhibitor. Such result was anticipated as BMT-153261 is formed via CYP1A2. While the decrease in BMT-153261 exposure was significant (up to 94%), the exposures of total circulating active species (calculated as sum of molar concentrations of deucravacitinib and BMT-153261, without adjustment for potency as these two have comparable potency) were not significantly affected (6% increase in C_{max} and 22% increase in AUC_{inf}). Since BMT-153261 accounts for only about 20% of circulating drug-related components in plasma at steady-state (Table 14), the observed changes in BMT-153261 exposures when coadministered with fluvoxamine, as well as changes of less magnitude observed in other drug interaction studies are not considered clinically meaningful. In addition, exposure-analysis (Section [19.4.2](#)) indicated that a 100% higher exposure and a 50% lower exposure in deucravacitinib are expected to result in only a modest increase in infection/infestations (~3%) and a modest decrease in efficacy response (~9% in PASI75), respectively. Therefore, no adjustment is recommended when deucravacitinib is coadministered with the drugs studied above.

Effect of Deucravacitinib on Other Drugs

The effect of deucravacitinib on the PK of coadministered drugs is summarized in [Figure 7](#) and described below. Overall, deucravacitinib did not result in clinically meaningful changes in PK of the coadministered drugs.

Figure 7. Effect of Deucravacitinib on the PK of Coadministered Drugs



Source: Figure 3.5.2.3-1, Module 2.7.2

Abbreviations: MMF=Mycophenolate mofetil, MPA=Mycophenolic acid, MTX=Methotrexate

- Loestrin 1.5/30 (1.5 mg norethindrone [NET]/ 30 µg ethinyl estradiol [EE]): Concomitant administration of deucravacitinib (12 mg BID) with Loestrin as oral contraceptive did not result in significant changes in exposures of NET and EE. The C_{max} and AUC of NET increased by 3% and 10%, respectively. The C_{max} of EE decreased by 1% and AUC of EE increased by 4%. No dose adjustment is recommended.
- Methotrexate (MTX; potential concomitant medication for the treatment of autoimmune disorders; a substrate of BCRP, OAT1 and OAT3): Concomitant administration of deucravacitinib (12 mg QD on Days 8 through 14) with MTX (7.5 mg on Days 1 and 12) did not result in significant changes in exposures of MTX. The C_{max} and AUC of MTX increased by 11% and 4%, respectively.
- Mycophenolate mofetil (MMF; potential concomitant medication for the treatment of autoimmune disorders; a substrate of CES1 and CES2): Concomitant administration of deucravacitinib (12 mg QD on Days 1 through 9) with MMF (1000 mg on Days 6 and 14) did not result in significant changes in exposures of mycophenolic acid (MPA), the predominant circulating active metabolite of the prodrug MMF. The C_{max} and AUC of MPA increased by 8% and 2%, respectively. No dose adjustment is recommended.
- Rosuvastatin (a substrate of BCRP, OATP1B1, OATP1B3 and OAT3): Multiple dose administration of deucravacitinib (12 mg QD on Days 5 through 12) did not result in significant changes in exposures of rosuvastatin (10 mg on Days 1 and 9) relative to those when rosuvastatin was administered alone. The concomitant administration resulted in 14% increases in C_{max} and AUC of rosuvastatin. No dose adjustment is recommended.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

In support of their NDA, the Applicant submitted the following 5 trials in addition to 19 clinical pharmacology studies:

- Two Phase 3 controlled trials in subjects with psoriasis:
 - IM011046
 - IM011046
- One ongoing, open-label, long-term safety trial in subjects with psoriasis:
 - IM011075
- Two Phase 2 placebo-controlled trials:
 - IM011011 in subjects with psoriasis
 - IM011084 in subjects with psoriatic arthritis

The table below provides a summary of the aforementioned trials submitted for deucravacitinib to treat moderate to severe psoriasis in adults who are candidates for systemic therapy or phototherapy, as well as a separate listing of clinical pharmacology studies.

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Table 27. Listing of Clinical Trials Relevant to this BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
IM011046	NCT03624127	Phase 3, randomized, PBO and active comparator controlled, DB	<u>DEUC</u> : 6 mg PO QD <u>APREM</u> : 30 mg BID PO (with initial titration per label) <u>PBO</u> : PO QD	<u>Co-primary efficacy</u> proportion of subjects who achieved PASI 75 response at Week 16 and the proportion of subjects with a PGA score of 0 ("cleared") or 1 ("minimal") at Week 16	Screening (up to 4 weeks), treatment (52 weeks), and a follow-up (4 weeks)	665	Subjects with moderate-to-severe plaque Ps; candidates for systemic or phototherapy; males and females ≥ 18 years of age; PASI ≥ 12, sPGA ≥ 3, BSA involvement ≥ 10%	154 sites US, China, Japan, EU (Germany, Poland, Spain, UK), and ROW (Canada, Russia, South Korea)
IM011047 -	NCT03611751	Phase 3, randomized, PBO and active comparator controlled, DB	<u>DEUC</u> : 6 mg PO QD <u>APREM</u> : 30 mg BID PO (with initial titration per label) <u>PBO</u> : PO QD	<u>Co-primary efficacy</u> proportion of subjects who achieved PASI 75 response at Week 16 and the proportion of subjects with a PGA score of 0 ("cleared") or 1 ("minimal") at Week 16	Screening (up to 4 weeks), treatment (24 weeks), randomized withdrawal and maintenance (28 weeks) and follow-up (4 weeks)	1018	Subjects with moderate-to-severe plaque Ps; candidates for systemic or phototherapy; males and females ≥ 18 years of age; PASI ≥ 12, sPGA ≥ 3, BSA involvement ≥ 10%	191 sites US, EU (Czech Republic, Finland, France, Germany, Hungary, Italy, Poland, Spain, Sweden, and UK) and ROW (Australia, Canada, Israel, New Zealand, and Puerto Rico) Completed

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
Studies to Support Safety								
IM011075	NCT04036435	Open-label, single-arm	<u>DEUC</u> : 6 mg PO QD	Long-term safety and efficacy	Up to 244 weeks	1452	Subjects with moderate-to-severe plaque Ps; candidates for systemic or phototherapy; males and females ≥ 18 years of age; PASI ≥ 12 , sPGA ≥ 3 , BSA involvement $\geq 10\%$	264 sites US, EU, and ROW
IM011011	NCT02931838	Randomized double-blind, placebo-controlled dose-ranging	<u>DEUC</u> : 3 mg QOD 3 mg QD 3 mg BID 6 mg BID 12 mg QD <u>PBO</u> : QOD, QD, or BID PO	Proportion of subjects who achieved PASI 75 response at Week 12	Treatment (12 weeks); Follow-up (4 weeks)	267	Subjects with moderate-to-severe plaque Ps; candidates for systemic or phototherapy; males and females ≥ 18 years of age; PASI ≥ 12 , sPGA ≥ 3 , BSA involvement $\geq 10\%$	67 sites in EU, North America (Canada and US), Australia, Mexico, and Japan

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
IM011084	NCT03881059	Randomized, Placebo-Controlled, Double-blind	<u>DEUC</u> 6 mg PO QD <u>DEUC</u> 12 PO mg QD <u>PBO</u> PO QD	ACR 20 response	Treatment (52 weeks); Follow-up (4 weeks)	314	Males and females diagnosed with PsA for at least 6 months before screening who met the Classification Criteria for Psoriatic Arthritis (CASPAR) at screening	67 sites in 7 countries (Czech Republic, Germany, Hungary, Poland, Russia, Spain, and the United States)

Abbreviations: BID = twice daily; BSA = body surface area; DEUC = deucravacitinib; EU = European Union; PO = by mouth; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; QD = once daily; QOD = every other day; ROW = rest of world; sPGA = Static Physicians Global Assessment; UK = United Kingdom; US = United States.

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Table 28. Clinical Pharmacology Studies Pertinent to the Review of Efficacy or Safety

Study Description	Study Number
Safety/Pharmacokinetics/Pharmacodynamics	
Single ascending doses in healthy subjects of any ethnic background (1 - 40 mg QD) Multiple ascending doses in healthy non-Japanese subjects (2 - 12 mg BID and 12 mg QD for 14 days) Multiple ascending doses in healthy Japanese subjects (2 - 12 mg BID and 12 mg QD for 14 days)	IM011002
Pharmacokinetics and metabolism of [¹⁴ C]-ADME (24 mg QD/100 µCi)	IM011016
Randomized, double-blind, positive-controlled, placebo-controlled, 4-period crossover study to investigate the electrocardiographic effects of DEUC (12 or 36 mg + 400 mg moxifloxacin + placebo)	IM011048
Special Populations	
Open-label, single-dose study for the evaluation of PK and safety of DEUC (12 mg) in subjects with varying degrees of renal impairment, and in subjects with end-stage renal disease on hemodialysis	IM011061
Open-label, single-dose study for the evaluation of PK and safety of DEUC (12 mg) in subjects with varying degrees of hepatic impairment	IM011062
Drug-Drug Interactions (deucravacitinib as a perpetrator)	
Open-label, single-sequence, drug-drug interaction study to assess the effect of coadministration of multiple doses of DEUC (12 mg) on the systemic exposure of rosuvastatin (10 mg)	IM011015
Open-label, single-sequence study to evaluate the effects of DEUC (12 mg) on the PK and safety and tolerability of methotrexate (7.5 mg)	IM011025
2-cycle, multiple-dose, single-sequence, crossover study designed to assess drug-drug interactions between DEUC (12 mg BID) and the oral contraceptive Loestrin (1.5 mg NET/30 µg EE)	IM011039
Open-label, single-sequence study to investigate the effects of multiple doses of DEUC, at 12 mg QD (steady state exposure) on the PK of single dose mycophenolate mofetil (500 mg)	IM011071
Drug-Drug Interactions (deucravacitinib as a victim)	
Open-label, single-sequence study to investigate the effects of cyclosporine (500 mg) on the PK of DEUC (6 mg) at steady state	IM011045
Open-label, single-sequence study to investigate the effects of cytochrome P450 1A2 induction by ritonavir (100 mg) on the PK of DEUC (12 mg)	IM011087

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Open-label, single-sequence study to investigate the effects of cytochrome P450 1A2 (100 mg) inhibition by fluvoxamine on the PK of DEUC (12 mg)	IM011088
Open-label, 2-treatment period, 1-sequence, crossover study in healthy male subjects designed to determine the effect of OCT1 inhibition by pyrimethamine (50 mg) on the PK of DEUC (6 mg)	IM011100
Open-label, single-sequence, crossover study to investigate the effects of UGT1A9 inhibitor diflunisal (500 mg), at steady state, on pharmacokinetics of a single dose of DEUC (6 mg)	IM011101
Biopharmaceutics	
Relative bioavailability (solution vs capsule), pH effect (famotidine) and food effect (high fat meal vs. fasted) in healthy subjects (12 mg)	IM011002
Open-label, single-dose, 6-period, 6-treatment crossover, bioavailability study in healthy subjects to investigate the systemic exposure of the DEUC (12 mg) tablet formulation as compared to the DEUC (12 mg) capsule formulation, the DEUC (3 mg) tablet formulation as compared to the DEUC (3 mg) capsule formulation, and the effects of a high fat/high calorie meal and increased gastric pH via famotidine (40 mg) pretreatment on the bioavailability of DEUC in the (12 mg) tablet.	IM011031
Open-label, non-randomized, single-period study to evaluate the absolute oral bioavailability of DEUC tablet in healthy male subjects (intravenous: 100 µg/oral: 12 mg)	IM011067
Open-label, single-sequence study to investigate the effects of gastric acid suppression by rabeprazole (20 mg) on the PK of DEUC (12 mg) in healthy males and females	IM011090
Relative bioavailability of the commercial image tablet (6 mg) to assess the pH effect (famotidine) and food effect (high-fat/high-calorie vs. fasted) in healthy subjects	IM011119

7.2. Review Strategy

The sources of data used for the evaluation of the efficacy and safety of deucravacitinib for the proposed indication included final trial reports submitted by the Applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)]. This application was submitted in electronic common technical document format and entirely electronic. The electronic submission included protocols, statistical analysis plans (SAPs), clinical trial reports, SAS transport datasets in Study Data Tabulation Model (SDTM), and Analysis Data Model (ADaM) format. The datasets were in the following network path:

Original submission: [\\CDSESUB1\evsprod\NDA214958\0001](#)

The Applicant submitted the required certification and disclosure information for participating investigators (Form 3454). Refer to Section [19.2](#). Financial Disclosure of this review for additional information.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial Design

The Applicant conducted two pivotal Phase 3 trials, IM011046 and IM011047, to evaluate the efficacy and safety of deucravacitinib (BMS-986165) tablets in adult subjects with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Both trials were 52-week, multicenter, randomized, double-blind, placebo- and active comparator-controlled trials with apremilast as the comparator. Trial IM011047 additionally had a randomized-withdrawal and maintenance period. It is noted that apremilast, an inhibitor of phosphodiesterase 4, was approved on September 23, 2014 (NDA 206088) for the treatment of patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Approximately 600 subjects in Trial IM011046 and 1000 subjects in Trial IM011047 from global sites were planned to be randomized in a 2:1:1 ratio to the following treatment arms:

- Deucravacitinib 6 mg once daily (OD)
- Placebo
- Apremilast 30 mg twice daily (BID) with initial titration per labeling:
 - Day 1: 10 mg tablet in the morning
 - Day 2: 10 mg tablet in the morning and evening
 - Day 3: 10 mg tablet in the morning and 20 mg tablet in the evening
 - Day 4: 20 mg tablet in the morning and the evening
 - Day 5: 20 mg tablet in the morning and 30 mg tablet in the evening
 - Day 6 and thereafter: 30 mg tablet in the morning and the evening

The protocols specified stratifying randomization by geographic region, previous biologic use (psoriasis, psoriatic arthritis, or other inflammatory disease only; yes/no), and body weight (≥ 90 kg and < 90 kg; body weight stratum not applied in Japan or China). The stratification by region differed between the two trials as follows:

- Trial IM011046: US, Japan, China (body weight stratum is not applied in China and Japan), and Rest of World. Note that there are no Chinese subjects in the apremilast group due to lack of market approval of the agent in China.
- Trial IM011047: US, Rest of World

The following were the key inclusion criteria for the two pivotal trials:

- Male or female ≥ 18 years old
- Diagnosed with a stable plaque psoriasis ≥ 6 months

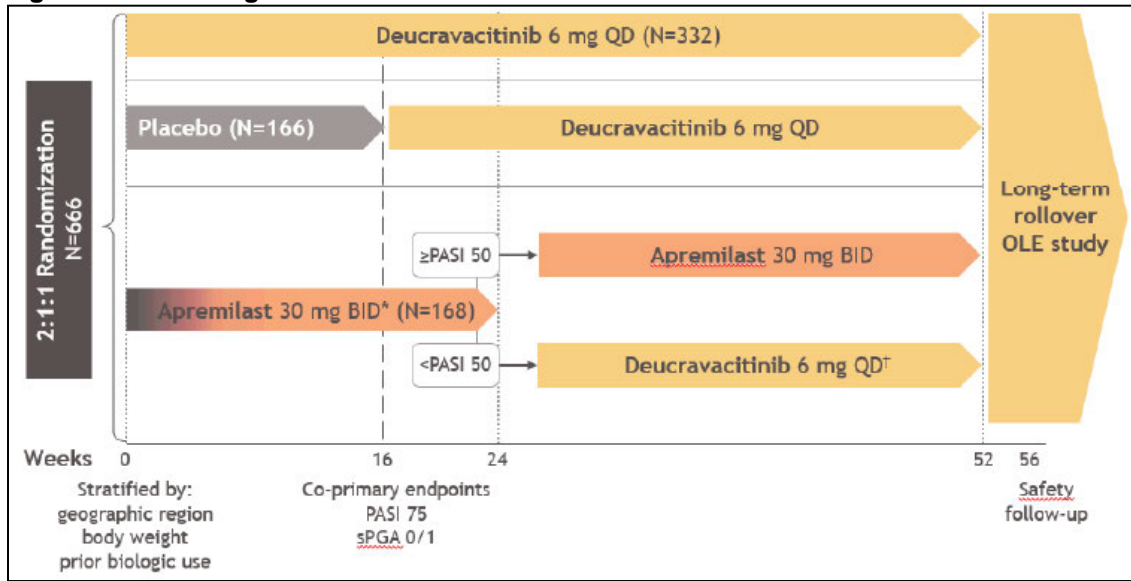
- Deemed by the Investigator to be eligible for phototherapy or systemic therapy
- Body surface area (BSA) involvement $\geq 10\%$ of at screening and baseline
- Psoriasis Area and Severity Index (PASI) score ≥ 12 at screening and baseline; see Section [8.1.2](#) for details on the PASI scale
- Static Physician's Global Assessment (sPGA) score ≥ 3 at screening and baseline; see Section [8.1.2](#) for details on the sPGA scale

•
Trial design schematics for Trials IM011046 and IM011047 are provided in [Figure 8](#) and [Figure 9](#), respectively. Trial IM011046 consisted of a screening period (up to 4 weeks), a treatment period (52 weeks), and a follow-up period (4 weeks). Trial IM011047 consisted of a screening period (up to 4 weeks), a treatment period (24 weeks), a randomized withdrawal and maintenance period (28 weeks) and a follow-up period (4 weeks). Subjects in both trials had visits at screening, baseline, Weeks 1, 2, 4, and every 4 weeks thereafter until Week 52. The subjects also had a safety follow-up visit at Week 56.

At Week 16, subjects randomized to placebo in both trials were switched in a blinded manner to deucravacitinib. All other subjects remained in the treatment group as initially randomized in a blinded fashion until Week 24, at which point the trial designs differed as follows:

- Trial IM011046: At Week 24, subjects originally randomized to apremilast who achieved PASI 50 response continued to receive apremilast, in a blinded manner, through Week 52 while subjects who did not achieve PASI 50 response were switched, in a blinded manner, to deucravacitinib through Week 52. Subjects originally randomized to deucravacitinib or placebo subjects re-randomized to deucravacitinib at Week 16, continued deucravacitinib to Week 52.
- Trial IM011047: At Week 24 (Randomized Withdrawal Treatment Period), subjects originally randomized to deucravacitinib who achieved PASI 75 response were re-randomized 1:1, in a blinded manner, to placebo or deucravacitinib, in order to evaluate maintenance and durability of response. If subjects re-randomized to placebo experienced a relapse (defined as at least a 50% loss of Week 24 PASI percent improvement from baseline) they switched in a blinded manner, to deucravacitinib until the end of the maintenance period (Week 52). Subjects originally randomized to deucravacitinib who did not achieve PASI 75 response continued to receive deucravacitinib, until the end of the maintenance period (Week 52). Subjects originally randomized to apremilast who achieved PASI 75 response were switched, in a blinded manner, to placebo and those who did not achieve PASI 75 response were switched in a blinded manner to deucravacitinib through Week 52. If subjects re-randomized to placebo experienced a relapse (defined as at least a 50% loss of Week 24 PASI percent improvement from baseline) they were switched, in a blinded manner, to deucravacitinib until the end of the maintenance period (Week 52). Subjects originally randomized to placebo and switched to deucravacitinib at Week 16, continued on deucravacitinib to Week 52.

Figure 8. Trial Design Schematic for Trial IM011046



Source: Clinical Study Report (CSR) for Trial IM011046; page 30.

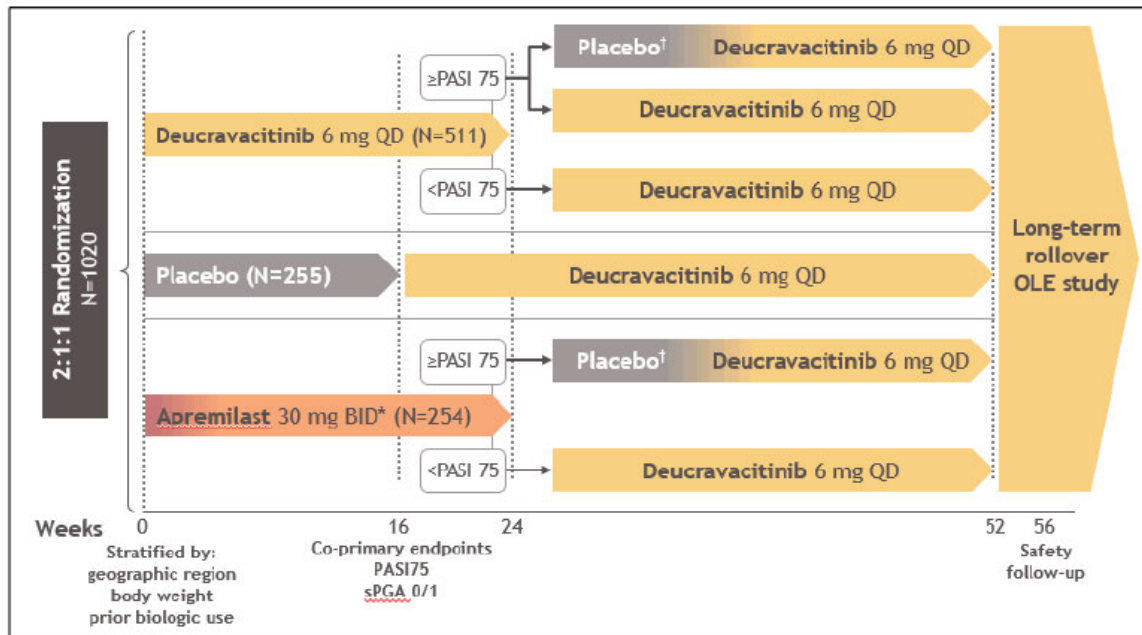
*Apremilast is titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.

† Subjects in the apremilast arm who did not achieve 50% improvement in the PASI score at Week 24 were switched in a blinded fashion to deucravacitinib

The co-primary endpoints are evaluated at Week 16.

Abbreviations: BID = twice daily; OLE = open label extension; PASI = Psoriasis Area and Severity Index; QD = once daily

Figure 9. Trial Design Schematic for Trial IM011047



Source: Clinical Study Report (CSR) for Trial IM011047; page 38.

*Apremilast is titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.

† Upon relapse (at least a 50% loss of Week 24 PASI percent improvement from baseline), subjects are switched to deucravacitinib 6 mg QD.

Abbreviations: BID = twice daily; OLE = open label extension; PASI = Psoriasis Area and Severity Index; QD = once daily

8.1.2. Objectives and Endpoints

The protocol-specified co-primary efficacy endpoints in all two pivotal trials are:

- sPGA 0/1: The proportion of subjects who achieve sPGA score of 0 (clear) or 1 (minimal) with at least 2 grade improvement from Baseline at Week 16.
- PASI 75: The proportion of subjects who achieve PASI 75 (i.e., at least 75% reduction from baseline in PASI score) at Week 16.

During the end-of-phase (EOP) 2 meeting held on 3/7/2018 and in the advice letters dated 10/29/2018 and 12/6/2019, the Agency noted that they consider sPGA 0/1 with at least 2-grade of improvement as the primary endpoint for establishing efficacy for the indication of plaque psoriasis.

The table below summarizes the key secondary objectives/endpoints for the US submission as specified in the latest version of statistical analysis plans (SAPs).

Table 29. Key Secondary Objectives and Endpoints for Trials 046/047

Objectives	Endpoint
5. Assess whether deucravacitinib is superior to placebo <u>at Week 16</u>	○ sPGA 0/1 (only for comparison to <u>apremilast</u>) ○ PASI 75 (only for comparison to <u>apremilast</u>) ○ PASI 90
6. Assess whether deucravacitinib is superior to apremilast <u>at Week 16</u>	○ PASI 100 (only for comparison to placebo) ○ sPGA 0
	Scalp psoriasis
	○ ss-PGA 0/1 among subjects with baseline ss-PGA ≥ 3
	Nail Psoriasis (only for comparison to <u>placebo</u>)
	○ PGA-F 0/1 among subjects with baseline PGA-F ≥ 3
	Other Patient Reported Outcomes (PROs)
	○ Change from baseline in PSSD symptom score (for comparison to <u>apremilast</u>)
	○ PSSD <u>Symptom</u> domain score of 0 among subjects with a baseline PSSD symptom score ≥ 1
• Assess whether deucravacitinib is superior to apremilast <u>at Week 24</u>	○ PASI 75 at Week 24 ○ PASI 90 at Week 24 ○ sPGA 0/1 at Week 24
• Assess whether deucravacitinib is superior to apremilast <u>at Week 52</u> - Only Trial IM011046	○ PASI 75 at Week 52 and at Week 24 ○ PASI 90 at Week 52 and at Week 24 ○ sPGA 0/1 at Week 52 and at Week 24 Note: Subjects must meet response criteria at both Weeks 24 and 52 in order to be considered a responder.

Source: Excerpts from the Statistical Analysis Plans (SAPs) for Trials IM011046/47

Abbreviations: PASI = Psoriasis Area and Severity Index; PGA-F = Physician's Global Assessment-Fingernails; PSSD = Psoriasis Symptoms and Signs Diary; sPGA = static Physician's Global Assessment; ss-PGA = scalp specific Physician's Global Assessment

The Agency noted several times (EOP2 meeting dated 3/7/2018, advice letters dated 10/29/2018 and 12/6/2019 and Pre-NDA meeting dated 5/12/2021) that establishing superiority

over apremilast based on endpoints and/or time points other than the endpoints used to establish efficacy of apremilast depends on clinical relevance along with control for multiplicity.

The protocols/SAPs also specified many “additional secondary” efficacy endpoints; however, such endpoints were not included in the multiplicity testing procedure (MTP). Therefore, the results of these endpoints are considered exploratory and are not included in this review.

Clinical Outcome Assessment Description(s)

Efficacy was assessed using several clinical outcome assessments (COAs), including the Static Physician’s Global Assessment (sPGA), Psoriasis Area and Severity Index (PASI), Scalp-specific Physician’s Global Assessment (ss-PGA), Physician’s Global Assessment-Fingernails (PGA-F), and the Psoriasis Symptoms and Signs Diary (PSSD). A description of each COA is given below.

Static Physician’s Global Assessment (sPGA)

The sPGA is a single item clinician-reported outcome (ClinRO) instrument designed to assess the overall psoriasis severity (based on lesions). The attributes or components of the lesions rated include erythema, induration, and scaling. Each component is rated using a 5-point verbal rating scale (VRS) ranging from 0 (“Clear”) to 4 (“Severe”). The recall period is current state. A copy of the instrument is provided in Appendix [19.5.1](#).

Each component generates a single score. The scores from each component are summed, averaged, and rounded to the nearest whole number to calculate the total sPGA score ranging from 0 to 4, with higher scores indicating more severe disease.

Psoriasis Area and Severity Index (PASI)

The PASI is a ClinRO instrument designed to assess severity and extent of psoriasis (based on lesions). The attributes or components of the lesions rated include erythema, induration, and scaling. Each component is rated using a 5-point VRS ranging from 0 (“None”) to 4 (“Very severe”). The recall period is current state. A copy of the instrument is provided in Appendix [19.5.1](#).

Each component generates a score that is weighted by the area of involvement (head, arms, trunk to groin, and legs to top of buttocks) and degree of body surface area involvement for each body region (rated from 0 [none] to 6 [90% - 100%]). The PASI generates a total score ranging from 0 to 72, with higher PASI scores indicating more severe disease.

Scalp-Specific Physician’s Global Assessment (ss-PGA)

The ss-PGA is a single item ClinRO instrument designed to assess overall scalp psoriasis severity using a 5-point VRS ranging from 0 (“Absence of disease”) to 4 (“Severe disease”). The recall period is current state. The ss-PGA generates a total score that is based on the clinical signs of erythema, induration, and scaliness. The ss-PGA is performed only in subjects with active scalp involvement at baseline.

Physician’s Global Assessment-Fingernails (PGA-F)

The PGA-F is a ClinRO instrument designed to assess the overall condition of the fingernails. The components rated include the nail bed signs and nail matrix signs. Each component is rated

using a 5-point VRS ranging from 0 (“Clear”) to 4 (“Severe”). The recall period is current state. The PGA-F generates a total score, which is assigned based on the higher of the nail bed/nail matrix score. The PGA-F is performed only in subjects with active psoriatic fingernail involvement at baseline.

Psoriasis Symptoms and Signs Diary (PSSD)

The PSSD is an 11-item PRO instrument designed to assess the severity of symptoms and signs of plaque psoriasis. It consists of two domains: Symptom (itch, pain, stinging, burning, and skin tightness) and Sign (skin dryness, cracking, scaling, shedding or flaking, redness, bleeding). Each item is rated on an 11-point numeric rating scale ranging from 0 (“Absent”) to 10 (“Worst imaginable”). The recall period is the previous 24 hours. A copy of the instrument is provided in Appendix [19.5.1](#).

The PSSD generates domain and total scores. However, the PSSD-based endpoint (adjusted for multiplicity) focused on the Symptom domain score. The PSSD Symptom domain score is derived by averaging the five symptoms items (i.e., itch, pain, stinging, burning, and skin tightness) and multiplying by 10. The PSSD Symptom domain score has a possible range of 0 to 100, where 0 represents the least severe symptom and 100 represents the most severe symptom. To obtain a symptom score on a given day, responses to at least 2 of the 5 questions must be available. If more than 3 questions were missing, the symptom score was considered to be missing.

To calculate the scores at each visit, the daily scores with 24-hour recall periods over the prior 7 days were used and the average score to each of the 11 questions was used as the score at that visit. In case missing data arose during the 7 days prior to the visit, daily scores of at least 4 days out of the 7 days were used. If greater than 3 days of the 7 were missing, the average score was set to missing. The baseline PSSD Symptom domain scores was calculated based on the daily diary data collected during the screening period.

8.1.3. Statistical Methodologies

Analysis Sets

The protocol-specified primary efficacy analysis population was the Full Analysis Set (FAS), defined as all randomized subjects.

The SAPs specified conducting supportive efficacy analyses for the co-primary endpoints using the Per Protocol Set (PPS), defined as a subset of the FAS who are compliant with trial treatment and who do not have any relevant protocol deviations that may impact the co-primary efficacy endpoint assessments. The SAPs specified the following relevant protocol deviations to be considered regarding exclusion of subjects from the PPS:

- Randomized but did not take any trial treatment
- No postbaseline PASI or sPGA
- Baseline BSA involvement < 10%
- Baseline PASI score < 1

- Baseline sPGA < 3
- Did not have non-plaque psoriasis at baseline
- Poor compliance to trial medication within the first 16 weeks of treatment, defined as <75% compliant with trial treatment
- Failure to adhere to prohibited concomitant medication restrictions prior to Week 16

All subjects with relevant protocol deviations were to be identified prior to database lock and unblinding of treatment assignment with the exception of subjects where actual treatment received is different than randomized treatment which is determined after treatment unblinding.

Analysis Methods for Co-Primary Endpoints:

The SAPs specified analyzing the co-primary endpoints (sPGA 0/1 and PASI 75 at Week 16) using the Cochran-Mantel-Haenszel (CMH) test stratified by randomization factors (i.e., geographical region, body weight and prior biologic use) to compare the response rates of deucravacitinib to placebo.

For Trial IM011046, the SAP noted that if there is not at least one subject per treatment group in each of the China and Japan strata, then these regions will be collapsed together to form the stratum of Asia for analyses.

Analysis Methods for Secondary Endpoints:

The SAPs specified analyzing the binary secondary endpoints using the same method as that for the co-primary endpoints (i.e., CMH test stratified by randomization factors). The SAPs specified analyzing the continuous secondary endpoints using the analysis of covariance (ANCOVA), with treatment and stratification factors as fixed effects, and baseline value as a covariate.

Multiplicity Testing Procedure (MTP):

The SAPs specified that each co-primary endpoint is tested at a 2-sided 5% level of significance ($\alpha = 0.05$). Both endpoints need to demonstrate statistical significance to result in a successful trial.

Statistical analysis of the key secondary endpoints is performed only if both coprimary endpoint are significant. In order to control for Type I error rate when testing for the key secondary endpoints, the SAPs specified separate testing branches with a 2-sided $\alpha=0.025$ for comparisons of deucravacitinib compared to placebo and deucravacitinib compared to apremilast as shown in [Table 30](#) for Trial IM011046 and in [Table 31](#) for Trial IM011047 (US submission). A hierarchical testing method within each testing branch will be implemented for the key secondary endpoints. Alpha-controlled testing may only proceed to the next key secondary endpoint within each testing branch if the null hypothesis is rejected at $\alpha=0.025$. If an endpoint fails at any step, then all subsequent comparisons will be considered descriptive. No further multiplicity adjustments will be done for any additional time points or endpoints.

Table 30. Testing Order of Key Secondary Endpoints for Trial IM011046 (U.S. Submission)

Comparisons to Placebo (at Week 16) ($\alpha=0.025$)	Comparisons to Apremilast ($\alpha=0.025$)
P1. PASI 90	A1. sPGA 0/1 with at least a 2-point improvement from baseline at Week 16
P2. ss-PGA 0/1 with at least a 2-point improvement from baseline among subjects with a baseline ss-PGA $\geq$ 3	A2. PASI 75 at Week 16
P3. sPGA 0	A3. PASI 90 at Week 16
P4. PASI 100	A4. sPGA 0/1 with at least a 2-point improvement from baseline at Week 24
P5. PSSD symptom score of 0 among subjects with baseline PSSD symptom score $\geq$ 1	A5. PASI 75 at Week 24
P6. PGA-F 0/1 with at least a 2-point improvement from baseline among subjects with a baseline PGA-F $\geq$ 3	A6. PASI 90 at Week 24
	A7. Change from baseline in PSSD symptom score at Week 16
	A8. ss-PGA 0/1 at Week 16 with at least a 2-point improvement from baseline among subjects with a baseline ss-PGA $\geq$ 3
	A9. sPGA 0/1 with at least a 2-point improvement from baseline at Week 52 and at Week 24
	A10. PASI 75 at Week 52 and at Week 24
	A11. PASI 90 at Week 52 and at Week 24
	A12. sPGA 0 at Week 16
	A13. PSSD symptom score of 0 at Week 16 among subjects with baseline PSSD symptom score $\geq$ 1

Source: SAP for Trial IM011046

Table 31. Testing Order of Key Secondary Endpoints for Trial IM011047 (U.S. Submission)

Comparisons to Placebo (at Week 16) ($\alpha=0.025$)	Comparisons to Apremilast ($\alpha=0.025$)
P1. PASI 90	A1. sPGA 0/1 with at least a 2-point improvement from baseline at Week 16
P2. ss-PGA 0/1 with at least a 2-point improvement from baseline among subjects with a baseline ss-PGA $\geq$ 3	A2. PASI 75 at Week 16
P3. sPGA 0	A3. PASI 90 at Week 16
P4. PASI 100	A4. sPGA 0/1 with at least a 2-point improvement from baseline at Week 24
P5. PSSD symptom score of 0 among subjects with baseline PSSD symptom score $\geq$ 1	A5. PASI 75 at Week 24
P6. PGA-F 0/1 with at least a 2-point improvement from baseline among subjects with a baseline PGA-F $\geq$ 3	A6. PASI 90 at Week 24
	A7. Change from baseline in PSSD symptom score at Week 16
	A8. ss-PGA 0/1 at Week 16 with at least a 2-point improvement from baseline among subjects with a baseline ss-PGA $\geq$ 3
	A9. sPGA 0 at Week 16
	A10. PSSD symptom score of 0 at Week 16 among subjects with baseline PSSD symptom score $\geq$ 1

Source: SAP for Trial IM011047

Abbreviations: PASI = Psoriasis Area and Severity Index; PGA-F = Physician's Global Assessment-Fingernails; PSSD = Psoriasis Symptoms and Signs Diary; sPGA = static Physician's Global Assessment; ss-PGA = scalp specific Physician's Global Assessment

The Agency noted in the advice letter dated 12/6/2019 that change in PSSD Symptom domain score may not be clinically meaningful. During the EOP 2 meeting dated 3/7/2018, the Agency noted that achieving a score of 0 on the PSSD total score, Symptom domain score, and Sign domain score are clinically meaningful endpoints, and requested further information on how the PSSD is scored in the registration trials.

Methods for Handling Missing Data:

The SAPs specified a non-responder imputation (NRI) method for the handling of missing data for the analysis of the co-primary and binary key secondary endpoints. In particular, any subject who discontinues treatment prior to or has missing Week 16 endpoint data for any reason (or Week 24 for certain endpoints) is considered as a non-responder. According to the protocols, subjects who discontinued treatment early were expected to remain in the trial for continued follow-up to Week 52. Therefore, subjects who discontinued treatment could still have efficacy assessments performed at subsequent visits; however, they are considered non-responders for the primary efficacy analyses.

For sensitivity analyses for the handling of missing data when analyzing the co-primary efficacy endpoints, the protocols/SAPs specified the following methods:

- (1) Last observation carried forward (LOCF): Last observation carried forward for subjects with missing values at Week 16. The SAPs added that subjects without a post-baseline are considered non-responders.
- (2) LOCF and NRI: LOCF for placebo subjects and NRI for deucravacitinib subjects. The SAPs added that placebo subjects without a post-baseline values are considered non-responders.
- (3) Multiple imputation (MI): Multiple imputation of missing data for PASI75 response and SPGA 0/1 response is performed by fully conditional specification (FCS) using PROC MI in SAS with the FCS option. The FCS MI specifies the multivariate imputation model on a variable-by-variable basis by a set of conditional densities. For each missing value at Week X, the FCS MI generates values from a conditional distribution for the missing data given the other data prior to Week X. The FCS MI model includes treatment group and stratification factors for randomization. A total of 1000 imputed (complete) datasets are generated for the MI analysis. The same test procedure used for the main analysis (CMH test), is used to analyze the responder endpoint from each imputed dataset. SAS PROC MIANALYZE is used to pool the results from the CMH tests and generate an overall result by Rubin's rules.
- (4) Tipping point analysis: Different number of events between treatment groups are assessed until the trial conclusion is changed. Each imputed value is initially imputed as a responder. The imputed values in the placebo group remains as responders while the deucravacitinib imputed values are replaced as non-responders one at a time, therefore changing the number of events between groups. Once all imputed values in the deucravacitinib group have been replaced with non-responder values, the data reset to where the deucravacitinib group imputed values are all responders and one by one the imputed values in the placebo group are replaced with a non-responder until all placebo

are non-responders and all BMS-986165 are responders. Furthermore, every pair of imputations between the placebo and deucravacitinib groups are assessed similarly, creating a matrix of possible patterns. At each iteration, the statistical analysis is assessed, and the direction of the analysis is recorded.

For continuous secondary efficacy endpoints, the SAPs specified using a modified baseline observation carried forward (mBOCF) method for the handling of missing data. The baseline observation was carried forward for subjects who discontinue treatment due to lack of efficacy and adverse events (AEs). Subjects who discontinue treatment for other reasons had the last valid observation carried forward (including the baseline value as applicable). Subjects with a missing baseline value will be excluded from this analysis.

For the endpoints of sPGA 0/1, PASI-75 and PASI-90 response at both Week 24 and Week 52 (only Trial IM011046), the SAP specified using the non-responder imputation for subjects who:

- Discontinue treatment or trial prior to Week 52.
- Have missing Week 52 or Week 24 endpoint data.
- Switch from apremilast to deucravacitinib at Week 24 for Week 24 PASI 50 non-responders.

Statistical Impacts Due to Coronavirus Disease 2019 (COVID-19)

According to the SAPs, there were no COVID-19-related impacts to the Week 16 efficacy endpoints as all subjects in the trials completed the Week 16 visit prior to COVID-19 site restrictions. However, efficacy endpoints involving Week 24 and later visits could be impacted by COVID-19 in the form of missing data and/or a treatment assignment defaulting to deucravacitinib. Because of the COVID-19 pandemic, and due to the inability of subjects to visit the investigator site, in both trials, investigators were permitted to conduct visits remotely; however, efficacy assessments were not conducted in remote visits.

At Week 24, when COVID-19-related issues resulted in subject visit being missed or conducted remotely, and therefore, missing PASI assessment, the treatment arm assigned was defaulted to deucravacitinib for the duration of the trial. Similarly, for all subsequent visits post Week 24, when COVID-19-related issues resulted in the subject visit being missed or conducted remotely, the treatment arm assignment was done as per the following:

- Missed visits: treatment assigned was the treatment assigned at the previous visit.
- Visits conducted remotely: treatment assigned was defaulted to deucravacitinib for the duration of the trial.

If a subject had missing data or switched to deucravacitinib from a different treatment due to COVID-19, the SAPs specified excluding such subject from the analysis of endpoints assessed at Week 24 through Week 52. To assess the impact of missing efficacy assessments due to COVID-19, the SAPs specified a sensitivity analysis for the PASI 75 and sPGA 0/1 endpoints where missing efficacy assessments due to COVID-19 are imputed using the last observed value.

The SAP for Trial IM011046 specified the following data handling rules for subjects with missing data, or for those subjects who switched to deucravacitinib from a different treatment, due to COVID-19:

- (5) If the subject is missing the Week 52 response value (i.e., sPGA 0/1, PASI 75, PASI 90), then the last observed response value during the Week 24 through Week 52 period is carried forward to the Week 52 value
- (6) If the subject is switched to deucravacitinib from a different treatment due to COVID-19, then the last observed response value prior to the switch will be carried forward to the Week 52 value

8.1.4. Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial IM011046 enrolled and randomized a total of 666 subjects at 154 investigational sites in 11 countries (Canada, China, Germany, Japan, Poland, Russia, South Korea, Spain, Taiwan, United Kingdom, and the United States). A total of 665 subjects were treated. According to the Applicant, one subject in the placebo arm was not treated because he was discontinued from the trial prior to treatment due to incorrect randomization (baseline PASI was < 12 and baseline sPGA score was < 3). However, due to findings of non-compliance with ICH Guidelines for Good Clinical Practice, Site 0092 was terminated by the Applicant, and therefore, the review team decided to exclude the two subjects enrolled in Site 0092 from the evaluation of efficacy and safety. More details as to why this site was removed from the safety and efficacy analyses are provided in the Section [4.1](#). The review team otherwise concluded that the conduct of the trials appears to be adequate, and the data generated appears to be acceptable to support the use of this product for the proposed indication.

Trial IM011047 enrolled and randomized a total of 1020 subjects at 191 investigational sites in 16 countries (Australia, Canada, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, New Zealand, Poland, Puerto Rico, Spain, Sweden, United Kingdom, and the United States). A total of 1018 subjects were treated.

[Table 32](#) presents the disposition of subjects during the first 16 weeks for the two pivotal trials. The discontinuation rate was slightly lower in the deucravacitinib arm compared to placebo and apremilast arms. The discontinuation rates are slightly higher in Trial IM011047 compared to IM011046. In Trial IM011046, the most common reasons for discontinuation were adverse event and other reasons. In Trial IM011047, the most common reasons for discontinuation were adverse event, other reasons, and withdrawal by subject. According to the Applicant, "other" reasons for discontinuation included a subject's request to discontinue for a variety of personal or work-related reasons, a subject's request to discontinue due to a perceived lack of efficacy or dissatisfaction with treatment, and eligibility criteria.

Table 32. Subject Disposition through Week 16 – Trials IM011046/47 (FAS*)

Subject Disposition	Trial IM011046			Trial IM011047		
	DEUC (N=330)	PBO (N=166)	APR (N=168)	DEUC (N=511)	Placebo (N=255)	APR (N=254)
Completed	305 (92%)	145 (88%)	145 (86%)	456 (89%)	212 (83%)	217 (85%)
Discontinued	25 (8%)	20 (11%)	23 (14%)	54 (11%)	42 (17%)	37 (15%)
Reasons of Discontinuation						
Adverse Event	5 (2%)	7 (4%)	10 (6%)	11 (2%)	7 (3%)	12 (5%)
Death	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)
Lack of Efficacy	0 (0%)	1 (<1%)	1 (<1%)	6 (1%)	9 (4%)	4 (2%)
Lost to Follow-up	7 (2%)	2 (1%)	4 (2%)	5 (1%)	6 (2%)	2 (1%)
Non-Compliance with Protocol	1 (<1%)	1 (<1%)	2 (1%)	5 (1%)	2 (1%)	1 (<1%)
Pregnancy	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Withdrawal by Subject	4 (1%)	3 (2%)	3 (2%)	14 (3%)	9 (4%)	9 (4%)
Other	8 (2%)	5 (3%)	3 (2%)	13 (3%)	9 (4%)	7 (3%)

Source: Reviewer's Analysis; ADSL.xpt

Abbreviations: APR = apremilast; DEUC = deucravacitinib; PBO = placebo

* Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed.

The disposition of subjects for the treatment period after Week 16 (i.e., Week 16-24) is presented in [Table 33](#). In Trial IM011046, a total of 595 subjects entered Week 16-24 period, including 145 subjects who were switched from placebo to deucravacitinib at Week 16. In Trial IM011047, a total of 884 subjects entered the Week 16-24 period, including 212 subjects who were switched from placebo to deucravacitinib at Week 16. The reader is referred to Section [8.1.11](#) for the disposition of subjects during the maintenance or randomized withdrawal period.

Table 33. Disposition of Subjects for Weeks 16-24 – Trials IM011046/47 (FAS*)

Characteristic	Trial IM011046		Trial IM011047	
	DEUC N=450	APR N=145	DEUC N=667	APR N=217
Entered Week 16-24 period				
Completed Week 24	440 (98%)	141 (97%)	642 (9%)	208 (96%)
Discontinued between Week 16 and Week 24	10 (2%)	4 (3%)	25 (4%)	9 (4%)
Adverse Event	1 (<1%)	1 (1%)	7 (1%)	2 (1%)
Lack of Efficacy	3 (1%)	0 (0%)	8 (1%)	1 (<1%)
Lost to Follow-up	0 (0%)	2 (1%)	2 (<1%)	0 (0%)
Non-Compliance with Protocol	1 (<1%)	0 (0%)	3 (<1%)	1 (<1%)
Pregnancy	0 (0%)	0 (0%)	1 (<1%)	1 (<1%)
Withdrawal by Subject	2 (<1%)	1 (1%)	2 (<1%)	2 (<1%)
Other	3 (1%)	0 (0%)	2 (<1%)	2 (<1%)
Due to COVID-19	0 (0%)	0 (0%)	1 (<1%)	1 (<1%)

Source: Reviewer's Analysis; ADSL.xpt

Abbreviations: APR = apremilast; DEUC = deucravacitinib

* Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed.

[Table 34](#) presents the demographics and baseline disease characteristics for the two pivotal trials. The demographics and baseline disease characteristics were generally balanced across the treatment arms within each trial and were comparable across trials. Trial IM011046 had higher proportion of Asian subjects and lower proportion of White subjects compared to Trial IM011047. The majority of subjects were White and male, with a mean age of about 46 years old and baseline sPGA score of 3 (moderate). One subjects in Trial IM011046 (in placebo arm) had baseline sPGA score of 2 (mild). Furthermore, the majority of subjects in both trials had psoriasis of scalp involvement of at least moderate (ss-PGA score $\geq$ 3) at baseline. A slightly higher

proportion of subjects had prior systemic therapy use for psoriasis in Trial IM011046 compared to Trial IM011047.

Table 34. Demographics and Baseline Disease Characteristics – Trials IM011046/47 (FAS*)

Characteristic	Trial IM011046			Trial IM011047		
	DEUC (N=330)	PBO (N=166)	APR (N=168)	DEUC (N=511)	PBO (N=255)	APR (N=254)
Age (years)						
Mean (SD)	45.8 (13.7)	47.9 (14.0)	44.7 (12.1)	46.9 (13.4)	47.3 (13.6)	46.4 (13.3)
Median	45	48	43	46	47	46
Range	18 – 80	19 – 81	20 – 77	18 – 84	18 – 83	18 – 79
Age Group, n (%)						
<65	304 (92%)	141 (85%)	158 (94%)	457 (89%)	229 (90%)	226 (89%)
≥65	26 (8%)	25 (15%)	10 (6%)	54 (11%)	26 (10%)	28 (11%)
Sex, n (%)						
Female	102 (30%)	53 (32%)	58 (35%)	175 (34%)	74 (29%)	97 (38%)
Male	230 (70%)	113 (68%)	110 (65%)	336 (66%)	181 (71%)	157 (62%)
Race, n (%)						
White	265 (80%)	128 (77%)	139 (83%)	474 (93%)	232 (91%)	229 (90%)
Black or African American	2 (1%)	3 (2%)	1 (1%)	8 (2%)	9 (4%)	9 (4%)
American Indian or Alaska Native	0 (0%)	0 (0%)	0 (0%)	2 (<1%)	2 (1%)	3 (1%)
Asian	59 (18%)	34 (20%)	28 (17%)	24 (5%)	8 (3%)	12 (5%)
Other	4 (1%)	1 (1%)	0 (0%)	3 (1%)	4 (2%)	1 (<1%)
Weight (Kg)						
Mean (SD)	88.0 (21.8)	89.1 (22.3)	87.5 (21.1)	92.3 (21.9)	91.5 (20.2)	93.5 (22.2)
Median	85	86	86	91	91	91
Range	36 – 173	46 – 182	46 – 187	40 – 180	48 – 160	50 – 173
Weight Group, n (%)						
<90 Kg	199 (60%)	99 (60%)	102 (61%)	241 (47%)	122 (48%)	117 (46%)
≥90 Kg	131 (40%)	67 (40%)	66 (39%)	270 (53%)	133 (52%)	137 (54%)
Region, n (%)						
US	107 (32%)	53 (32%)	56 (33%)	163 (32%)	80 (31%)	79 (31%)
Non-US	223 (68%)	113 (68%)	112 (67%)	348 (68%)	175 (69%)	175 (69%)
Prior Systemic Therapy for Psoriasis/Psoriatic Arthritis						
Yes	199 (60%)	109 (66%)	109 (65%)	274 (54%)	139 (55%)	140 (55%)
No	131 (40%)	57 (34%)	59 (35%)	237 (46%)	116 (45%)	114 (45%)
Disease Duration (years)						
Mean (SD)	17.0 (12.4)	17.3 (12.8)	17.7 (11.8)	18.6 (13.1)	19.2 (13.5)	17.6 (12.1)
Median	13	15	16	16	17	15
Range	1 – 58	1 – 62	1 – 56	1 – 61	2 – 62	1 – 55
sPGA						
2 – Mild	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 – Moderate	255 (77%)	128 (77%)	139 (83%)	408 (80%)	217 (85%)	196 (77%)
4 – Severe	75 (23%)	37 (22%)	29 (17%)	103 (20%)	38 (15%)	58 (23%)
PASI						
Mean (SD)	21.8 (8.6)	20.7 (8.0)	21.4 (9.0)	20.7 (7.5)	21.1 (9.0)	21.6 (8.4)
Median	20	18	19	19	18	19
Range	12 – 59	10 – 48	12 – 52	12 – 56	12 – 67	12 – 52
BSA						
Mean (SD)	26.6 (15.9)	25.3 (16.9)	26.6 (16.1)	26.3 (15.8)	25.3 (15.6)	28.3 (16.5)
Median	21	18	20	20	20	22
Range	10 – 90	10 – 90	10 – 85	10 – 84	10 – 92	10 – 75
ss-PGA						
<3	121 (37%)	45 (27%)	58 (35%)	206 (40%)	82 (32%)	88 (35%)
≥3	209 (63%)	121 (73%)	110 (65%)	305 (60%)	173 (68%)	166 (65%)

Characteristic	Trial IM011046			Trial IM011047		
	DEUC (N=330)	PBO (N=166)	APR (N=168)	DEUC (N=511)	PBO (N=255)	APR (N=254)
PGA-F						
<3	287 (87%)	132 (80%)	151 (90%)	442 (86%)	217 (85%)	207 (81%)
≥3	43 (13%)	34 (20%)	17 (10%)	69 (14%)	38 (15%)	47 (19%)

Source: Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt

Abbreviations: APR = Apremilast; BSA = Body Surface Area; DEUC = deucravacitinib; PASI = Psoriasis Area and Severity Index; PBO = placebo, PGA F = Physician's Global Assessment-Fingernails; pp-PGA = palmoplantar PGA; sPGA = static Physician's Global Assessment; ss-PGA = scalp specific Physician's Global Assessment

* Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed

8.1.5. Results for the Co-Primary Efficacy Endpoints

[Table 35](#) presents the results for the co-primary efficacy endpoints at Week 16 for Trials IM011046 and IM011047. Deucravacitinib was statistically superior to placebo (p-values < 0.001) for both co-primary efficacy endpoints in both trials. The results for the PPS and FAS populations were very similar (results for PPS not presented herein). The results presented in [Table 35](#) for Trial IM011046 do not include Site 0092. However, the results with this site included were very similar to those in [Table 35](#), see [Table 100](#) in Appendix [19.5.2](#).

Table 35. Results for the Co-Primary Endpoints at Week 16 – Trials IM011046/47 (FAS; NRI¹)

Endpoint	Trial IM011046		Trial IM011047	
	DEUC (N=330)	PBO (N=166)	DEUC (N=511)	PBO (N=255)
sPGA 0/1	178 (54%)	12 (7%)	253 (50%)	22 (9%)
Difference (95% CI) ²	47% (40%, 53%)		41% (35%, 46%)	
P-Value ²	<0.001		<0.001	
PASI-75	193 (58%)	21 (13%)	271 (53%)	24 (9%)
Difference (95% CI) ²	46% (39%, 53%)		44% (38%, 49%)	
P-Value ²	<0.001		<0.001	

Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASBSA.xpt

Abbreviations: CI = Confidence Interval; DEUC=deucravacitinib; PBO=placebo

¹ Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed; missing data are imputed using the non-responder imputation (NRI) described in Section [8.1.3](#).

² Estimate, 95% CI and p-value for the difference are based on CMH test stratified for region, body weight and prior biologic use; Note: body weight stratum not applied in Japan or China.

[Table 36](#) presents the number of subjects with missing data for the co-primary efficacy endpoints by week, treatment arm, and trial up to Week 16. The amount of missing data was relatively small. The amount of missing data at Week 16 was higher in the placebo arm compared to the deucravacitinib arm in both trials. No subjects had missing data due to COVID-19 during the first 16 weeks of the trials.

Table 36. Missing Data for the Co-Primary Endpoints by Week up to Week 16 – Trials IM011046/47 (FAS¹)

Week	Trial IM011046		Trial IM011047	
	DEUC (N=330)	PBO (N=166)	DEUC (N=511)	PBO (N=255)
Week 1	12 (4%)	10 (6%)	31 (6%)	23 (9%)
Week 2	14 (4%)	13 (8%)	26 (5%)	14 (5%)
Week 4	9 (3%)	13 (8%)	23 (4%)	13 (4%)

Week	Trial IM011046		Trial IM011047	
	DEUC (N=330)	PBO (N=166)	DEUC (N=511)	PBO (N=255)
Week 8	15 (4%)	16 (10%)	35 (7%)	24 (9%)
Week 12	21 (6%)	19 (11%)	46 (9%)	33 (13%)
Week 16	23 (7%)	21 (13%)	54 (11%)	37 (14%)

Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASBSA.xpt

Abbreviations: DEUC=deucravacitinib; PBO=placebo

* Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed.

The primary method of handling missing data specified in the protocol was non-responder imputation (NRI). For sensitivity analyses for the handling of missing data when analyzing the co-primary efficacy endpoints, the SAPs specified the following methods: (i) LOCF, (ii) LOCF and NRI, (iii) MI/ FCS and (iv) tipping point analysis. This reviewer conducted an additional analysis under the worst-case scenario (i.e., missing data for deucravacitinib is imputed as non-responders and missing data for placebo is imputed as responders) before the tipping point analysis. [Table 37](#) and [Table 38](#) present the results for the co-primary efficacy endpoints by the various imputation methods in Trials IM011046 and IM011047, respectively. For both trials, the results were very similar across the various methods. In the extreme case (i.e., worst case scenario), deucravacitinib remained statistically significant to placebo (p-values < 0.001) for both co-primary efficacy endpoints. Therefore, the reviewer did not conduct the tipping point analysis.

Table 37. Results for the Co-Primary Endpoints at Week 16 With Different Approaches of Handling the Missing Data at Week 16 – Trial IM011046 (FAS¹)

Approach to Missing Data	DEUC (N=332)	PBO (N=166)	Difference (P-value) ²
sPGA 0/1			
NRI (Primary)	54%	7%	47% (<0.001)
LOCF	55%	7%	48% (<0.001)
LOCF + NRI	54%	7%	47% (<0.001)
MI/FCS	58%	8%	50% (<0.001)
Worst Case Scenario	54%	20%	34% (<0.001)
PASI-75			
NRI (Primary)	58%	13%	46% (<0.001)
LOCF	60%	13%	47% (<0.001)
LOCF + NRI	58%	13%	46% (<0.001)
MI/FCS	63%	14%	49% (<0.001)
Worst Case Scenario	59%	25%	34% (<0.001)

Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASBSA.xpt.

Abbreviations: DEUC=deucravacitinib; PBO=placebo

¹ Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed.

² Estimate and p-value for the difference are based on CMH test stratified for region, body weight and prior biologic use; Note: body weight stratum not applied in Japan or China.

Table 38. Results for the Co-Primary Endpoints at Week 16 With Different Approaches of Handling the Missing Data at Week 16 – Trial IM011047 (FAS¹)

Approach to Missing Data	DEUC (N=511)	PBO (N=255)	Difference (P-value) ²
IGA 0/1			
NRI (Primary)	50%	9%	42% (<0.001)
LOCF	51%	9%	43% (<0.001)
LOCF and NRI	50%	9%	42% (<0.001)
MI/FCS	55%	10%	46% (<0.001)
Worst Case Scenario	5%	23%	27% (<0.001)

Approach to Missing Data	DEUC (N=511)	PBO (N=255)	Difference (P-value)²
PASI-75			
NRI (Primary)	53%	9%	44% (<0.001)
LOCF	55%	10%	45% (<0.001)
LOCF and NRI	53%	10%	43% (<0.001)
MI/FCS	60%	11%	49% (<0.001)
Worst Case Scenario	54%	24%	30% (<0.001)

Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASBSA.xpt.

Abbreviations: DEUC=deucravacitinib; PBO=placebo

¹ Full Analysis Set (FAS), defined as all randomized subjects.

² Estimate and p-value for the difference are based on CMH test stratified for region, body weight and prior biologic use; Note: body weight stratum not applied in Japan or China.

8.1.6. Results for Secondary Efficacy Endpoints

This section summarizes the results for the investigator-reported secondary efficacy endpoints. The results for the secondary efficacy endpoints based on patient reported outcomes (PROs) are summarized in Section [8.1.9](#).

8.1.7. Results for Secondary Efficacy Endpoints Against Placebo

The results for the investigator-reported secondary efficacy endpoints at Week 16 in comparison to placebo are presented in [Table 39](#). In both trials, deucravacitinib was statistically superior to placebo (p-values < 0.001) for secondary endpoints based on PASI and sPGA at Week 16.

To evaluate the impact of treatment with deucravacitinib on psoriasis located on the scalp, the Applicant assessed a secondary efficacy endpoint based on the Scalp Specific Physician's Global Assessment (ss-PGA) scale. Specifically, the Applicant evaluated the proportion of subjects with an ss-sPGA score of 0 or 1 with at least a 2-grade improvement from baseline at Week 16 for deucravacitinib compared to placebo. This analysis was prespecified to include only subjects with a baseline ss-PGA score of at least 3 (moderate) and the results are included in [Table 39](#). Approximately 66% and 63% of subjects had an ss-IGA score $\geq$ 3 at baseline and were included in the analysis for Trials IM011046 and IM011047, respectively. In both trials, deucravacitinib was statistically superior to placebo (p-values < 0.001) for this endpoint at Week 16.

To evaluate the impact of treatment with deucravacitinib on psoriasis located on the nails, the Applicant included a secondary efficacy endpoint based on the Physician's Global Assessment-Fingernails (PGA-F). Specifically, the Applicant evaluated the proportion of subjects with an PGA-F score of 0 or 1 with at least a 2-grade improvement from baseline at Week 16 for deucravacitinib compared to placebo. This analysis was prespecified to include only subjects with a baseline PGA-F score of at least 3 (moderate) and the results are included in [Table 39](#). Only about 14% and 15% of subjects had PGA-F score $\geq$ 3 at baseline and were included in the analysis for Trials IM011046 and IM011047, respectively. In both trials, although there was a greater proportion of subjects who had PGA-F 0/1 response in the deucravacitinib treatment group compared with placebo, statistical significance was not achieved (p-values >0.1) with this endpoint at Week 16.

Table 39. Results for the Investigator-Reported Secondary Endpoints at Week 16 Against Placebo – Trials IM011046/47 (FAS; NRI¹)

Endpoint	Trial IM011046		Trial IM011047	
	DEUC (N=330)	PBO (N=166)	DEUC (N=511)	PBO (N=255)
P1. PASI-90 at Week 16	118 (36%)	7 (4%)	138 (27%)	7 (3%)
Difference (95% CI) ²	32% (26%, 38%)		24% (20%, 29%)	
P-Value ² (Significant per MTP ³)	<0.001 (Y)		<0.001 (Y)	
P2. ss-PGA 0/1 at Week 16	147/209 (70%)	21/121 (17%)	182/305 (60%)	30/173 (17%)
Difference (95% CI) ²	53% (44%, 62%)		42% (34%, 50%)	
P-Value ² (Significant per MTP ³)	<0.001 (Y)		<0.001 (Y)	
P3. sPGA 0 at Week 16	58 (18%)	1 (1%)	80 (16%)	3 (1%)
Difference (95% CI) ²	17% (13%, 21%)		14% (11%, 18%)	
P-Value ² (Significant per MTP ³)	<0.001 (Y)		<0.001 (Y)	
P4. PASI-100 at Week 16	47 (14%)	1 (1%)	52 (10%)	3 (1%)
Difference (95% CI) ²	14% (10%, 18%)		9% (6%, 12%)	
P-Value ² (Significant per MTP ³)	<0.001 (Y)		<0.001 (Y)	
P6. PGA-F 0/1	9/43 (21%)	3/34 (9%)	14/69 (20%)	3/38 (8%)
Difference (95% CI) ²	14% (3%, 31%)		15% (1%, 30%)	
P-Value ² (Significant per MTP ³)	0.1049 (N)		0.3891 (N)	

Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASBSA.xpt, ADSSPGA.xpt, ADPFMNAP.xpt.

Abbreviations: CI = Confidence Interval; DEUC=deucravacitinib; PBO=placebo

¹ Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed; missing data are imputed using the non-responder imputation (NRI) described in Section 8.1.3.

² Estimate, 95% CI and p-value for the difference are based on CMH test stratified for region, body weight and prior biologic use; Note: body weight stratum not applied in Japan or China.

³ Multiplicity Testing Procedure (MTP): the protocols specified a sequential testing to control the Type I error rate for testing multiple treatment groups and endpoints; see Table 30 and Table 31.

8.1.8. Results for the Secondary Efficacy Endpoints Against Apremilast

The investigator-reported endpoints at Week 16 in comparison to apremilast specified in the SAPs were the same with those in comparison to placebo, with the exception of the endpoint based on the Physician's Global Assessment-Fingernails (PGA-F) and PASI-100. The SAPs did not specify such endpoints in comparison to apremilast.

The results for the investigator-reported secondary efficacy endpoints at Week 16 in comparison to apremilast are presented in Table 40. In both trials, deucravacitinib was statistically superior to apremilast (p-values < 0.001) for all the pre-specified efficacy endpoints at Week 16.

Table 40. Results for the Investigator-Reported Secondary Endpoints at Week 16 Against Apremilast – Trials IM011046/47 (FAS; NRI¹)

Endpoint	Trial IM011046		Trial IM011047	
	DEUC (N=330)	APR (N=168)	DEUC (N=511)	APR (N=254)
A1. sPGA 0/1 at Week 16	178 (54%)	54 (32%)	253 (50%)	86 (34%)
Difference (95% CI) ²	22% (13%, 30%)		16% (9%, 23%)	
P-Value ² (Significant per MTP ³)	<0.001 (Y)		<0.001 (Y)	
A2. PASI-75 at Week 16	193 (58%)	59 (35%)	271 (53%)	101 (40%)
Difference (95% CI) ²	23% (14%, 32%)		13% (6%, 21%)	
P-Value ² (Significant per MTP ³)	<0.001 (Y)		<0.001	
A3. PASI-90 at Week 16	118 (36%)	33 (20%)	138 (27%)	46 (18%)
Difference (95% CI) ²	16% (8%, 24%)		9% (3%, 15%)	
P-Value ² (Significant per MTP ³)	<0.001 (Y)		0.0046 (Y)	

Endpoint	Trial IM011046		Trial IM011047	
	DEUC (N=330)	APR (N=168)	DEUC (N=511)	APR (N=254)
A8. ss-PGA 0/1 at Week 16	147/209 (70%)	43/110 (39%)	182/305 (60%)	61/166 (37%)
Difference (95% CI) ²	30% (19%, 41%)		23% (14%, 33%)	
P-Value ² (Significant per MTP ³)	<0.001 (Y)		<0.001 (Y)	
A12. sPGA 0 at Week 16	58 (17%)	8 (5%)	80 (16%)	16 (6%)
Difference (95% CI) ²	13% (8%, 18%)		9% (5%, 14%)	
P-Value ² (Significant per MTP ³)	<0.001 (Y)		<0.001 (Y)	

Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASBSA.xpt, ADSSPGA.xpt

Abbreviations: DEUC=deucravacitinib; APR = apremilast; CI = Confidence Interval;

¹ Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed; missing data are imputed using the non-responder imputation (NRI) described in Section 8.1.3.

² Estimate, 95% CI and p-value for the difference are based on CMH test stratified for region, body weight and prior biologic use; Note: body weight stratum not applied in Japan or China.

³ Multiplicity Testing Procedure (MTP): the protocols specified a sequential testing to control the Type I error rate for testing multiple treatment groups and endpoints; see Table 30 and Table 31.

As noted in Section 8.1.3, the SAPs also specified several investigator-reported secondary endpoints against apremilast at Week 24. The results for these endpoints are presented in Table 41. It should be noted that in Trial IM011047, 7 subjects in deucravacitinib arm (14%) missed Week 24 visit due to COVID-19, while no subjects in Trial IM011046 missed Week 24 visit due to COVID-19. The SAP specified excluding subjects with missing data due to COVID-19 from the efficacy analyses between Week 24 through Week 52. However, Table 41 presents the results where subjects with missing data for any reason (including missing data due to COVID-19) are imputed using the pre-specified primary method for handling missing data, i.e., NRI. The statistical reviewer considered the analysis with missing data due to COVID-19 removed as exploratory analysis to assess the impact of missing data due to COVID-19. The results for this exploratory analysis were very similar to the results presented in Table 41 (see Table 101 in Appendix 19.5.3).

Table 41. Results for the Investigator-Reported Secondary Endpoints at Week 24 Against Apremilast – Trials IM011046/47 (FAS; NRI¹)

Endpoint	Trial IM011046		Trial IM011047	
	DEUC (N=330)	APR (N=168)	DEUC (N=511)	APR (N=254)
A4. sPGA 0/1 at Week 24	194 (59%)	52 (31%)	251 (49%)	75 (30%)
Difference (95% CI) ²	27% (19%, 36%)		20% (13%, 27%)	
P-Value ² (Significant per MTP ³)	<0.001 (Y)		<0.001 (Y)	
A5. PASI-75 at Week 24	228 (69%)	64 (38%)	296 (58%)	96 (38%)
Difference (95% CI) ²	31% (22%, 40%)		20% (13%, 27%)	
P-Value ² (Significant per MTP ³)	<0.001 (Y)		<0.001 (Y)	
A6. PASI-90 at Week 24	140 (42%)	37 (22%)	164 (32%)	50 (20%)
Difference (95% CI) ²	20% (12%, 28%)		13% (6%, 19%)	
P-Value ² (Significant per MTP ³)	<0.001 (Y)		<0.001 (Y)	

Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASBSA.xpt

Abbreviations: DEUC=deucravacitinib; APR = apremilast; CI = Confidence Interval;

¹ Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed; missing data are imputed using the non-responder imputation (NRI) described in Section 8.1.3.

² Estimate, 95% CI and p-value for the difference are based on CMH test stratified for region, body weight and prior biologic use; Note: body weight stratum not applied in Japan or China.

³ Multiplicity Testing Procedure (MTP): the protocols specified a sequential testing to control the Type I error rate for testing multiple treatment groups and endpoints; see Table 30 and Table 31.

For Trial IM011046, the SAP also specified secondary endpoints based on sPGA0/1, PASI-75 and PASI-90 response assessed at both Week 24 and Week 52 against apremilast. Subjects should meet response criteria at both Weeks 24 and 52 in order to be considered responders for these endpoints. The results for these endpoints are presented in Table 42.

Table 42. Results for the Investigator-Reported Secondary Endpoints at Weeks 24 and 52 Against Apremilast – Trials IM011046/47 (FAS; NRI¹)

Endpoint	Trial IM011046	
	DEUC (N=330)	APR (N=168)
A9. sPGA 0/1 at Week 24 and Week 52*	151 (46%)	67 (22%)
Difference (95% CI) ²	23% (15%, 31%)	
P-Value ² (Significant per MTP ³)	<0.001 (Y)	
A10. PAS-75 at Week 24 and Week 52*	187 (57%)	51 (30%)
Difference (95% CI) ²	26% (17%, 34%)	
P-Value ² (Significant per MTP ³)	<0.001 (Y)	
A11. PAS-90 at Week 24 and Week 52*	103 (31%)	26 (15%)
Difference (95% CI) ²	15% (8%, 23%)	
P-Value ² (Significant per MTP ³)	<0.001 (Y)	

Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASBSA.xpt

Abbreviations: DEUC=deucravacitinib; APR = apremilast; CI = Confidence Interval;

¹ Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 removed; missing data are imputed using non-responder imputation (NRI).

² Estimate, 95% CI and p-value for the difference are based on CMH test stratified for region, body weight and prior biologic use; Note: body weight stratum not applied in Japan or China.

³ Multiplicity Testing Procedure (MTP): the protocols specified a sequential testing to control the Type I error rate for testing multiple treatment groups and endpoints; see Table 30 and Table 31.

* Subjects must meet response criteria at both Weeks 24 and 52 in order to be considered a responder.

8.1.9. Patient Reported Outcomes (PROs)

The protocols for both trials specified three secondary efficacy endpoints based on the patient reported outcome (PRO) of Psoriasis Symptom and Sign Diary (PSSD) at Week 16:

- (1) PSSD Symptom domain score of 0 at Week 16 among subjects with baseline PSSD Symptom domain score ≥ 1 [deucravacitinib vs. placebo].
- (2) Change from baseline in PSSD Symptom domain score at Week 16 [deucravacitinib vs. apremilast for superiority].
- (3) PSSD Symptom domain score of 0 among subjects with baseline PSSD Symptom domain score ≥ 1 [deucravacitinib vs. apremilast for superiority].

The PSSD Symptom domain is one of two domains in the 11-item PSSD. The Symptom domain is designed to assess the severity of five symptoms, which include itch, pain, stinging, burning, and skin tightness. Each symptom is rated on an 11-point NRS ranging from 0 (“Absent”) to 10 (“Worst imaginable”) over the past 24 hours. The PSSD Symptom domain score ranges from 0 to 100, where 0 represents the least severe symptom and 100 represents the most severe symptom (refer to Section 8.1.2 regarding scoring details). To calculate the scores at each visit, the daily PSSD Symptom domain scores were averaged over at least 4 daily scores of the previous 7 days. If more than 3 daily scores were missing, the average score was set to missing.

[Table 43](#) presents the results for the absolute change from baseline in PSSD Symptom domain score to Week 16 for deucravacitinib against apremilast. In both trials, deucravacitinib was statistically superior to apremilast (p-values < 0.001) for this endpoint. It should be noted that in the advice letters dated 10/29/2018 and 12/6/25019 and at the Pre-NDA meeting #2 (meeting minutes dated 6/10/2021, the Agency stated that mere change from baseline in PSSD Symptom domain may not translate to clinically meaningful treatment effect.

Table 43. Absolute Change From Baseline in PSSD Symptom_Domain Score at Week 16 – Trials IM011046/47 (FAS; mBOCF¹)

PSSD Symptom Score	Trial IM011046		Trial IM011047	
	DEUC (N=332)	APR (N=168)	DEUC (N=511)	APR (N=254)
Baseline				
N ²	304	158	466	233
Mean (SD)	51.7 (25.2)	56.2 (25.2)	52.3 (26.3)	51.9 (25.4)
Median	53.2	58.6	52.9	53.1
Range	0 – 100	2 – 100	1 – 100	0 – 100

PSSD Symptom Score	Trial IM011046		Trial IM011047	
	DEUC (N=332)	APR (N=168)	DEUC (N=511)	APR (N=254)
Change from Baseline to Week 16				
N ²	304	158	466	233
Mean	-29.3	-22.8	-28.9	-21.5
LS Mean ³	-26.5	-17.8	-28.3	-21.1
Difference (95% CI) ³	-8.7 (-12.6, -4.8)		-7.2 (-10.5, -3.9)	
P-Value ³ (MTP) ⁴	<0.001 (Y)		<0.001 (Y)	

Source: Statistical Reviewer's Analysis; ADPSSD.xpt

Abbreviations: DEUC=deucravacitinib; APR = apremilast; CI = Confidence Interval; DEUC = deucravacitinib

¹ Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 removed; missing data are imputed using the mBOCF method described in Section 8.1.3. Subjects with a missing baseline value were excluded from the analysis of this endpoint.

² Subjects with baseline PSSD Symptom domain score.

³ Least square (LS) means, difference (95% CI) and p-value are based on ANCOVA model with treatment and stratification factors as fixed effects and baseline value as covariate; Note: body weight stratum not applied in Japan or China.

⁴ Multiplicity Testing Procedure (MTP): the protocols specified a sequential testing to control the Type I error rate for testing multiple treatment groups and endpoints; see Table 30 and Table 31.

Table 44 presents the results for the proportion of subjects with a PSSD Symptom domain score of 0 at Week 16 for deucravacitinib against placebo and against apremilast. The analysis of such endpoint included subjects who had PSSD Symptom domain score ≥ 1 at baseline. Approximately 92% of the subjects in both trials met this criterion. In both trials, deucravacitinib was statistically superior to placebo (p-values<0.002). However, although the proportion of subjects achieving PSSD Symptom domain score 0 at Week 16 was numerically higher with deucravacitinib compared to apremilast, deucravacitinib was not statistically superior to apremilast (p-values>0.09).

Table 44. Proportion of Subjects With a PSSD Symptom Domain Score of 0 at Week 16 – Trials IM011046/47 (FAS; NRI¹)

Against Placebo	Trial IM011046		Trial IM011047	
	DEUC (N=330)	PBO (N=166)	DEUC (N=511)	PBO (N=255)
n/N (%)	24/305 (8%)	1/149 (1%)	35/466 (8%)	3/238 (1%)
Difference (95% CI) ²	7% (4%, 11%)		6% (3%, 9%)	
P-Value ² (Significant per MTP ³)	0.0013 (Y)		<0.001 (Y)	
Against Apremilast	Trial IM011046		Trial IM011047	
	DEUC (N=330)	APR (N=168)	DEUC (N=511)	APR (N=254)
N (%)	23/303 (8%)	7/158 (4%)	35/466 (8%)	10/232 (4%)
Difference (95% CI) ²	3% (-1%, 7%)		3% (<0%, 0.7%)	
P-Value ² (Significant per MTP ³)	0.2107 (N)		0.0928 (N)	

Source: Statistical Reviewer's Analysis; ADPSSD.xpt

Note: PSSD Symptom domain score of 0 responder defined as a PSSD Symptom domain score of 0 among subjects with a baseline PSSD Symptom domain score ≥ 1

Abbreviations: DEUC=deucravacitinib; APR = apremilast; CI = Confidence Interval

¹ Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed; missing data are imputed using the non-responder imputation (NRI) described in Section 8.1.3.

² Estimate, 95% CI and p-value for the difference are based on CMH test stratified for region, body weight and prior biologic use; Note: body weight stratum not applied in Japan or China.

³ Multiplicity Testing Procedure (MTP): the protocols specified a sequential testing to control the Type I error rate for testing multiple treatment groups and endpoints; see Table 30 and Table 31.

Review of PRO Measure for Evaluation of Clinical Benefit

The FDA reviewed the Applicant's qualitative and quantitative evidence for the PSSD Symptom domain score. The PSSD Symptom domain score was reviewed for content validity and other

measurement properties (reliability, construct validity, responsiveness), as well as score interpretability. Note that the Applicant did not submit an evidence dossier in the NDA submission to support the content validity and other measurement properties of the PSSD Symptom domain. The review of this instrument was based on evidence submitted in the IND phase.

Content Validity

The Applicant documented previous qualitative research (i.e., concept elicitation and cognitive interviews) used to develop the PSSD. The submitted qualitative data supports that the plaque psoriasis symptoms measured in the PSSD Symptom domain (i.e., itch, burning, stinging, pain, and skin tightness) are relevant and important to the target population. Further, the symptoms measured in the PSSD are consistent with Voice of the Patient report (November 2016) from the Patient-Focused Drug Development meeting for psoriasis held on March 17, 2016.

Refer to the full COA review by Yasmin Choudhry, M.D., the Division of Clinical Outcome Assessment (DCOA) for detailed results of the content validity of the PSSD Symptom domain.

Other Measurement Properties (Reliability, Construct Validity, Responsiveness)

The Applicant documented the other measurement properties of the PSSD that included data from a non-interventional study and guselkumab phase 3 clinical trials. Note that the target populations within these studies are consistent with the trial population for Trials IM011-046 and -047. For the assessment of reliability and other measurement properties of the PSSD Symptom domain, the results were generally within acceptable and within reasonable range.

Refer to the full review by Yasmin Choudhry, M.D., DCOA for detailed discussion of the other measurement properties of the PSSD Symptom domain.

Score Interpretability

The Applicant performed a pre-specified analysis (secondary endpoint) evaluating the proportion of subjects achieving a PSSD Symptom domain score of 0 (symptom absent).

The Applicant performed the following analyses to support the threshold(s) for meaningful within-subject score change in the PSSD Symptom domain score:

- Anchor-based analyses
 - Distribution of change on the target COAs by change on anchors
 - Anchor-based empirical cumulative distribution function and probability density function curves
- Distribution-based analyses

The Applicant proposed the following thresholds for meaningful within-subject score change for the PSSD Symptom domain score ([Table 45](#)).

Table 45. Summary of PSSD Symptom Domain Meaningful Change Thresholds for Improvement Estimates

PSSD Score	Anchor-based Estimates	Distribution-based Estimates		MCT Recommendations		
		0.5 SD	SEM	Smallest meaningful change	Concordance between anchors	Hyper-responder threshold
Symptom score	14.8, 23.7	12.8	5.8	15	25	30

Source: Table 9 in Section 5.2.4 of Appendix 9.2 PRO Report.

The results for the anchor-based analyses are not discussed in this unireview as the pre-specified secondary PRO endpoint assesses clinical benefit via the targeted response of complete resolution of signs. The distribution-based analyses are also not discussed in this unireview as distribution-based methods (e.g., effect sizes, certain proportions of the standard deviation and/or standard error of measurement) are only considered supportive to anchor-based methods.

Refer to the full COA review by the DCOA for detailed results of the score interpretability of the PSSD Symptom domain.

Conclusions

The Applicant has documented the content validity and the other measurement properties for the PSSD Symptom domain. The PSSD Symptom domain and its corresponding endpoint(s) assesses clinical benefit via the targeted response of complete resolution of symptoms; this endpoint appears to adequately support labeling claims.

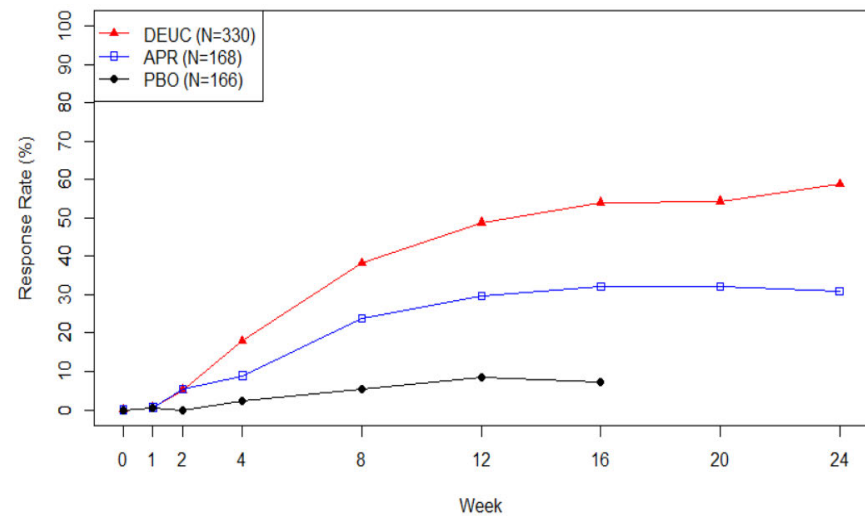
8.1.10. Efficacy Over Time

8.1.10.1. Initial Treatment Period

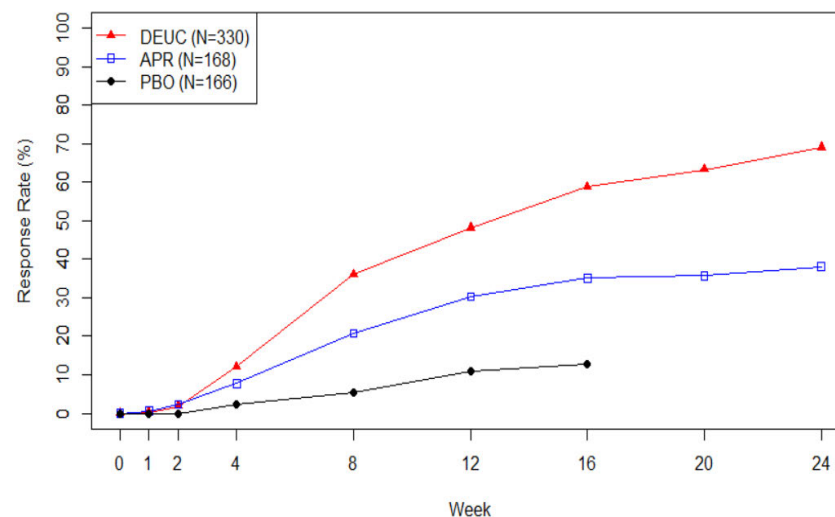
[Figure 10](#) presents the results for sPGA score of 0 or 1 and PASI-75 through Week 24 for Trials IM011046 and IM011047.

Figure 10. Results for sPGA 0/1 and PASI 75 Through Week 24 – Trials IM011046/47 (FAS; NRI¹)

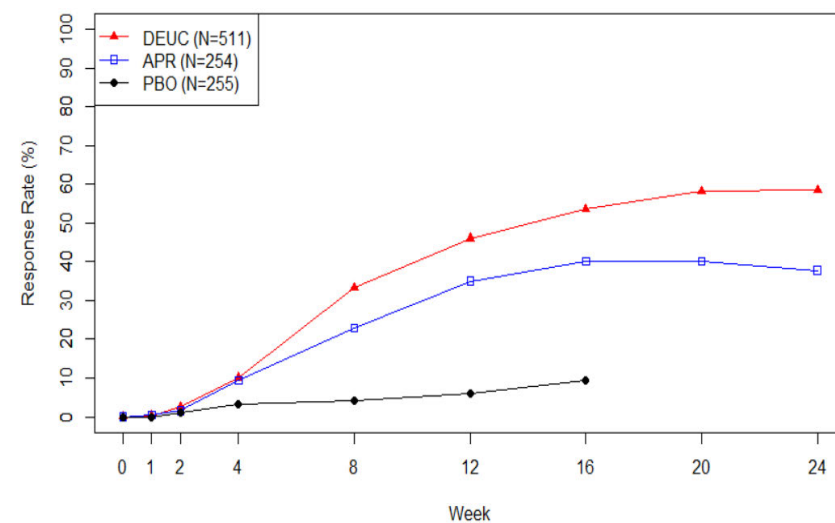
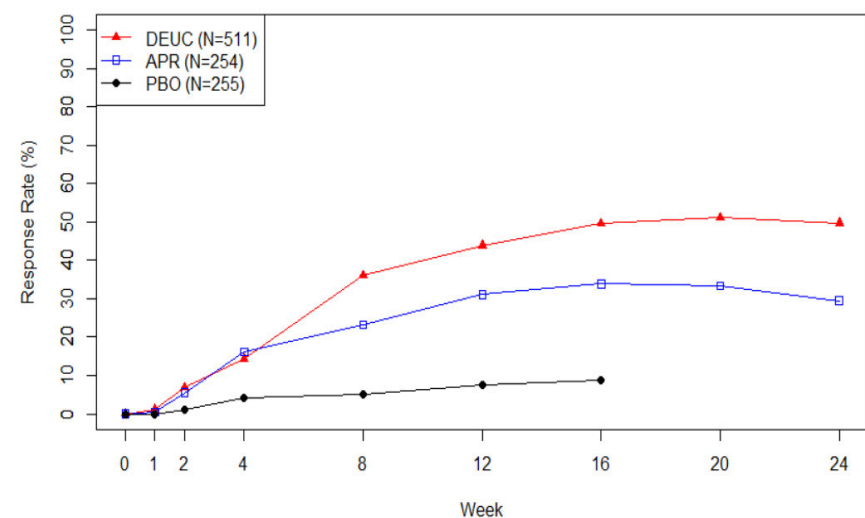
Trial IM011046



PASI-75



Trial IM011047



Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASBSA.xpt

Abbreviations: DEUC=deucravacitinib; APR = apremilast ; DEUC = deucravacitinib; PBO = placebo

¹ Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed; missing data are imputed using the non-responder imputation (NRI) described in Section 8.1.3.

8.1.11. Maintenance Period or Randomized Withdrawal Period

The disposition of subjects for the maintenance or randomized withdrawal period (i.e., Week 24-52) is presented in [Table 46](#).

In Trial IM011046, at Week 24, 145 subjects originally randomized to placebo switched to deucravacitinib and 305 subjects originally randomized to deucravacitinib continued on the same treatment during the maintenance period. Furthermore, a total of 54 subjects were switched from apremilast to deucravacitinib, as per trial design, because they did not achieve PASI 50 response at Week 24, while 87 subjects who achieved PASI 50 response remained on apremilast arm.

In Trial IM011047, at Week 24, 203 subjects originally randomized to placebo switched to deucravacitinib at Week 24. A total of 142 subjects originally randomized to deucravacitinib who did not achieve PASI 75 response at Week 24 continued to receive deucravacitinib, until the end of the maintenance period. A total of 298 subjects originally randomized to deucravacitinib achieved PASI 75 response and were re-randomized 1:1, in a blinded manner, to placebo (N = 150) or deucravacitinib (N = 148). A total of 97 subjects originally randomized to apremilast who achieved PASI 75 response at Week 24 were switched in a blinded manner to placebo and 111 subjects who did not achieve PASI 75 response were switched in a blinded manner to deucravacitinib.

Table 46. Disposition of Subjects for Weeks 16-52 – Trials IM011046/ IM011047 (FAS*)

Subject Disposition	Trial IM011046		Trial IM011047	
	DEUC	APR	DEUC	PBO
Entered Week 24-52 period	N=494	N=87	N=604	N=247
Completed Week 52	444 (90%)	83 (95%)	535 (89%)	214 (87%)
Discontinued between Week 24 and Week 52	50 (10%)	4 (5%)	69 (11%)	33 (13%)
Adverse Event	8 (2%)	1 (1%)	14 (2%)	7 (3%)
Lack of Efficacy	6 (1%)	0 (0%)	8 (1%)	8 (3%)
Lost to Follow-up	5 (1%)	1 (1%)	9 (1%)	4 (2%)
Non-Compliance with Protocol	2 (<1%)	0 (0%)	2 (<1%)	0 (0%)
Pregnancy	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Withdrawal by Subject	10 (2%)	0 (0%)	8 (1%)	6 (2%)
Other	19 (4%)	2 (2%)	28 (5%)	7 (3%)
Due to COVID-19	7 (1%)	1 (1%)	8 (1%)	3 (1%)

Source: Reviewer's Analysis; ADSL.xpt

Abbreviations: APR = apremilast; DEUC = deucravacitinib; PBO = placebo

* Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed.

As noted in Section [8.1.3](#), disruptions in the trials' visit schedule and subjects receiving treatment due to the COVID-19 pandemic affected the maintenance or randomized withdrawal period for both trials. [Table 47](#) presents the number of subjects with missing data due to COVID-19 for the co-primary efficacy endpoints by week, original treatment arm, and trial between Week 24 and Week 52. The amount of missing data due to COVID19 is very small.

Table 47. Missing Data Due to COVID-19 for the Co-Primary Endpoints by Week Between Week 24 and Week 52/56 – Trials IM011046/47 (FAS¹)

Week	Trial IM011046			Trial IM011047		
	DEUC (N=330)	PBO (N=166)	APR (N=168)	DEUC (N=511)	PBO (N=255)	APR (N=254)
Week 24	0 (0%)	0 (0%)	0 (0%)	7 (1%)	3 (1%)	0 (0%)
Week 28	0 (0%)	1 (1%)	0 (0%)	8 (2%)	1 (<1%)	2 (1%)
Week 32	2 (1%)	1 (1%)	0 (0%)	7 (1%)	1 (<1%)	0 (0%)
Week 36	6 (2%)	0 (0%)	1 (1%)	8 (2%)	0 (0%)	2 (1%)
Week 40	11 (3%)	3 (2%)	2 (1%)	9 (2%)	2 (1%)	0 (0%)
Week 44	8 (2%)	1 (1%)	3 (2%)	8 (2%)	2 (1%)	2 (1%)
Week 48	7 (2%)	0 (0%)	2 (1%)	11 (2%)	2 (1%)	0 (0%)
Week 52	1 (<1%)	0 (0%)	1 (1%)	5 (1%)	1 (<1%)	1 (<1%)

Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASBSA.xpt

Abbreviations: APR = apremilast; DEUC = deucravacitinib; PBO = placebo

¹ Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed.

In Trial IM011046, among Week 24 responders who received deucravacitinib, the response rates at Week 52 were 78% (151/194) for sPGA 0/1, 82% (187/228) for PASI-75 and 74% (103/140) for PASI-90. Subjects with missing data in this analysis are imputed with the NRI method described in Section 8.1.3.

In Trial IM011047, subjects originally randomized to deucravacitinib at baseline and who were PASI 75 responders at Week 24 were re-randomized to either continue treatment with deucravacitinib or be withdrawn from therapy (i.e., placebo). Table 48 presents the proportion of responders (sPGA 0/1 and PASI-75) at Week 52 among subjects who were responders at Week 24.

Table 48. Response at Week 52 Among Week 24 Responders – Trial IM011047 (FAS; NRI¹)

Endpoint	DEUC/DEUC (N=148)	DEUC/PBO (N=150)
sPGA 0/1 among Week 24 sPGA 0/1 responders	83/118 (70%)	28/119 (24%)
PASI-75 among Week 24 PASI-75 responders	119/148 (80%)	47/150 (31%)

Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASBSA.xpt

Abbreviations: DEUC = deucravacitinib; PBO = placebo

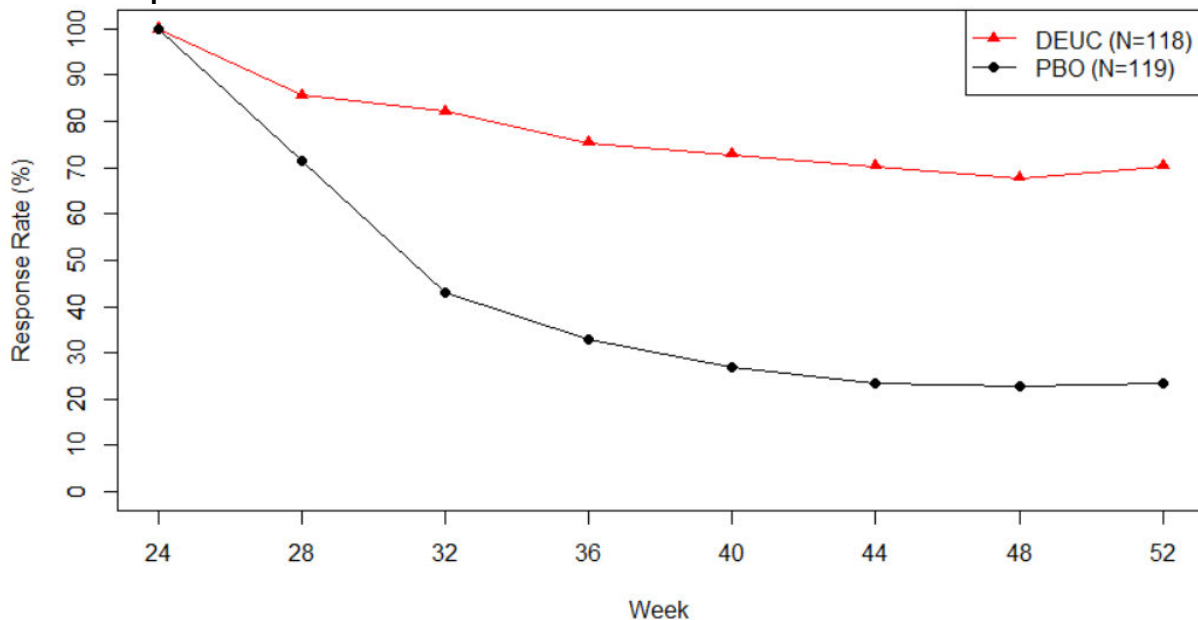
¹ Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed; missing data are imputed using the non-responder imputation (NRI) described in Section 8.1.3.

Note: For re-randomization at Week 24, the percent change from baseline in PASI for PASI 75 response was rounded up due to interactive response technology (IRT) specifications.

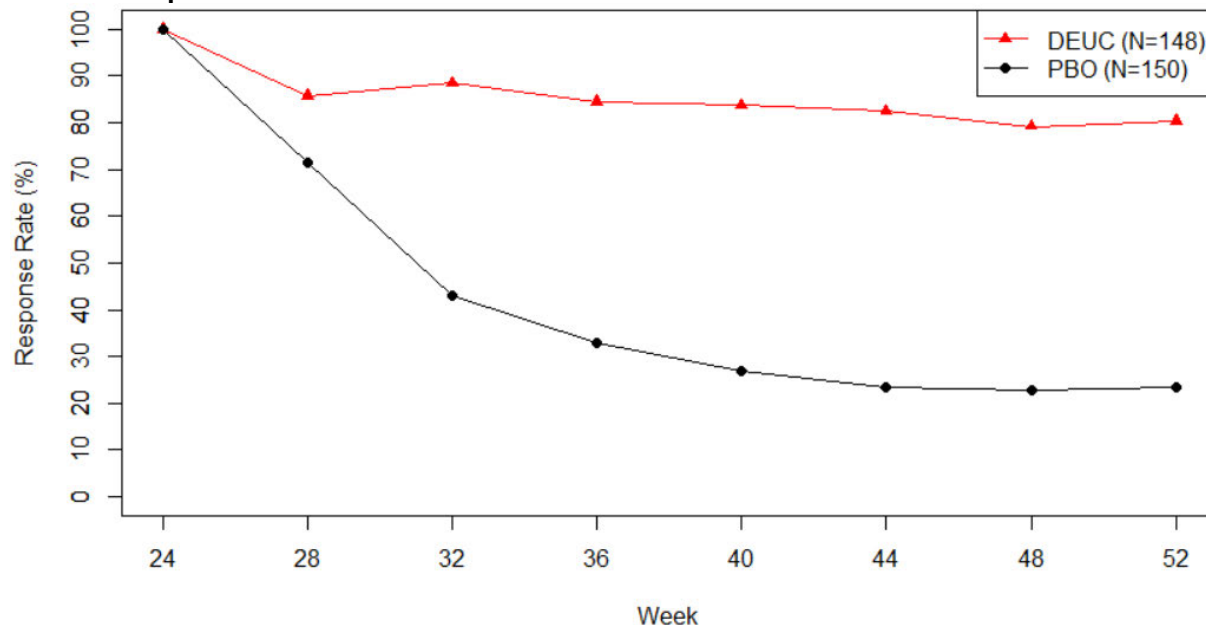
For responders at Week 24 who were re-randomized to treatment withdrawal, the median time to loss of sPGA 0/1 response was approximately 57 days and the median time to loss of PASI-75 response was approximately 85 days. Figure 11 presents the sPGA 0/1 and PASI-75 response rates during the randomized-withdrawal period (Weeks 24 to 52) for the re-randomized subjects (i.e., continue deucravacitinib or switch to placebo).

Figure 11. sPGA 0/1 and PASI-75 Response Rates During the Randomized-Withdrawal Period - Trial IM011047 (FAS; NRI¹)

IGA 0/1 Response Rates Over Time



PASI-75 Response Rates Over Time



Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASBSA.xpt

Abbreviations: DEUC = deucravacitinib; PBO=placebo

¹ Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed; missing data are imputed using the non-responder imputation (NRI) described in Section 8.1.3.

8.1.12. Findings in Special/Subgroup Populations

8.1.13. Sex, Race, Age, Weight, Baseline Disease Severity and Prior Use of Systemic Therapy

Table 49 and Table 50 present, respectively, the results for the co-primary efficacy endpoints (i.e., sPGA score of 0 or 1 at Week 16 and PASI 75 at Week 16) by age (18-64 and ≥65 years),

sex, race (White, Black of African American, Asian, Other), weight (<90 kg, ≥90 kg), baseline sPGA score (moderate, severe) and prior use of systemic therapy for psoriasis for psoriasis/psoriatic arthritis (Yes, No) for Trial IM011046. The same results for Trial IM011047 are presented in [Table 51](#) and [Table 52](#).

In both trials, the majority of subjects were White (87%) and less than 65 years of age (approximately 90%); therefore, it would be difficult to detect any differences in efficacy for the Non-White (i.e., Black of African American, Asian and Other) and ≥ 65 years of age subgroups. For sex, the treatment effect was in general comparable between males and females for both co-primary efficacy endpoints in both trials. For baseline weight, the treatment effect was higher in subjects with baseline weight < 90 kg compared to those with baseline weight ≥90 kg for both co-primary endpoints and in both trials, except for the PASI-75 endpoint in Trial IM011046, for which the treatment effect was comparable across these two subgroups. For baseline disease severity, the treatment effect for both co-primary endpoints tended to be higher for subjects with more severe disease at baseline (i.e., sPGA score of 4 [severe]) in Trial IM011046; however, it should be noted that the sample size for the severe disease was relatively small. In Trial IM011047, the treatment effect was comparable across the two baseline disease severity subgroups for both endpoints. The treatment effect was generally consistent across the prior use of systemic therapy for psoriasis/psoriatic arthritis subgroups for both endpoints in both trials.

The statistical reviewer further explored results for the co-primary efficacy endpoints at Week 16 in subjects who had treatment failure or who were intolerant to prior systemic therapy for Psoriasis/Psoriatic arthritis (see results in [Table 53](#)). The treatment effect in this subpopulation was generally similar to the treatment effect in the overall population (see [Table 35](#)).

Table 49. sPGA 0/1 at Week 16 by Age, Sex, Race, Weight, Baseline sPGA Score and Prior Use of Systemic Therapy – Trial IM011046 (FAS; NRI¹)

Subgroups (n[DEUC], n[PBO])	DEUC (N=330)	PBO (N=166)	Difference (95% CI)
Age (years)			
18-64 (304, 141)	163 (54%)	10 (7%)	47% (40%, 54%)
≥65 (26, 25)	15 (58%)	2 (8%)	50% (28%, 71%)
Sex			
Male (230, 113)	115 (50%)	6 (5%)	45% (37%, 52%)
Female (100, 53)	63 (63%)	6 (11%)	52% (39%, 64%)
Race			
White (265, 10)	135 (51%)	10 (8%)	43% (36%, 51%)
Black/African American (2, 3)	1 (50%)	0 (0%)	-
Asian (59, 34, 28)	40 (68%)	2 (6%)	62% (48%, 76%)
Other (4, 1, 0)	2 (50%)	0 (0%)	50% (-19%, 100%)
Baseline Weight			
<90 kg (199, 99)	124 (62%)	11 (11%)	51% (42%, 60%)
≥90 kg (131, 67)	54 (41%)	1 (1%)	40% (31%, 49%)
Baseline sPGA			
Moderate (255, 128)	134 (53%)	11 (9%)	44% (36%, 52%)
Severe (75, 37)	44 (59%)	1 (3%)	56% (44%, 68%)
Prior Systemic Therapy for Psoriasis/Psoriatic Arthritis			
Yes (199, 109)	108 (54%)	9 (8%)	46% (37%, 55%)
No (131, 57)	70 (53%)	3 (5%)	48% (38%, 59%)
Overall	178 (54%)	12 (7%)	47% (40%, 53%)

Table 50. PASI-75 Response at Week 16 by Age, Sex, Race, Weight, Baseline sPGA Score and Prior Use of Systemic Therapy – Trial IM011046 (FAS; NRI¹)

Subgroups (n[DEUC], n[PBO])	DEUC (N=330)	PBO (N=166)	Difference (95% CI)
Age (years)			
18-64 (304, 141)	177 (58%)	20 (14%)	44% (36%, 52%)
≥65 (26, 25)	16 (62%)	1 (4%)	58% (37%, 78%)
Sex			
Male (230, 113)	130 (57%)	11 (10%)	47% (38%, 55%)
Female (100, 53)	63 (63%)	10 (19%)	44% (30%, 58%)
Race			
White (265, 10)	147 (55%)	17 (13%)	42% (34%, 51%)
Black/African American (2, 3)	2 (100%)	0 (0%)	-
Asian (59, 34)	42 (71%)	4 (12%)	59% (44%, 75%)
Other (4, 1)	2 (50%)	0 (0%)	50% (1%, 99%)
Baseline Weight			
<90 kg (199, 99)	128 (64%)	19 (19%)	45% (35%, 55%)
≥90 kg (131, 67)	65 (50%)	2 (3%)	47% (37%, 56%)
Baseline sPGA			
Moderate (255, 128)	144 (56%)	18 (14%)	42% (34%, 51%)
Severe (75, 37)	49 (65%)	3 (8%)	57% (43%, 71%)

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Subgroups (n[DEUC], n[PBO])	DEUC (N=330)	PBO (N=166)	Difference (95% CI)
Prior Systemic Therapy for Psoriasis/Psoriatic Arthritis			
Yes (199, 109)	118 (59%)	9 (8%)	51% (43%, 60%)
No (131, 57)	75 (57%)	12 (21%)	36% (23%, 50%)
Overall	193 (58%)	21 (13%)	46% (39%, 53%)

Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASBSA.xpt

Abbreviations: CI = Confidence Interval ; DEUC = deucravacitinib; PBO = placebo

¹ Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 removed; missing data are imputed using the non-responder imputation (NRI) described in Section 8.1.3.

Table 51. sPGA 0/1 at Week 16 by Age, Sex, Race, Weight, Baseline sPGA Score and Prior Use of Systemic Therapy - Trial IM011047 (FAS; NRI¹)

Subgroups (n[DEUC], n[PBO])	DEUC (N=511)	PBO (N=255)	Difference (95% CI)
Age (years)			
18-64 (457, 229)	225 (49%)	20 (9%)	41% (35%, 46%)
≥65 (54, 26)	28 (52%)	2 (8%)	44% (27%, 61%)
Sex			
Male (336, 181)	159 (47%)	15 (8%)	39% (32%, 46%)
Female (172, 74)	94 (54%)	7 (9%)	44% (34%, 54%)
Race			
White (474, 232)	238 (50%)	20 (9%)	42% (36%, 47%)
Black/African American (8, 9)	2 (25%)	1 (11%)	14% (-22%, 50%)
Asian (24, 8)	11 (46%)	1 (13%)	33% (3%, 64%)
Other (5, 6)	2 (40%)	0 (0%)	40% (-3%, 83%)
Baseline Weight			
<90 kg (241, 122)	145 (60%)	14 (11%)	50% (41%, 58%)
≥90 kg (270, 133)	108 (40%)	8 (6%)	35% (28%, 42%)
Baseline sPGA			
Moderate (408, 217)	208 (51%)	21 (10%)	41% (35%, 48%)
Severe (103, 58)	45 (44%)	1 (3%)	41% (30%, 52%)
Prior Systemic Therapy for Psoriasis/Psoriatic Arthritis			
Yes (274, 139)	134 (49%)	11 (8%)	41% (34%, 48%)
No (237, 116)	119 (50%)	11 (9%)	41% (32%, 49%)
Overall	253 (50%)	22 (9%)	41% (35%, 46%)

Table 52. PASI-75 Response at Week 16 by Age, Sex, Race, Weight, Baseline sPGA Score and Prior Use of Systemic Therapy - Trial IM011047 (FAS; NRI¹)

Subgroups (n[DEUC], n[PBO])	DEUC (N=511)	PBO (N=255)	Difference (95% CI)
Age (years)			
18-64 (457, 229)	242 (53%)	20 (9%)	44% (38%, 50%)
≥65 (54, 26)	29 (54%)	4 (15%)	38% (19%, 58%)
Sex			
Male (336, 181)	163 (49%)	16 (9%)	40% (33%, 46%)
Female (172, 74)	108 (62%)	8 (11%)	51% (41%, 61%)
Race			
White (474, 232)	253 (53%)	23 (10%)	43% (38%, 49%)
Black/African American (8, 9)	2 (25%)	1 (11%)	14% (-22%, 50%)
Asian (24, 8)	13 (54%)	0 (0%)	54% (34%, 74%)
Other (5, 6)	3 (60%)	0 (0%)	60% (17%, 100%)
Baseline Weight			
<90 kg (241, 122)	127 (47%)	10 (8%)	48% (40%, 57%)
≥90 kg (270, 133)	144 (60%)	14 (11%)	40% (32%, 47%)

Baseline sPGA			
Moderate (408, 217)	221 (54%)	22 (10%)	44% (38%, 50%)
Severe (103, 58)	50 (59%)	2 (5%)	43% (31%, 55%)
Prior Systemic Therapy for Psoriasis/Psoriatic Arthritis			
Yes (274, 139)	138 (50%)	8 (6%)	45% (38%, 52%)
No (237, 116)	133 (56%)	16 (14%)	42% (33%, 51%)
Overall	271 (53%)	24 (9%)	44% (38%, 49%)

Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASBSA.xpt

Abbreviations: CI = Confidence Interval; DEUC = deucravacitinib; PBO = placebo

¹ Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed; missing data are imputed using the non-responder imputation (NRI) described in Section 8.1.3.

Table 53. Response Rates at Week 16 in Subgroup Who Had Treatment Failure or Intolerance to Prior Systemic Therapy for Psoriasis/Psoriatic Arthritis - Trials IM011046/047 (FAS; NRI¹)

Trial (Sample Sizes)	DEUC	PBO	Difference, % (95% CI)
sPGA 0/1 at Week 16			
IM011046 (117, 66)	59 (50%)	6 (9%)	41% (30%, 53%)
IM011047 (166, 87)	78 (47%)	5 (6%)	41% (32%, 50%)
PASI-75 at Week 16			
IM011046 (117, 66)	68 (58%)	6 (9%)	49% (38%, 60%)
IM011047 (166, 87)	82 (49%)	5 (6%)	44% (35%, 53%)

Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASBSA.xpt, ADCM.xpt

Abbreviations: CI = Confidence Interval; DEUC = deucravacitinib; PBO = placebo

Note: Prior systemic treatment use in psoriasis/psoriatic arthritis using C_{MIN}D variable in ADCM.xpt.

¹ Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed; missing data are imputed using non-responder imputation (NRI).

8.1.14. Geographic Location (Country)

Trial IM011046 was conducted in 11 countries (Canada, China, Germany, Japan, Poland, Russia, South Korea, Spain, Taiwan, United Kingdom, and the United States). Trial IM011047 was conducted in 16 countries (Australia, Canada, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, New Zealand, Poland, Puerto Rico, Spain, Sweden, United Kingdom, and the United States). A total of 1018 subjects were treated. [Table 54](#) and [Table 55](#) present the results for the coprimary endpoints at Week 16 by country for Trials IM011046 and IM011047, respectively. Across the two trials, the treatment effect varied across the countries; however, this may be due to the relatively small sample sizes in many of the countries.

Table 54. sPGA 0/1 and PASI-75 Response at Week 16 by Country - Trial IM011046 (FAS; NRI¹)

Country (n[DEUC], n[PBO])	DEUC (N=511)	PBO (N=255)	Difference (95% CI)
sPGA 0/1 Response			
Canada (26, 20)	13 (50%)	2 (10%)	40% (17%, 63%)
China (4, 2)	2 (50%)	0 (0%)	50% (1%, 99%)
Germany (1, 0)	0 (0%)	-	-
Spain (3, 1)	1 (33%)	0 (0%)	33% (-20%, 87%)
Great Britain (13, 4)	6 (46%)	0 (0%)	46% (19%, 73%)
Japan (32, 17)	24 (75%)	2 (12%)	63% (42%, 85%)
Korea (14, 7)	10 (71%)	0 (0%)	71% (48%, 95%)
Poland (94, 44)	54 (57%)	6 (14%)	44% (30%, 58%)
Russia (36, 13)	22 (61%)	1 (8%)	53% (32%, 75%)
Taiwan (0, 5)	-	0 (0%)	-

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

USA (107, 53)	46 (43%)	1 (2%)	41% (31%, 51%)
Overall	178 (54%)	12 (7%)	47% (40%, 53%)
PASI-75 Response			
Canada (26, 20)	62%	15%	47% (22%, 71%)
China (4, 2)	75%	0%	75% (33%, 100%)
Germany (1, 0)	0%	-	-
Spain (3, 1)	33%	0%	33% (-20%, 87%)
Great Britain (13, 4)	46%	25%	21% (-29%, 72%)
Japan (32, 17)	78%	12%	66% (45%, 87%)
Korea (14, 7)	64%	14%	50% (14%, 86%)
Poland (94, 44)	66%	14%	52% (38%, 66%)
Russia (36, 13)	67%	15%	51% (26%, 76%)
Taiwan (0, 5)	-	0%	-
USA (107, 53)	44%	11%	33% (20%, 45%)
Overall	193 (58%)	21 (13%)	46% (39%, 53%)

Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASBSA.xpt

Abbreviations: CI = Confidence Interval; DEUC = deucravacitinib; PBO = placebo;

¹ Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 removed; missing data are imputed using the non-responder imputation (NRI) described in Section 8.1.3.

Table 55. sPGA 0/1 and PASI-75 Response at Week 16 by Country - Trial IM011047 (FAS; NRI¹)

Country (n[DEUC], n[PBO])	DEUC (N=511)	PBO (N=255)	Difference (95% CI)
sPGA 0/1 Response			
Australia (23, 18)	39%	6%	33% (10%, 56%)
Canada (43, 28)	33%	7%	25% (8%, 42%)
Czech Republic (29, 16)	72%	6%	66% (46%, 86%)
Germany (21, 7)	43%	0%	43% (22%, 64%)
Spain (12, 1)	58%	0%	58% (30%, 86%)
Finland (6, 1)	33%	0%	33% (-4%, 71%)
France (6, 3)	33%	0%	33% (-4%, 71%)
Great Britain (25, 11)	68%	0%	68% (50%, 86%)
Hungary (38, 13)	68%	15%	53% (28%, 78%)
Israel (4, 1)	100%	0%	100%
New Zealand (2, 3)	100%	0%	100%
Poland (131, 66)	62%	12%	50% (38%, 61%)
Puerto Rico (1, 4)	0%	0%	0%
Sweden (7, 4)	57%	0%	57% (20%, 94%)
USA (163, 80)	34%	10%	24% (14%, 33%)
Overall	253 (50%)	22 (9%)	41% (35%, 46%)
PASI-75 Response			
Australia (23, 18)	57%	0%	57% (36%, 77%)
Canada (43, 28)	47%	7%	39% (22%, 57%)
Czech Republic (29, 16)	69%	0%	69% (52%, 86%)
Germany (21, 7)	33%	0%	33% (13%, 54%)
Spain (12, 1)	83%	0%	83% (62%, 100%)
Finland (6, 1)	33%	0%	33% (-4%, 71%)
France (6, 3)	33%	33%	0% (-65%, 65%)
Great Britain (25, 11)	68%	0%	68% (50%, 86%)
Hungary (38, 13)	71%	15%	56% (31%, 80%)
Israel (4, 1)	100%	0%	100%
New Zealand (2, 3)	50%	0%	50% (-19%, 100%)
Poland (131, 66)	61%	12%	49% (37%, 60%)

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Puerto Rico (1, 4)	0%	0%	0%
Sweden (7, 4)	71%	25%	46% (-8%, 100%)
USA (163, 80)	39%	13%	26% (16%, 37 [^])
Overall	271 (53%)	24 (9%)	44% (38%, 49%)

Source: Statistical Reviewer's Analysis; ADSPGA.xpt, ADPASBSA.xpt

Abbreviations: CI = Confidence Interval; DEUC = deucravacitinib; PBO = placebo

¹ Full Analysis Set (FAS), defined as all randomized subjects, with Site 0092 (Trial IM011046) removed; missing data are imputed using the non-responder imputation (NRI) described in Section [8.1.3](#).

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety of deucravacitinib for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy and phototherapy was assessed primarily using data from two Phase 3 trials (IM011046 and IM011047) and an open-label long-term extension trial (IM011075). A Phase 2 dose-ranging trial (IM01101) provided additional supportive data. Refer to Section [7.1](#) for details of trials pertinent to the evaluation of efficacy and safety.

The review team analyzed various pools of short-term and long-term data comparing deucravacitinib to placebo and an active comparator (apremilast) to support the safety of deucravacitinib in the target population. The relevance of the known and potential safety risks associated with the class of JAK inhibitors was also considered while evaluating safety. To understand whether deucravacitinib's TYK2 inhibition poses similar safety risks as JAK inhibitors approved for inflammatory conditions, data from the development program in terms of common adverse reactions, adverse events of interest, and laboratory parameters were compared to the adverse reactions (ARs) described in labeling for JAK inhibitor products.

Furthermore, nonclinical findings identified during drug development were considered as part of the safety evaluation for the drug. Safety signals arising from nonclinical repeat-dose toxicity studies, such as a dose-dependent increase in severity and/or incidences of skin abnormalities (epidermal erosion, hyperkeratosis, and crust; dermal mixed cell infiltration) in monkeys, informed the clinical safety review approach. Additionally, the nonclinical key findings from rat toxicity studies showed a reduction of immune cell populations and decreases in hematopoietic cellularity in the bone marrow (which were largely resolved after recovery) along with an increased incidence of lymphoid depletion in the spleen. These observations warranted particular attention while assessing the risk of serious infections and deucravacitinib's impact on hematological parameters.

Overall cardiovascular (CV) effects in monkeys were not considered notable; however, unexplained myocardial inflammation during the one-month oral toxicity study in monkeys treated with deucravacitinib was observed. This (CV) finding, however, was absent during the 3-month and 9-month monkey studies, and in the 1-month monkey study, two control animals also developed minimal subacute myocardial inflammation. Nonetheless, cardiovascular risk was evaluated as part of this safety review given the risk of MACE labeled for JAK inhibitors that are indicated for the treatment of chronic inflammatory conditions, as well as the association between psoriasis and CV disease and metabolic syndrome.

Although deucravacitinib was not carcinogenic based on nonclinical studies, the risk of malignancies labeled for other JAK inhibitors was considered during the review of safety data.

In attempts to attain reliable estimates of important safety parameters, the data from the Phase 3 clinical trials were pooled as follows:

- The Controlled Safety Pool consists of data from the two Phase 3 trials (IM011046 and IM011047).
- The Phase 3 Safety Pool is comprised of data from the two Phase 3 psoriasis trials plus the long-term safety data from the extension trial as of the safety cutoff date (June 15, 2021).
- Additional data from the 120 day safety had a cut-off date of October 1, 2021.

To address treatment switching, comparisons were based on subjects who did not switch treatment. Therefore, comparative assessments between deucravacitinib and placebo were performed at 16 weeks of exposure, and deucravacitinib compared to apremilast was based on 16, 24, as well as 52 weeks of exposure. Because subjects did not stay on apremilast for 52 weeks in Trial IM011047, only the subjects who did not switch treatment in Trial IM011046 (i.e., excluding subjects who switched from placebo to deucravacitinib at Week 16 and subjects who switched from apremilast to deucravacitinib at Week 24) were used in the comparative safety analysis between deucravacitinib and apremilast at 52 weeks of exposure.

While the analyses using the Controlled Safety Pool are useful to compare overall AEs, as well as laboratory assessments between treatment groups, rare events and events with long latency might not be seen. The Phase 3 Safety Pool provides information on the total number of events (e.g., malignancies and deaths) that occurred in the the controlled trials, as well as in the extension trial. While acknowledging that the number of events is useful, the relationship to treatment cannot be fully ascertained due to the open-label trial design. In some cases, comparisons were made with epidemiological data from source databases; others were done by cross-comparisons with clinical trials for other JAK inhibitor products and other products for the systemic treatment of psoriasis. Both of these approaches have limitations on the interpretation.

Primary safety analyses evaluated treatment-emergent adverse events (AEs), deaths, serious AEs (SAEs), AEs leading to discontinuation, and laboratory abnormalities in the Phase 3 trials. Additional analyses of AEs of special interest were conducted. These were chosen based on the mechanism and targeted pathway of deucravacitinib and include AEs seen with similar precedent immunomodulatory products, namely those of the JAK inhibitor family.

8.2.2. Review of the Safety Database

Overall Exposure

As of June 15, 2022, the data cut-off date used for this application, the psoriasis development program included 1519 subjects who received at least one dose of deucravacitinib 6 mg daily for a total of 2166.9 patient years (PY) of deucravacitinib exposure.

Subjects with exposure to deucravacitinib without treatment switching included:

- 1312 subjects for at least 6 months
- 1068 subjects for at least 1 year
- 296 subjects for at least 2 years

The 120 day safety update provided additional data through October 1, 2021 comprising of 1519 subjects with a total exposure of 2482 PY. Of the 1519 subjects, those who received deucravacitinib without switching treatment included:

- 1312 subjects for at least 6 months
- 1179 subjects for at least 1 year
- 584 subjects for at least 2 years

Relevant Characteristics of the Safety Population

The deucravacitinib psoriasis clinical safety population was predominantly white and male. The median age was 47 years with 10% of subjects at least 65 years old. The median body mass index (BMI) was 30 kg/m². Over half of the safety population used prior systemic therapy. The population appears to be representative of the US target population based on race and age. There is no clear sex predilection for psoriasis; however, trials have indicated differences in the severity of disease, with females having less severe psoriasis (Hagg et al. 2017). Baseline demographics and disease characteristics were balanced across treatment groups in the Controlled Safety Pool, and concomitant medication use was generally similar across treatment groups.

Adequacy of the Safety Database

While the safety database presented by the Applicant is of sufficient size to assess the safety of deucravacitinib for the treatment of moderate to severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy, it is not sufficient to identify risks that may arise with long-term use of deucravacitinib. The database is also not considered adequate to identify adverse pregnancy, fetal, or infant outcomes or determine risk-benefit in the pediatric population as deucravacitinib use in these populations was not studied. The demographics of the safety population are sufficiently representative of the target population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data quality and fitness were evaluated in conjunction with the Office of Computational Science (OCS) JumpStart team who audited results against the Applicant's study reports. The team confirmed that adverse events matched to MedDRA version 23.0 for Trial IM011046 and MedDRA version 23.1 for Trials IM011047, IM011075, and the Integrated Summary of Safety (ISS). Dataset modifications were required to update the subject level (ADSL) dataset as the presence of multiple treatment period dates/time variables caused JMP Clinical to attempt

“Crossover Detection” in many reports, resulting in incorrect counts.

During the course of the review, multiple requests were sent to the Applicant requesting information and tables for adverse events of special interest (AESI) and laboratory abnormalities for subjects who did not switch treatment in order to better detect an association between drug use and an adverse event. Information across all deucravacitinib programs (e.g., systemic lupus erythematosus and inflammatory bowel disease) was also requested for MACE, malignancy including lymphoma, thrombosis, and aneurysm to gain a broader picture of potential risks.

The team also collaborated with the Office of Scientific Investigations (OSI) to select sites for clinical inspections.

Due to non-compliance issues, the review team decided to exclude data from Trial IM011046/Site 0092 and requested the Applicant provide reanalysis of data to exclude the 2 subjects enrolled at this site. Refer to Section [4.1](#) for details.

Categorization of Adverse Events

According to the Applicant, an adverse event (AE) was defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a subject administered study drug and that does not necessarily have a causal relationship with study treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

For Trials IM011046, IM011047, and the Integrated Summary of Safety (ISS), the Applicant defined treatment emergent adverse events (TEAEs) as events that occurred after the first dose of study treatment through 30 days after the final dose of the study treatment or subject’s participation in the trial if the last scheduled visit occurred at a later time. This is not unreasonable given the known PK/PD characteristics of the drug (e.g., PK $t_{1/2}$ ~10h hours and slightly longer PD effect). Nonetheless, analysis of the entire database beyond this defined scope was assessed for AEs.

For Trial IM011075, the Applicant defined an adverse event as treatment emergent if it occurred after the first dose of study drug was given during the IM011075 study and through 30 days after the last dose of study drug in the IM011075 trial. Events that were ongoing during the parent trial (IM011046 or IM011047) and worsened once the study drug was initiated in the IM011075 trial were considered TEAEs.

A serious AE (SAE) was defined as any AE that results in any of the following outcomes:

- Death
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or permanent damage

- Congenital anomaly/birth defect
- An important medical event (defined as a medical event(s) that may not be immediately
- life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1. Each AE was coded to a system organ class (SOC) and preferred term (PT). Laboratory values were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0). The coding of adverse events and grading of laboratory values in the NDA submission appeared adequate and in general allowed for reasonable estimation of AE risks. An exception was the designation of suicidality and depression which were not consistently assessed as AEs despite worsening of these preexisting medical conditions. This issue was discussed in more detail in the review by Dr. Roberta Rasetti of the Division of Psychiatry.

Investigators conducted assessments for AEs at study visits and recorded all observations and other data pertinent to the investigation on each subject treated or entered as a control. Data that was derived from source documents and reported on the case report form (CRF) had to be consistent with the source documents or discrepancies explained. For sites using the Applicant or designee electronic data capture tool, electronic CRFs were prepared for all data collection fields except for fields specific to SAEs and pregnancy, which were reported on the electronic SAE form and paper Pregnancy Surveillance Form, respectively. SAEs, whether related or not related to study drug, and pregnancies were required to be reported to the Medical Monitor within 24 hours of awareness of the event.

If limited information was initially available, follow-up reports were required. If an ongoing SAE changed in its severity or relationship to study drug or if new information became available, the SAE report had to be updated and submitted within 24 hours to the Applicant (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs were required to be followed to "resolution or stabilization".

The definitions of AE, TEAE, and SAE are acceptable. The method of categorizing severity, as well as assessment of causality were adequate. The Applicant's identification and presentation of AEs of special interest were reasonable.

Routine Clinical Tests

The Applicant's safety assessments included clinical evaluation of AEs, SAEs, vital signs, physical examinations, concomitant medications, ECGs, clinical laboratory evaluation (chemistry,

hematology, and urinalysis). Safety assessments also included pregnancy testing at Screening and periodically throughout the trials. Suicidality and depression were assessed using electronic Columbia–Suicide Severity Rating Scale (eC–SSRS) and eight-item Patient Health Questionnaire depression scale (PHQ-8). Subjects received a pretreatment evaluation for tuberculosis (TB). The schedules of safety assessments were similar among the trials.

8.2.4. Safety Results

8.2.4.1. Deaths

As of the 120-day safety update clinical data cut-off (October 1, 2021), a total of 12 deaths were reported in the deucravacitinib psoriasis development program. Of these, 10 occurred in deucravacitinib-, one in placebo-, and one in apremilast-treated subjects.

The Applicant defined a fatal event as a death if it occurred following the first dose of study treatment through 30 days after the final dose of the study treatment or 30 days after a subject's participation in the study if the last scheduled visit occurred at a later time. This is not unreasonable given the known PK/PD characteristics of the drug (e.g., PK $t_{1/2}$ –10h hours and slightly longer PD effect). Nonetheless, analysis of the entire database beyond this defined scope did not identify any additional deaths than what the Applicant reported.

Ten of the 12 deaths in the psoriasis program occurred in subjects who were receiving deucravacitinib, 6 of which were due to COVID-19 and were reported during the long-term extension (LTE) trial that coincided with the pandemic. Although psoriasis development programs for other products cannot be directly compared, excluding deaths due to COVID-19, the proportion of deaths is comparable to the rate observed for most approved Ps products.

Of the other 4 deaths in deucravacitinib -treated subjects, 2 were adjudicated as cardiovascular (CV) deaths (cardiac arrest/cardiac failure in the setting of sepsis that occurred after 4 days of exposure and thoracic aortic aneurysm rupture/hemopericardium after 66 weeks of exposure), one was a cancer death [hepatocellular carcinoma (HCC) after 42 weeks], and one was of unknown cause that was reported on Day 420 (Week 60) but occurred on an unspecified day during the LTE trial.

Summaries of the deaths in deucravacitinib-treated subjects are provided below. The death of the apremilast-treated subject was due to metastatic lung adenocarcinoma (15 weeks), and the death of the placebo subject was caused by "hypertensive heart disease" (Day 17) according to the death certificate.

Subject IM011047-(b) (6): Heart Failure and Sepsis (Day 4)

75-year-old White female with a history of obesity, hypertension, stroke, rheumatoid arthritis (on methotrexate), hypothyroidism and s/p pacemaker placement, received deucravacitinib 6 mg on Day 1. On Day 4, study drug was discontinued because the subject was discovered to be taking a prohibited concomitant medication (leflunomide). On Day 8 no AEs were reported and physical examination including vital signs were within normal limits during an early termination

visit. On trial Day 12, the subject was reported by a family member to have had multiple episodes of “cardiac arrest with resuscitation by emergency medical personnel” and was hospitalized. On trial Day 13, the subject was reported by a family member to have died due to “heart failure” and “sepsis”. Medical records were not available and the information provided could not be independently verified. An autopsy was not performed. The death was considered as not related to study treatment by the investigator.

The contribution of study drug cannot be determined based on limited information, 4 days of exposure to study treatment, multiple comorbidities, and advanced age.

Subject IM011047- (b) (6): Hepatocellular Carcinoma (Day 220/32 weeks)

54-year-old Asian male with a history of type 2 DM, Hepatitis C (reportedly treated), latent tuberculosis (treated (b) (6)), prior tobacco use, and prior use of adalimumab and ustekinumab, was diagnosed with hepatocellular carcinoma (HCC) after receiving treatment with deucravacitinib for 32 weeks.

During Week 32, due to abdominal pain and distention, an abdominal CT Scan with contrast showed cirrhosis with signs of portal hypertension, including para-esophageal and gastric varices, splenomegaly, moderate ascites, as well as thrombosis of the splenic, superior mesenteric, main portal and right portal veins. There was no discrete hypervascular mass to suggest hepatocellular carcinoma. Due to upper GI bleeding, endoscopy was performed. It revealed scarring from prior banding seen in the distal esophagus and 3 columns of grade 2 varices. Colonoscopy showed a liver mass. The following week, the subject developed ascites and an MRI revealed a 5 cm malignant neoplasm of the liver. Study treatment was discontinued. At Week 35, peripancreatic lymph node biopsy confirmed poorly differentiated carcinoma and no lymphoid tissue was identified. Following unspecified immunotherapy, albumin, spironolactone, furosemide, and paracentesis the subject’s health continued to decline and he was transitioned to hospice care. He died during Week 42 with cause of death reported hepatocellular carcinoma.

Although details were not available regarding the subject’s treatment course of hepatitis C, the prior banding suggests previous esophageal varices as a sequelae of portal hypertension and hepatic fibrosis. The subject had multiple risk factors for HCC which were more likely to be contributory to the cause of death than the study drug.

The Drug-Induced Liver Injury (DILI) team determined that this subject’s liver injury is not hepatotoxicity due to deucravacitinib and the HCC is likely a result of background cirrhosis due to hepatitis C. However, the team conveyed that it is plausible for deucravacitinib to have possibly accelerated the course of cancer growth in this subject in a manner similar to the other JAK inhibitors. Dr. Paul Hayashi, DILI Team Lead, Division of Hepatology & Nutrition, identified a case report (Migita et al. 2022) of a 76-year-old male with a history of RA, alcohol use, and cirrhosis who developed rapidly progressive liver cancer following use of JAK inhibitors for 6 months. Based on this case and what is known about the safety profile of JAK inhibitors, Dr. Hayashi recommended the team consider labeling that i) reflects the higher rate of cancers

observed in subjects treated with another JAK inhibitor (i.e., during the tofacitinib PMR trial A3921133), ii) emphasizes imaging in cirrhosis patients prior to treatment, and iii) encourages adherence to liver cancer screening guidelines.

As described in [8.2.5.2](#), an association between deucravacitinib and an overall increased risk for malignancy was not observed. However, a potential lymphoma signal was identified, similar to what is described in labeling for other JAK inhibitors that are approved for the treatment of inflammatory conditions. Therefore, product and patient labeling will reflect the potential lymphoma risk. Additionally, postmarketing evaluation will be recommended to further assess the long-term risk of malignancy in patients with moderate to severe psoriasis receiving deucravacitinib.

After 52 weeks of blinded study treatment, the following subjects transitioned to the LTE trial and received open-label deucravacitinib. Due to different treatment arm assignments during the parent trials, exposure to deucravacitinib varied among these subjects:

Subject IM011075-(b) (6) (IM011046-(b) (6), Placebo Week 0-16, Deucravacitinib Week 16-52): Hemopericardium, Ruptured Thoracic Aortic Aneurysm (66 weeks)

59-year-old White male with history of tobacco use, obesity, hypertension, and sinus tachycardia was found dead at home after receiving 66 weeks of treatment with deucravacitinib. Postmortem findings revealed a ruptured aortic aneurysm, but the details of the autopsy report were not made available to trial site staff. The subject's death certificate listed hemopericardium and thoracic aortic aneurysm rupture.

The subject had underlying disease that may have contributed to his death. The paucity of information does not allow an assessment as to whether study drug was a factor leading to his death.

Subject IM011075-(b) (6) (IM01104-(b) (6), Deucravacitinib Week 0-52): Unknown Cause (60 weeks)

58-year-old White male with a history of excessive alcohol use died on an unspecified day of unknown causes. The subject had an ongoing event of elevated liver enzymes with onset at Day 1 of the LTE trial. His alcohol intake had increased and he was seeking treatment for alcohol abuse, as per the report from his last study visit at which study drug was discontinued due to this event of worsening alcohol abuse. The subject's family informed the trial site on Day 420 of the subject's death—no further information was garnered from an obituary probe or death registry search.

The subject's alcohol dependence might have contributed to his death; however, the paucity of information does not allow assessment as to whether study drug was a factor leading to his death.

Subject IM011075- (b) (6) (IM011047- (b) (6), Deucravacitinib Week 0-52): COVID-19 (73 weeks)

59-year-old White male with a history of morbid obesity was diagnosed with COVID-19 after 73 weeks of treatment with deucravacitinib and died at home soon thereafter.

Subject IM011075- (b) (6) (IM011047- (b) (6), Deucravacitinib Week 0-52): COVID-19 Pneumonia (65 weeks)

84-year-old White male with a history of hypertension, coronary artery disease, and pulmonary fibrosis was diagnosed with COVID-19 after receiving 65 weeks of treatment with deucravacitinib. He required hospitalization due to acute hypoxemic respiratory failure. At Week 67, he was discharged home and died the same day.

Subject IM011075- (b) (6) (IM011047- (b) (6), Deucravacitinib Week 0-52): COVID-19 (89 weeks)

61-year-old White male with a history of hypertension, hyperlipidemia, and DM Type 2 was diagnosed with COVID-19 after receiving 89 weeks of deucravacitinib. Multiorgan failure ensued and the subject died during Week 91.

Subject IM011075- (b) (6) (IM011047- (b) (6), Apremilast Week 0-24, Deucravacitinib Week 24-52): COVID-19 (56 weeks)

64-year-old Asian female with a history of tobacco use, obesity, hypertension, and diabetes mellitus missed her LTE Week 36 visit. Site staff discovered her death upon reading the obituaries. The subject had a positive PCR test after receiving 56 weeks of treatment with deucravacitinib and died at home due to COVID-19 complications.

Subject IM011075- (b) (6) (IM011047- (b) (6), Apremilast Week 0-24, Placebo Week 24-52): COVID-19 (24 weeks)

60-year-old White male with a history of hypertension had a positive COVID-19 test after 24 weeks of receiving deucravacitinib treatment. He was hospitalized for hypoxemic respiratory failure and died during Week 26.

Subject IM011075- (b) (6) (IM011046- (b) (6), Deucravacitinib Week 0-52): COVID-19 (64 weeks)

53-year-old White male with a history of having received a single dose of COVID-19 vaccine, began to develop respiratory symptoms 29 days later. He was diagnosed with bilateral COVID pneumonia and multiple small pulmonary emboli requiring mechanical ventilation and admission to the ICU, then died on Day 472 following 64 weeks of deucravacitinib exposure.

Although this subject did not have comorbid conditions that may have placed him at higher risk for death due to COVID-19, it is difficult to determine the contribution of study drug, if any, in the setting of an active COVID-19 pandemic.

All but one of the subjects who died of COVID-19 had received deucravacitinib during the controlled Phase 3 trials. However, a higher mortality risk due to COVID-19 cannot be directly

attributed to deucravacitinib exposure given the disproportionately greater number of subjects who received deucravacitinib and higher total exposure to deucravacitinib compared to apremilast and placebo (i.e., more subjects could receive deucravacitinib throughout the controlled trials based on the 2:1:1 randomization scheme; at Week 16, all subjects originally randomized to placebo were blindly switched to deucravacitinib; and subjects who did not achieve prespecified PASI thresholds at Week 24, were expected to blindly switch to deucravacitinib).

Furthermore, all of the subjects who died of COVID-19 had existing comorbidities that are associated with increased mortality from severe COVID-19 infection. Due to the limited understanding of this disease caused by a novel virus which lacks long-term characterization, and the unknown effects of TYK2 inhibition in the progression of severe COVID-19, it is difficult to know how the virus impacts and behaves in subjects taking a tyrosine kinase 2 immunomodulating agent. The immunosuppressive potential of deucravacitinib cannot be discounted, but determining the extent of its effect is challenging.

Although COVID-19 testing and reporting may likely be more thorough in a clinical trial setting relative to real world practice, uniform COVID-19 testing during the Phase 3 psoriasis trials was not performed, therefore infection fatality rate (IFR) cannot be confidently estimated. Moreover, the open label design and timing of the LTE trial relative to the pandemic onset does not provide added confidence in assessing the incidence rate of COVID-19 infection in deucravacitinib-treated subjects.

8.2.4.2. Adverse Events

Serious Adverse Events

A number of the serious adverse events are also safety topics of special interest, which include infections, in particular viral reactivation as well as opportunistic; malignancies, inclusive of lymphomas; cardiovascular (CV) events; lipid elevations; gastrointestinal (GI) bleeding; hematological events; as well as hepatic, renal, and muscular events. These findings are described in Section [8.2.5](#).

Dropouts and/or Discontinuations Due to Adverse Effects

During the placebo-controlled period (Week 0-16), a lower proportion of deucravacitinib-treated subjects (20/842, 2.4%) discontinued treatment due to AEs compared to 16/419 (3.8%) and 22/422 (5.2%) in the placebo and apremilast groups, respectively. In the placebo group, AEs leading to treatment discontinuation in 2 or more subjects were psoriasis (4 subjects, 1.0%) and headache (2 subjects, 0.5%). In the apremilast group, AEs leading to treatment discontinuation in 2 or more subjects included diarrhea (6 subjects, 1.4%), nausea (4 subjects, 0.9%), anxiety and headache (3 subjects each, 0.7%) and abdominal pain, myalgia, vomiting (2 subjects each, 0.5%). At Week 16, the most common SOCs for AEs leading to discontinuation in deucravacitinib-treated subjects were Psychiatric Disorders and Investigations, with 5 (0.6%) subjects in each SOC. Two subjects with insomnia and single subjects with depressed mood, altered mood, plus panic attack comprised the Psychiatric Disorders AEs that led to study

discontinuation. Although these events led to treatment discontinuation, Dr. Roberta Rasetti of the Division of Psychiatry determined that there was insufficient evidence of increased risk of suicidal ideation and behavior or other psychiatric adverse reactions with deucravacitinib compared to placebo to warrant language in labeling (Review dated May 9, 2022).

Protocol specified criteria for withdrawal of subjects with a GFR $\leq$ 45 mL/min accounted for the majority of cases (4) in the Investigations SOC. Because apremilast's label requires dose reduction when patients have a GFR $<$ 30 mL/min, the protocols for Trials IM011046 and IM011047 required that randomized subjects have a baseline GFR $\geq$ 45 mL/min and that study treatment be discontinued if a subject's GFR decreased to $<$ 45 mL/min (confirmed by repeat). The 4 subjects during this period, as well as others who had longer exposure and discontinued treatment due to a reduced GFR, are discussed under Renal Events, Section [8.2.5.8](#).

Because subjects did not remain on apremilast for 52 weeks in Trial IM011047, and to minimize bias in the long-term (Weeks 0-52) comparisons between deucravacitinib and apremilast, the Applicant was requested to provide analyses using only the subjects who remained on the same treatment in Trial IM011046 (i.e., excluding subjects who switched from placebo to deucravacitinib at Week 16 and subjects who switched from apremilast to deucravacitinib at Week 24). For deucravacitinib-treated subjects who remained on the same treatment from Weeks 0-52, the distribution of AEs leading to discontinuation by SOC was similar to that of the 16-week placebo controlled period. The following table demonstrates that i) a lower proportion of deucravacitinib-treated subjects compared to apremilast, discontinued treatment due to an AE, ii) the majority of AEs leading to treatment discontinuation occurred in single subjects, and iii) the Psychiatric SOC continued to comprise the most subjects.

Table 56. AEs Leading to Discontinuation of Study Treatment for Subjects in IM011046 Who Were Randomized to and Continued on the Same Active Treatment Controlled Safety Pool Excluding IM011046 Site 0092 – As-Treated Population Week 0 Through Week 52 - Exposure Adjusted Incidence Rate

System Organ Class Preferred Term	DEUC 6 mg QD N=330			Apremilast N=114		
	n (%)	P-Y	IR/ 100 P-Y	n (%)	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	10 (3.0)	297.9	3.4	9 (7.9)	92.4	9.7
Psychiatric disorders	3 (0.9)	298.8	1.0	2 (1.8)	93.1	2.1
Affect lability	1 (0.3)	299.1	0.3	0	93.2	0
Depression	1 (0.3)	299.0	0.3	0	93.2	0
Mood altered	1 (0.3)	299.0	0.3	0	93.2	0
Anxiety	0	299.1	0	1 (0.9)	93.1	1.1
Negative thoughts	0	299.1	0	1 (0.9)	93.1	1.1
Suicidal ideation	0	299.1	0	1 (0.9)	93.1	1.1
Cardiac disorders	2 (0.6)	299.0	0.7	1 (0.9)	93.1	1.1
Myocardial infarction	1 (0.3)	299.0	0.3	1 (0.9)	93.1	1.1
Pericarditis	1 (0.3)	299.0	0.3	0	93.2	0
Infections and infestations	2 (0.6)	298.6	0.7	1 (0.9)	93.1	1.1
Folliculitis	1 (0.3)	298.7	0.3	0	93.2	0
Postoperative wound infection	1 (0.3)	299.0	0.3	0	93.2	0
Cellulitis	0	299.1	0	1 (0.9)	93.1	1.1
Blood and lymphatic system disorders	1 (0.3)	299.0	0.3	0	93.2	0
Lymphopenia	1 (0.3)	299.0	0.3	0	93.2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	299.1	0.3	0	93.2	0
Hodgkin's disease	1 (0.3)	299.1	0.3	0	93.2	0
Pregnancy, puerperium and perinatal conditions	1 (0.3)	299.1	0.3	0	93.2	0
Abortion spontaneous	1 (0.3)	299.1	0.3	0	93.2	0
Skin and subcutaneous tissue disorders	1 (0.3)	299.0	0.3	2 (1.8)	93.0	2.1
Psoriasis	1 (0.3)	299.0	0.3	1 (0.9)	93.1	1.1
Erythema	0	299.1	0	1 (0.9)	93.1	1.1
Gastrointestinal disorders	0	299.1	0	4 (3.5)	92.8	4.3
Diarrhoea	0	299.1	0	2 (1.8)	93.0	2.2
Gastrointestinal pain	0	299.1	0	1 (0.9)	93.1	1.1
Lip swelling	0	299.1	0	1 (0.9)	93.1	1.1
Nausea	0	299.1	0	2 (1.8)	93.0	2.1
Vomiting	0	299.1	0	1 (0.9)	93.1	1.1
Nervous system disorders	0	299.1	0	2 (1.8)	93.0	2.1
Headache	0	299.1	0	2 (1.8)	93.0	2.1

Source: Modified Applicant's Table 3.4.2 from response to information request (IR) dated March 11, 2022.

Abbreviations: DEUC, deucravacitinib; n, number of subjects with event; %, percentage of subjects with event; P-Y, patient years; incidence rate per 100 person-years of exposure (IR/100 P-Y)

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

With longer exposure to deucravacitinib during the entire Phase 3 program (i.e., including subjects who rolled over into the open label extension Trial IM011075), the EAIR of AEs leading to treatment discontinuation were relatively consistent compared to the incidence rate at 52 weeks for subjects who were randomized and remained on the same treatment (5.4/100 PY for pooled Trials IM011046 and IM011047 and 3.4/100 PY for Trial IM011046 only). The following table shows the number, proportion, and EAIRs of subjects who discontinued treatment due to an AE for the entire Phase 3 Safety pool at the time of pre-specified safety data cut-offs.

Table 57. Adverse Events Leading to Treatment Discontinuation ≥ 2 Subjects – Phase 3 Safety Pool – As-Treated Population

Preferred Term	Phase 3 Safety Pool Through 15-Jun-2021 N = 1519 Total P-Y = 2166.9		Phase 3 Safety Pool Through 01-Oct-2021 N = 1519 Total P-Y = 2482.0	
	n (%)	IR/100 P-Y	n (%)	IR/100 P-Y
Total Subjects with an Event	66 (4.3)	3.0	69 (4.5)	2.8
COVID-19	5 (0.3)	0.2	6 (0.4)	0.2
Glomerular filtration rate decreased	5 (0.3)	0.2	5 (0.3)	0.2
Psoriasis	4 (0.3)	0.2	4 (0.3)	0.2
Blood creatine phosphokinase increased	3 (0.2)	0.1	3 (0.2)	0.1
Diarrhea	3 (0.2)	0.1	3 (0.2)	0.1
Rash	3 (0.2)	0.1	3 (0.2)	0.1
Fatigue	2 (0.1)	0.1	2 (0.1)	0.1
Insomnia	2 (0.1)	0.1	2 (0.1)	0.1
Lymphadenopathy	2 (0.1)	0.1	2 (0.1)	0.1
Malignant melanoma	2 (0.1)	0.1	2 (0.1)	0.1
Vomiting	2 (0.1)	0.1	2 (0.1)	0.1

Source: Applicant's 120-day safety updated report (SUR) Table 2.6-1

Abbreviations: n, number of subjects with event; %, percentage of subjects with event; P-Y, patient years; incidence rate per 100 person-years of exposure (IR/100 P-Y)

Significant Adverse Events

According to the ICH guideline for industry E3 Structure and Content of Clinical Study Reports, significant adverse events include: marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy, other than those reported as serious adverse events.

The majority of these adverse events are discussed in Section [8.2.5](#).

Adverse events affecting the skin (folliculitis and acne) and mucosal surfaces (mouth ulcerations), as well as events of hypersensitivity will be discussed in this section, separate from the issues considered to be areas of safety interest due to deucravacitinib's understood inhibition of signaling downstream of Type I IFNs, IL-12, and the IL-23/IL-17 pathway and concerns with the JAK inhibitor class.

Folliculitis and Acne

Results of nonclinical studies ($\geq$ 3-month monkey studies) submitted by the Applicant demonstrated a variety of skin changes including swelling, dryness, flaking, papule, redness, or scabbing at doses at or above 4 times the human exposure at the 6 mg once daily (QD). These skin findings were observed on oral mucosal surfaces (buccal mucosa, lips, and gums), dorsum, fore- and hindlimbs, fore- and hindpaws, interscapular area, genitals, and tail. While no definitive microbial pathogens were deemed to be causative or contributing factors, the Applicant considered that the skin changes were likely caused by microbial pathogens given that the lesions generally improved following antibiotic treatment and occurred in the context of immunosuppression. According to the Applicant, "the skin changes did not result in any preterminal deaths or unscheduled euthanasia, were clinically monitorable and manageable with veterinary treatments, and trended towards reversibility during recovery".

During the placebo-controlled period (Week 0-16), the incidence of skin AEs was higher in the deucravacitinib group (8.6%) compared with the placebo (2.4%) and apremilast (2.8%) groups as shown in the following table. The most common events were folliculitis and acne which typically occurred on the face or torso, resolved spontaneously or with topical/oral antimicrobial agents, and mostly occurred within the first 8 weeks of treatment. None of the skin AEs were serious. A single event each of folliculitis and rosacea led to treatment discontinuation.

Table 58. Skin Adverse Events of Interest - Controlled Safety Pool (Week 0-16) – As-Treated Population

Preferred Term [n (%) m]	BMS-986165 6 mg QD N = 842	Placebo N = 419	Apremilast N = 422
TOTAL SUBJECTS WITH AN EVENT	72 (8.6) 84	10 (2.4) 13	12 (2.8) 16
FOLLICULITIS	14 (1.7) 15	0	0
ACNE	10 (1.2) 10	1 (0.2) 1	0
PRURITUS	9 (1.1) 10	4 (1.0) 4	5 (1.2) 5
RASH	8 (1.0) 10	0	1 (0.2) 1
ROSACEA	8 (1.0) 8	0	2 (0.5) 2
ECZEMA	5 (0.6) 5	1 (0.2) 1	1 (0.2) 1
SKIN INFECTION	3 (0.4) 3	0	0
BLISTER	2 (0.2) 2	0	0
DERMATITIS ACNEIFORM	2 (0.2) 2	0	0
PARONYCHIA	2 (0.2) 2	2 (0.5) 2	0
PERIORAL DERMATITIS	2 (0.2) 2	0	0
SUBCUTANEOUS ABSCESS	2 (0.2) 2	0	0
URTICARIA	2 (0.2) 2	1 (0.2) 4	2 (0.5) 2
DERMATITIS	1 (0.1) 1	1 (0.2) 1	0
DERMATITIS CONTACT	1 (0.1) 2	0	1 (0.2) 1
INTERTRIGO	1 (0.1) 1	0	0
MECHANICAL URTICARIA	1 (0.1) 1	0	0
PUSTULE	1 (0.1) 1	0	0
RASH PUSTULAR	1 (0.1) 2	0	0
SEBORRHOEIC DERMATITIS	1 (0.1) 1	0	0
SKIN ULCER	1 (0.1) 2	0	0
DERMATITIS ATOPIC	0	0	1 (0.2) 1
ECZEMA ASTEATOTIC	0	0	1 (0.2) 1
PRURITUS ALLERGIC	0	0	1 (0.2) 1
URTICARIA PAPULAR	0	0	1 (0.2) 1

Source: Applicant's SCS table 2.7.1.3-1.

Abbreviations: BMS-986165 = deucravacitinib; n = number of subjects; m = number of events.

After 52-weeks of exposure, skin AEs continued to be reported at higher frequencies in subjects receiving deucravacitinib compared to those receiving apremilast. Acne and folliculitis remained the most common skin AE. None of the skin AEs were serious. It's unclear if the events of folliculitis represent infectious folliculitis or drug-induced follicular eruptions. The latter seems less likely as the majority of the events spontaneously resolved despite continuation of study drug or improved with antimicrobial intervention.

With longer exposure, skin AEs did not appear to increase with time based on EAIRs. Both acne and folliculitis will be described in labeling as adverse reactions occurring in $\geq 1\%$ of deucravacitinib-treated subjects.

Mucosal Ulcers

As described above, nonclinical studies in monkeys demonstrated a variety of changes such as swelling, dryness, flaking, papules, redness, or scabbing on oral mucosal surfaces (buccal mucosa, lips, and gums) at doses at or above 4 times the human exposure at the 6 mg QD. Although the pathophysiology of these lesions is unknown, the Applicant purports a microbial etiology.

The review team pooled preferred terms (PTs): aphthous ulcer, stomatitis, mouth ulceration and tongue ulceration to gain a better understanding of the frequencies at which these events occurred.

During the trials IM011046 and IM011047, mouth ulcerations occurred at a higher rate in subjects treated with deucravacitinib compared to other treatment groups as shown in the following tables.

Table 59. Mouth Ulceration Reported Summary (Week 0 through Week 16) Treatment Based on Actual Treatment Regimens Without Switching

	BMS-986165 6 mg QD N=840				Apremilast 30 mg BID N=422				Placebo N=419			
	n	%	PY	EAIR	n	%	PY	EAIR	n	%	PY	EAIR
Mouth ulceration	16	1.9	248.5	6.4	0	0.0	125.4	0.0	0	0.0	123.0	0.0

Source: Statistical Reviewer generated analysis based on Applicant submitted data (adae.xpt, adsl.xpt).

Number of subjects in Trials IM011046 and IM011047 calculated by actual treatment received and using SAFFL == "Y".

Number of adverse events calculated using SAFFL == "Y", TRTEMFL == "Y" and (APERIOD == 1) and AEDECOD includes Aphthous ulcer, Stomatitis, Mouth ulceration, Tongue ulceration.

Abbreviations: n = Number of subjects with event; % = Proportion of subjects with event out of number of subjects assigned by actual treatment; PY = Patient-Year; EAIR = Exposure-Adjusted Incidence Rate

Patient year calculated by: 1) If subject did not experience AE and treatment status is discontinued, then exposure time = time in treatment + 30 days 2) If subject did not experience AE and treatment status is completed, then exposure time = time in treatment 3) If subject experienced an AE, exposure time = treatment time up to analysis start date.

Subjects who were discontinued at Week 16 are included.

Subjects from Trial IM011046, Site 0092, are omitted.

Table 60. Mouth Ulceration Reported Summary (Week 0 through Week 24) Treatment Based on Actual Treatment Regimens Without Switching

	BMS-986165 6 mg QD N=840				Apremilast 30 mg BID N=422			
	n	%	PY	EAIR	n	%	PY	EAIR
Mouth ulceration	17	2.0	361.3	4.7	1	0.2	180.3	0.6

Source: Reviewer generated analysis based on Applicant submitted data (adae.xpt, adsl.xpt).

Number of subjects in Trials IM011046 and IM011047 calculated by actual treatment received and using SAFFL == "Y".

Number of adverse events calculated using SAFFL == "Y", TRTEMFL == "Y" and (APERIOD == 1 or APERIOD == 2) and AEDECOD includes Aphthous ulcer, Stomatitis, Mouth ulceration, Tongue ulceration.

Abbreviations: n = Number of subjects with event; % = Proportion of subjects with event out of number of subjects assigned by actual treatment; PY = Patient-Year; EAIR = Exposure-Adjusted Incidence Rate

Patient year calculated by: 1) If subject did not experience AE and treatment status is discontinued, then exposure time = time in treatment + 30 days 2) If subject did not experience AE and treatment status is completed, then exposure time = time in treatment 3) If subject experienced an AE, exposure time = treatment time up to analysis start date.

Subjects who were discontinued at Week 24 are included.

Subjects from Trial IM011046, Site 0092, are omitted.

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Table 61. Mouth Ulceration Reported Summary (Week 0 through Week 52) Treatment Based on Actual Treatment Regimens Without Switching

AESI	BMS-986165 6 mg QD N=330				Apremilast 30 mg BID N=114			
	n	%	PY	EAIR	n	%	PY	EAIR
Mouth ulceration	10	3.0	293.1	3.4	0	0.0	93.2	0.0

Source: Reviewer generated analysis based on Applicant submitted data (adae.xpt, adsl.xpt).

Number of subjects in Trials IM011046 calculated by actual treatment received and using SAFFL == "Y".

Number of adverse events calculated using SAFFL == "Y", TRTEMFL == "Y" and (APERIOD == 1 or APERIOD == 2 or APERIOD == 3) and AEDECOD includes Aphthous ulcer, Stomatitis, Mouth ulceration, Tongue ulceration.

Abbreviations: n = Number of subjects with event; % = Proportion of subjects with event out of number of subjects assigned by actual treatment; PY = Patient-Year; EAIR = Exposure-Adjusted Incidence Rate

Patient year calculated by: 1) If subject did not experience AE and treatment status is discontinued, then exposure time = time in treatment + 30 days 2) If subject did not experience AE and treatment status is completed, then exposure time = time in treatment 3) If subject experienced an AE, exposure time = treatment time up to analysis start date.

Subjects who were discontinued at Week 52 are included.

Subjects from Trial IM011046, Site 0092, are omitted.

Given the frequency (i.e., $\geq 1\%$ during the first 16 weeks) and significant imbalance between treatment arms, mouth ulcers will be labeled in Section 6 as an adverse reaction in deucravacitinib-treated subjects. The mechanism by which deucravacitinib impacts the mucosa is not clear. The majority of ulcerative lesions were labeled as aphthous ulcers. While the etiology of aphthous ulcers is idiopathic and multifactorial, it likely involves activation of the cell-mediated immune system (Plewa and Chatterjee 2022). There were no other events involving mucosal surfaces suggestive of an immune mediated mechanism. In particular, there were no events of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

Additionally, there were no mucosal events suggesting severe immunosuppression as a potential mechanism, aside from some cases of herpetic viral reactivation (e.g., multidermatomal zoster). Of the few cases of enterocolitis in subjects receiving deucravacitinib, one was secondary to a viral infection and none directly led to interruption or discontinuation of study drug. Furthermore, a case of cytomegalovirus (CMV) infection involving the gastrointestinal tract (described in Section [8.2.5.1](#) Infections) was reported in a subject with a history of colorectal cancer and colostomy. The subject received symptomatic care with acetaminophen and loperamide and resumed study treatment following temporary interruption of dosing.

Other than the aforementioned oral ulcers, events related to disruption of a mucosal surface were infrequent and none were severe or appeared to signify severe immunosuppression or an immune mediated mechanism. This is dissimilar to other JAK inhibitors indicated for various inflammatory conditions which are labeled for GI perforation. GI perforation was not reported in any subject with psoriasis treated with deucravacitinib.

Gastrointestinal Bleeding

Gastrointestinal bleeding (GIB) was reviewed as a safety issue of concern because of the increased frequency of AEs involving mucosal surfaces (e.g., mouth ulcerations and aphthous ulcers) in the deucravacitinib group relative to the placebo and apremilast groups, as well as events of gastrointestinal perforation reported in clinical trials with JAK inhibitors in the treatment of chronic inflammatory conditions (although the role of JAK inhibition in these events is not known), further evaluation of gastrointestinal bleeding (GIB) was conducted. The review team's analyses did not demonstrate a significantly disproportionate number of subjects with GIB events in the deucravacitinib group. Additionally, the deucravacitinib-treated subjects with events had confounding factors (i.e., malignancy and excessive alcohol use) that made it difficult to attribute causality. Refer to [8.2.5.5](#) for discussion of GIB.

Hypersensitivity

Preferred terms of hypersensitivity, drug hypersensitivity, anaphylactic reaction, urticaria, mechanical urticaria, urticaria papular, face edema, swelling face, eyelid edema, and lip swelling were pooled in attempts to identify subjects who experienced hypersensitivity reactions and to more clearly assess the frequencies at which these reactions occurred.

In the first 16 weeks of treatment, the proportions of subjects who reported an event of hypersensitivity were comparable across treatment groups (5, 0.6% for deucravacitinib; 2, 0.5% for placebo; and 4, 0.9% for apremilast). The majority of AEs associated with deucravacitinib during this period were mild, transient cases of urticaria that resolved without change in dosing of study drug and were considered unrelated. One subject (IM011047- (b) (6)) had an anaphylactic reaction that was severe and serious but unrelated to drug treatment (due to multiple wasp stings). Another hypersensitivity event that led to study discontinuation is described below.

Subject IM011047- (b) (6): Facial Allergic Reaction Leading to Treatment Discontinuation

60-year old White male with a history of hypertension and hypercholesterolemia was reported to have mild hypersensitivity (related, verbatim: facial allergic reaction) on Study Day 2. The subject did not receive treatment for this event. Study drug was discontinued due to hypersensitivity, with the last dose of study treatment received on Day 5. On Day 8, hypersensitivity was reported as resolved. The subject discontinued from the study on Day 44 due to this adverse event.

While this report of hypersensitivity was described as mild by the investigator, it led to discontinuation of study drug. An information request was sent to the Applicant to retrieve details specific to the presence or absence of associated facial swelling. According to the Applicant, no concurrent angioedema or swelling was reported.

After 52 weeks of exposure, 4 more subjects in the Controlled Safety Pool who did not switch treatment, reported *moderate, unrelated hives* (IM011046- (b) (6)); *moderate, unrelated skin dermographism/mechanical urticaria* (IM011046- (b) (6)); *mild, related urticaria* (IM011046- (b) (6)); and *mild, unrelated hives generalized* (IM011047- (b) (6)). None of the events were considered serious, led to study discontinuation, or resulted in dose interruption. One subject (IM011047- (b) (6)), a 40-year-old white female reported sudden onset moderate facial swelling during Week 24-52, after 37 weeks of exposure to deucravacitinib that was not serious and did not lead to study discontinuation. No other symptoms and no precipitating events or new concomitant medications were reported. A computed tomography (CT) scan of the head and a CT angiogram were performed and were normal. The subject received prednisolone and aspirin for the AEs. Both AEs resolved without interruption or modification of drug dosing. Laboratory values for IgE and eosinophils remained within normal limits. The subject continued on deucravacitinib into the OLE trial with no further AEs of facial swelling.

The etiology of this subject's facial swelling is unknown. The event resolved and did not recur despite continuation of study drug. Based on the information, it is unlikely that the facial swelling was drug-induced.

For subjects who switched treatment, there was one subject (IM011047- (b) (6)) who experienced severe urticaria that led to treatment discontinuation 6 days after switching from apremilast to deucravacitinib. Her brief narrative follows.

Subject IM011047- (b) (6): Urticaria Leading to Treatment Discontinuation

51-year old White female with a history of drug allergies developed severe urticaria (verbatim: diffuse allergic urticaria) during Week 25, 6 days after transitioning from apremilast to deucravacitinib. Her lesions were on the face, chest, back, abdomen, and upper extremity, which was disseminated, erythematous, and associated with pruritus. The subject did not experience a similar event previously. She received treatment with triamcinolone, loratadine, and intramuscular betamethasone. Two days later, she discontinued from the study due to urticaria. The event was unresolved at the early termination visit on Day 178.

This report of a disseminated allergic reaction classified by the investigator under the High Level Group Term, Angioedema and urticaria, involved the skin and subcutaneous tissue and resulted in treatment discontinuation. Involvement of the subcutaneous tissue is consistent with angioedema; thus, this case clinically represents a case of probable drug induced angioedema. Angioedema can be severe and life threatening when it involves the respiratory tract. Labeling should inform for the potential of this serious adverse reaction.

The information provided in the SUR identified 2 subjects who developed face edema/swelling during the long-term OLE trial, IM011075.

Subject IM011047- (b) (6)

47-year-old White female who initially received placebo then transitioned to deucravacitinib at Week 16 during Trial IM011047, reported face edema after 50 weeks of exposure to deucravacitinib.

The information provided for this subject within the datasets and case report form disclosed concurrent facial redness. Worsening psoriasis was also reported around the same time and might account for the facial signs and symptoms, therefore, this case does not appear to be consistent with drug-induced angioedema.

Subject IM011046- (b) (6)

36 year-old White female who initially received apremilast through Week 24 then transitioned to deucravacitinib during Trial IM011046, reported transient facial swelling lasting less than 1 day during the OLE trial after 43 weeks of exposure to deucravacitinib. The event was not considered serious and did not lead to study drug discontinuation. The subject was also reported to have had a nonserious AE of drug hypersensitivity due to robaxacet initiated for an AE of neurologic amyotrophy (Parsonage Turner Syndrome) but no further events of facial swelling occurred.

Based on the information provided, this report of a "swollen face" is not consistent with drug-induced angioedema.

Overall, while hypersensitivity AEs were infrequent in the deucravacitinib group, there were events of urticaria, allergic reactions, and a case consistent with drug-induced angioedema that led to discontinuation of study drug.

These events indicate a potentially significant risk as patients with even mild symptoms of mast cell/basophil activation (e.g., urticaria and localized angioedema) can develop fulminant, life threatening anaphylaxis with repeated re-exposure over time.

Therefore, inclusion of hypersensitivity reactions in Section 4 Contraindications, Section 5 Warnings and Precautions, (b) (6) of the full prescribing information (FPI), as well as in the Medication Guide, is recommended.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment-emergent AEs (TEAEs) are defined as events that occurred after the first dose of study treatment through 30 days after the final dose of the study treatment or subject's participation in the study if the last scheduled visit occurred at a later time.

Adverse events were summarized as both subject incidence rates and exposure-adjusted incidence rates per 100 PYs. The former provided the basis of assessment for the 16 week Controlled Safety Pool while the latter provided for a more adequate assessment of the long term safety data given the varied duration of exposure across different treatment groups. The exposure adjusted rates also enabled comparison of data across the short-term and long-term analysis sets.

The review team pooled preferred terms (PTs) which likely describe the same AE to obtain a clearer understanding of the frequencies at which these events occurred. The following table demonstrates the pooled terms:

Table 62. Pooled Preferred Terms

System Organ Class (SOC)	Preferred Term (PT)	Pooled terms
Infections and infestations	Upper Respiratory Infections	upper respiratory tract infection (viral, bacterial, and unspecified), nasopharyngitis, pharyngitis (including viral, bacterial, streptococcal, and unspecified), sinusitis (includes acute, viral, bacterial), rhinitis, rhinotracheitis, tracheitis, laryngitis, tonsillitis (including bacterial, streptococcal, and unspecified), pharyngotonsillitis
Cardiac disorders	Acute coronary syndrome	myocardial infarction, acute myocardial infarction, coronary artery occlusion, myocardial ischemia, coronary artery disease, cardiac arrest, coronary artery stenosis, arteriosclerosis coronary artery, angina unstable

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Vascular disorders	Thrombosis	thrombosis, deep vein thrombosis, pulmonary embolism, peripheral arterial occlusion, peripheral arterial occlusive disease, iliac artery occlusion
Skin and subcutaneous tissue disorders	Acne	acneiform rash, acne cystic, dermatitis acneiform
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	myalgia, myopathy, musculoskeletal pain, musculoskeletal stiffness, muscle spasms, pain in extremity, myofascial pain syndrome, muscle injury, arthralgia, back pain, bone pain, neck pain, spinal pain, joint stiffness
Immune system disorder	Hypersensitivity	hypersensitivity, drug hypersensitivity, anaphylactic reaction, urticaria, mechanical urticaria, urticaria papular, face edema, swelling face, eyelid edema, lip swelling
Gastrointestinal disorders	Gastrointestinal bleed	hematochezia, gastrointestinal hemorrhage, hematemesis, rectal hemorrhage
	Mouth ulceration	mouth ulceration, aphthous ulcer, tongue ulceration, lip ulceration, angular cheilitis, stomatitis

As described in Section [8.2.1](#), to address treatment switching, comparisons between treatment groups were based on subjects who did not switch treatment. Therefore, within this section, comparative assessments between deucravacitinib, placebo, and apremilast at 16 weeks, and deucravacitinib compared to apremilast at 52 weeks of exposure will be described. Because subjects did not stay on apremilast for 52 weeks in Trial IM011047, only the subjects who did not switch treatment in Trial IM011046 (i.e., excluding subjects who switched from placebo to deucravacitinib at Week 16 and subjects who switched from apremilast to deucravacitinib at Week 24) were used in the comparative safety analysis between deucravacitinib and apremilast at 52 weeks of exposure.

In the first 16 weeks of treatment, 469 (55.7%) subjects in the deucravacitinib group experienced at least 1 AE, which was comparable to apremilast and placebo groups in which 243 (57.6%) and 208 (49.6%) subjects, respectively, experienced an AE. The proportions of subjects reporting AEs in the SOCs of Infections and Infestations and Skin and Subcutaneous Tissue Disorders were higher in the deucravacitinib group compared with the placebo and apremilast groups, primarily driven by PTs of Upper Respiratory Infections, folliculitis, and acne. A higher incidence of hypertension PT in the deucravacitinib group compared to the placebo group was reported; however, blood pressure was assessed separately and there was no

clinically meaningful change from baseline in blood pressure observed in any treatment group as further discussed in Section 8.2.5.3. Therefore, labeling for hypertension is not recommended despite the imbalance reported for the PT.

Common adverse events reported in the Controlled Safety Pool are shown in the table below.

Table 63. Most Frequent Adverse Events Reported in ≥ 1% of Subjects, by Frequency of PT in 16 Weeks (Controlled Safety Pool)

Preferred Term	BMS-986165 6 mg QD N=840				Apremilast 30 mg BID N=422				Placebo N=419			
	n	%	PY	EAIR	n	%	PY	EAIR	n	%	PY	EAIR
Upper Respiratory Infections	163	19.4	224.2	72.7	74	17.5	113.2	65.4	63	15.0	113.3	55.6
Musculoskeletal pain	47	5.6	244.3	19.2	35	8.3	118.6	29.5	20	4.8	119.9	16.7
Headache	38	4.5	242.7	15.7	45	10.7	115.2	39.1	19	4.5	118.8	16.0
Diarrhea	37	4.4	243.1	15.2	50	11.8	113.9	43.9	25	6.0	117.2	21.3
Blood creatine phosphokinase increased	23	2.7	247.1	9.3	3	0.7	124.7	2.4	5	1.2	121.7	4.1
Mouth ulceration	16	1.9	248.5	6.4	0	0.0	125.4	0.0	0	0.0	123.0	0.0
Hypertension	15	1.8	248.2	6.0	11	2.6	123.5	8.9	1	0.2	122.8	0.8
Nausea	14	1.7	247.4	5.7	42	10.0	115.5	36.4	7	1.7	121.1	5.8
Folliculitis	14	1.7	249.3	5.6	0	0.0	125.4	0.0	0	0.0	123.0	0.0
Psoriasis	12	1.4	249.1	4.8	9	2.1	123.5	7.3	14	3.3	120.5	11.6
Fatigue	12	1.4	249.4	4.8	2	0.5	125.0	1.6	5	1.2	121.6	4.1
Acne	12	1.4	248.9	4.8	0	0.0	125.4	0.0	1	0.2	123.0	0.8
Oral herpes	11	1.3	249.9	4.4	1	0.2	125.1	0.8	1	0.2	122.8	0.8
Cough	10	1.2	250.2	4.0	3	0.7	124.6	2.4	5	1.2	121.8	4.1
Pruritus	9	1.1	249.3	3.6	5	1.2	124.2	4.0	4	1.0	121.9	3.3
Oropharyngeal pain	9	1.1	250.1	3.6	2	0.5	125.1	1.6	3	0.7	122.6	2.4
Urinary tract infection	8	1.0	250.4	3.2	3	0.7	124.5	2.4	4	1.0	121.9	3.3
Rosacea	8	1.0	249.8	3.2	2	0.5	125.2	1.6	0	0.0	123.0	0.0
Rash	8	1.0	250.0	3.2	1	0.2	125.3	0.8	0	0.0	123.0	0.0

Source: Statistical Reviewer's Analysis.

During the Week 0-52 exposure period in Trial IM011046, AEs were most commonly reported in the SOCs of Infections and Infestations and Musculoskeletal and Connective Tissue Disorders.

With longer duration of treatment, frequently reported AEs remained essentially unchanged. The most frequent AEs reported in ≥ 1% of deucravacitinib compared to apremilast in Trial IM011046 is shown in the table below.

Table 64. Most Frequent Adverse Events Reported in ≥ 1% of Subjects, by Frequency of PT in 52 Weeks, As-Treated Population, Trial IM011046

Preferred Term	BMS-986165 6 mg QD N=330				Apremilast 30 mg BID N=114			
	n	%	PY	EAIR	n	%	PY	EAIR
Upper Respiratory Infections	135	40.9	224.0	60.3	28	24.6	76.9	36.4
Musculoskeletal pain	39	11.8	277.9	14.0	16	14.0	85.6	18.7
Headache	29	8.8	282.4	10.3	17	14.9	83.2	20.4
Diarrhea	23	7.0	286.0	8.0	16	14.0	84.1	19.0
Cough	13	3.9	293.5	4.4	2	1.8	91.7	2.2
Acne	13	3.9	289.7	4.5	0	0.0	93.2	0.0
Blood creatine phosphokinase increased	12	3.6	292.3	4.1	3	2.6	91.8	3.3
Mouth ulceration	10	3.0	293.1	3.4	0	0.0	93.2	0.0

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Preferred Term	BMS-986165 6 mg QD N=330				Apremilast 30 mg BID N=114			
	n	%	PY	EAIR	n	%	PY	EAIR
Pruritus	8	2.4	294.5	2.7	3	2.6	91.9	3.3
Influenza	8	2.4	294.9	2.7	2	1.8	92.6	2.2
Psoriasis	8	2.4	295.4	2.7	2	1.8	92.2	2.2
Nausea	7	2.1	292.6	2.4	19	16.7	81.5	23.3
Hypertension	7	2.1	293.1	2.4	8	7.0	89.4	8.9
Folliculitis	7	2.1	295.4	2.4	1	0.9	92.7	1.1
Urinary tract infection	7	2.1	295.6	2.4	0	0.0	93.2	0.0
Hypersensitivity	5	1.5	296.0	1.7	3	2.6	91.7	3.3
Fatigue	5	1.5	295.9	1.7	2	1.8	91.8	2.2
Toothache	5	1.5	296.4	1.7	2	1.8	92.0	2.2
Abdominal pain	5	1.5	296.6	1.7	1	0.9	92.4	1.1
Alanine aminotransferase increased	5	1.5	295.8	1.7	1	0.9	92.8	1.1
Nasal congestion	5	1.5	297.3	1.7	1	0.9	93.1	1.1
Oral herpes	5	1.5	296.3	1.7	1	0.9	92.7	1.1
Oropharyngeal pain	5	1.5	295.9	1.7	1	0.9	92.7	1.1
Constipation	5	1.5	295.8	1.7	0	0.0	93.2	0.0
Rosacea	5	1.5	295.2	1.7	0	0.0	93.2	0.0
Abdominal pain upper	4	1.2	296.6	1.3	4	3.5	91.3	4.4
Vomiting	4	1.2	297.5	1.3	4	3.5	91.9	4.4
Contusion	4	1.2	297.6	1.3	2	1.8	91.5	2.2
Dental caries	4	1.2	296.7	1.3	1	0.9	93.0	1.1
Blood triglycerides increased	4	1.2	296.0	1.4	0	0.0	93.2	0.0
C-reactive protein increased	4	1.2	297.6	1.3	0	0.0	93.2	0.0
Hypoesthesia	4	1.2	297.3	1.3	0	0.0	93.2	0.0
Ligament sprain	4	1.2	297.7	1.3	0	0.0	93.2	0.0
Pyrexia	4	1.2	297.9	1.3	0	0.0	93.2	0.0
Spinal osteoarthritis	4	1.2	297.3	1.3	0	0.0	93.2	0.0

Source: Statistical Reviewer's Analysis.

Laboratory Findings

Clinical safety laboratory evaluations were performed in the Phase 3 psoriasis trials at Baseline, Week 1, Week 2, Week 4, and then every 4 weeks through the end of study in Trials IM011046 and IM011047 and at every visit in Trial IM011075.

Laboratory findings were assessed as a comparison between deucravacitinib and placebo at Week 16 and between deucravacitinib and apremilast at Weeks 24 and 52. These parameters are discussed in detail in Section [8.2.5](#) Analysis of Submission-Specific Safety Issues with evaluation of mean change from baseline, AEs based on laboratory abnormalities, worst toxicity CTCAE grades, and shifts ≥ 2 CTCAE grade from baseline. A brief summary of findings is provided below:

- Cytopenias were rare, primarily low-grade, and there was no mean change in hemoglobin or cell counts for lymphocytes, natural killer cells, and neutrophils.
- Evaluation of lipids did not show a significant increase in the atherogenic index assessed by ratios of Total Cholesterol:HDL and LDL-C:HDL; however, a notable increase in mean triglyceride levels, as well as hypertriglyceridemia TEAEs and higher toxicity grade hypertriglyceridemia were observed.

- The differences in liver enzyme elevations between the deucravacitinib, apremilast, and placebo groups varied without a clear concern for liver injury risk with deucravacitinib. Specifically, during the placebo- and active-controlled period, subjects in the deucravacitinib group had the highest AST elevation (1.5%, $\geq 3 \times$ ULN) among all subjects. By Week 24, deucravacitinib-treated subjects experienced more ALT, AST and bilirubin elevation compared to apremilast-treated subjects, but the difference for ALT was not sustained at $>5 \times$ ULN. For AST, the differences persisted at $>5 \times$ ULN but more modestly than at $>3 \times$ ULN.
- The effect of deucravacitinib on renal function appeared inconsistent as the mean change in serum creatinine was stable and comparable across treatment groups and there was not a clear imbalance of serum creatinine events upon assessment of TEAEs, toxicity grade and shifts ≥ 2 CTCAE grades; however, more deucravacitinib-treated subjects reported a reduction in glomerular filtration rate (GFR) and discontinued treatment due to a reduced GFR of < 45 mL/min compared to the apremilast and placebo groups. Further, in deucravacitinib-treated subjects with already reduced GFRs, worsening proteinuria was observed.
- Treatment with deucravacitinib was associated with an increased incidence of CPK elevation compared to treatment with placebo and apremilast. There was also a higher proportion of Grade 4 CPK elevations ($>10 \times$ ULN) with deucravacitinib treatment and reports of associated rhabdomyolysis and myopathy (including pain and muscle weakness) occurring with higher grade events.

During clinical trials conducted with JAK inhibitors for the treatment of inflammatory conditions, there have been particular laboratory findings that appear to be shared by this class of drugs and are labeled as adverse reactions. These include hematologic abnormalities (neutropenia, lymphopenia, anemia, thrombocytopenia, as well as platelet elevations), lipid elevations, liver enzyme elevations, creatine phosphokinase (CPK) elevations, and elevated serum creatinine.

While comparisons were made with other JAK inhibitors, cross-comparisons with clinical trials for JAK inhibitors in other indications have significant limitations on the interpretation. The data from the psoriasis clinical trials did not demonstrate the same impact for deucravacitinib on the bone marrow as is seen with other JAK inhibitors. Other laboratory findings overlapped with those labeled for the JAK inhibitor class approved for inflammatory conditions. The findings are summarized as below:

- Deucravacitinib's impact on hematological AEs, higher grade effects, and mean change showed little to no effect on lymphocytes, neutrophils, hemoglobin, and platelets; however, approved JAK inhibitors indicated for the treatment of chronic inflammatory conditions are labeled for a number of various cytopenias.
- Deucravacitinib's effect on lipids appears to only result in elevation of triglycerides whereas hyperlipidemia AEs paralleled mean increases in cholesterol for other JAK inhibitors approved for inflammatory conditions.

- Elevated transaminases in the deucravacitinib group were reported, but there was no evidence of liver injury as assessed by the Drug Induced Liver Injury (DILI) team.
- Similar to what has been observed for other JAK inhibitors approved for inflammatory conditions, treatment with deucravacitinib was associated with an increased incidence of CPK elevation relative to comparator groups.
- There was no mean change for serum creatinine although increases in this laboratory parameter was seen with other JAK inhibitors approved for inflammatory conditions.

Vital Signs

There were no clinically meaningful changes in vital sign parameters (blood pressure, respiratory rate, pulse rate, or temperature) in the Controlled Safety Pool or in the safety update reporting period. A higher incidence of hypertension PT in the deucravacitinib group compared to the placebo group was reported; however, there was no clinically meaningful change from baseline in blood pressure observed in any treatment group as further discussed in Section [8.2.5.3](#).

Mean change from baseline in weight (kg) at Week 16 was small (0.12, -0.25, and -1.41) in the deucravacitinib, placebo and apremilast groups, respectively, and not clinically significant. The negative average rate of change in the apremilast group is expected as *weight decrease* is an adverse reaction labeled for apremilast.

Electrocardiograms (ECGs)

Serial ECGs across all treatment groups showed no clinically relevant change from baseline in mean values for PR, QRS, QTcB, or QTcF intervals in the deucravacitinib group compared with the placebo and apremilast groups. There were no cumulative trends through 52 weeks in the deucravacitinib or apremilast groups.

QT

Dr. Girish Bende of the Interdisciplinary Review Team for Cardiac Safety Studies reviewed the Applicant's QT evaluation and concluded that there was "no significant QTcF prolongation effect of deucravacitinib detected" in the thorough QT study (IM011048), which was a double-blind, randomized, single-dose (12 mg and 36 mg), placebo- and positive-controlled, crossover study conducted in healthy subjects. Dr. Bende also stated that the "Assay sensitivity was established using moxifloxacin. The highest dose evaluated was 36 mg, which covers the high clinical exposure scenario (hepatic impairment). Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that deucravacitinib is associated with significant QTc prolonging effect."

Dr. Bende's proposed edits to the label are as shown below with **additions** in blue font and **deletions** in strikethrough red font.

Figure 12. Proposed Edits to the Label, Pharmacodynamics

12.2 Pharmacodynamics <u>Cardiac Electrophysiology</u> <i>At a dose 6 (b) (4) times the (b) (4) recommended dose of the 6 mg once daily (b) (4) in psoriasis patients, (b) (4) <TRADENAME> does not prolong the QTc interval to any clinically relevant extent.</i> <i>We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.</i>

Immunogenicity

Deucravacitinib is a small molecule which is not expected to be associated with immunogenicity. Therefore, the Applicant did not assess the potential for antibody formation.

8.2.5. Analysis of Submission-Specific Safety Issues

Some AEs were considered to be areas of safety interest due to deucravacitinib’s understood inhibition of signaling downstream of Type I IFNs, IL-12, and the IL-23/IL-17 pathway; unknown mechanisms for the toxicities identified with other products targeting the JAK/STAT pathway; observed signals during nonclinical and Phase 2 studies, as well as known comorbidities associated with psoriasis.

These specific AEs of safety interest, will be summarized in detail as follows:

- Infections (including serious, opportunistic, and viral reactivation)
- Malignancies (including all possible malignancies, malignant tumors, nonmelanoma skin cancer [NMSC], and malignant tumors excluding NMSC)
- Cardiovascular (CV) events (including major adverse cardiovascular events (MACE), extended MACE, thrombosis, and other CV events)
- Lipid Elevations
- Gastrointestinal bleed/GI perforation
- Hematological events
- Hepatic events
- Renal events
- Neuropsychiatric events [including depression and suicidal ideation and behavior(SIB)]
- Muscular events
- Retinal detachment

8.2.5.1. Infections

Based on in vitro data, inhibition of TYK2 by deucravacitinib has been shown to affect the signaling cascade that originates upon binding of type I IFNs, IL-12, and the IL-23/IL-17 cytokines. A major effect of type I IFNs (e.g., IFN α/β) is their antiviral action; they act on all cells to inhibit viral replication as well as cellular proliferation (McNab et al. 2015). IL-12 and IL-23 are produced by inflammatory myeloid cells and promote the development of TH1 cell and IL-17-producing T helper (TH17) cell responses, respectively. Patients deficient in IL-12/23p4 or IL-12R β 1 have been shown to be more susceptible to infections caused by the pathogens, Bacille Calmette-Guérin (BCG), Salmonella, and Candida (Teng et al. 2015). Therefore, TYK2 inhibition by deucravacitinib is purported to blunt the effects of these cytokines, theoretically resulting in an increased risk of viral, mycobacterial, salmonella, and mucocutaneous candida infections.

The Applicant thus developed a pre-defined custom MedDRA query for preferred terms (PTs) associated with herpes viral infections, opportunistic infections (including fungal infections), and tuberculosis (TB) to identify and monitor these AE incidences. Furthermore, all infection AESIs were reviewed by an independent, blinded Adjudication Committee who classified events as herpes viral infections (zoster or simplex), influenza, TB (pulmonary or extrapulmonary), and opportunistic infections (fungal, bacterial, viral, parasitic, or other). The analysis appears acceptable, and the Applicant's data are summarized in this section.

Because treatment of inflammatory disease with any immunosuppressive agent carries the potential risk of impaired host defense responses to pathogens, deucravacitinib was evaluated for infections, serious infections, opportunistic infections, and viral reactivation.

To participate in the Phase 3 trials, subjects were excluded if they had the following:

- Active bacterial, viral, fungal, mycobacterial infection, or other infection that required hospitalization or treatment with IV antibiotics within 60 days of screening.
- Any ongoing evidence of chronic bacterial infection.
- Herpes zoster lesions at screening or on Day 1.
- A history of serious herpes zoster or serious herpes simplex infection (e.g., disseminated herpes, herpes encephalitis).
- Positive screening tests for viral hepatitis or HIV.
- Active or latent TB.
- A history of opportunistic infections (e.g., Pneumocystis jirovecii pneumonia, histoplasmosis, or coccidioidomycosis).

In the first 16 weeks of treatment, more subjects (29.1%) in the deucravacitinib group reported AEs of infection compared to 21.5% in the placebo and 22.0% in the apremilast groups. The most common adverse reactions of infections in the deucravacitinib group ($\geq 1\%$ of subjects) included upper respiratory infections, herpes simplex, and folliculitis, all of which occurred at a higher frequency in the deucravacitinib group compared with placebo and apremilast groups.

During Trials IM011046, IM011047, and IM011075 through the safety update cut off, 52 % (792/1519; 63.1/100 PY) of the deucravacitinib-treated subjects reported AEs of infection, of which 3.9% (2.8/100 PY) were serious.

8.2.5.1.1. Serious Infections

Placebo- and Apremilast-controlled Period, Week 0-16

In the first 16 weeks of treatment, serious infections were reported in 5 (0.6%) subjects treated with deucravacitinib, 2 (0.5%) subjects treated with placebo (cellulitis and diverticulitis), and 2 (0.5%) subjects treated with apremilast (cellulitis and polymicrobial diabetic foot wound following trauma).

During this period, the serious infections in deucravacitinib-treated subjects included sepsis, diverticulitis, upper respiratory tract infection, pyelonephritis, and streptococcal bacteremia. The case of sepsis was fatal as previously described in the section detailing Deaths (Section [8.2.4.1](#)); however, 4 days of exposure to study treatment, multiple comorbidities, and advanced age made it difficult to attribute sepsis to deucravacitinib. The subjects with diverticulitis, upper respiratory tract infection, and pyelonephritis had predisposing risk factors of multiple diverticula, asthma, and pelviureteric stricture, respectively. Their dosing of study drug was interrupted due to these AEs; however, all three subjects resumed treatment and rolled into the LTE trial. The subject with streptococcal bacteremia withdrew from the trial as described below.

Subject IM011047- (b) (6): Streptococcal Bacteremia

19-year-old White female with a history of tobacco use, developed a febrile illness after receiving 4 days of treatment with deucravacitinib. She required hospitalization on Day 9. During her stay, a blood culture was positive for *Streptococcus pseudoporcinus*. Her hospital stay was complicated by a right radial vein thrombosis following cannulation of this vessel for infusion of intravenous antibiotics. Her infection was reported to have resolved by Day 18 and she was discharged from the hospital. On Day 23, the subject withdrew from the trial. She had received the last dose of study treatment on Day 4.

Streptococcus pseudoporcinus is usually associated with infections in swine. Reports of isolation of *S. pseudoporcinus* from humans is rare and has primarily been isolated from the female genitourinary tract (Facklam et al. 1995). This species is biochemically similar to *Streptococcus agalactiae* and serologically cross-reacts with group B streptococcal reagent suggesting human infections or colonization by *S. porcinus* may be underestimated (Bekal et al. 2006). Although *S. pseudoporcinus* has been isolated from multiple specimen types, including blood, the epidemiological information of this organism and its role in human disease is lacking.

While the rates of serious infections during the placebo-controlled period were comparable across treatment groups, the isolation of a presumed rare streptococcal species from the bloodstream of an acutely ill young, otherwise healthy subject, suggests the potential for an added susceptibility to disseminated infection.

Apremilast-controlled Period, Week 0-24

For subjects who were treated with either apremilast or deucravacitinib through 24 weeks without switching, there was 1 additional apremilast-treated subject (*Mycoplasma pneumoniae*) and 2 more deucravacitinib-treated subjects who reported serious infections. One of the deucravacitinib-treated subjects (IM011046-^{(b) (6)}) was a 19-year-old male with a history of hidradenitis suppurativa who required a brief hospitalization for surgical removal of a pilonidal cyst. Dosing of study drug was interrupted. The subject resumed treatment and rolled into the LTE trial. The other subject (IM011047-^{(b) (6)}) was a 52-year-old female with no significant PMH who was hospitalized for 5 days for right lower lobe pneumonia. No action was taken with study drug. The subject improved without sequelae following intravenous antibiotics and eventually transitioned into the LTE trial.

Apremilast-controlled Period, Week 0-52 – Trial IM011046

With longer exposure from Week 24 to Week 52, there was 1 more apremilast-treated subject (bilateral COVID-19 pneumonia) and 1 additional deucravacitinib-treated subject (infectious mononucleosis) in Trial IM011046 who did not switch treatment and reported serious infections. The narrative for the subject who received deucravacitinib and required hospitalization for infectious mononucleosis after 41 weeks of exposure is provided within this section.

To capture events outside of the periods and pools discussed above, analyses were performed for deucravacitinib-treated subjects including those who switched treatment during both controlled Phase 3 trials (IM011046 and IM011047).

After 52-weeks of exposure, a total of 17/1364 (1.2%) deucravacitinib-treated subjects experienced serious infections (1.3/100 PY). This includes 7 subjects described above plus 2 more cases of pneumonia, 2 cases of COVID-19 (IM011046-^{(b) (6)}, IM011047-^{(b) (6)} ^{(b) (6)}) and single cases of pharyngotonsillitis, carbuncle, anal abscess, infectious mononucleosis, vascular graft infection, and purulence at the pancreatic head in the setting of chronic pancreatitis. The subject with a perianal abscess (IM011047-^{(b) (6)}) requiring incision and drainage was a 43-year-old white male with a history of anal fissures who withdrew from the study after receiving deucravacitinib for a total of 18 weeks. The other subjects continued to receive study treatment. Details of select cases are provided below.

Subject IM011047-^{(b) (6)}: Pneumonia

55-year-old White female with a history of morbid obesity, hypertension, prior tobacco use (23 pack years, quit 9 years prior), obstructive sleep apnea, glucose intolerance, fatty liver, monoclonal gammopathy of unknown significance, and previous biologic use, was initially randomized to placebo then transitioned to deucravacitinib at Week 16. She required hospitalization for multiorgan failure and septic shock secondary to bilateral pneumonia. Study drug was interrupted. She had received treatment with deucravacitinib for 29 weeks. Following intravenous antibiotics, fluids, and positive pressure ventilation, her condition improved and on hospital day 7, she was able to be discharged. Shortly thereafter, she resumed study treatment and eventually transitioned into the LTE trial.

Subject IM011047- (b) (6): Pneumonia

49-year-old White male with a history of chronic tobacco use (25 years) was hospitalized with right middle and lower lobe pneumonia after receiving deucravacitinib treatment for 9 weeks. He was initially randomized to placebo then transitioned to deucravacitinib at Week 16. Other than mild, transient reduction of lymphocytes [16.2% (RR: 25-45%)], his reported laboratory studies remained within normal range. Following IV antibiotics and hydration, his condition improved, and he was discharged on hospital day 7. No action was taken with study drug. The subject continued in the study and transitioned into to LTE trial.

Subject IM011047- (b) (6): Vascular Graft Infection

66-year-old male with a history of tobacco use, chronic obstructive pulmonary disease (COPD), hypertension, and right bundle branch block was originally randomized to placebo then blindly transitioned to deucravacitinib at Week 16. During the first 16 weeks of study treatment, he was diagnosed with significant right femoral artery sclerosis and right iliac artery occlusion during a 5-day hospitalization for acute COPD exacerbation. Several weeks later (Week 16), he underwent right sided iliofemoral bypass surgery. During Weeks 18-20, he was hospitalized for severe Staphylococcus aureus vascular graft infection requiring graft removal and IV antibiotics. He had leukocytosis (peak WBC count $14.6 \times 10^9/L$, baseline $10.5 \times 10^9/L$; rr $4.1-12.3 \times 10^9/L$), neutrophilia (peak neutrophil count $11.11 \times 10^9/L$, baseline $8.25 \times 10^9/L$; rr $2.03-8.36 \times 10^9/L$), and reactive thrombocytosis (peak platelet count $587 \times 10^9/L$, baseline $239 \times 10^9/L$; rr $140-450 \times 10^9/L$). His differential otherwise remained within normal range.

No action was taken with study drug. The subject's infection resolved and limb perfusion was satisfactory. He eventually transitioned into the LTE trial.

Subject IM011047- (b) (6): Purulence at the Pancreatic Head

60-year-old White male with a history of hypertension, hypercholesterolemia, and recurrent episodes of acute pancreatitis developed epigastric pain after receiving treatment with deucravacitinib without treatment switching for 32 weeks. Study drug was temporarily interrupted. Abdominal imaging demonstrated a heterogenous mass in the region of the duodenum and pancreatic head. Endoscopic ultrasound and biopsy were performed. Histopathology showed acute purulent granulation tissue. Study drug was temporarily interrupted. A medical certificate indicated that the prior episodes of acute pancreatitis resulted in a post-inflammatory cyst in the region of the head of pancreas. Study drug was restarted on an unspecified day. The subject completed the study and rolled into the LTE trial.

Subject IM011046- (b) (6): Infectious Mononucleosis

26-year-old Asian female with no significant past medical history required hospitalization after 41 weeks of treatment with deucravacitinib without treatment switching due to infectious mononucleosis which was preceded approximately one month by a non-serious influenza A infection. During her 3-day hospital stay, she received IV fluids, antibiotic therapy, and supportive care. Her white blood cell count and differential were within normal range, and her hemoglobin reflected mild anemia (9.7 g/dL; reference range 11.6-16.2 g/dL).

Seventeen subjects who received deucravacitinib reported serious infections during the controlled trials, 3 of which discontinued study drug: 1 due to sepsis after 4 days of treatment, 1 as a result of streptococcal bacteremia after 4 days of treatment, and a third due to a perianal abscess after 18 weeks of treatment. Because of confounding factors and limited exposure, it is difficult to attribute these serious infections that led to discontinuation to deucravacitinib use. However, there were serious infections in the Phase 3 Safety Pool that justify labeling in Section 5 of the FPI with the most common being pneumonia and COVID-19, all of which necessitated acute inpatient care and interventions such as frequent intravenous antimicrobial infusions, mechanical ventilation, and continuous assessments in the Intensive Care Unit (ICU) setting.

The cases of transient streptococcal bacteremia in a young subject with no other comorbidities and acute pyelonephritis reflective of an infection that could not be locally contained, support labeling of serious infections, but do not warrant inclusion in product labeling.

TYK2 belongs to the JAK family. The adverse reactions (ARs) described in labeling for JAK inhibitors (tofacitinib, baricitinib, upadacitinib, and abrocitinib) that are approved for chronic inflammatory conditions include serious infections such as BK virus encephalitis, esophageal candidiasis, cryptococcus, acute histoplasmosis, and pneumocystis jirovecii pneumonia which are described in a Boxed Warning. Overall, the types of serious infections reported in deucravacitinib-treated subjects with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy did not include these invasive fungal infections. Therefore, a Boxed Warning for serious infections is not justified at this time. Serious infections will be adequately described in Warnings and Precautions and under Adverse Reactions. Because the mechanism for JAK inhibitor-associated adverse reactions is not well understood, the potential risks related to JAK inhibition observed in a large, randomized, postmarketing safety trial of a JAK inhibitor in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor, will also be described in Warnings and Precautions.

To address the uncertainty regarding the long-term safety of deucravacitinib and to identify a potential serious risk for opportunistic infections, a long-term randomized trial with an active comparator will be required.

As of the safety SCS data cut-off date (June 15, 2021), 42 more subjects reported 44 serious infections. The majority of events were due to COVID-19 and COVID-19 pneumonia as shown in the table below.

Table 65. Infection Serious Adverse Events, Controlled Safety Pool (Week 0-52) and Phase 3 Safety Pool - All Treated Subjects

System Organ Class Preferred Term	CONTROLLED SAFETY POOL				PHASE 3 SAFETY POOL			
	BMS-986165 6 mg QD N = 1364				BMS-986165 6 mg QD N = 1519			
	n (%)	P-Y	IR/ 100 P-Y		n (%)	P-Y	IR/ 100 P-Y	
Infections and infestations	1/ (1.2)	981.1	1.7		59 (3.9)	2143.2	2.8	
Pneumonia	3 (0.2)	985.4	0.3		4 (0.3)	2173.2	0.2	
COVID-19	2 (0.1)	986.2	0.2		27 (1.8)	2167.9	1.2	
Anal abscess	1 (0.1)	986.6	0.1		1 (0.1)	2177.0	0.0	
Carbuncle	1 (0.1)	986.5	0.1		1 (0.1)	2176.0	0.0	
Diverticulitis	1 (0.1)	985.9	0.1		2 (0.1)	2174.4	0.1	
Infectious mononucleosis	1 (0.1)	986.5	0.1		1 (0.1)	2175.7	0.0	
Pharyngotonsillitis	1 (0.1)	986.7	0.1		1 (0.1)	2176.0	0.0	
Pilonidal cyst	1 (0.1)	986.1	0.1		1 (0.1)	2175.5	0.0	
Furuncle	1 (0.1)	986.3	0.1		1 (0.1)	2176.1	0.0	
Eyelonephritis	1 (0.1)	986.0	0.1		1 (0.1)	2175.3	0.0	
Sepsis	1 (0.1)	986.6	0.1		1 (0.1)	2177.0	0.0	
Streptococcal bacteremia	1 (0.1)	986.6	0.1		1 (0.1)	2177.0	0.0	
Upper respiratory tract infection	1 (0.1)	986.4	0.1		1 (0.1)	2175.7	0.0	
Vascular graft infection	1 (0.1)	986.0	0.1		1 (0.1)	2175.8	0.0	
COVID-19 pneumonia	0				13 (0.9)	2171.5	0.6	
Gastroenteritis	0				1 (0.1)	2175.7	0.0	
Pneumonia viral	0				1 (0.1)	2176.6	0.0	
Tubo-ovarian abscess	0				1 (0.1)	2176.4	0.0	
Post procedural sepsis	0				1 (0.1)	2176.8	0.0	

Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time for the selected AE under each treatment.

MedDRA: 23.1

Note: Exposure in p-y is presented in the table only for those PTs where there is at least one event.

Source: Applicant's SCS Table 2.7.2.4-2.

In all 3 psoriasis Phase 3 clinical trials (IM011046, IM011047, and the ongoing open-label long-term extension trial, IM011075), serious infections were reported in 59 subjects (2.8/100 patient-years) treated with deucravacitinib. The most commonly reported serious infections were COVID-19/COVID-19 pneumonia, pneumonia, and diverticulitis.

COVID-19 is a novel disease caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2) that became epidemic during the OLE portion of the deucravacitinib program. It is unclear if deucravacitinib contributed to these serious COVID-19 infections. While there may be viral susceptibility with deucravacitinib treatment as described under Section 8.2.5.1.2, it is not unexpected that a greater than usual portion of the population would become seriously ill from the virus alone given the lack of immunity at the time.

Calculation of the exposure-adjusted incidence rate (EAIR) of serious infections excluding COVID-19 events is useful in order to conduct appropriate comparisons to other systemic therapies for the treatment of psoriasis. In this case, the EAIR is 0.9/100 PY.

In a large prospective cohort analysis to assess the rate and types of serious infections among subjects with moderate to severe psoriasis receiving systemic treatments, the IR was 1.63/100 PY for those being actively treated with a biologic agent (adalimumab, etanercept, infliximab, ustekinumab, golimumab, certolizumab, tocilizumab, abatacept, anakinra, and rituximab) and 1.79/100 PY for those undergoing nonbiologic therapy (methotrexate, retinoids, cyclosporine, hydroxyurea, mycophenolate mofetil, sulfasalazine, and thioguanine) (Dobry et al. 2017). Although there has been varying published results regarding serious infections among subjects with systemically treated psoriasis, the overall exposure-adjusted rate of serious infections

(excluding COVID-19) seen during the deucravacitinib program does not appear to exceed the rate observed for other systemic treatments.

Given that the rate, as well as types of serious infections, and lack of opportunistic infections through 52-weeks of exposure (as discussed under Section [8.2.5.1.3](#)) were not suggestive of potent immunosuppression, a Boxed Warning to describe serious infections is not justified at this time. Serious infections will be adequately described in Warnings and Precautions and under Adverse Reactions, as well as further characterized in a required randomized postmarketing trial.

8.2.5.1.2. Viral (Herpes Simplex, Zoster, Influenza)

8.2.5.1.2.1. Herpes simplex virus (HSV)

Placebo- and Apremilast-controlled Period, Week 0-16

In the first 16 weeks of treatment, the proportion of subjects with herpes simplex AEs was highest for deucravacitinib (17/842, 2.0%) compared to placebo (1/419, 0.2%) and apremilast (2/422, 0.5%). None of the events were considered serious. Dosing was interrupted for one deucravacitinib-treated subject who resumed treatment and continued to the LTE trial.

Apremilast-controlled Period, Week 0-24

For pooled subjects who received either apremilast or deucravacitinib through Week 24 without switching, there were 2 additional deucravacitinib-treated subjects and 1 more apremilast-treated subject with HSV AEs. None of these events were reported as serious or severe. There were no changes made to study drug dosing, and none of the subjects discontinued the study due to a HSV AE.

Apremilast-controlled Period, Week 0-52 – Trial IM011046

Deucravacitinib-treated subjects in Trial IM011046, who did not switch treatment, had a higher rate of HSV AEs (7/330, 2.0%) compared to apremilast subjects who did not switch treatment (1/114, 0.9%).

To capture HSV events outside of the periods and pools discussed above, events that occurred in *both* controlled trials through 52-weeks of exposure were evaluated--17 more deucravacitinib -treated including subjects who switched treatment through 52 weeks reported HSV AEs, for a total of 36/1364 (2.6%) subjects, the majority of whom had oral herpes events. All of the cases were mild to moderate in severity and did not result in change to study treatment.

During the LTE trial, 9 more subjects who received deucravacitinib reported HSV AEs, for a total of 42/1519 (2.0/100 PY) subjects as of the safety cut-off date (June 15, 2021).

The 120 day safety update included 1 new event of herpes simplex resulting in an essentially unchanged EAIR (1.8/100 PY).

Comparative analyses between appropriate pools and periods demonstrate a higher frequency of herpes simplex infections in deucravacitinib-treated subjects relative to placebo and active control groups. Although there were no cases of disseminated HSV, this imbalance reflects the important impact of deucravacitinib's effect on immune surveillance and will be labeled in Sections 5 and 6 of the FPI.

8.2.5.1.2.2. Herpes Zoster (HZV)

Placebo- and Apremilast-controlled Period, Week 0-16

During the first 16 weeks of treatment, the incidence rate of herpes zoster events in the Controlled Safety Pool were similar between the deucravacitinib (2/840, 0.2%) and the placebo (1/419, 0.2%) groups. There were no events reported in the apremilast group. Both of the events in the deucravacitinib-treated subjects were considered non-serious, moderate in severity, and neither led to study drug discontinuation.

Apremilast-controlled Period, Week 0-24

For those who were treated with either apremilast or deucravacitinib through 24 weeks without switching, there were no additional apremilast-treated subjects with an AE of herpes zoster, but there was 1 more deucravacitinib-treated subject (IM011047-(b) (6)) who reported an AE of ophthalmic zoster. The subject was a 56-year-old female with no significant past medical history, who was diagnosed with painful trigeminal herpes zoster (VI) assessed as moderate in severity after treatment with deucravacitinib for 22 weeks. Ophthalmologic evaluation demonstrated eyelid swelling without herpetic involvement of the cornea or other orbital structures. Acyclovir was started and study drug was interrupted then resumed after resolution of zoster. After 34 weeks of study treatment, the subject discontinued the trial reportedly due to concerns with the pandemic and unsatisfactory study treatment efficacy.

Apremilast-controlled Period, Week 0-52 – Trial IM011046

In Trial IM011046, 3/330 (0.9%) deucravacitinib-treated subjects who did not switch treatment through 52 weeks reported AEs of herpes zoster—1 of these subjects developed herpes zoster infection during the first 16 weeks and is included in the Week 0-16 numbers above; 2 additional subjects reported events of herpes zoster during Week 24-52. There were no subjects treated apremilast without switching who reported AEs of herpes zoster.

To capture AEs of herpes zoster outside of the aforementioned periods and pools, events that occurred in both controlled trials through 52-weeks of exposure were evaluated. After 52-weeks, a total of 9/1364 (0.7%) subjects receiving deucravacitinib, regardless of whether they switched treatment or not, experienced AEs of herpes zoster (0.9/100 PY).

During the LTE trial, 6 additional subjects reported 7 AEs of herpes zoster yielding an EAIR of 0.6/100 PY at the safety data cut-off date (June 15, 2021).

Details of the AEs of herpes zoster that occurred during trials IM011046, IM011047, and IM011075 are provided in the table below.

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Table 66. Adverse Events of Herpes Zoster - Phase 3 Psoriasis Trials

PID	Age/Sex/ Race	Treatment Sequence	Preferred Term	Study Day of Event	Severity/ SAE (yes/no)	Received Antivirals for Event? (Yes/No)	Action Taken with Study Treatment
(b) (6)	48/M/W	DEUC (W0-52); DEUC (075)	Herpes zoster (2 events, one in each study)	329 (31)	Moderate/ No Mild/ No	Yes Yes	Drug interrupted Drug Interrupted
	27/F/W	DEUC (W0-52)	Herpes zoster	94	Moderate/ No	Yes	None
	27/M/A	Placebo (W0-16); DEUC (W16-52)	Herpes zoster	340	Mild/ No	Yes	None
	44/M/A	DEUC (W0-52)	Herpes zoster	347	Moderate/ No	Yes	Drug interrupted
	36/M/A	Placebo (W0-16); DEUC (W16-52)	Herpes zoster	318	Moderate/ No	Yes	Drug interrupted
	67/M/W	DEUC (W0-52)	Herpes zoster	222	Mild/ No	Yes	Drug interrupted
	58/F/W	DEUC (W0-52)	Herpes zoster	88	Moderate/ No	Yes	Drug interrupted
	56/F/W	DEUC (W0-52)	Ophthalmic herpes zoster	154	Moderate/ No	Yes	Drug interrupted
	55/F/W	Placebo (W0-16); DEUC (W16-52)	Herpes zoster (2 events)	102; 156	Moderate/ No Severe/ No	Yes Yes	Drug interrupted Drug interrupted
	38/M/A	Placebo (W0-16) DEUC (W16-52) DEUC (075 LTE)	Herpes zoster	(216)	Moderate/No/ Related	Yes	Drug interrupted
	39/F/W	Apremilast (W0- 24) DEUC (W 24-52) DEUC (075 LTE)	Herpes zoster	(31)	Moderate/ No	Yes	None
	46/M/W	Apremilast (W0- 24) Placebo (W24-52) DEUC (075 LTE)	Herpes zoster	(34)	Moderate/ No	Yes	None
	30/M/W	Apremilast (W0- 52) DEUC (075 LTE)	Herpes zoster	(33)	Moderate/ No	Yes	None
	64/F/W	PBO (W 0-16) DEUC (W 16 - 52) DEUC (075 LTE)	Herpes zoster	(509)	Moderate/No	Yes	Drug interrupted
	49/F/W	Apremilast (W 0- 52) DEUC (075 LTE)	Herpes zoster	(364)	Mild/No	Yes	None

Source: Applicant's SCS Table 2.7.2.5-1.

Bolded treatment is treatment at time of event. DEUC=deucravacitinib. PBO=placebo

For IM011075 events, the parent study PID is provided in parentheses

^a Subject also experienced an AE of malignant melanoma.

^b Subject also experienced an AE of unstable angina pectoris.

^c Subject also experienced an AE of blood creatinine increased.

^d Subject also experienced an AE of pericarditis.

Based on information from the 120-day safety updated report (SUR), 3 more subjects reported herpes zoster infections, none of which had events that were disseminated, serious, severe, or led to treatment discontinuation. The EAIR for AEs of herpes zoster as of the SUR data cut-off date (October 1, 2021) was 0.7/100 PY.

Although none of the events of herpes zoster were reported as serious by investigators, two subjects are considered by the review team as having had clinically significant events--one (IM011047-^{(b) (6)}) was associated with ophthalmic involvement (described above), and the other subject (IM011046-^{(b) (6)}) had herpes zoster lesions that crossed multiple cervical (C5-C8) dermatomes. This subject was a 37-year-old Asian male with no significant past medical history. He enrolled into the LTE trial, and after receiving a total of 50 weeks of deucravacitinib, developed herpes zoster involving his right upper extremity. Study drug was interrupted. As of the SUR, the subject was reported to have developed post-herpetic neuralgia.

Based on exposure-response (E-R) analyses by the Applicant, as well as by Drs. Ye Xiong and Youwei Bi of the Division of Pharmacometrics, an exposure related trend for herpes zoster infection was not demonstrated, as exposures were comparable between subjects who had and subjects who did not have herpes zoster.

While there is a lack of E-R trend and the EAIR for herpes zoster events during the Phase 3 trials is comparable to that found in a retrospective cohort study from large research databases (Harpaz and Leung 2019), analyses of the submitted data showed that 10 of the 15 subjects who reported herpes zoster AEs were under 50 years of age, 6 of whom were between the ages of 27 and 39 years.

Age is the most significant risk factor for developing herpes zoster with a dramatic increase in the incidence of herpes zoster beginning at approximately age 50 years (Yawn et al. 2007). Notwithstanding the unexplained rising incidence of zoster worldwide, it is still relatively rare in young adults.

A description of this significant finding is recommended for Warnings and Precautions under the subsections of Infections and Immunizations (as below) to communicate the risk of this viral reactivation that is not typically seen in younger patients and will include steps to take to prevent, mitigate, and/or manage herpes zoster:

- Infections: Multidermatomal herpes zoster was reported in a subject who received SOTYKTU. During PSO-1, PSO-2, and the open-label extension trial in which subjects who completed the controlled trials could enroll, the majority of subjects who reported events of herpes zoster while receiving SOTYKTU were under 50 years of age.
- Immunizations: Prior to initiating therapy with [SOTYKTU], consider completion of all age-appropriate immunizations according to current immunization guidelines including prophylactic herpes zoster vaccination.

8.2.5.1.2.3. Influenza

Placebo- and Apremilast-controlled Period, Week 0-16

During the first 16 weeks of treatment in the Controlled Safety Pool, 4/842 (0.5%) deucravacitinib-subjects reported an AE of influenza compared to 3/419 (0.7%) of subjects in the placebo group. No subject in the apremilast group had an event of influenza.

Apremilast-controlled Period, Week 0-24

For those who were treated with either apremilast or deucravacitinib without switching through 24 weeks, 1/422 (0.2%) subject in the apremilast group reported an event that was considered non-serious, moderate in severity, and did not lead to change in study treatment. This rate is similar to that of the deucravacitinib group which included 2/842 (0.2%) subjects whose influenza events were reported as non-serious, mild, and did not lead to discontinuation of study drug.

Apremilast-controlled Period, Week 0-52 - Trial IM011046

In Trial IM011046, analysis of subjects who were treated with either deucravacitinib or apremilast without switching demonstrated 9/330 (2.7%) subjects in the deucravacitinib group and 2/114 (1.8%) subject in the apremilast group who experienced AEs of influenza. All of the events were nonserious and mild or moderate in severity. All subjects except one in the deucravacitinib group did not have dosing changed. The single deucravacitinib-treated subject whose dosing was interrupted, resumed study treatment after several days and eventually entered the LTE trial.

In the Controlled Safety Pool, after 52-weeks of exposure, a total of 23 (1.7%, 2.4/100 PY) deucravacitinib-treated subjects reported influenza-related AEs regardless of whether they switched treatment or not--10 were confirmed to be influenza by the Infection Adjudication Committee.

In the LTE trial, 6 additional subjects had influenza AEs. Of these, 2 were confirmed to be influenza by the Infection Adjudication Committee resulting in a total of 12/1519 (0.8%) adjudicated events of influenza with an EAIR of 0.6/100 PY (2163.7 PY) in the deucravacitinib group up to the data cutoff date (June 15, 2021).

Information from the SUR identified 2 more subjects with influenza events, none of which were serious or led to treatment discontinuation; 1 of the events was reported as severe.

Overall, comparative analyses between appropriate pools and periods did not demonstrate a significantly higher frequency of influenza infections in deucravacitinib-treated subjects relative to placebo and active control groups. There were also no cases of serious influenza events.

8.2.5.1.3. Opportunistic Infections

As previously outlined, subjects were not permitted to participate in the Phase 3 trials if they had active or latent tuberculosis (TB) or a history of opportunistic infections (e.g., Pneumocystis jirovecii pneumonia, histoplasmosis, or coccidioidomycosis). Those with a positive screening IFN

gamma release assay (IGRA) were eligible if they did not have current signs or symptoms of active TB and the subject had received appropriate treatment for latent TB infection (LTBI) within 5 years of screening or had started prophylactic treatment for LTBI per local guidelines plus was rescreened after 1 month of treatment. To continue in the study, subjects must have completed a locally-recommended course of treatment for LTBI; however, use of rifampin was not recommended because according to the apremilast US prescribing information, rifampin could reduce efficacy of apremilast.

Placebo- and Apremilast-controlled Period, Week 0-16

During the first 16 weeks in the Controlled Safety Pool, 1 (0.1%) deucravacitinib-treated subject (IM011047-^{(b) (6)}) reported an AE of oral candidiasis, and 2 (0.5%) subjects in the apremilast group had events of pseudomonas wound infection and blastocystis hominis infection. The deucravacitinib-treated subject was a 52-year-old female with no significant past medical history who was previously described in [Section 8.2.5.1.1](#) for an event of pneumonia that was diagnosed after receiving 20 weeks of treatment with deucravacitinib. The subject's event of *oral candidiasis*, however, occurred during the first 16 weeks of treatment and was reportedly mild in severity; it did not result in change to study treatment. There were no opportunistic infections reported in the placebo group.

Apremilast-controlled Period, Week 0-24

For subjects who were treated with either apremilast or deucravacitinib through 24 weeks without switching, 1 (0.1%) additional subject in the deucravacitinib group had an infection of ophthalmic herpes zoster that although a formal ophthalmological examination demonstrated eyelid swelling without herpetic involvement of the cornea or other orbital structures. As previously described in [Section 8.2.5.1.2.2](#), the subject was a 56-year-old female with no significant past medical history, who was diagnosed with painful trigeminal herpes zoster (VI) assessed as moderate in severity after treatment with deucravacitinib for 22 weeks. No additional subject in the apremilast group was reported with an opportunistic infection.

Apremilast-controlled Period, Week 0-52 - Trial IM011046

In Trial IM011046, there were no additional subjects who were treated with either deucravacitinib or apremilast without switching that experienced opportunistic infections.

To capture events outside of these periods and pools, analyses were performed including subjects who switched treatment through 52 weeks of treatment. Five additional subjects reported opportunistic infections while receiving deucravacitinib: oral candidiasis/thrush (3), infectious mononucleosis (1), and chlamydia pneumonia (1).

Fungal infections will be discussed in more detail within [Section 8.2.5.1.4](#).

The AE of mononucleosis (previously discussed in [8.2.5.1.1](#)) in an otherwise immunocompetent subject does not likely represent an OI. A brief narrative of the subject with atypical pneumonia provided below similarly does not suggest an OI.

Subject IM011047- (b) (6): Chlamydia Pneumonia

A 59-year-old White male with obesity (BMI 34), and a history of prior biologic use for the treatment of severe plaque psoriasis, was reported to have non-serious chlamydia pneumonia following 18 weeks of deucravacitinib exposure. No other details were provided.

During the LTE trial, 14 subjects reported AEs considered potential opportunistic infections by investigators including cytomegalovirus (CMV) infection (1), pulmonary TB (1), latent TB (3), positive quantiferon test (5), and oral thrush/oral fungal infection/oral candidiasis (4). None of these AEs were reported as serious. The event of pulmonary TB led to study discontinuation while the others did not. Narratives of the subjects with CMV and TB infections are provided below.

Subject IM011046- (b) (6): CMV Infection of the GI Tract

67-year-old White female with a past medical history of basal cell carcinoma and colorectal cancer requiring surgical resection and colostomy (not actively receiving treatment) was reported to have “moderate cytomegalovirus infection, not related to study drug” after receiving treatment with deucravacitinib for 41 weeks. She presented with fever and diarrhea. Her cytomegalovirus antibodies (IgG and IgM) were positive. According to the Applicant, “the Infection Adjudication committee was unable to arrive at a unanimous consensus due to lack of information”. The subject received symptomatic care with acetaminophen and loperamide and resumed study treatment following temporary interruption of dosing. Of note, her ALT and AST were transiently greater than 5 times upper limit of normal (ULN) at 416 U/L (baseline 10 U/L; reference range 0-33 U/L) and 180 U/L (baseline 13 U/L; RR 0-31) respectively; however, the investigator did not report the elevated transaminases as AEs. Within the SUR, no further clinically important safety data were reported for this subject.

Subject IM011046- (b) (6): Pulmonary TB

33-year-old White male from Russia with no significant past medical history was diagnosed with “infiltrative tuberculosis of the upper lobe of the right lung” after receiving 54 weeks of treatment with deucravacitinib during the LTE trial. He had received apremilast throughout the controlled trial (IM011046). The AE of tuberculosis led to study drug discontinuation. According to the SUR, no further clinically significant safety information was provided following treatment with rifabutin, isoniazid, and ethambutol.

Other tuberculosis-related AEs (latent TB and positive quantiferon test) are outlined in the table below. All 8 AEs occurred during the open label LTE trial. To be eligible for this trial, a subject must not have active signs or symptoms of TB as assessed by the investigator. At the baseline visit, approximately yearly thereafter, and as indicated, in addition to a complete history and physical examination, all subjects completed a TB questionnaire comprised of the following 3 yes/no questions: 1) Recent close or prolonged contact with someone with infectious TB disease (defined as within 12 months), 2) High-risk profession or situations, like being patient-facing, e.g., healthcare providers, and 3) Recent travel to or from a high burden country for TB OR residing in a high burden country for TB. The 4 subjects with LTBI were all from Russia, had

no active TB symptoms, had deucravacitinib dosing interrupted during treatment for LTBI, and did not have progression to active TB based on information provided within the safety update.

Table 67. Tuberculosis-Related Adverse Events

Subject ID	Age (yrs)	Treatment Sequence*	AE	Deucravacitinib Exposure Prior to AE (Wks)
(b) (6)	42	DEUC-DEUC-DEUC-DEUC	Latent TB	52
(b) (6)	54	DEUC-DEUC-DEUC-DEUC	Latent TB	100
(b) (6)	43	APR-APR-APR-DEUC	Latent TB	24
(b) (6)	70	PBO-DEUC-DEUC-DEUC	Latent TB	48
(b) (6)	60	DEUC-DEUC-DEUC-DEUC	Positive quantiferon test	53
(b) (6)	53	DEUC-DEUC-DEUC-DEUC	Quantiferon positive test	52
(b) (6)	72	APR-APR-PBO-DEUC	Positive quantiferon	1 day
(b) (6)	22	DEUC-DEUC-DEUC-DEUC	'POSITIVATION OF THEQUANTIFERON"	68

Source: Reviewer's analysis.

*Treatment sequence = Week 0 to 16 – Week 16 to 24 – Week 24 to 52 – LTE to October 1, 2021 (120 day data cut-off date)

€ Subject IM011046- (b) (6) was reported with LTBI in the 120-day SUR.

'Subject IM011046 (b) (6) also had a subsequent AE of varicella reported 88 weeks after first dose of deucravacitinib.

Abbreviations: DEUC=deucravacitinib; APR=apremilast; PBO=placebo

8.2.5.1.4. Fungal Infections

During trials IM011046, IM011047, and IM011075, 42 subjects treated with deucravacitinib experienced a total of 49 fungal infections. None of the fungal infections were reported as serious or led to discontinuation of study drug. The majority of cases were mucocutaneous events: 16 vaginal infections, 9 oral, 2 skin, and 1 balanitis. Fourteen tinea infections were also reported.

The additional information provided in the safety update showed that the rate and pattern of opportunistic and fungal infections remained generally unchanged.

None of the opportunistic infections identified by the review team were considered by the investigators as serious or related to study drug. As previously assessed under serious infections (Section 8.2.5.1.1), the opportunistic infections observed in subjects with psoriasis who received deucravacitinib were different compared to those described in labeling for other JAK inhibitors that are approved for inflammatory conditions such as extrapulmonary TB, disseminated herpes zoster, as well as invasive fungal infections including esophageal candidiasis, pneumocystis jirovecci pneumonia, cryptococcosis, and aspergillus pneumonia.

8.2.5.1.5. Overall Infection Assessment

Compared to placebo, subjects treated with deucravacitinib experienced more infections; however, the incidence of serious infections was similar.

Three of 17 subjects who received deucravacitinib discontinued study drug due to serious

infections during the controlled trials. These cases (sepsis after 4 days of exposure resulting in death, streptococcal bacteremia after 4 days of treatment in a young subject with no other comorbidities, and a perianal abscess after 18 weeks in a subject with known anal fissures), as well as a case of acute pyelonephritis reflective of an infection that could not be locally contained, support labeling of serious infections, but do not warrant inclusion in the full prescribing information (FPI) due to confounding factors and/or limited exposure.

The most common serious infections in the Phase 3 Safety Pool that justify labeling of serious infections in Section 5 of the FPI include pneumonia and COVID-19, all of which necessitated acute inpatient care and interventions such as frequent intravenous antimicrobial infusions, mechanical ventilation, and continuous assessments in the Intensive Care Unit (ICU) setting.

Viral reactivation assessments showed that the frequency of herpes simplex infections in deucravacitinib-treated subjects was higher than in placebo-treated subjects.

A case of herpes zoster affecting multiple dermatomes was reported in a subject who received deucravacitinib. During Trials IM011046, IM011047 and IM011075, 10 of the 15 subjects who reported AEs of herpes zoster were under 50 years of age.

Of 4 subjects with latent tuberculosis (TB) who were treated with deucravacitinib and received appropriate TB prophylaxis, no subjects developed active TB (during the mean follow-up of 34 weeks). One subject, who did not have latent TB, developed active TB while receiving deucravacitinib.

TYK2 belongs to the JAK family. The adverse reactions (ARs) described in labeling for JAK inhibitors (tofacitinib, baricitinib, upadacitinib, and abrocitinib) that are approved for chronic inflammatory conditions include serious infections such as BK virus encephalitis, esophageal candidiasis, cryptococcus, acute histoplasmosis, and pneumocystis jirovecii pneumonia which are described in a Boxed Warning. Overall, the types of serious infections reported in deucravacitinib-treated subjects with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy did not include these invasive fungal infections.

The findings of infections observed during the development program will be adequately communicated in Section 5 (Warnings and Precautions) and Section 6 (Adverse Reactions) of the full prescribing information, as well as in the Medication Guide. A Boxed Warning for serious infections is not justified at this time. Because the mechanism for JAK inhibitor-associated adverse reactions is not well understood, the potential risks related to JAK inhibition observed in a large, randomized, postmarketing safety trial of a JAK inhibitor in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor, will also be described in Warnings and Precautions.

To address the uncertainty regarding the long-term safety of deucravacitinib and to identify a potential serious risk for opportunistic infections, a long-term randomized trial with an active comparator will be required.

8.2.5.2. Malignancies

Due to deucravacitinib's immunosuppressive potential, the risk of malignancy associated with deucravacitinib use, especially in a population with moderate to severe chronic inflammation, is a concern.

The Phase 3 trials, IM011046, IM011047, and IM011075, excluded subjects if they had cancer or history of cancer (solid organ or hematologic including myelodysplastic syndrome) or lymphoproliferative disease within the previous 5 years. Subjects with resected cutaneous basal cell or squamous cell carcinoma or carcinoma of cervix in situ that was treated with no evidence of recurrence, were permitted to participate in the trials. Prior phototherapy, systemic therapy, or biologic therapy for psoriasis was reported in 40.2%, 41.1%, and 34.8% of randomized subjects.

Data were evaluated by malignancy categories [malignancy excluding nonmelanoma skin cancer (NMSC) and NMSC] at 16 weeks, 52 weeks, and up to October 1, 2021 (120-day SUR cutoff date providing a total exposure of 2482.0 patient-years), with some subjects (584) exposed continuously for 2 years.

In the first 16 weeks of trials IM011046 and IM011047, no subject in the pooled deucravacitinib or placebo groups reported AEs of non-NMSC malignant tumor. In the apremilast group, there was one subject (0.2%) who had a reported AE of lung adenocarcinoma.

NMSCs were reported in 1/842 (0.1%) deucravacitinib subject (malignant sweat gland neoplasm described below) and 1/422 (0.2%) apremilast subject (squamous cell carcinoma). No placebo subject reported an NMSC during Week 0-16.

Subject IM011046- (b) (6) – NMSC of Malignant Sweat Gland Neoplasm of the Scalp

72-year-old White male with no prior systemic or phototherapy use was reported to have a malignant sweat gland tumor of the scalp after receiving deucravacitinib treatment for 30 days. He also had concomitant AEs of actinic keratoses in multiple areas. Study drug was interrupted for 6 days and the neoplasm was treated. The event was reported as recovered/resolved.

Malignant sweat gland tumors are rare cutaneous neoplasms that comprise the largest group of skin adnexal carcinomas. Although the incidence of these tumors is rising, information regarding prognostic factors and long-term outcomes is limited and mainly reliant on small case series and single-institution reports (Martinez et al. 2011).

The brief duration of exposure to deucravacitinib makes it unlikely that this subject's NMSC was a result of treatment with study drug.

Beyond Week 16, no malignancies were reported for apremilast.

After 52 weeks of exposure to deucravacitinib (969.0 PY), additional malignancies were reported in 9 subjects--3 had non-NMSC malignancies [breast cancer, hepatocellular cancer (HCC), and Hodgkin disease] and 6 had NMSCs, with basal cell carcinoma (BCC) reported in 4 subjects and squamous cell carcinoma (SCC) in 2 subjects.

As of the safety update cutoff date of October 1, 2021 (total exposure of 2482.0 patient-years), a total of 22/1519 (1.5%, 0.9/100 PY) subjects who received a dose of deucravacitinib in trials IM011046, IM011047, and IM011075 reported events of malignancy, of which 8 were solid tumors, 4 were hematological malignancies, and 11 were NMSCs (2 subjects had both basal cell carcinoma and squamous cell carcinoma). A summary of AEs of malignancy is shown in the table below. Of the 11 non-NMSC malignancies, breast carcinoma (PTs of breast cancer, intraductal proliferative breast lesion, and invasive ductal breast carcinoma), malignant melanoma, and colorectal cancer were reported in 2 subjects each; HCC and lung adenocarcinoma occurred in one subject each.

Table 68. Malignant Tumor and Nonmelanoma Skin Cancer AEs in Deucravacitinib-Treated Subjects - Phase 3 Safety Pool

Malignancy type	Phase 3 Safety Pool Through 15-Jun-2021	Phase 3 Safety Pool Through 01-Oct-2021
	N = 1519 Total P-Y = 2166.9	N = 1519 Total P-Y = 2482.0
	n (%) IR/100 p-y	n (%) IR/100 p-y
Total malignancies	19 (1.3) 0.9	22 (1.4) 0.9
Malignancies excluding NMSC	10 (0.7) 0.5	12 (0.8) 0.5
Solid tumors	6 (0.4) 0.3	8 (0.5) 0.3
Breast cancer ^a	2 (0.1) 0.1	2 (0.1) 0.1
Malignant melanoma	2 (0.1) 0.1	2 (0.1) 0.1
Colorectal cancer	1 (0.1) 0.0	2 (0.1) 0.1
Hepatocellular carcinoma	1 (0.1) 0.0	1 (0.1) 0.0
Lung adenocarcinoma	0	1 (0.1) 0.0
Hematologic	4 (0.3) 0.2	4 (0.3) 0.2
Acute promyelocytic leukemia	1 (0.1) 0.0	1 (0.1) 0.0
Lymphoma	3 (0.2) 0.1	3 (0.2) 0.1
B-cell lymphoma	1 (0.1) 0.0	1 (0.1) 0.0
Hodgkin's disease	1 (0.1) 0.0	1 (0.1) 0.0
Nodal marginal zone B-cell lymphoma	1 (0.1) 0.0	1 (0.1) 0.0
NMSC ^b	10 (0.7) 0.5	11 (0.7) 0.4
Basal cell carcinoma	7 (0.5) 0.3	8 (0.5) 0.3
Squamous cell carcinoma ^c	4 (0.3) 0.2	4 (0.3) 0.2
Malignant sweat gland neoplasm	1 (0.1) 0.0	1 (0.1) 0.0

Source: Applicant's 120-day SUR Table 2.7.3-1.

^a Includes preferred terms of breast cancer, intraductal proliferative breast lesion, and invasive ductal breast carcinoma.

^b 2 subjects had basal cell carcinoma and squamous cell carcinoma.

^c Includes preferred terms of squamous cell carcinoma, squamous cell carcinoma of skin, and Bowen's disease

Abbreviations: DEUC, deucravacitinib; IR, incidence rate; N, total number of subjects in the treatment group; n, number of subjects with the specific adverse event; p-y, person-years of exposure based on time to first onset.

Note: Phase 3 Safety Pool: deucravacitinib N = 1519; 2167 p-y at 15-Jun-2021 and deucravacitinib N = 1519; 2482 p-y at 01-Oct-2021.

8.2.5.2.1. Non-NMSC Malignancies

Details of malignancies excluding NMSC are described below.

8.2.5.2.1.1. Breast Carcinoma (2 Cases)

Subject IM011046- (b) (6)

64-year-old White female with a history of obesity and a family history of breast cancer (mother), had received multiple prior immunosuppressive agents (methotrexate, brodalumab, certolizumab, and UVB phototherapy) and was diagnosed with "invasive carcinoma of no

special type (NST)" after receiving treatment with deucravacitinib for 24 weeks. She received apremilast during Week 0-24 then deucravacitinib Week 24-52. Study drug was discontinued.

Subject IM011075- (b) (6) (IM011047- (b) (6))

55-year-old White female with a history of obesity, prior tobacco use, and monoclonal gammopathy of unknown significance, had received etanercept, alefacept, efalizumab, guselkumab, ixekizumab, infliximab, and adalimumab from (b) (6) and was reported to have "intraductal proliferative breast lesion" and "invasive ductal breast carcinoma" after receiving treatment with deucravacitinib for 46 weeks. She received placebo during Week 0-16 and deucravacitinib from Week 16 to 52 then transitioned to the LTE trial. Study drug was discontinued.

Both subjects had multiple risk factors for breast carcinoma making it difficult to determine deucravacitinib's role, if any, in the development of these malignancies.

8.2.5.2.1.2. Lung Adenocarcinoma (1 Case)

Subject IM011075- (b) (6) (IM011047- (b) (6))

53-year-old Asian male without prior known use of immunosuppressive agents or a predisposing family history, was diagnosed with metastatic lung adenocarcinoma to brain and bone after 85 weeks of exposure to deucravacitinib. He had received apremilast during Week 0-24 and deucravacitinib Week 24-52 then transitioned to the LTE trial. At the time of the safety update database freeze, the subject had not received treatment for his lung adenocarcinoma. Study drug was discontinued due to lung adenocarcinoma.

While lung adenocarcinoma is the second most common cancer in both men and women, this subject had no predisposing factors placing him at higher risk for this malignancy. Whether the 85-week (1.6 years) duration of deucravacitinib exposure impacted the progression of his malignancy to include distant metastases cannot be determined.

8.2.5.2.1.3. Colorectal Cancer (2 Cases)

Subject IM011075- (b) (6) (IM011046- (b) (6))

43-year-old Asian male with a history of tobacco use, family history of colon cancer (mother) and prior history of treatment with NB-UVB, certolizumab, and etretinate, developed colorectal cancer after receiving treatment with deucravacitinib for 14 weeks (open label extension study). He received apremilast throughout Study IM011046.

This subject, who despite being relatively young, was an active smoker with risk factors that collectively may have contributed to the development of colon cancer. The 14 weeks of exposure to deucravacitinib makes it unlikely that this subject's cancer was a result of treatment with study drug.

Subject IM011046- (b) (6)

64-year-old White male without prior known use of immunosuppressive agents or a predisposing family history, was diagnosed with metastatic colon cancer after receiving

treatment with deucravacitinib treatment for 103 weeks. He received deucravacitinib throughout Trial IM011046. Study drug was discontinued.

Other than his age, this subject did not have other reported risk factors for colon cancer, which has had an overall decreasing incidence in the US for several years. A causality link cannot be determined in this case wherein exposure to study drug was 2 years.

8.2.5.2.1.4. Hepatocellular Carcinoma (1 Case)

Subject IM011047- (b) (6)

54-year-old Asian male with a past medical history of cirrhosis due to hepatitis C infection, tobacco use, and prior treatment with adalimumab and ustekinumab, was diagnosed with hepatocellular carcinoma after receiving 32 weeks of deucravacitinib. He subsequently died with cause of death reported due to hepatocellular carcinoma. Refer to the section of Deaths (Section [8.2.4.1](#)) for further details.

8.2.5.2.1.5. Malignant Melanoma (2 Cases)

Subject IM011075- (b) (6) (IM011047- (b) (6))

51-year-old White male with Fitzpatrick skin Type 1, prior treatment with NB-UVB ((b) (6)) and acitretin, had malignant melanoma reported after receiving a total of 62 weeks of deucravacitinib treatment (deucravacitinib throughout Trial IM011047 and during the LTE trial). Study drug was discontinued.

Subject IM011075- (b) (6) (IM011046- (b) (6))

48-year-old White male with a prior history of malignant melanoma ((b) (6)) was diagnosed with malignant melanoma after receiving treatment with deucravacitinib for 84 weeks (deucravacitinib throughout Trial IM011046 and during the LTE trial). Study drug was discontinued.

Both subjects had multiple risk factors for melanoma making it difficult to determine deucravacitinib's role, if any, in the development of these malignancies.

Of note, during the Phase 2 dose-ranging study (IM011011), there was one case of in situ malignant melanoma (stage 0) that was diagnosed via skin biopsy of an atypical nevus after 13 weeks of deucravacitinib 3 mg daily. The paucity of information makes it difficult to assess deucravacitinib's effect on this early stage melanoma. Further, the brief duration of exposure to deucravacitinib makes it unlikely that this subject's melanoma was a result of treatment with study drug.

The most common types of non-NMSC malignancies reported in deucravacitinib's drug development program correspond to the most common cancers seen in the United States (US). Breast carcinoma is the most common cancer in the US followed by lung, prostate, and colon cancers. Additionally, the incidence of melanoma of the skin has been rising.

There did not appear to be an association between deucravacitinib exposure and a particular malignancy. For the 2 subjects who did not have reported risk factors for cancer, it is difficult to establish if TYK2 inhibition might have contributed to their development of lung adenocarcinoma and colon cancer.

8.2.5.2.1.6. Leukemia (1 Case)

Subject IM011075- (b) (6) (IM011046- (b) (6))

56-year-old Asian male with a history of tobacco use, active vaping, and a family history of acute leukemia (maternal grandmother at age 88 years), was diagnosed with acute promyelocytic leukemia on Day 239 (34 weeks) of the LTE trial. There was no history of prior systemic therapy or phototherapy. The subject received placebo during Week 0-16 followed by deucravacitinib from Week 16 to 52 and during the LTE trial. Study drug was discontinued. He received all-trans-retinoic acid and dexamethasone. Subsequently, 7 weeks following diagnosis, his bone marrow showed mature neutrophils and no monotonous proliferation of blasts. Information provided in the SUR described the subject as undergoing maintenance chemotherapy with persistent bone marrow evidence of complete remission.

8.2.5.2.1.7. Lymphoma (3 Cases)

Subject IM011046- (b) (6): Hodgkin Lymphoma

48-year-old White male with a history of hypertension, dyslipidemia, and type 2 DM had no prior history of systemic therapy or phototherapy. He was diagnosed with Stage III classic Hodgkin lymphoma (cHL) on Day 177 after 25 weeks of exposure to deucravacitinib. He received adriamycin, bleomycin, palonosetron, doxorubicin, dacarbazine, vinblastine, dexamethasone for treatment of his cHL. During Week 39 the subject discontinued from the trial due to cHL with the last dose received at the time of diagnosis (Day 171, Week 24). Twenty-three weeks after diagnosis, his PET-scan showed evidence of complete response with no abnormal radiotracer uptake and no abnormal lymph nodes.

Subject IM011075- (b) (6) (IM011046- (b) (6)): Non-Hodgkin Lymphoma

58-year-old White male with a history of hypertension, hyperlipidemia, tobacco use (one pack per day for 36 years), prior phototherapy and systemic therapy including methotrexate, efalizumab, and ustekinumab, who had received 98 weeks of deucravacitinib (initially placebo then deucravacitinib from Week 16 onward) was diagnosed with low grade follicular B-cell Non-Hodgkin lymphoma. Study drug was discontinued and last dose received was on Day 413.

Subject IM011075- (b) (6) (IM011047- (b) (6)): Non-Hodgkin Lymphoma

72-year-old White male with a history of prior phototherapy, numerous squamous and basal cell carcinomas, as well as a family history of leukemia (father) and ovarian cancer (mother), was diagnosed with nodal marginal zone B-cell on Day 183 of the LTE trial following 77 weeks of exposure to deucravacitinib. Study drug was discontinued due to lymphoma with the last dose of study treatment received on Day 183. On Day 254, the subject started treatment with rituximab and bendamustine for lymphoma. End of study visit was performed on Day 317.

Noteworthy, is a case of Hodgkin lymphoma (HL) reported during a regional Phase 2, single-arm, open-label study (Study IM011066) in Japan. The subject was a 46-year-old Asian male with erythrodermic psoriasis but no prior history of systemic therapy or phototherapy use. At baseline his T- and B-cell flow cytometry (TBNK) showed elevated B cells. He had received 36 weeks of deucravacitinib and underwent cervical node biopsy at Week 37 that confirmed HL.

Non-Hodgkin lymphoma (NHL) is the fifth most common cancer in the United States (US) with a rising incidence rate. In the US (and in Europe, as well as other economically developed countries), the majority of lymphomas are NHL while HL accounts for approximately 10 percent of all lymphomas (Baris and Zahm 2000). Published literature describes that patients with psoriasis have an increased relative risk of lymphoma potentially due to psoriasis's pathophysiology and/or its treatments (Gelfand et al. 2006).

While the events of lymphoma reported during deucravacitinib's psoriasis development program were few in number, occurring after differing durations of exposure (i.e., 25, 77, and 98 weeks of treatment), and each case included potential confounding factors, the exposure-adjusted incidence rate of lymphoma observed with deucravacitinib during the development program is higher than the rate observed in patients with psoriasis (0.04-0.06/100 PY) (Gelfand et al. 2006) and is comparable to that of tofacitinib 10 mg twice a day (0.11/100 PY) used during clinical trials for the treatment of rheumatoid arthritis (Pfizer 2021).

It is difficult to determine deucravacitinib's role in each of these cases of lymphoma. The mechanism generating the increased risk of lymphoma is not known. There was no nonclinical evidence of lymphoproliferative disorders or malignancies in the chronic 9-month toxicology study in cynomolgus monkeys at doses up to 5 mg/kg/day (65× recommended human dose AUC at 6 mg QD). While a potential risk of lymphoma is identified, there is not a demonstrated increase in overall malignancy risk.

TYK2 belongs to the JAK family. The adverse reactions (ARs) described in labeling for JAK inhibitors (tofacitinib, baricitinib, upadacitinib, and abrocitinib) that are approved for chronic inflammatory conditions consist of malignancies, including lymphoma, which are described in a Boxed Warning.

The EAIR (0.1/100 PY) of lymphoma observed for deucravacitinib-treated subjects with moderate to severe psoriasis is comparable to the rate for rheumatoid arthritis subjects treated with tofacitinib 10 mg twice a day during clinical trials (Pfizer 2021). This EAIR is also 5 fold higher than the rate of lymphoma expected in the general U.S. population based on the 5-Year Age-Adjusted Incidence Rates, 2015-2019 Surveillance, Epidemiology, and End Results (SEER) Database.

Based on the available data to date, the risk of lymphoma will be communicated to healthcare providers as a Warning & Precaution and Adverse Reaction in order to mitigate potential risk, and will also be adequately described for patients in the Medication Guide.

Additionally, the potential risks related to JAK inhibition from a large randomized, postmarketing safety trial of a JAK inhibitor in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor that confirmed the safety signal of malignancy, will also be conveyed as a Warning and Precaution.

Because the duration of deucravacitinib's development program did not allow detection of events with long latency periods such as malignancy, long-term data are needed to identify a potential serious risk of malignancy. A postmarketing, active-controlled randomized trial will be required to more fully assess the risk of overall malignancy.

The overall incidence rate for malignancies (excluding NMSC) in subjects who received deucravacitinib during the psoriasis development program is 0.5/100 PY. In comparison, the rates of malignant tumors (excluding NMSC) reported in clinical programs for other systemic therapies [including ustekinumab (IL-12/IL-23 blocker), ixekizumab (IL-17A blocker), secukinumab (IL-17A blocker), and guselkumab (IL-23 blocker)] ranged from 0.31 – 0.49/100 PY. The published rate for subjects with moderate to severe psoriasis who received tofacitinib during clinical trials was 1.15/100 PY (95% CI, 0.78-1.63, for all doses in the total tofacitinib exposure pool) (Papp et al. 2016). Moreover, the rate of first malignancy among patients who did not have a history of malignancy (excluding NMSC) reported for biologics in the Psoriasis Longitudinal Assessment and Registry (total PYs, 46,041) was 0.55/100 P-Y (95% CI, 0.48-0.62) (Fiorentino et al. 2017).

The data to date demonstrate that the exposure-adjusted incidence rate for malignancies (excluding NMSC) is on par with what has been seen during other psoriasis programs for biologics and is notably less than what was seen with the tofacitinib-psoriasis program (Strober et al. 2019).

8.2.5.2.2. Non-melanoma Skin Cancers (NMSC)

The incidence rate for NMSC at the SUR data cut-off date was 0.4/100 p-y, which is comparable to incidence rates of NMSC in real world populations of psoriasis patients using psoriasis drug products (range: 0.4-2.4/100 p-y) (Kimball et al. 2015).

Of the 10 subjects with squamous cell carcinoma (SCC) or basal cell carcinoma (BCC), 7 had a prior history of NMSC. Other subjects had risk factors of advanced age, actinic keratosis, Fitzpatrick Skin Type 1 or 2, history of phototherapy use with ultraviolet A light, or prior tumor necrosis factor (TNF) inhibitor use.

Skin cancer is the most common class of malignancies, and the elevated risk of skin cancers in chronically immunosuppressed individuals is well-established from studies in organ transplant patients. The ratio of SCC:BCC in nontransplant patients is 0.2:1.0. Following transplant, the ratio changes as the incidence of SCC significantly increases, but the incidence of BCC only slightly increases, resulting in an inverted SCC:BCC ratio of 1.8:1.015 (Penn 1997).

Of the 13 NMSC malignancies reported in subjects who received deucravacitinib during the Phase 3 development program, squamous cell carcinoma/Bowen's disease combined included 4 events while basal cell carcinoma events (8) were more common. The SCC:BCC ratio is 1:2. While the ratio is not as wide as seen in nontransplant patients, it does not invert due to an increase of SCC, indicating a potentially less immunosuppressive affect relative to that seen in transplant patients.

Furthermore, of the 10 subjects who experienced an NMSC in the Phase 3 Safety Pool, 7 had a medical history of prior NMSC. Other reported risk factors (in addition to psoriasis) included actinic keratosis, older age, Fitzpatrick Skin Type 1 or 2, phototherapy with ultraviolet A light, or prior TNF inhibitor use.

8.2.5.2.3. Overall Malignancy Assessment

Although the event rate for malignancy in general was consistent with that seen for other systemic therapies in the treatment of psoriasis, deucravacitinib is a new small molecule with immunomodulating properties that might impact tumorigenesis.

Based on the available data to date, an increase in overall malignancy risk was not demonstrated; however, there was a potential risk of lymphoma identified in deucravacitinib-treated subjects with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy.

TYK2 belongs to the JAK family, and the adverse reactions (ARs) described in labeling for JAK inhibitors (tofacitinib, baricitinib, upadacitinib, and abrocitinib) that are approved for chronic inflammatory conditions consist of malignancies (including lymphoma) which are described in a Boxed Warning. The EAIR (0.1/100 PY) of lymphoma observed for deucravacitinib-treated subjects with moderate to severe psoriasis is comparable to the rate observed for rheumatoid arthritis subjects treated with tofacitinib 10 mg twice a day during clinical trials (Pfizer 2021).

While the precise mechanism of action is unknown, natural killer (NK) cells appear to play a crucial role in tumor surveillance and the lack of mean change during the deucravacitinib program might account, at least in part, for the different malignancy risk to date as seen with JAK inhibitors approved for inflammatory conditions such as tofacitinib, wherein NK cells were reduced (Valenzuela et al. 2015).

While deucravacitinib will not carry the same labeled risk of malignancy as the other JAK inhibitors approved for inflammatory diseases, the risk of lymphoma will be communicated to healthcare providers in the Warnings & Precautions and Adverse Reactions sections and will also be adequately described for patients in the Medication Guide in order to mitigate potential risk.

Additionally, the potential risks related to JAK inhibition from the large randomized, postmarketing safety trial of a JAK inhibitor in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor that confirmed the safety signal of malignancy, will also be conveyed as a Warning and Precaution.

The duration of deucravacitinib's development program may not have allowed for detection of events with long latency periods such as malignancy, therefore, to address uncertainties regarding the long-term safety of deucravacitinib, a long-term postmarketing, active-controlled randomized trial will be required to more fully assess the risk of overall malignancy.

8.2.5.3. Cardiovascular (CV) Events

Analysis of major adverse cardiovascular events (MACE) to assess cardiovascular safety was of interest for several reasons: (1) the association between psoriasis and CV comorbidities, (2) the potential relationship between anti-cytokine therapies used in the treatment of moderate to severe psoriasis and CV events, (3) animal models in another TYK2 program that identified the heart as a target organ, and (4) the known CV safety issues associated with the class of JAK inhibitors. The Applicant conducted analyses on adjudicated MACE, extended MACE, other CV events, and thrombosis that were considered serious. MACE included events of nonfatal myocardial infarction (MI), nonfatal stroke, and CV death. Extended MACE was defined as MACE plus unstable angina requiring hospitalization. Other serious adjudicated CV events included revascularization procedures, heart failure, dysrhythmias, heart blocks, all deaths, as well as thrombotic events. In this section, MACE and extended MACE will be discussed together, followed by "other CV events", with a review of thrombosis discussed separately.

The eligibility criteria in the two Phase 3 clinical trials excluded participants who had the following:

- Unstable cardiovascular disease, defined as a recent clinical cardiovascular event (e.g., unstable angina, myocardial infarction, stroke, rapid atrial fibrillation) during the last 3 months prior to Screening, or a cardiac hospitalization (e.g., revascularization procedure, pacemaker implantation) within 3 months prior to Screening.
- Uncontrolled arterial hypertension characterized by a systolic blood pressure (BP) >160 mm Hg or diastolic BP >100 mm Hg which was determined by 2 consecutive elevated readings.
- Class III or IV congestive heart failure by New York Heart Association Criteria.

Randomized subjects were predominantly male (67%) with a mean age of 47 years with approximately 10% of subjects $\geq$ 65 years of age. Median body mass index (BMI) was 29 kg/m². Across the two Phase 3 trials, the mean (median) duration of psoriasis was approximately 19 (16) years, with a mean age at disease onset of approximately 29 years. Baseline cardiovascular risk factors and baseline history of cardiovascular disease were in general, evenly distributed among the deucravacitinib arm and the control arms of the trials comprising the safety pools.

8.2.5.3.1. MACE and Extended MACE

As described above, MACE included events of nonfatal myocardial infarction (MI), nonfatal stroke, and CV death. Extended MACE was defined as MACE plus unstable angina requiring hospitalization. Dr. Charu Gondotra of the Division of Cardiology and Nephrology (DCN) was consulted to provide an assessment of the adequacy of the Applicant's analyses and to help

determine the CV risk in the psoriasis population treated with deucravacitinib. She determined that the overall number of CV SAEs is small and the incidence of MACE was low in the Controlled, as well as Phase 3 safety pools, therefore, she could not conclude that there is an increased risk of MACE with deucravacitinib.

Placebo- and Apremilast-Controlled Period, Week 0-16

During the Week 0-16, the incidence rates for serious MACE and extended MACE events were the same for deucravacitinib (2/842, 0.2%) and apremilast (1/422, 0.2%) and highest for placebo (3/419, 0.7%).

One of the two deucravacitinib-treated subjects (IM011046-(b) (6)) had a non-ST elevation myocardial infarction (NSTEMI) on Day 16 that was considered by the investigator to be related to study drug. The subject was a 60-year-old male with a PMH of obesity, hypertension, hyperlipidemia, and diabetes mellitus who discontinued from the study following percutaneous transluminal coronary angioplasty (PTCA) with stent insertion. His creatine kinase level was 199 U/L [reference range (RR): 39-308] up from a baseline level of 112 U/L, and his troponin ranged from 299 ng/L to 534 ng/L (reference range: 0-33 ng/L) during the initial hours of presentation. His total cholesterol was 225.06 mg/dL (RR: <200 mg/dL) up from a baseline value of 195 mg/dL. Serum triglycerides were increased at 6.98 mmol/L (RR: 0-1.69 mmol/L) relative to baseline (4.51 mmol/L).

Given this subject's numerous cardiovascular risk factors, it is difficult to determine deucravacitinib's role, if any, in this subject's acute myocardial infarct (AMI).

The observed lipid changes are not unexpected as fluctuations in serum lipid profile are observed after AMI with the most common abnormal parameter noted to be elevated triglycerides (Kumar et al. 2019).

The other deucravacitinib-treated subject (IM011047-(b) (6)) had fatal events of 'cardiac arrest' and 'cardiac failure' in the setting of 'sepsis' as discussed previously under Deaths (Section [8.2.4.1](#)).

One placebo-treated subject with a PT of unstable angina was adjudicated to myocardial infarction (MI). The other two placebo subjects included a 71-year-old male with numerous CV risk factors who had an acute MI, and the other placebo subject died from "hypertensive heart disease" as previously described under Deaths (Section [8.2.4.1](#)). The apremilast-treated subject had an MI. Additionally, there was a subject receiving apremilast who had a PT of stroke that was determined by the adjudication committee to not be a stroke. This subject had ischemic strokes reported in the setting of metastatic lung cancer and died of lung adenocarcinoma as commented under Deaths (Section [8.2.4.1](#)).

Apremilast-controlled Period, Week 0-24

Between Week 16 to Week 24, for subjects treated with either apremilast or deucravacitinib *without switching*, there was one additional subject in each of the apremilast and

deucravacitinib groups equating to a total of 2/422 (0.5%) apremilast-treated subjects and 3/842 (0.4%) deucravacitinib-treated subjects who had MACE or extended MACE events during Week 0-24.

Noteworthy is that the apremilast-treated subject (IM011046-(b) (6)) received several deucravacitinib tablets in error:

- The subject was a 47-year-old White male with a PMH of hypertension, hyperlipidemia, diabetes, and obesity who was diagnosed with an acute brainstem infarct. During Week 20, the subject was hospitalized for left partial paresis and numbness. His initial brain MRI did not demonstrate focal cerebral abnormalities but there were features of left vertebral artery occlusion. CT angiogram showed right vertebral artery stenosis and left vertebral artery occlusion with some areas of established perfusion from collaterals. A repeat cranial MRI showed a hyperintense focus in the medulla oblongata 5 days later.
- It was noted that at the Week 16 visit, the subject was dispensed 2 bottles of apremilast, 1 bottle of 'matching placebo', and mistakenly, 1 bottle (16 tablets) of deucravacitinib. At the Week 20 visit all of the bottles were returned empty.
- The radiographic evidence of collaterals reflects that the subject's diminished posterior circulation was chronic. The role of either of the 2 active study treatments (individually or collectively) on the acute brainstem infarct cannot be established.

The subject in the deucravacitinib group (IM011046-(b) (6)) had a MACE event that occurred during Week 16-24 but also had related CV events beyond Week 24 that led to study discontinuation during Week 31 (Day 220).

- He was a 76-year-old male with a history of obesity, hypertension, hyperlipidemia chronic kidney disease stage 3 and known coronary artery disease with prior MI requiring coronary artery stenting, who developed unstable angina during Week 21 following an outpatient cardiac catheterization. The following week, coronary artery bypass grafting (CABG) was performed due to multi-vessel disease. During his hospitalization he developed atrial fibrillation. His clinical course was complicated by a postoperative sternal staphylococcal wound infection and pericarditis during Weeks 27 to 29. During Week 30, he was rehospitalized for pericarditis and discontinued treatment. The investigator did not consider the post-operative wound infection and pericarditis related to study drug.
- The CV events and complicated clinical course following CABG is difficult to attribute to study drug given the subject's numerous pre-existing comorbid conditions.

Apremilast-controlled Period, Week 0-52 – Trial IM011046

With longer exposure from Week 24 to Week 52, there were no subjects with MACE or extended MACE events in trial 046 who did not switch treatment.

For completeness and to capture any events beyond Week 24 through Week 52 *outside* of the periods and pools discussed above, analyses were performed for subjects who did not switch treatment during *both* controlled Phase 3 trials (IM011046 and IM011047). This analysis yielded

one additional subject who received deucravacitinib and experienced a MACE event. No events were reported in the apremilast group.

Subject IM011047- (b) (6): Stroke

73-year-old female with a history of obesity, hypertension, and atrial fibrillation not on anticoagulation therapy received deucravacitinib throughout Trial IM011047 and required hospitalization during Week 37 due to an acute posterior cerebral artery stroke plus rapid atrial fibrillation with a heart rate in the 180 BPM range. CT angiogram of the head and neck showed near complete occlusion of the right posterior cerebral artery. The subject withdrew from the study after 42 weeks of exposure to deucravacitinib.

The subject's history of atrial fibrillation without anticoagulation therapy is more likely to be contributory to the cause of stroke than the study drug.

In the LTE trial (IM011075), 7 additional events in subjects receiving open label deucravacitinib were adjudicated to serious MACE and extended MACE events. They are summarized in the discussion below with relevant updates based on the 120-day safety update.

Subject IM011075- (b) (6) (IM011047- (b) (6), Deucravacitinib Week 0-52): Ischemic Stroke

35-year-old female with a history of tobacco use (half a pack per day) received deucravacitinib throughout Trial IM011047 and had also received her first of two COVID-19 vaccine injections approximately 2 weeks prior to her CV event. She had an ischemic stroke during Week 35 of the LTE trial (i.e., following 87 weeks of deucravacitinib exposure). She presented with sudden onset collapse, left sided paralysis, and inability to speak. Study drug was interrupted. A cranial MRI confirmed a subacute infarct involving the right middle cerebral artery territory. Following "clot busting treatment" (details unknown) and intensive physiotherapy the subject's mobility and speech improved but residual left hemiparesthesias persisted. As of the safety update October 1, 2021 database lock, there was no new information for this subject who had resumed study drug.

Given the subject's young age and lack of significant cardiovascular risk factors, there is elevated concern regarding deucravacitinib's role in the pathogenesis of this subject's stroke.

Subject IM011075- (b) (6) (IM011046- (b) (6), Placebo Week 0-16, Deucravacitinib Week 16-52): Unstable Angina Requiring Hospitalization

37-year-old male with history of tobacco use, hyperlipidemia and a family history of "congenital heart disease" described as dilated cardiomyopathy (father) presented to the hospital on Week 24 of the LTE trial (i.e., after 60 weeks of deucravacitinib exposure) with chest pain, tightness, and an elevated blood pressure. Coronary angiography showed atherosclerotic heart disease thus coronary artery balloon dilation and stent implantation were performed.

During his hospitalization he was also documented with adverse events of type 2 diabetes, fatty liver disease, and moderate abnormal liver function. Additionally, a brain MRI scan was

performed and showed multiple localized stenoses of the left posterior cerebral artery although there was no indication as to why cranial imaging was pursued, the subject was specifically described as not experiencing any neurological deficits.

There was no new information for this subject who remained on study drug as of the safety update October 1, 2021 database lock.

Although this subject is young, he had numerous cardiovascular risk factors. It is difficult to determine *deucravacitinib's* role, if any, in this subject's atherosclerotic plaque progression.

Subject IM011075- (b) (6) (IM011047- (b) (6)), Deucravacitinib Week 0-52): NSTEMI 44-year-old White male with a history of hypertension, hyperlipidemia, and tobacco use was admitted to hospital with chest pain on Day 2 of the LTE trial (i.e., following 52 weeks of deucravacitinib exposure). ECG showed regular sinus rhythm and normal axis without ischemic changes, but laboratory studies showed evidence of myocardial infarction [troponin-T value of 0.991 µg/L (baseline: NA; reference range: 0-0.014 µg/L) and creatinine kinase of 9.20 µg/L (reference range: 0.10-4.94 µg/L)].

Angiography showed critical left anterior descending (LAD) stenosis requiring angioplasty and stent placement. On Day 6, MI resolved and echo showed a left ventricular ejection fraction (EF) of 50%. The MI was considered not related by investigator. Safety update information from the 120 day report described the subject as having undergone a "normal" exercise stress test. He also pursued cardiac rehabilitation with "good general" health under the care of a cardiologist while remaining on study drug.

Although this subject is relatively young, he had several cardiovascular risk factors. Therefore, it is difficult to determine what impact, if any, deucravacitinib had on this subject's atherosclerotic plaque progression to acute thrombosis.

Subject IM011075- (b) (6) (IM011046- (b) (6)), Apremilast Week 0-52): NSTEMI 47-year-old male with a history of hypertension, obesity, and tobacco use with a reported family history of premature coronary artery disease (father and grandfather) presented to the hospital with dyspnea and left arm pain during Week 56 of the LTE trial. Coronary angiography with angioplasty and implantation of drug eluting stents (DES) of the LAD and circumflex arteries were performed during his hospitalization. Safety update information reported the subject in "good/stable" condition under the care of a cardiologist while remaining on study drug.

Subject IM011075- (b) (6) (IM011046- (b) (6)), Deucravacitinib Week 0-52): NSTEMI 71-year-old White female with a history of tobacco use, hyperlipidemia was hospitalized during Week 17 of the LTE trial (i.e., following 69 weeks of deucravacitinib exposure) due to acute myocardial infarction considered not related by the investigator. Her laboratory studies were consistent with myocardial infarction [creatinine Kinase (CK) level of 236 U/L (reference value: 29-168 U/L); CK MB of 33 U/L (reference value: 0-25), and troponin I level of 718.10 ng/L

(reference range: 0-15.6 ng/L)]. Angiogram showed 99% stenosis of right coronary artery (RCA) requiring percutaneous intervention (PCI) and stent placement. Echocardiography showed hypokinesis of the inferior left ventricular wall. Five days after admission, the subject was discharged. There was no new information for this subject who remained on study drug as of the safety update October 1, 2021 database lock.

Subject IM011075- (b) (6) (IM011046- (b) (6)), Placebo Week 0-16, Deucravacitinib Week 16-52): NSTEMI, Congestive Heart Failure

76-year-old overweight White male with a history of obesity, hypertension, hyperlipidemia, type 2 diabetes, prior tobacco use, and latent tuberculosis (treated) was admitted to the hospital during Week 34 of the LTE trial (i.e., after 70 weeks of deucravacitinib exposure) with peripheral edema and severe dyspnea including paroxysmal nocturnal dyspnea. In the emergency room, he had severe heart failure, left bundle branch block on EKG, an elevated brain natriuretic peptide (BNP) level (6127 ng/mL, 0-300 ng/L), and high troponin T value (0.328 ng/mL, 0-0.018 ng/mL). Echocardiogram showed an ejection fraction (EF) of 15-20%, aortic sclerosis, and moderate-to-severe tricuspid regurgitation. Cardiac catheterization showed severe 3 vessel coronary artery disease.

Cardiac MRI followed by dobutamine ECHO did not add further diagnostic insight. Cardiac surgery consultation did not recommend CABG or PCI. The subject also developed hematuria during his hospitalization and cystoscopy revealed bladder stones along with significant benign prostatic hypertrophy. Study drug was interrupted. After approximately 40 days following admission to the hospital, the subject was discharged and his events of coronary artery disease and CHF were considered resolved.

According to the safety update report, the event of coronary artery disease was downgraded by the principal investigator from an SAE to an AE because the subject did not undergo PCI or CABG.

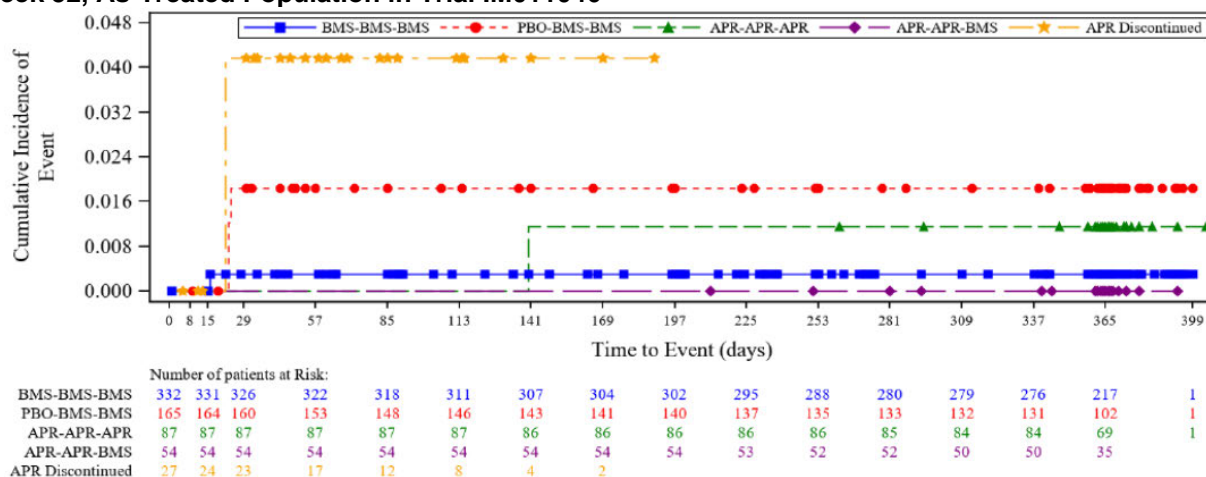
Subject IM011075- (b) (6) (IM011046- (b) (6)), Placebo Week 0-16, Deucravacitinib Week 16-52): Thoracic Aortic Aneurysm Ruptured and Hemopericardium

This subject was previously discussed under Deaths (Section [8.2.4.1](#)).

Other than the young female subject who suffered an acute stroke, all of the subjects with reported MACE or extended MACE events had at least 2 cardiovascular risk factors. Given these confounders, causality cannot be definitively attributed to study treatment.

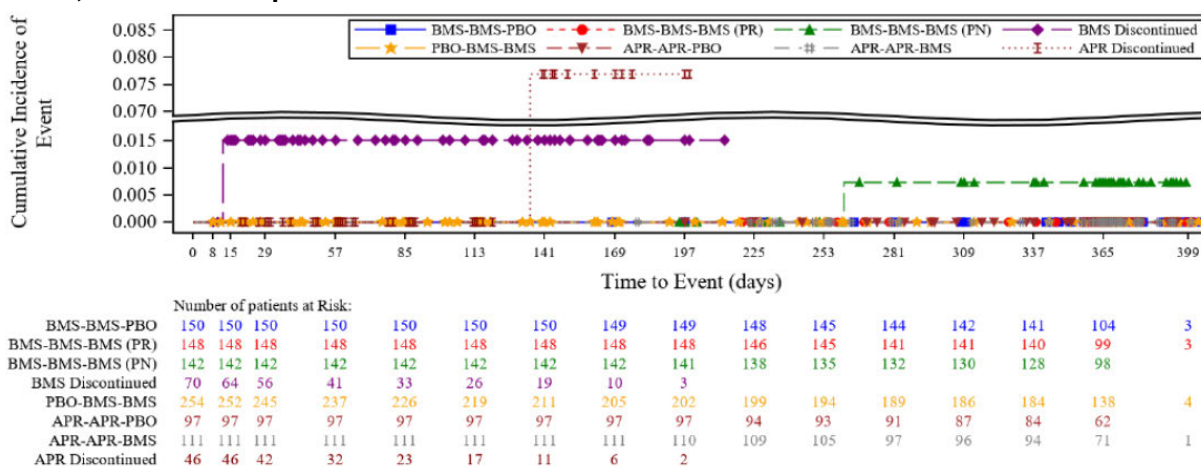
To understand the incidence of MACE over time in various treatment groups, an Information Request was sent on May 9, 2022 for the Applicant to provide Kaplan–Meier (K-M) curves for MACE and extended MACE (without creatinine kinase elevation) for the As-Treated Population, Controlled Safety. [Figure 13](#) and [Figure 14](#) below are the K-M plots for MACE in trials IM011046 and IM011047.

Figure 13. Kaplan-Meier Plot for Cumulative Incidence of Subjects With MACE Event, Week 0 Through Week 52, As-Treated Population in Trial IM011046



Includes events with a start date between first dose and +30 days post last dose date or upon rollover into IM011075.
 Subjects are summarized according to treatment sequence. 'APR Discontinued' includes subjects who discontinued prior to treatment switching at Week 24.
 Program Source: \\BMSSTATS-BSTATS\SAS\Report\SCS120D\rg-km-ae52-ebr.sas 13MAY2022:15:48:42

Figure 14. Kaplan-Meier Plot for Cumulative Incidence of Subjects With MACE Event, Week 0 Through Week 52, As-Treated Population in Trial IM011047



Includes events with a start date between first dose and +30 days post last dose date or upon rollover into IM011075.
 Subjects are summarized according to treatment sequence. PR and PN represent PASI75 Responders and Nonresponders at Week 24 (per IRT response), respectively.
 'BMS Discontinued' and 'APR Discontinued' include subjects who discontinued prior to treatment switching at Week 24.
 Program Source: \\BMSSTATS-BSTATS\SAS\Report\SCS120D\rg-km-ae52-ebr.sas 13MAY2022:15:48:50

Dr. Gondotra concluded, and the review team concurs, that the curves for Trial IM01104 indicate a lower incidence of MACE in subjects on deucravacitinib compared to subjects who were switched from placebo to deucravacitinib or those on apremilast and the K-M Curves for trial 047 indicate a lower incidence of MACE for subjects on deucravacitinib versus subjects who were discontinued from deucravacitinib but slightly higher than the subjects on other treatment sequences. After approximately 250 days of treatment, the incidence of MACE

appeared to increase raising some concern about CV safety of long-term use of deucravacitinib. However, Dr. Gondotra reiterated that the number of MACE is low to definitively conclude an increased CV risk with deucravacitinib.

In attempts to understand the risk of MACE with longer duration of exposure beyond 52 weeks, the Applicant assessed overall MACE for deucravacitinib-treated subjects in the Phase 3 safety pool in response to an IR dated March 11, 2022. An EAIR of 0.4/100 PY (95% CI, 0.2-0.7, n=9, N=1519, exposure 2482 PY) was calculated, which is on par with published rates in psoriasis patients and is comparable to the EAIR reported during the tofacitinib-psoriasis program [0.37/100 PY (95% CI, 0.22-0.57, n=19, N=3623, exposure 5203 PY)] (Wu et al. 2016). However, given potential differences in subject edibility criteria, demographics, baseline characteristics, durations of treatments, study design and conduct, such comparisons should be made and interpreted with caution.

While the rate of MACE and extended MACE was low for deucravacitinib-treated subjects with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy, and there was no increase with longer duration of treatment, literature suggests an association between psoriasis and cardiovascular disease and metabolic syndrome (Oliveira Mde et al. 2015). Therefore, risk of MACE with deucravacitinib should be kept in mind as deucravacitinib will be used in patients with underlying CV risk factors and for longer duration than the controlled trials.

Based on the submitted data, it cannot be concluded that there is an increased risk of MACE with deucravacitinib at this time. Although uncertainties remain, deucravacitinib's different pharmacological class and differences in overall safety profile including limited impact on lipids, support labeling that will reflect the risks related to JAK inhibition, exclusively referencing the higher rate of MACE demonstrated in a large, randomized, postmarketing safety study of a JAK inhibitor in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor.

To better define the long-term safety profile of deucravacitinib as a new molecular entity, we have determined that a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of cardiovascular events. This required postmarketing trial is further discussed in Section [13](#).

8.2.5.3.2. Other Serious Adjudicated CV Events

As previously described, other serious CV events that were adjudicated include revascularization procedures, heart failure, dysrhythmias, heart blocks, all deaths, as well as thrombotic events. Peripheral venous and arterial thrombotic events will be discussed separately.

Placebo- and Apremilast-controlled Period, Week 0-16

During Week 0-16, 2/842 (0.2%) subjects who received deucravacitinib reported other serious CV events of ventricular tachycardia (IM011046-(b) (6)) and malignant hypertension

(IM011047- (b) (6)). Both of these subjects had underlying CV risk factors--the former was a 64-year-old male with CAD, prior MI, ventricular tachycardia requiring an implantable defibrillator, sleep apnea, and CKD stage 3, and the other subject was a 38-year-old male with morbid obesity (BMI of 47 kg/m²) and hypertension who ran out of his blood pressure medications. Following treatment in the hospital setting, both continued to receive study treatment and were enrolled in the LTE study. No subjects in the placebo or apremilast groups had other serious CV events reported during this period.

Apremilast-controlled Period, Week 0-24

During Week 16-24, three subjects who received deucravacitinib without switching (i.e., excludes placebo subjects who switched treatment), had serious CV events that were adjudicated as supraventricular tachycardia, atrial fibrillation, and myocardial ischemia.

A fourth deucravacitinib-treated subject had a serious CV event of "transient ischemic attack" during this period (Week 16-24); however, he had initially received placebo then transitioned to deucravacitinib at Week 16. There were no subjects in the apremilast group that reported a serious CV event during this period.

Apremilast-controlled Period, Week 0-52 – Trial IM011046

A longer-term assessment of subjects treated with deucravacitinib or apremilast in Trial 046 without switching through 52 weeks identified 2 additional serious CV cases of pericarditis in the deucravacitinib group as described below. There were no subjects in the apremilast group with serious CV events.

Subject IM011046- (b) (6) – Acute Pericarditis

76-year-old male with history of hypertension, hyperlipidemia, and CAD requiring prior angioplasty ((b) (6)) and stent insertion ((b) (6)), reported a post-operative wound infection and acute pericarditis following coronary artery bypass grafting (CABG) after 30 weeks of deucravacitinib exposure. He discontinued study treatment.

Subject IM011046- (b) (6) – Acute Pericarditis

64-year-old-male with history of hyperlipidemia reported an acute GI infection plus acute pericarditis after 31 weeks of exposure to deucravacitinib. He withdrew from the trial.

Both subjects' events of acute pericarditis were in the setting of concurrent illnesses that were *likely more contributory than study drug*.

In the LTE trial (IM011075), 9 additional events in subjects receiving open label deucravacitinib were adjudicated to serious CV events: pericarditis (IM011075- (b) (6)), angina (IM011075- (b) (6)), uncontrolled hypertension (IM011075- (b) (6)), malignant hypertension (IM011075- (b) (6)), coronary artery stenosis (IM011075- (b) (6)), congestive heart failure (IM011075- (b) (6) and IM011075- (b) (6)), atrial flutter (IM011075 (b) (6) (b) (6)), and ventricular tachycardia (IM011075- (b) (6)).

In the SUR, 1 additional serious CV event of transient ischemic attack (IM011075- (b) (6) (b) (6) was reported.

Analyses of the ADAE database evaluating the number of AEs under cardiac and vascular disorder system organ class by preferred term and by treatment arm performed by the review team and Dr. Gondotra did not demonstrate an increased risk of other CV events with deucravacitinib. A higher incidence of hypertension PT in the deucravacitinib group compared to the placebo group was seen; however, there was no clinically meaningful change from baseline in blood pressure observed in any treatment group. As such, Dr. Gondotra recommended, and the team concurs, that hypertension will not be included in Sections 5 or 6.

8.2.5.3.3. Venous Thrombosis and Peripheral Arterial Occlusion

Thrombosis (including venous thromboembolic and peripheral arterial events) is considered to be an area of safety interest for deucravacitinib given this risk has been observed for other JAK inhibitors indicated for the treatment of chronic inflammatory conditions. Dr. Fadi Nossair of the Division of Nonmalignant Hematology was consulted to assist in the assessment of the thrombosis risk with deucravacitinib. After review of the Applicant's analyses, as well as examination of the detailed narratives, he determined that none of the thrombotic events were thought to have strong association with exposure to the drug and that it was difficult to attribute causality of any of the events to drug exposure, especially given the variable duration of exposure, some of which were as short as 1 week.

Placebo- and Apremilast-controlled Period, Week 0-16

In the first 16 weeks of treatment of the controlled trials, one subject in each treatment group was reported to have experienced thrombosis (1/842, 0.1% in the deucravacitinib group, 1/419, 0.2% in the placebo group, and 1/422, 0.2% in the apremilast group). The thrombotic events in the placebo- and apremilast-treated subjects were distal arterial occlusive events in the setting of underlying peripheral atherosclerosis.

In the deucravacitinib group, a 19-year-old White female (IM011047- (b) (6)) with a history of tobacco and oral contraceptive use developed a deep vein thrombosis (DVT). The subject was hospitalized on Day 9 for streptococcal bacteremia (unknown source) and was treated with systemic antibiotics via a peripheral right radial intravenous (IV) line. On Day 16, she had an ultrasound of the right upper extremity which showed a non-compressible radial vein with signs of thrombosis. Enoxaparin was started. On Day 23, the subject withdrew from the study. Her last dose of study treatment was on Day 4. The thrombosis was not considered serious by the Investigator and was reported resolved on Day 24.

Given thrombosis of the right radial vein occurred following cannulation of the vessel, DVT secondary to study drug is less probable.

Apremilast-controlled Period, Week 0-24

With further exposure up to Week 24 in subjects who did not switch treatment, there were no additional cases of thrombosis.

Apremilast-controlled Period, Week 0-52 – Trial IM011046

After 52 weeks of exposure, 1 additional subject in the deucravacitinib group who did not switch treatment experienced a thrombotic event as discussed below. No other subjects in the placebo or apremilast groups were reported with thrombosis.

Subject IM011046- (b) (6) – Saddle Thrombus/Pulmonary Embolism (PE)

48-year-old male with a history of tobacco use, obesity and hypertension was hospitalized during Week 38 with an acute aortic dissection and concurrent PE. A pulmonary CT angiogram demonstrated a Type A dissection from the aortic root to the upper abdominal aorta, with saddle thrombosis/pulmonary embolus extending into lower right middle lobe and left upper lobe. An aortic graft repair and aortic valve replacement were performed. One week later, the subject was discharged and resumed study treatment. No further thrombotic or other CV events were reported into the long-term extension trial.

This subject's extensive PE cannot be definitively attributed to study drug as case reports have described intraoperative and post-mortem findings of pulmonary artery thrombus in the setting of ascending aortic dissections.

For completeness and to capture events of thrombosis outside of the pools and periods for subjects who did not switch treatment, events that occurred through 52-weeks of exposure in subjects who switched treatment groups were evaluated. Two subjects who developed thromboses while receiving deucravacitinib were identified and are described below. There continued to be no subjects in the placebo or apremilast groups with reported thromboses.

Subject IM011047- (b) (6) – Arterial Thrombosis (Ischemic Clot of the Right Leg)

64-year-old White man with a history of hypertension, peripheral arterial disease, tobacco use, and chronic obstructive pulmonary disease (COPD) initially received placebo (Week 0 to Week 16) followed by deucravacitinib (Week 16 to Week 52). He was hospitalized at Week 27 due to SAEs of a large thrombosed right proximal popliteal artery aneurysm measuring up to 6 cm transversely and lower limb compartment syndrome complicated by regional rhabdomyolysis considered unrelated to treatment by the investigator. Extensive surgery including right femorotibial bypass, embolectomy, and right lower leg fasciotomies were performed. Elevated AST of 380 U/L was reported as hepatitis (no other test results were provided) and considered to be related to rhabdomyolysis. Study treatment was discontinued on the same day.

At Week 27, the subject developed post-procedural hemorrhage which required suture repair of the vein graft and evacuation of the hematoma. Two weeks later, the subject underwent debridement of right foot and lower leg fasciotomy wounds with coverage using split-thickness skin graft. On an unspecified date, the subject developed gangrene of right foot dorsal and toe, and on at Week 32, amputation of his right toes with skin grafts over fasciotomy sites were required.

At Week 34, he was discharged from the hospital with hepatitis, rhabdomyolysis, and the thrombosis event having resolved. The subject discontinued from the study at Week 36 due to the thrombosis adverse event.

Subject IM011047- (b) (6) – Leriche Syndrome

57-year-old White male smoker with a history of obesity, hypertension, hyperlipidemia, and hepatic steatosis presented with claudication and at Week 37 received a diagnosis of Leriche syndrome, an aortoiliac occlusive disease caused by severe atherosclerosis affecting the distal abdominal aorta, iliac arteries, and femoro-popliteal vessels that manifests with a triad of claudication, impotence, and absence of femoral pulses. Ultrasound demonstrated obstruction of the common femoral and superficial femoral arteries. The AE was not considered serious. At Week 48, the diagnosis was further confirmed by abdominal angiography findings of infrarenal aortic obstruction with a 25 mm long thrombus, obstructed common and external iliac arteries, and obstructed superficial femoral arteries. Study drug was interrupted but the subject completed trial 047 and enrolled into the LTE trial. He completed Week 48 visit in the LTE trial and is on meds for an AE of type 2 diabetes mellitus.

In both of these subjects with arterial thrombosis, multiple confounding factors including arterial aneurysm and existing peripheral arterial occlusive disease, make it difficult to determine the degree, if any, that deucravacitinib contributed to the reported AEs of peripheral arterial occlusion.

During the LTE trial, an additional serious thrombotic event was reported in a 48-year-old white male (IM011075- (b) (6); IM011047- (b) (6)) with a history of Factor V Leiden mutation and prior PE who had received deucravacitinib during Week 0-24 followed by placebo Week 24-52. After being diagnosed with COVID-19 pneumonia, the subject developed left leg superficial thrombophlebitis after receiving 16 days of deucravacitinib during the LTE trial. The DVT progressed to a DVT 56 days later (Week 10) requiring hospitalization. He received enoxaparin. At Week 11, thrombosis was reported as “recovered with sequelae” and the subject was discharged from the hospital.

Given the subject’s hypercoagulable state and concurrent COVID-19 infection, it cannot be determined that thrombophlebitis progression to deep venous clot formation was due to study drug.

With the January 6, 2022 submission of the 120-day safety update report (SUR) which provided approximately 7 months of additional safety data from the data cutoff for the initial submission (June 15, 2021) and includes all data up to October 1, 2021 (SUR data cutoff), one additional event of deep vein thrombosis was reported as a non-serious AE by the investigator in a subject who was hospitalized for treatment of an SAE of COVID-19.

Subject IM011047- (b) (6) – COVID-19, Deep Vein Thrombosis (DVT)

63-year-old female with a history of morbid obesity, hypertension, hyperlipidemia, Type 2 DM, and coronary artery disease received deucravacitinib throughout Trial IM011047. She was

hospitalized on Day 443 (Week 63) due to COVID-19. She required prolonged mechanical ventilation for respiratory failure. Study drug was interrupted at Week 64 at which time she developed a right lower extremity DVT that was treated with enoxaparin. At Week 72, COVID-19 infection was reported to have resolved. The subject was eventually able to discharge from the hospital with apixaban for DVT prophylaxis. Due to the subject's numerous comorbidities placing her at increased risk for hypercoagulable complications in the setting of an acute COVID-19 infection, it cannot be determined if the AE of DVT was in part a result of study drug.

Over the Phase 3 clinical psoriasis program as of October 1, 2021 (total exposure of 2482.0 patient-years), 6/1519 (0.4%, 0.2/100 PY) subjects who received a dose of deucravacitinib and were followed through to the end of exposure (including the ongoing LTE study) reported thrombosis events. Because of confounding comorbidities within each case, attribution to study drug is difficult to determine.

Based on the submitted data, Dr. Nossair concluded, and the team concurred, that the current findings did not support the identification of a venous or arterial thrombosis safety signal with deucravacitinib based on the submitted data, thus labeling for VTE risk is not supported.

8.2.5.4. Lipid Elevations

Lipid elevation was identified as a specific concern as JAK-STAT signaling is involved in lipid metabolism.

During trials IM011046 and IM011047, measurements of fasting lipid profiles [total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels] were performed at baseline, Week 8, Week 16, Week 24, and Week 52.

Within this section, cholesterol and triglycerides are reviewed separately. Comparisons are made between treatment groups for appropriate pools and periods for mean change from baseline, AEs, worst toxicity CTCAE grade, and shifts ≥ 2 CTCAE grades.

To analyze lipid elevation as a treatment emergent adverse event, the review team pooled the following PTs: blood cholesterol increased, hypercholesterolemia, dyslipidemia, hyperlipidemia, lipids increased, low density lipoprotein increased, and type V hyperlipidemia. Events of blood triglycerides increased and hypertriglyceridemia were analyzed separately.

Placebo- and Apremilast-controlled Period, Week 0-16

The mean total cholesterol, as well as mean HDL and LDL levels during the first 16 weeks of treatment were comparable between treatment groups. However, there was an observed increase in triglycerides with a mean change from baseline at Week 16 of 11.0 mg/dL for the deucravacitinib group compared to 0.4 mg/dL and -6.8 mg/dL for the placebo and apremilast groups, respectively.

The proportion of TEAEs of lipid elevation reported in deucravacitinib-treated subjects (5/840, 0.6%) was comparable to placebo-treated subjects (3/419, 0.7%) and apremilast-treated

subjects (2/422, 0.5%). No subject had CTCAE Grade 3 (>400 – 500 mg/dL) or Grade 4 (> 500 mg/dL) high cholesterol, and no subjects had a shift in cholesterol levels of ≥ 2 grades from baseline.

Despite the increase in mean triglyceride levels from baseline for subjects in the deucravacitinib group, TEAEs of blood triglycerides increased and hypertriglyceridemia were reported at comparable rates between treatment groups: 7/840 (0.8%) in deucravacitinib-treated subjects, 4/419 (1.0%) in placebo-treated subjects, and 4/422 (0.9%) in apremilast-treated subjects. The proportion of subjects with Grade 3 hypertriglyceridemia (>500 – 1000 mg/dL) was also comparable between treatment groups [deucravacitinib 12/813 (1.5%), placebo 6/394 (1.5%), and apremilast 8/405 (2.0%)]; however, Grade 4 (>1000 mg/dL) hypertriglyceridemia occurred in deucravacitinib-treated subjects (2/842, 0.2%) but not in any placebo or apremilast subjects. One subject with Grade 4 hypertriglyceridemia had Grade 2 levels at baseline and the other subject had Grade 3 hypertriglyceridemia at baseline. The incidence of shifts of ≥ 2 CTCAE grade increase was similar between deucravacitinib (1.9%) and PBO (1.8%) and higher than apremilast (1.2%).

Apremilast-controlled Period, Week 0-24

Mean total cholesterol, HDL, and LDL through Week 24 continued to be comparable between treatment groups. The mean triglyceride change from baseline at Week 24 remained stable at 11.2 mg/dL for deucravacitinib-treated subjects compared to -1.6 mg/dL for apremilast subjects.

For those who did not switch treatment during this period, 5 additional subjects in the deucravacitinib group and none in the apremilast group had an AE of lipid elevation. All of these lipid-related events were mild or moderate in severity, and dosing was not changed due to any of the events. There continued to be no subjects with CTCAE Grade 3 or Grade 4 high cholesterol. One (0.1%) deucravacitinib subject had a ≥ 2 CTCAE grade increase while no APREM subjects reported this shift.

Adverse events of blood triglycerides increased and hypertriglyceridemia occurred in 2 (0.2%) deucravacitinib-treated subjects compared to no apremilast subject. Both events were mild, non-serious, and did not result in change to dosing. Although the proportion of subjects with Grade 3 hypertriglyceridemia was comparable between treatment groups [20/813 (2.5%) deucravacitinib-treated subjects and 12/422 (3.0%) apremilast subjects], Grade 4 hypertriglyceridemia was reported in 3 (0.4%) deucravacitinib-treated subjects but no apremilast subjects.

Subject IM011046- (b) (6)

A 55-year-old male with a history of hyperlipidemia, diabetes mellitus, hypertension, and obesity who had Grade 1 hypertriglyceridemia at baseline. At Week 25, his triglycerides increased to Grade 4 levels but 11 days later returned to Grade 1 around the time his atorvastatin dose was increased.

Subject IM011046- (b) (6)

A 43-year-old male who was overweight (BMI 29.7 kg/m²) at baseline and had a history of hyperlipidemia and hypertension. At baseline, he had Grade 4 hypertriglyceridemia that fluctuated down to Grade 1 during the study while receiving deucravacitinib. At Week 24 Grade 4 hypertriglyceridemia was recorded but not reported as an AE. Subsequent values were Grade 2.

Subject IM011047- (b) (6)

A 32-year-old male with a history of obesity (BMI 33.8 kg/m²) and tobacco use who had Grade 2 hypertriglyceridemia at baseline and during Week 17 developed Grade 4 levels. At Week 24, his levels returned to Grade 2 without change in dosing of study drug.

Although the triglyceride levels in all three subjects fluctuated and at times decreased in toxicity grade despite continued treatment with study drug, there was an imbalance across treatment groups and lack of findings (Grade 4 hypertriglyceridemia, as well as AEs of blood triglycerides increased and hypertriglyceridemia and increase in mean change) in the apremilast group.

The incidence of shifts of ≥ 2 CTCAE grade increase during this period was higher in the deucravacitinib group (3.6 %) compared to 2.0% in the apremilast group.

Apremilast-controlled Period, Week 0-52 – Trial IM011046

With longer exposure, the mean total cholesterol, HDL, and LDL remained stable and comparable between those who received deucravacitinib and apremilast without switching during Trial IM011046. The mean triglyceride change from baseline further increased to 17.8 mg/dL in the deucravacitinib group and 10.7 mg/dL for the apremilast group.

An AE of lipid elevation was reported in 7/330 (2.1%, 2.4/100 PY) deucravacitinib-treated subjects while no event was reported in subjects who received apremilast without treatment switching. There were no Grade 3 or Grade 4 high cholesterol events or ≥ 2 CTCAE grade increases for either treatment group.

Adverse events of blood triglycerides increased and hypertriglyceridemia occurred in 6 (1.8%, 2.0/100 PY) subjects who received deucravacitinib but not in any apremilast subjects. The total number of subjects with Grade 3 and Grade 4 hypertriglyceridemia during Trial IM011046 from Week 0 to 52 were greater in the deucravacitinib group [13 (3.9%) and 3 (0.9%), respectively] compared to the APREM group [4 (3.5%) and 0, respectively]. The narratives of 2 deucravacitinib-treated subjects with Grade 4 hypertriglyceridemia were previously provided. The third subject, who was briefly mentioned under Week 0-16 had Grade 2 hypertriglyceridemia at baseline. During Week 52, he again developed Grade 4 levels in the setting of medication nonadherence due to “insurance issues”. The proportion of subjects with ≥ 2 CTCAE grade increases was greater for those who received deucravacitinib (6.5%) compared to those who received apremilast (2.8%).

To capture Grade 4 hypertriglyceridemia beyond the periods and pools discussed above, all subjects in trials IM011046 and IM011047 exposed to deucravacitinib during Week 0 to 52 regardless of whether they switched treatment or not, were evaluated. One additional subject (IM011046- (b) (6)) was identified. He was a 45-year-old male with a history of obesity (BMI 30.11 kg/m²) and tobacco use who was initially randomized to placebo then transitioned to deucravacitinib at Week 16. His triglyceride levels were normal at baseline but after 60 days of exposure to deucravacitinib, he developed transient Grade 4 hypertriglyceridemia (which was not reported as an AE) with levels improving to Grade 1 within a week.

Long-term Extension

During the LTE trial IM011075, 23 subjects reported an AE of lipid elevation and 8 subjects reported elevated triglyceride events. Similar to the subjects in the Controlled Safety Pool, all of the events were mild or moderate in severity, none were serious nor lead to drug interruption or withdrawal. One subject, IM011047- (b) (6) (IM011075- (b) (6)), was a 55-year-old male with hyperlipidemia, diabetes mellitus, hypertension, obesity, and tobacco use who received deucravacitinib throughout trial IM011047. He had Grade 1 hypertriglyceridemia at baseline and most triglyceride values during trial IM011047 were Grade 2. Approximately 49 weeks after transitioning to the LTE trial, he developed Grade 4 hypertriglyceridemia (which was not reported as an AE). Study treatment was discontinued early due to site closure. During his follow-up visit 6 weeks later, Grade 4 hypertriglyceridemia persisted.

120-day Safety Update Report (SUR)

With submission of the SUR, which provided approximately 7 months of additional safety data, 2 additional subjects with worst toxicity of Grade 3 and no other subjects with worst toxicity of Grade 4 increased triglycerides were reported. There was also 1 additional shift in hypertriglyceridemia of > 2 Grades (from Grade 1 to Grade 4).

Although the mean change in total cholesterol, HDL, and LDL was comparable between treatment groups, with longer exposure there was an unexplained imbalance of TEAEs with a higher proportion of lipid elevation AEs reported in the deucravacitinib group relative to the comparator group. The atherogenic index, however, did not show a significant increase as assessed by ratios of Total Cholesterol:HDL and LDL-C:HDL.

An increase in mean triglyceride levels, as well as TEAEs and hypertriglyceridemia of higher toxicity grade was observed. The clinical impact of the 9% increase of mean triglycerides and imbalance of Grade 4 events is unclear as the majority of cardiovascular events were reported in subjects with other known CV risk factors, and the single event of pancreatic injury occurred in a subject with reported obstructive pancreatitis in the context of preexisting cholelithiasis.

The effect of hypertriglyceridemia on cardiovascular morbidity and mortality has not been determined for deucravacitinib in patients with psoriasis.

The changes in lipid parameters observed with JAK inhibitors (tofacitinib, baricitinib, upadacitinib, and abrocitinib) that are approved for chronic inflammatory conditions carry a

Boxed Warning for increased risk of MACE and are labeled for lipid abnormalities in the Warnings and Precautions section. Deucravacitinib's inhibition of TYK2 appears to result in only elevation of triglycerides. This effect is different from other JAK inhibitor programs, where hyperlipidemia AEs paralleled increases in cholesterol. Therefore, the specific findings of increased triglycerides will be communicated to healthcare providers in Section 5 (Warnings and Precautions) and Section 6 (Adverse Reactions) of the FPI in order to mitigate potential CV risk:

- Treatment with [SOTYKTU] was associated with increases in triglyceride levels. The effect of this elevated parameter on cardiovascular morbidity and mortality has not been determined. Periodically evaluate serum triglycerides according to the clinical guidelines for hyperlipidemia while patients are receiving treatment with SOTYKTU. Manage patients according to clinical guidelines for the management of hyperlipidemia [see Adverse Reactions (6.1)].

Section 6 (Adverse Reactions) will also include triglyceride findings:

- Mean triglycerides increased by (b) (4) mg/dL during the 16-week treatment period in subjects treated with SOTYKTU and by (b) (4) mg/dL during the 52-week treatment period.

8.2.5.5. Gastrointestinal Bleed/Gastrointestinal Perforation

Given the increased frequency of AEs involving mucosal surfaces (e.g., mouth ulcerations and aphthous ulcers) in the deucravacitinib group relative to the placebo and apremilast groups, as well as events of gastrointestinal perforation reported in clinical trials with JAK inhibitors in the treatment of chronic inflammatory conditions (although the role of JAK inhibition in these events is not known), further evaluation of gastrointestinal bleeding (GIB) was conducted.

Placebo- and Apremilast-controlled Period, Week 0-16

During the placebo-controlled period, the proportion of subjects with events of GIB, ulceration, or gastrointestinal perforation was the same (0.2%) for each treatment group. A single subject in the apremilast group was reported to have had a GIB—this subject died of lung adenocarcinoma during the first 16 weeks of Trial IM011047. The subject in the placebo group had a small bowel perforation in the setting of umbilical hernioplasty. The 2 deucravacitinib-treated subjects experienced GI bleeding reported as hematochezia and serious GIB. Their brief narratives are provided below.

Subject IM011047- (b) (6): Hematochezia

46-year-old White male passed 3 stools in one day containing “fresh blood” which occurred 3 days after starting deucravacitinib. The event was considered mild and nonserious. It was not associated with thrombocytopenia, anemia, or significant change from his baseline hemoglobin value. No action was taken with study drug. The subject continued to receive deucravacitinib during Trial IM011047 and transitioned into the LTE trial.

This episode of hematochezia was transient and limited in nature without reported signs or symptoms of anemia secondary to acute blood loss.

Subject IM011047- (b) (6): Gastrointestinal Hemorrhage (Serious)

42-year old White male with a history of obesity, gout (on ibuprofen), alcohol dependence, and tobacco use, presented to the hospital during Week 16-17 after vomiting bright red blood and clots associated with dark stools and dizziness. He was diagnosed with an upper GIB, acute blood loss anemia, and melena. Refer to [Table 69](#) for his laboratory values. The subject received 4 units of packed red blood cells, 1 unit of fresh frozen plasma, octreotide, and pantoprazole.

Esophagogastroduodenoscopy with biopsy showed severe acute esophagitis, moderate gastritis in the antrum body, and acute on chronic duodenitis without active bleeding or varices. Study treatment was discontinued due to gastrointestinal hemorrhage.

The numerous confounders (ibuprofen use, alcohol dependence, and tobacco use) make it difficult to determine deucravacitinib's role, if any, on the onset or severity of GIB.

Table 69. Hemoglobin, Hematocrit, and Platelet Lab Results of Subject With Serious Gastrointestinal Hemorrhage

HGB	HCT	PLAT
g/dL	%	10 ⁹ /L
13-17.5	40-52	140-450
15.3	48.1	352
13.2	41.5	463
15	46.1	617
14.9	48.8	412
15.1	48.2	296
15	47.3	409
14	43.8	280
5.7	18	NULL
8.7	26	NULL
8.5	25	NULL
8.3	25	NULL
8.6	28.7	909

*Hospital laboratory reference ranges: Hgb (13.0-17.5 g/dL), Hct (39-53%), Plat 140-450 10⁹/L

Apremilast-controlled Period, Week 0-24

During Week 16-24, analysis of pooled subjects who were treated with either deucravacitinib or apremilast without switching, identified 1 subject who was suspected to have a gastric ulcer and iron deficiency anemia in the setting of Stage III Hodgkin's lymphoma. He was previously discussed within Section [8.2.5.2.1.7](#). There were no subjects who received continuous treatment with apremilast and reported an AE of GIB/ulceration/perforation.

Apremilast-controlled Period, Week 0-52 – Trial IM011046

During Study IM011046, 2 subjects who were treated with deucravacitinib without switching had one event each (possible gastric ulcer and hematochezia) and were previously described

within this section--neither events were serious or led to change in study treatment. There were no events of GIB/ulceration/perforation in subjects received apremilast without switching throughout Trial IM011046.

To capture events of GIB outside of the aforementioned pools and periods, subjects in trials IM011046 and IM011047 were evaluated regardless of whether they switched treatment or not. Two subjects reported GIB while receiving deucravacitinib. One had mild, nonserious hematochezia that did not lead to change in study treatment, and the other subject had rectal bleeding in the setting of hepatocellular carcinoma. The latter subject was discussed under Section [8.2.5.2.1.4](#).

During the LTE trial, 2 subjects reported hematochezia and one had hematemesis. None of the events were considered serious or led to study drug interruption or discontinuation. Hemoglobin and platelet levels remained stable and within reference range for all 3 subjects.

Within the safety update, there were no new events of GIB/ulceration/perforation.

Evaluation by the review team did not demonstrate a significantly disproportionate number of subjects with GI events in the deucravacitinib group. Additionally, the deucravacitinib-treated subjects with events had confounding factors (i.e., malignancy and excessive alcohol use) that make it difficult to attribute causality. Characterization of any potential role for deucravacitinib-associated GIB can be assessed through routine postmarketing pharmacovigilance.

8.2.5.6. Hematological Events

Because lymphocyte abnormalities, neutropenia, anemia, and thrombocytopenia are observed with JAK inhibition as a result of interference with signaling of particular cytokine(s) (e.g., suppression of IL-6), select bone marrow indices will be discussed in this section as an area of safety interest. Furthermore, nonclinical key findings from a 6-month rat oral toxicity study with a 2-month recovery demonstrated that at ≥ 5 mg/kg/day, deucravacitinib caused immunosuppression (reduction of immune cell populations) and decreases in hematopoietic cellularity in the bone marrow, which were largely resolved after recovery. At 50 mg/kg/day, deucravacitinib increased the incidence of minimal lymphoid depletion in the white pulp of the spleen of both sexes which was correlated with small size and decreased weights of the spleen.

Clinical safety laboratory evaluations were performed at Baseline, Week 1, Week 2, Week 4, and then every 4 weeks through the end of trial in trials IM011046 and IM011047 and at every visit in IM011075.

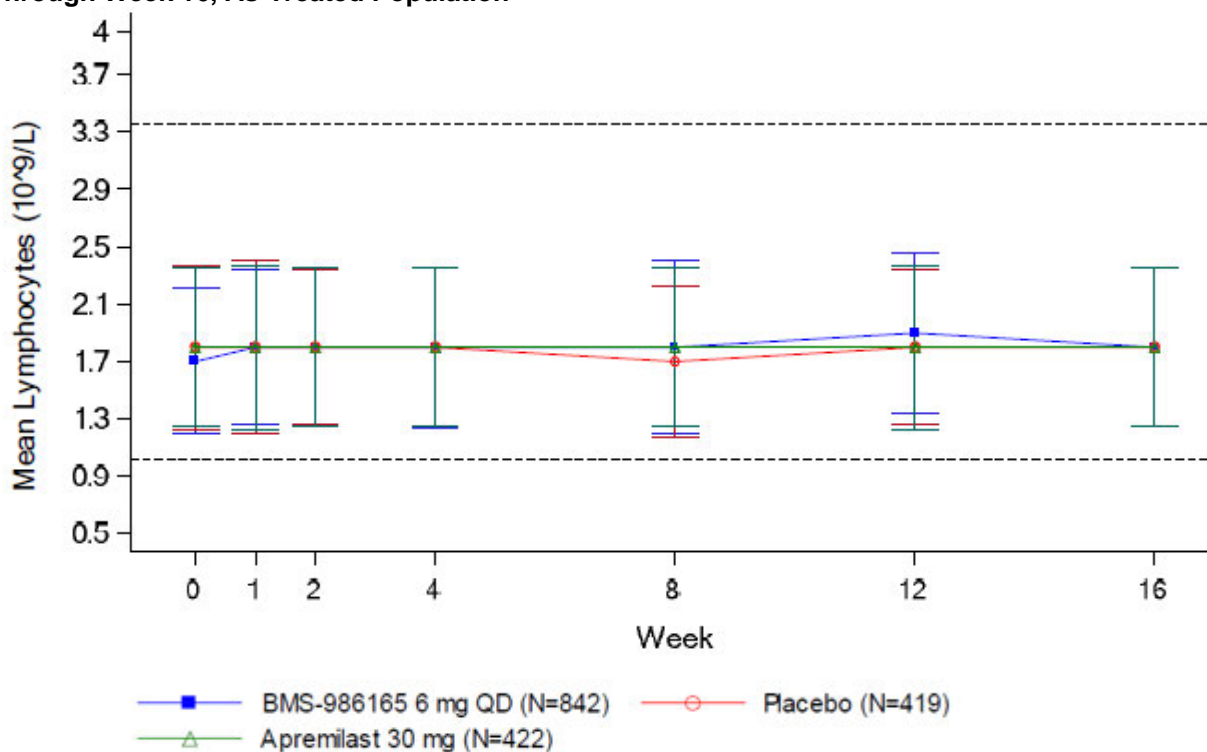
Within this section, each hematological parameter (lymphocytes, neutrophils, hemoglobin, and platelets) will be discussed separately, highlighting i) mean change from baseline, ii) shifts ≥ 2 CTCAE grade from baseline, iii) worst toxicity CTCAE grades, and iv) AEs based on laboratory abnormalities. Comparisons will be made between treatment groups for appropriate pools and periods.

8.2.5.6.1. Lymphocytes

Placebo- and Apremilast-controlled Period, Week 0-16

In the first 16 weeks of treatment, the mean change from baseline in lymphocyte counts was similar between the treatment groups (placebo: -0.016, deucravacitinib: 0.102, and apremilast: 0.017).

Figure 15. Mean Lymphocytes ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 16, As-Treated Population



Source: Figure 3.1.1-1 ISS.

During this period, there were no significant decreases in NK cell counts observed with deucravacitinib.

Decreased lymphocyte counts shifts of ≥ 2 CTCAE grades from baseline were reported in 14/831 (1.7%) subjects in the deucravacitinib group, 10/413 (2.4%) in the placebo group, and 4/418 (1.0%) in the apremilast group. Grade 1 and Grade 2 decreases in lymphocyte count were comparable across treatment groups. The proportions of Grade 3 ($<500 - 200/mm^3$) lymphopenia were comparable between the deucravacitinib (1/831, 0.1%) and placebo (1/413, 0.2%) groups; there were no subjects with Grade 3 lymphopenia in the apremilast group during this period. Further, no infection AEs were reported for the deucravacitinib-treated subject with Grade 3 lymphopenia. No Grade 4 lymphopenia ($<200/mm^3$) was observed in any treatment group.

For AEs of decreased lymphocyte count and lymphopenia, there was a higher proportion of subjects in the deucravacitinib group (5/840, 0.6%) (subjects IM11046-^{(b) (6)}, IM011047-^{(b) (6)}, IM011047-^{(b) (6)}, IM011047-^{(b) (6)}, IM011047-^{(b) (6)}) compared to placebo (1/419, 0.2%) (IM011046-^{(b) (6)}) and apremilast groups (0/422, 0%). None of the events were serious; however, 1 of the 5 deucravacitinib-treated subjects (IM011046-^{(b) (6)}) discontinued study drug and 1 subject (IM011047-^{(b) (6)}) required dose interruption. The narrative for the subject who discontinued study treatment (IM011046-^{(b) (6)}) is provided below.

Subject IM011046-^{(b) (6)}: Lymphopenia (Discontinued)

40-year-old white male with a PMH of a positive quantiferon test and “leukocytopenia” in ^{(b) (6)} developed mild, nonserious lymphopenia after treatment with deucravacitinib for 3 weeks ($0.45 \times 10^9/L$, reference range: $1.02-3.36 \times 10^9/L$) down from a baseline lymphocyte count of 0.8×10^9 . He did not receive treatment for this event. At Week 16, the subject discontinued from the study due to lymphopenia—he received his last dose during Week 8 at which time his lymphocytes were $0.58 \times 10^9/L$. The safety update report did not provide information regarding this subject.

The contribution of study drug cannot be definitively determined based on limited information and prior history of remote diminished white cell count. However, given that the lymphocyte count continued to fluctuate and eventually decreased from baseline with continuous exposure to deucravacitinib, with lymphopenia as an AE which subsequently led to discontinuation of the study drug, it is reasonable to consider the reported grade 3 lymphopenia AE as a possible AR, attributable to the study drug.

Table 70. Hematology Laboratory Test Results

Actual Treatment	Lab Date	Study Day	LEUK (10 ⁹ /L)	LYMPH (10 ⁹ /L)	NEUT (10 ⁹ /L)	HGB (g/L)	PLAT (10 ⁹ /L)
RANGE			4.1-12.3	1.02-3.36	2.03-8.36	130-175	140-450
	^{(b) (6)}	-27	3	1.07	1.57	144	284
BMS-986165 6 mg QD		1	3.2	0.8	2.03	140	266
BMS-986165 6 mg QD		10	3.3	0.61	2.31	155	292
BMS-986165 6 mg QD		15	2.4	0.58	1.57	143	265
BMS-986165 6 mg QD		23	2.4	0.45	1.56	146	232
BMS-986165 6 mg QD		30	2.6	0.74	1.54	147	255
BMS-986165 6 mg QD		39	2.7	0.94	1.26	150	284
BMS-986165 6 mg QD		58	2.3	0.58	1.37	149	255
		85	2.4	0.6	1.53	149	251
		113	3.7	0.64	2.79	147	287

Source: Applicant’s response to FDA IR dated 15-Jun-2022.

Subject IM011047- (b) (6)

This subject, whose dose was interrupted, had a range of baseline lymphocyte counts of $0.49 \times 10^9/L$ to $0.93 \times 10^9/L$ during the screening period. Upon resumption of the study drug, his lymphocyte counts remained stable on the study drug, then increased during the LTE trial, making the reported AE of decreased lymphocyte count unlikely to be related to study drug.

Subject IM011047- (b) (6)

Lymphocyte count was $1.94 \times 10^9/L$ at screening. At Week 2 on study drug treatment, the lymphocyte count decreased to $0.68 \times 10^9/L$. The lymphocyte count recovered at Week 4 to $2.13 \times 10^9/L$ while the subject continued study drug treatment and remained stable while the subject continued study drug treatment until Week 24, making the reported AE of decreased lymphocyte count unlikely to be related to study drug.

Subject IM011047- (b) (6)

Lymphocyte count was $1.87 \times 10^9/L$ at screening. At an unscheduled visit at Week 12 on study drug treatment, the lymphocyte count decreased to $0.89 \times 10^9/L$. The lymphocyte count recovered at Week 16 to $1.97 \times 10^9/L$ while the subject continued study drug treatment and remained stable while the subject continued study drug treatment until Week 24, making the reported AE of decreased lymphocyte count unlikely to be related to study drug.

Subject IM011047- (b) (6)

Lymphocyte count was $1.14 \times 10^9/L$ at screening. At Week 8 on study drug treatment, the lymphocyte count decreased to $0.85 \times 10^9/L$. The lymphocyte count recovered at Week 12 to $1.07 \times 10^9/L$ while the subject continued study drug treatment and remained stable while the subject continued study drug treatment until Week 16. However, the lymphocyte count decreased again at Week 20 and 24 to $0.97 \times 10^9/L$ and $0.86 \times 10^9/L$, respectively, while the subject continued study drug treatment. The subject was subsequently switched to blinded placebo treatment at Week 28 at which time lymphocyte counts were $1.06 \times 10^9/L$ and ranged from $0.9 \times 10^9/L$ (Week 52) to $1.22 \times 10^9/L$ (Week 40) while on placebo until Week 52. During the LTE trial, the subject was on study drug from Week 52 to 88 with no recorded decreased lymphocyte counts (range $1.07 \times 10^9/L$ (Week 88) to $1.51 \times 10^9/L$ (Week 60), making the reported AE of decreased lymphocyte count less likely to be related to study drug.

Subject IM011046- (b) (6), Placebo

The subject had a range of baseline lymphocyte counts of $1.01 \times 10^9/L$ to $1.91 \times 10^9/L$ during the screening period. At Week 12 while on placebo treatment, the lymphocyte count decreased to $0.4 \times 10^9/L$. The lymphocyte count was repeated at Week 12 and was $1.51 \times 10^9/L$, making the reported decreased lymphocyte count likely a laboratory error.

Summary of Deucravacitinib Effects on Lymphocyte Counts

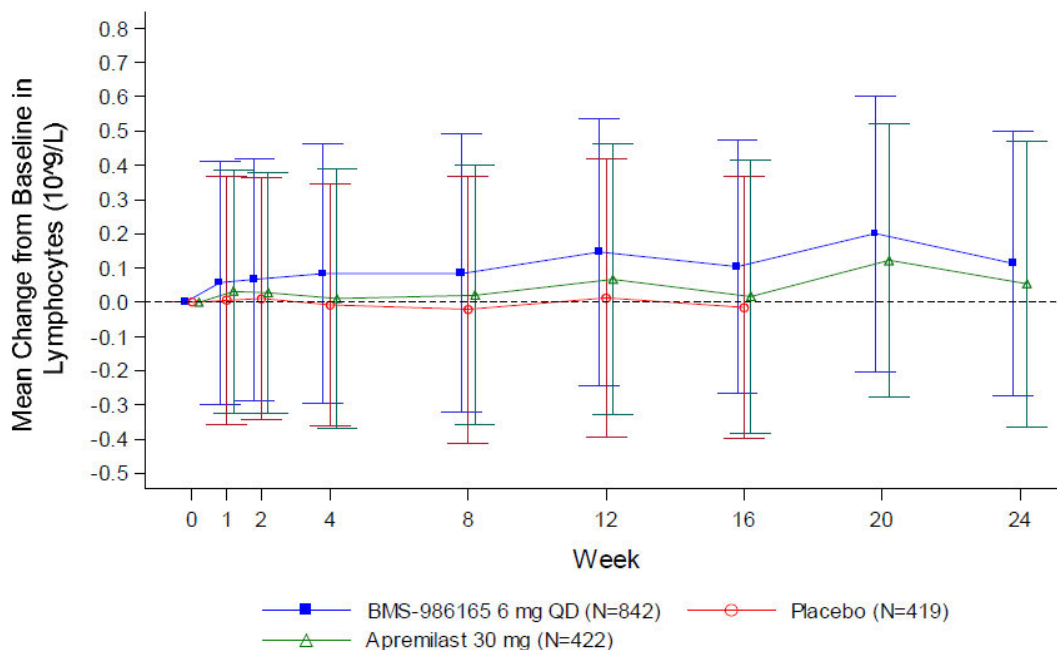
Assessment of the aforementioned reported AEs of lymphopenia demonstrated that the rates across treatment groups were similar [$1/840$, 0.1% for deucravacitinib (subject IM11046- (b) (6)); $0/419$, 0% for placebo; and $0/422$, 0% for apremilast]. There was one case of grade 3

lymphopenia identified in a deucravacitinib-treated subjects (IM11046-^{(b) (6)}). Based on these findings, labeling of lymphopenia is not indicated.

Apremilast-controlled Period, Week 0-24

In the Controlled Safety Pool who were continuously treated with either apremilast or deucravacitinib through 24 weeks, the mean change from baseline in lymphocyte counts for deucravacitinib was 0.113 and for apremilast was 0.054.

Figure 16. Mean Change From Baseline in Lymphocytes ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 24, Subjects Who Were Randomized to and Remained on the Same Treatment



Source: Applicant response to information request dated 31-May-2022.

From Applicant: Baseline through Week 16 visits include observed records of all subjects treated with BMS-986165, Placebo, or Apremilast in Period 1. Week 20 through Week 24 visits include observed records of all subjects continuously treated with BMS-986165 or Apremilast in Period 1 and Period 2.

Includes data from IM011046 and IM011047.

Error bars represent standard deviation of the mean changes from baseline.

Program Source: /gbs/prod/clin/programs/im/011/ebr16-fda/20220531/rpt

Program Name: rg-lb-mcfb-0-24-v01.sas 02JUN2022:16:46:09

Decreased lymphocyte counts shifts of ≥ 2 CTCAE grades from baseline were reported in 18/831 (2.2%) subjects in the deucravacitinib group, and 8/418 (1.9%) in the apremilast group. Grade 1 and Grade 2 decreases in lymphocyte count were comparable between treatment groups. The proportions of Grade 3 ($<500 - 200/mm^3$) lymphopenia were comparable between the deucravacitinib (1/831, 0.1%) (IM011046-^{(b) (6)}) and apremilast (1/418, 0.2%) groups. Further, no infection AEs were reported for the deucravacitinib-treated subject with Grade 3 lymphopenia. No Grade 4 lymphopenia ($<200/mm^3$) was observed in either treatment group.

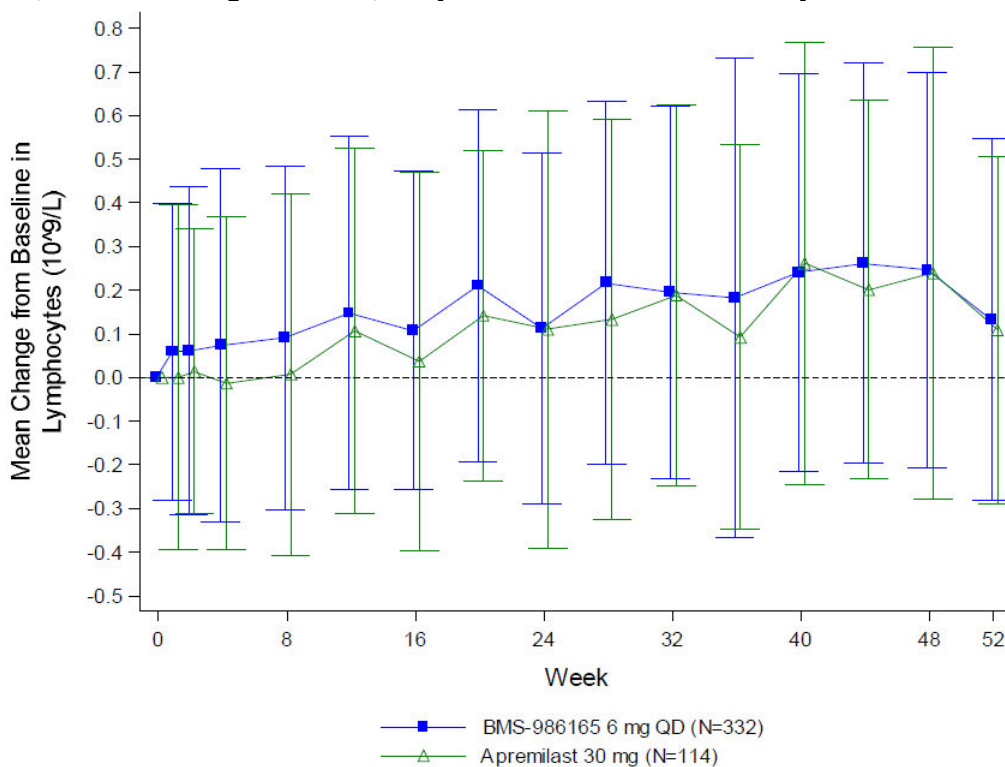
One additional subject (IM011047-^{(b) (6)}) in the apremilast group had a mild, nonserious event of lymphopenia that did not require change in study treatment (1/422, 0.2%) during this

period. IM011047- (b) (6) had a lymphocyte count of $0.92 \times 10^9/L$ at screening. At Week 16 on apremilast treatment, the lymphocyte count decreased to $0.83 \times 10^9/L$ and remained stable until Week 52 while the subject continued apremilast treatment. There were no additional subjects continuously treated with deucravacitinib who had an AE of lymphopenia or decreased lymphocyte count.

Apremilast-controlled Period, Week 0-52 – Trial IM011046

In the 52-week active-controlled period in Trial IM011046, there was a small increase in mean change from baseline in lymphocyte counts for deucravacitinib but mostly unchanged and comparable to apremilast (the mean change from baseline in lymphocyte counts for deucravacitinib was 0.132 and for apremilast was 0.109).

Figure 17. Mean Change From Baseline in Lymphocytes ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 52, Subjects Who Were Continuously Treated in IM011046



Source: Applicant response to information request dated 31-May-2022.
From Applicant: Includes observed records of all subjects continuously treated with BMS-986165 or Apremilast in Period 1, Period 2, and Period 3.
Includes data from IM011046.
Error bars represent standard deviation of the mean changes from baseline.
Program Source: /gbs/prod/clin/programs/im/011/abr16-fda/20220531/rpt
Program Name: rg-lb-mcfb-0-52-v01.sas 02JUN2022:16:42:50

Summary of Deucravacitinib Effects on CTCAE Grade Shifts

Decreased lymphocyte counts shifts of ≥ 2 CTCAE grades from baseline were reported in 11/328 (3.4%) subjects in the deucravacitinib group, and 4/111 (3.6%) in the apremilast group. A

greater proportion of subjects in the deucravacitinib group shifted from grade 0 to grade 1 (34/311, 10.9%), 41% (14/34 subjects) of whom also had a reported AE of infection, compared to the proportion of subjects in the apremilast group (5/104, 4.8%). The proportion of Grade 3 (<500 - 200/mm³) lymphopenia was greater in the deucravacitinib group (2/328, 0.6%) (IM011046-^{(b) (6)}-see above for discussion on case narrative, and IM011046-^{(b) (6)}) compared to the apremilast (0/111) group. For subject IM011046-^{(b) (6)}, the subject had an isolated, transient Grade 3 lymphocyte count decrease in the setting of pre-existing liver disease, leukopenia, increase to sertraline dose, and the lymphocyte count decrease resolved spontaneously while on study drug treatment and did not recur with continue study drug treatment, making this case unlikely related to the study drug. No infection AEs were reported for the deucravacitinib-treated subject with Grade 3 lymphopenia. No Grade 4 lymphopenia (<200/mm³) was observed in either treatment group.

No additional subjects had a reported AE of lymphopenia or decreased lymphocyte counts during this period. Lymphopenia was reported in 1/330 subject (0.3 per 100 PY) continuously treated with deucravacitinib which was previously reported during the 0-16 week period and 0 subjects treated with apremilast.

Overall, with further exposure through Week 52 weeks, no events were reported for subjects receiving deucravacitinib, and there continued to be no Grade 4 events of lymphopenia.

Within the safety update, 1 new AE each of decreased lymphocytes and lymphopenia was reported. Both were nonserious and did not result in change to study treatment.

Overall, during the Phase 3 program, continuous administration of deucravacitinib was associated with a gradual increase in mean lymphocyte counts over time with stabilization beyond Week 28 when the mean count plateaued at $1.91 \times 10^9/L$ (baseline mean lymphocyte count was $1.712 \times 10^9/L$).

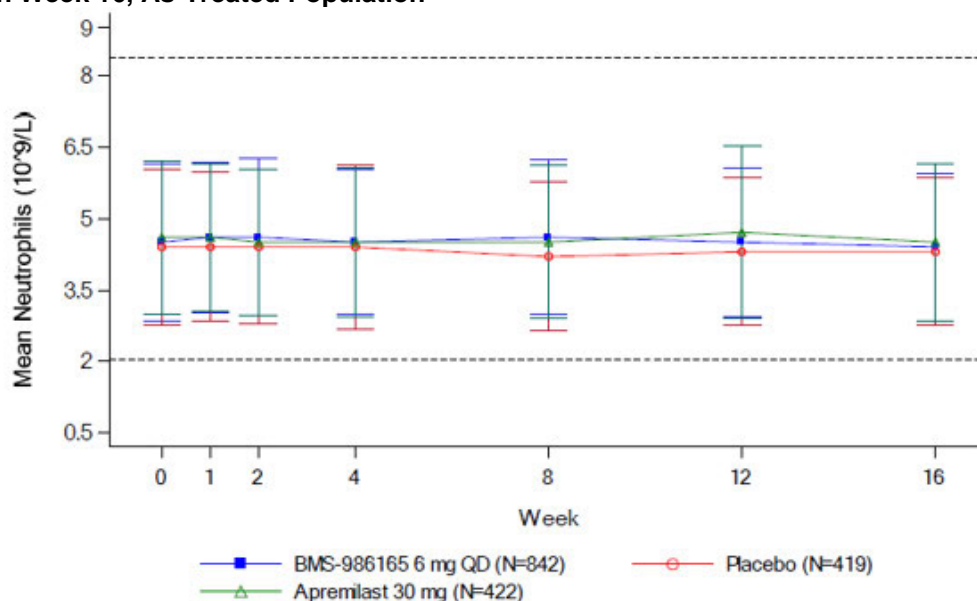
Therefore, we do not recommend including lymphopenia in the PI as an adverse reaction. Continued monitoring of potential effects of deucravacitinib on lymphocyte counts will be conducted in the postmarketing setting.

8.2.5.6.2. Neutrophils (Count Decreased)

Placebo- and Apremilast-controlled Period, Week 0-16

During the first 16 weeks of treatment the mean change from baseline in neutrophil counts was similar between the treatment groups (placebo: -0.110, deucravacitinib: -0.100, and apremilast: -0.032).

Figure 18. Mean Neutrophils ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 16, As-Treated Population



Error bars represent standard deviation for the mean.

The reference range for males was used because the majority of subjects in the study(ies) were male.

Source: Figure 3.1.1-2 ISS.

The proportion of subjects with shifts ≥ 2 CTCAE grade from baseline were also comparable (3/831, 0.4% for deucravacitinib; 1/413, 0.2% for placebo; and 4/418 (0.9%) for apremilast). Grade 1 and Grade 2 decreases in neutrophil count were comparable across treatment groups. The proportions of Grade 3 ($<1000 - 500/mm^3$) neutropenia were comparable between the deucravacitinib group (1/831, 0.1%) and placebo group (1/413, 0.2%); Grade 3 neutropenia was not reported in the apremilast group. The deucravacitinib-treated subject with Grade 3 neutropenia had Grade 3 neutropenia at baseline and no infection AEs were reported for the deucravacitinib-treated subject with Grade 3 neutropenia. No Grade 4 neutropenia ($<500/mm^3$) occurred in any treatment group.

For adverse events of decreased neutrophil count and neutropenia, the proportion of subjects in the deucravacitinib group (2/840, 0.2%) (IM011046-^{(b) (6)} and IM011047-^{(b) (6)}) was equal to the apremilast group (1/422, 0.2%) (IM011047-^{(b) (6)}). There were no placebo subjects with events of decreased neutrophil count or neutropenia.

Subject IM011046-^{(b) (6)}

The subject had a range of neutrophil counts of $1.8 \times 10^9/L$ to $2.3 \times 10^9/L$ (reference range: $2.03 - 8.36 \times 10^9/L$) during the screening period. At Week 8 on study drug treatment, the neutrophil count decreased to $1.38 \times 10^9/L$. The neutrophil count trended towards recovery at Week 12 to $2.02 \times 10^9/L$ while the subject continued study drug treatment and remained stable while the subject continued study drug treatment until Week 28 when the neutrophil count decreased to $1.52 \times 10^9/L$ while on study drug treatment. The neutrophil count recovered at Week 32 to $2.63 \times 10^9/L$ while the subject continued study drug treatment and remained stable while the

subject continued study drug treatment until Week 88 (LTE study), making the reported AE of decreased neutrophil count unlikely to be related to study drug.

Subject IM011047- (b) (6)

The subject had a range of neutrophil counts of $2.04 \times 10^9/L$ to $2.57 \times 10^9/L$ during the screening period. The subject discontinued study treatment on Day 7 due to chest pain and insomnia. At Week 1, the neutrophil count decreased to $1.9 \times 10^9/L$. On Day 8, the subject was diagnosed with moderate events of leukopenia and neutropenia. The subject did not receive any treatments for these events. The neutrophil count recovered at Week 4 to $2.5 \times 10^9/L$ while off of study drug treatment. The subject was discontinued from the study on Day 29 due to the adverse events. It is possible that this case of neutropenia may be related to study drug treatment given spontaneous resolution of neutropenia while off of study drug treatment, however, no definitive conclusions can be made.

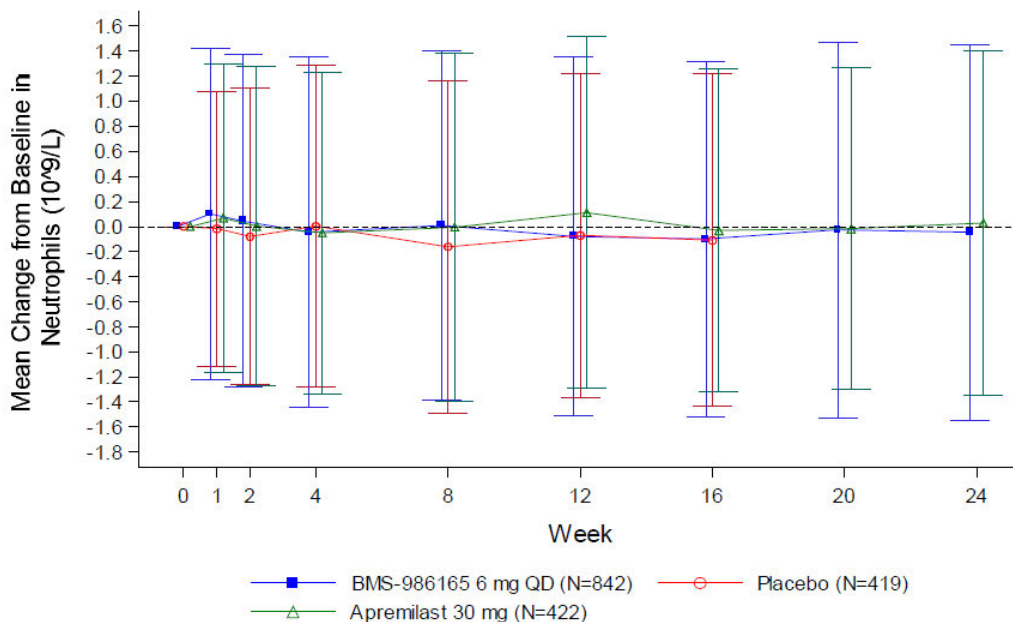
Subject IM011047- (b) (6), Apremilast

The subject had a range of neutrophil counts of $2.85 \times 10^9/L$ to $4.13 \times 10^9/L$ during the screening period. At Week 2 on apremilast treatment, the neutrophil count decreased to $1.99 \times 10^9/L$. The neutrophil count recovered at Week 8 to $2.28 \times 10^9/L$ then decreased at Week 16 to $1.99 \times 10^9/L$ then recovered at Week 20 to $2.34 \times 10^9/L$ and remained stable while the subject continued apremilast treatment until Week 24, making the reported AE of decreased neutrophil count unlikely to be related to apremilast.

Apremilast-controlled Period, Week 0-24

For subjects in the Controlled Safety Pool who were continuously treated with either deucravacitinib or apremilast through 24 weeks, the mean change in neutrophil count for deucravacitinib was -0.046 and for placebo was 0.027.

Figure 19. Mean Change From Baseline in Neutrophils ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 24, Subjects Who Were Randomized to and Remained on the Same Treatment



Source: Applicant response to information request dated 31-May-2022.

From Applicant: Baseline through Week 16 visits include observed records of all subjects treated with BMS-986165, Placebo, or Apremilast in Period 1. Week 20 through Week 24 visits include observed records of all subjects continuously treated with BMS-986165 or Apremilast in Period 1 and Period 2.

Includes data from IM011046 and IM011047.

Error bars represent standard deviation of the mean changes from baseline.

Program Source: /gbs/prod/clin/programs/im/011/ebr16-fda/20220531/rpt

Program Name: rg-lb-mcfb-0-24-v01.sas 02JUN2022:16:46:10

Summary of Deucravacitinib Effects on Neutrophil CTCAE Grade Shifts

Decreased neutrophil counts shifts of ≥ 2 CTCAE grades from baseline were reported in 6/831 (0.7%) subjects in the deucravacitinib group and 9/418 (2.2%) in the apremilast group. Grade 1 and Grade 2 decreases in neutrophil count were comparable between treatment groups. The proportion of Grade 3 ($<1000 - 500/mm^3$) neutropenia was greater in the deucravacitinib group (1/831, 0.1%) compared to the apremilast group (0/418). However, the deucravacitinib-treated subject with Grade 3 neutropenia (IM011046-^{(b) (6)}) had Grade 3 neutropenia at baseline. During the long-term extension trial, the subject with Grade 3 neutropenia had a reported mild infective gastroenteritis that did not lead to withdrawal of study drug and resolved in 5 days. No Grade 4 neutropenia ($<500/mm^3$) occurred in either treatment group.

One additional deucravacitinib-treated subject (IM011046-^{(b) (6)}) had a nonserious AE of Grade 2 neutropenia that did not result in drug interruption or discontinuation (total 3/840, 0.4%) during this period. There were no additional AEs of neutropenia or neutrophil count decreased reported for the apremilast group during this period (total 1/422, 0.2%).

Subject IM011046- (b) (6)

The subject had a range of neutrophil counts of $3.56 \times 10^9/L$ to $4.44 \times 10^9/L$ during the screening period. At Week 20 on study drug treatment, the neutrophil count decreased to $1.46 \times 10^9/L$. The neutrophil count recovered at Week 24 to $2.9 \times 10^9/L$ then decreased at Week 28 to $1.94 \times 10^9/L$ then recovered at Week 32 to $4.02 \times 10^9/L$ then decreased at Week 36 to $1.82 \times 10^9/L$ then recovered at Week 40 to $3.56 \times 10^9/L$ then decreased at Week 44 to $1.8 \times 10^9/L$ then recovered at Week 48 to $3.58 \times 10^9/L$ and remained stable until Week 76 (LTE study) when the neutrophil count decreased from a range of $0.74 \times 10^9/L$ to $1.51 \times 10^9/L$ during Weeks 76 to 88 (LTE study) then recovered at Week 100 to $3.43 \times 10^9/L$ (LTE study) while on study drug treatment. The fluctuating nature of decreased neutrophil counts while continuing study drug treatment makes this case appear more possibly related to study drug treatment.

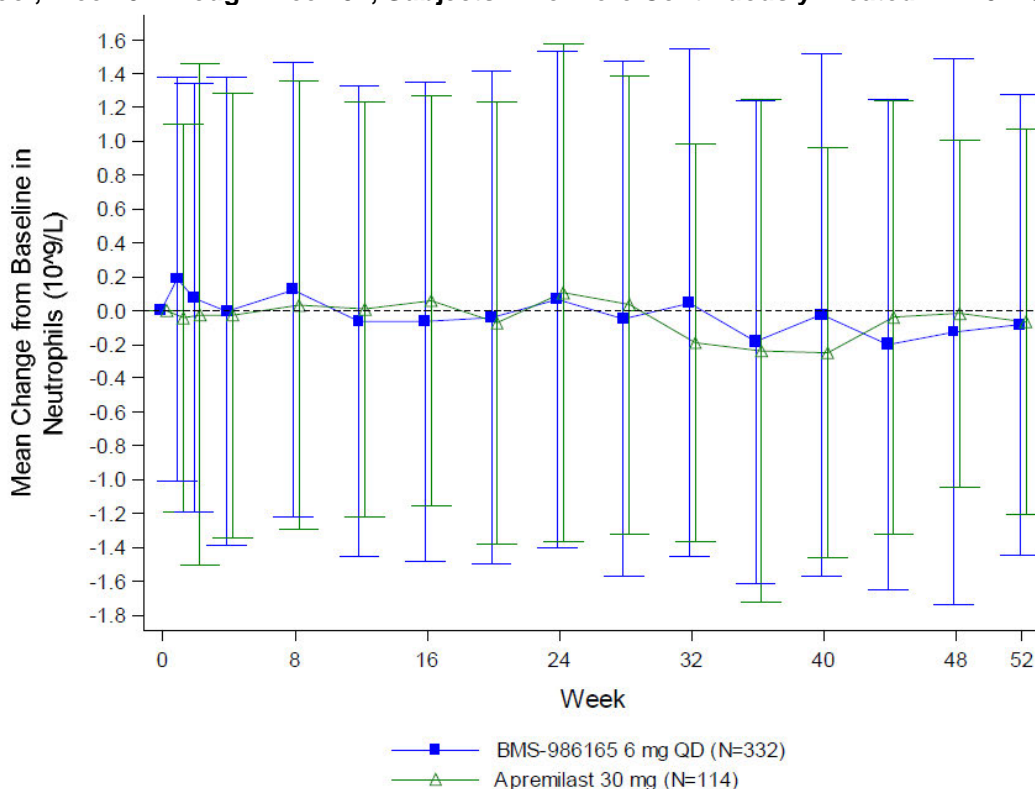
Summary of Deucravacitinib Effects on Neutrophil Counts

Assessment of the aforementioned reported AEs of neutropenia/decreased neutrophil count demonstrated comparable rates between deucravacitinib (2/840, 0.2%; IM011046- (b) (6)) and IM011047- (b) (6)) and apremilast (1/422, 0.2%; IM011047- (b) (6)). Therefore, labeling of neutropenia is not warranted at this time.

Apremilast-controlled Period, Week 0-52 – Trial IM011046

In the 52-week active-controlled period in Trial IM011046, the mean change in neutrophil count for deucravacitinib was -0.085 and for placebo was -0.067.

Figure 20. Mean Change From Baseline in Neutrophils ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 52, Subjects Who Were Continuously Treated in IM011046



Source: Applicant response to information request dated 31-May-2022.

From Applicant: Includes observed records of all subjects continuously treated with BMS-986165 or Apremilast in Period 1, Period 2, and Period 3.

Includes data from IM011046.

Error bars represent standard deviation of the mean changes from baseline.

Program Source: /gbs/prod/clin/programs/im/011/ebr16-fda/20220531/rpt

Program Name: rg-lb-mcfb-0-52-v01.sas 02JUN2022:16:42:51

Decreased neutrophil counts shifts of ≥ 2 CTCAE grades from baseline were reported in 8/328 (2.4%) subjects in the deucravacitinib group and 7/111 (6.3%) in the apremilast group. Grade 1 and Grade 2 decreases in neutrophil count were comparable between treatment groups. The proportion of Grade 3 ($<1000 - 500/mm^3$) neutropenia was greater in the deucravacitinib group (3/328, 0.9%) compared to the apremilast group (0/111). One of the 3 deucravacitinib-treated subjects with Grade 3 neutropenia had Grade 3 neutropenia at baseline, making the grade 3 neutropenia unlikely to be attributable to the study drug, and 2/323 (0.6%) deucravacitinib-treated subjects shifted from Grade 0 neutropenia at baseline to Grade 3 neutropenia during this period (IM011046-^{(b) (6)} and IM011046-^{(b) (6)}). For subjects IM011046-^{(b) (6)} and IM011046-^{(b) (6)}, the decrease in neutrophil counts resolved spontaneously on deucravacitinib and did not recur with continue deucravacitinib treatment, making the grade 3 neutropenia unlikely to be attributable to the study drug. No infection AEs were reported for the deucravacitinib-treated subjects who shifted from Grade 0 neutropenia at baseline to Grade 3 neutropenia. No Grade 4 neutropenia ($<500/mm^3$) occurred in the deucravacitinib group compared to 1/111 (0.9%) subject with Grade 4 neutropenia (shifted from Grade 0 at baseline) in the apremilast group.

With further exposure through Week 52 weeks, there were no additional subjects with reported AEs of neutropenia or neutrophil count decreased in either deucravacitinib or apremilast continuously treated subjects (2/330, 0.6% deucravacitinib continuously-treated subjects with 3 events were previously reported in the aforementioned preceding periods vs. 0/114, 0% apremilast continuously treated subjects), all of which were nonserious, mild or moderate in severity, and did not result in change to study treatment. There continued to be no Grade 4 events of neutropenia.

In the LTE trial, 4 subjects reported mild to moderate neutropenia/decreased neutrophil counts with no shifts more than 2 CTCAE grades. None of the events were serious or led to change in study medication.

Within the safety update, there were no new events of neutropenia/decreased neutrophil count.

Overall, there was a small decrease in mean change from baseline in neutrophil count for deucravacitinib, however, mostly unchanged and similar to apremilast.

Therefore, we do not recommend including neutropenia in the PI as an adverse reaction. Continued monitoring of potential effects of deucravacitinib on neutrophil counts will be conducted in the postmarketing setting.

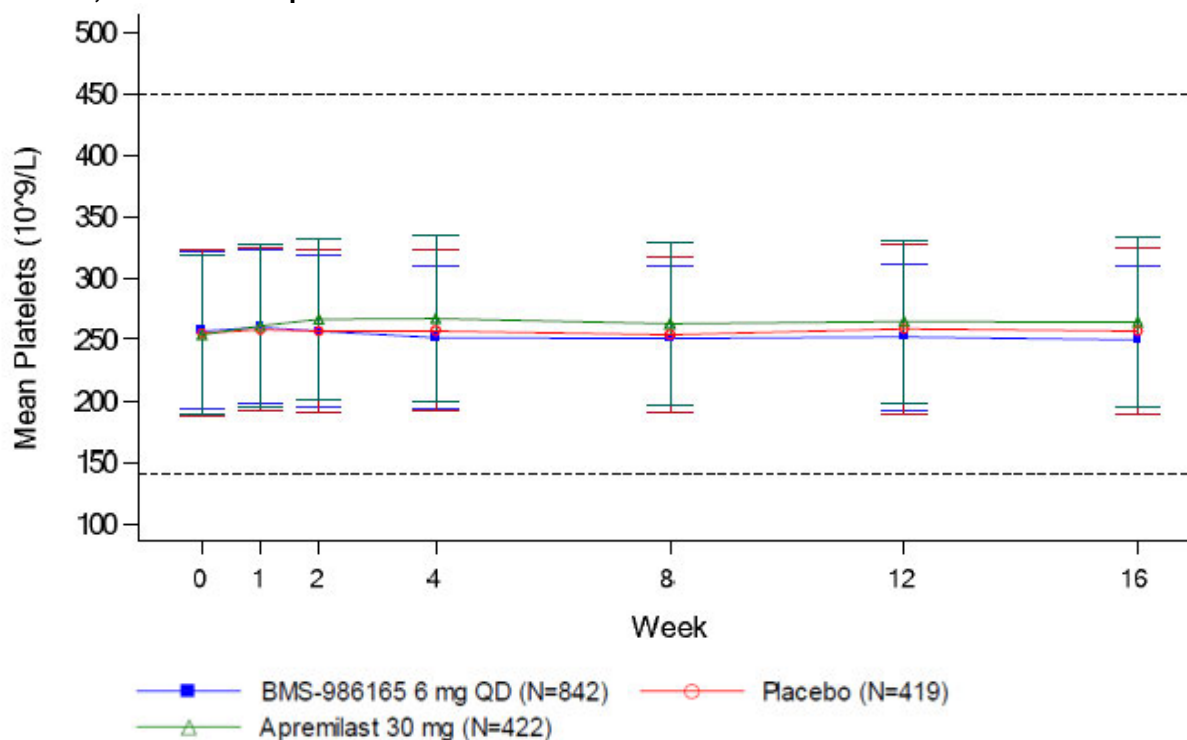
8.2.5.6.3. Platelets

8.2.5.6.3.1. Decrease in Platelet Counts

Placebo- and Apremilast-controlled Period, Week 0-16

During Week 0-16, the mean platelet count decreased by 6600 cells/mm³ (SE 1.32) in the deucravacitinib group in contrast to a mean increase of 1900 cells/mm³ (SE 1.8) observed in the placebo group and a mean increase of 10500 cells/mm³ (SE 1.87) seen in the apremilast group. There was a decrease in mean change in platelet counts noted at Week 16 in the deucravacitinib group (-6.6) compared to placebo (1.9) and apremilast (10.5).

Figure 21. Mean Platelets ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 16, As-Treated Population



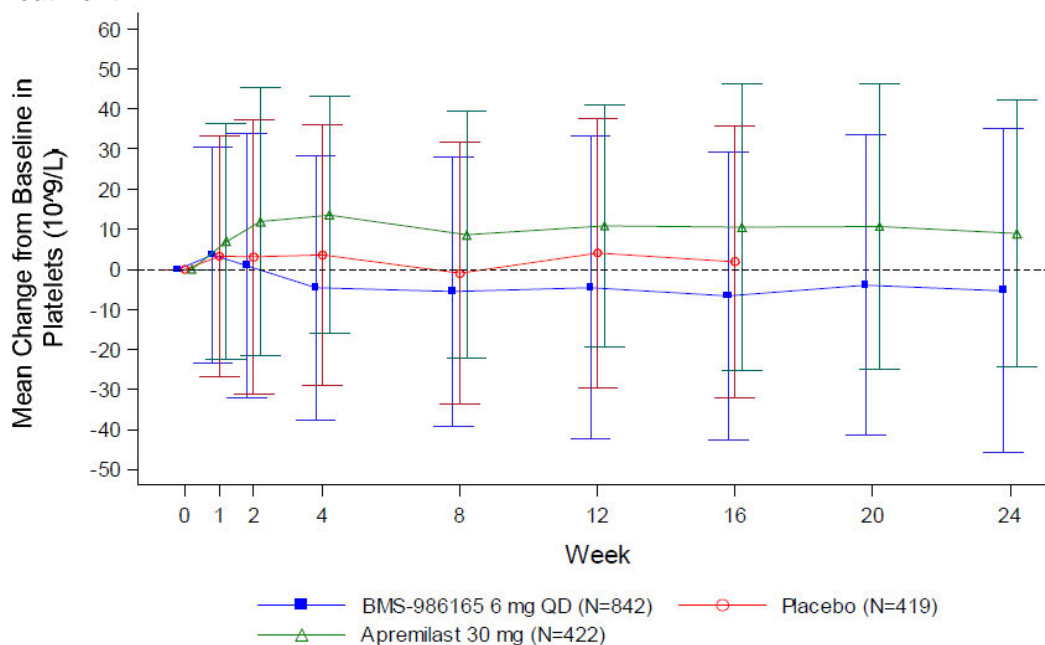
Source: Figure 3.1.1-4 ISS.

A single subject, who received placebo, had a ≥ 2 CTCAE grade shift from baseline. There was no Grade 3 ($<50,000 - 25,000/mm^3$) or 4 ($<25,000/mm^3$) thrombocytopenia for any treatment group, and no Grade 2 ($<75,000 - 50,000/mm^3$) thrombocytopenia for subjects in the deucravacitinib and apremilast groups during the first 16 weeks of treatment. For adverse events of decreased platelet count and thrombocytopenia, only one subject in the placebo group reported an event.

Apremilast-controlled Period, Week 0-24

For subjects in the Controlled Safety Pool who were continuously treated with either deucravacitinib or apremilast through 24 weeks, the mean change in platelet counts for deucravacitinib was -5.3 and for apremilast was 8.9.

Figure 22. Mean Change From Baseline in Platelets ($10^9/L$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 24, Subjects Who Were Randomized to and Remained on the Same Treatment



Source: Applicant response to information request dated 31-May-2022.

From Applicant: Baseline through Week 16 visits include observed records of all subjects treated with BMS-986165, Placebo, or Apremilast in Period 1. Week 20 through Week 24 visits include observed records of all subjects continuously treated with BMS-986165 or Apremilast in Period 1 and Period 2.

Includes data from IM011046 and IM011047.

Error bars represent standard deviation of the mean changes from baseline.

Program Source: /gbs/prod/clin/programs/im/011/abr16-fda/20220531/rpt

Program Name: rg-lb-mcfb-0-24-v01.sas 02JUN2022:16:46:09

No decreased platelet counts shifts of ≥ 2 CTCAE grades from baseline were reported in either treatment group. Grade 1 decreases in platelet counts were comparable between treatment groups. There was no Grade 2 ($<75,000 - 50,000/mm^3$), Grade 3 ($<50,000 - 25,000/mm^3$) or Grade 4 ($<25,000/mm^3$) thrombocytopenia for either treatment group.

A single subject in the Controlled Safety Pool who was continuously treated with apremilast through 24 weeks had a mild, nonserious event of thrombocytopenia. There were no events reported for the subjects who were continuously treated with deucravacitinib during this period.

Apremilast-controlled Period, Week 0-52 – Trial IM011046

In the 52-week active-controlled period in Trial IM011046, the mean change in platelet counts for deucravacitinib was -6.9 and for apremilast was 11.6.

One subject in the LTE trial reported an event of Grade 0 to 1 thrombocytopenia that was considered mild, nonserious, and did not lead to change in study drug.

With the safety update, there was one new AE of mild, nonserious, Grade 0 to 1 thrombocytopenia that did not lead to treatment discontinuation.

Overall, there was a decrease in mean change in platelet counts for deucravacitinib compared to placebo (up to week 16) and apremilast (up to week 52).

8.2.5.6.3.2. Elevation in Platelet Counts

Placebo- and Apremilast-controlled Period, Week 0-16

During the placebo-controlled period (Week 0-16), 1/840 (0.1%) in the deucravacitinib group and 2/419 (0.5%) in the placebo group reported platelet counts $>600,000$ cells/mm³. No subjects in the apremilast group reported platelet counts $>600,000$ cells/mm³ during this period. There were no reported AEs of thrombocytosis in any treatment group during this period.

Apremilast-controlled Period, Week 0-24

For subjects in the Controlled Safety Pool who were continuously treated with either deucravacitinib or apremilast through 24 weeks, 1/840 (0.1%) in the deucravacitinib group reported platelet counts $>600,000$ cells/mm³. No subjects in the apremilast group reported platelet counts $>600,000$ cells/mm³ during this period. There were no reported AEs of thrombocytosis in any treatment group during this period.

Apremilast-controlled Period, Week 0-52 – Trial IM011046

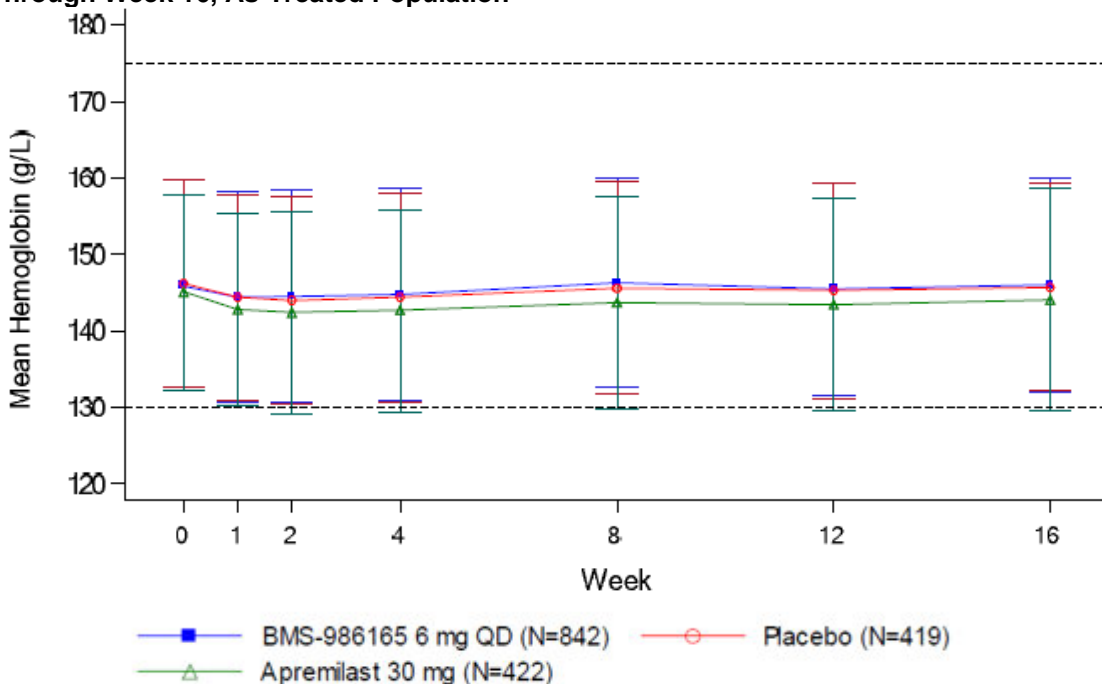
In the 52-week active-controlled period in Trial IM011046, no subjects in either treatment group reported platelet counts $>600,000$ cells/mm³ during this period. There were no reported AEs of *thrombocytosis* in any treatment group during this period.

8.2.5.6.4. Anemia

Placebo- and Apremilast-controlled Period, Week 0-16

During the placebo-controlled period (Week 0-16), the mean change in hemoglobin values from baseline were similar between the treatment groups (placebo: -0.07, deucravacitinib: 0.01, and apremilast: -0.09).

Figure 24. Mean Hemoglobin (10⁹/L) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 16, As-Treated Population



Source: Figure 3.1.1-3 ISS.

One subject each in the deucravacitinib (1/831, 0.1%) and apremilast (1/418, 0.2%) groups reported hemoglobin shifts ≥ 2 CTCAE grades from baseline. There were no placebo subjects with hemoglobin shifts equal to or exceeding 2 grades from baseline. Assessment of worst toxicity grade showed the proportion of subjects with Grade 1 anemia (Hemoglobin (Hgb) $<LLN - 10.0$ g/dL; $<LLN - 6.2$ mmol/L; $<LLN - 100$ g/L) was lowest for the deucravacitinib group [61/831 (7.3%)] compared to 39/413 (9.4%) for placebo subjects and 37/418 (8.9%) for those who received apremilast. Grade 2 anemia (Hgb $<10.0 - 8.0$ g/dL; $<6.2 - 4.9$ mmol/L; $<100 - 80$ g/L) occurred at the same rate among the treatment groups (0.5%). Grade 3 anemia (Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated) was reported in a single subject in the apremilast group.

According to the Applicant there were no Grade 4 events of anemia (CTCAE version 5 does not have a corresponding hemoglobin value (i.e., Grade 4 anemia is characterized as “life-threatening consequences; urgent intervention indicated”). For adverse events of *anemia* (note, excluded reported AEs of *anemia vitamin B12 deficiency* and *iron deficiency anemia*), 2/840 (0.2%) subjects in the deucravacitinib group and 2/422 (0.5%) subjects in the apremilast group reported mild to moderate, nonserious events that did not lead to change in study treatment. There were no AEs of anemia in the placebo group.

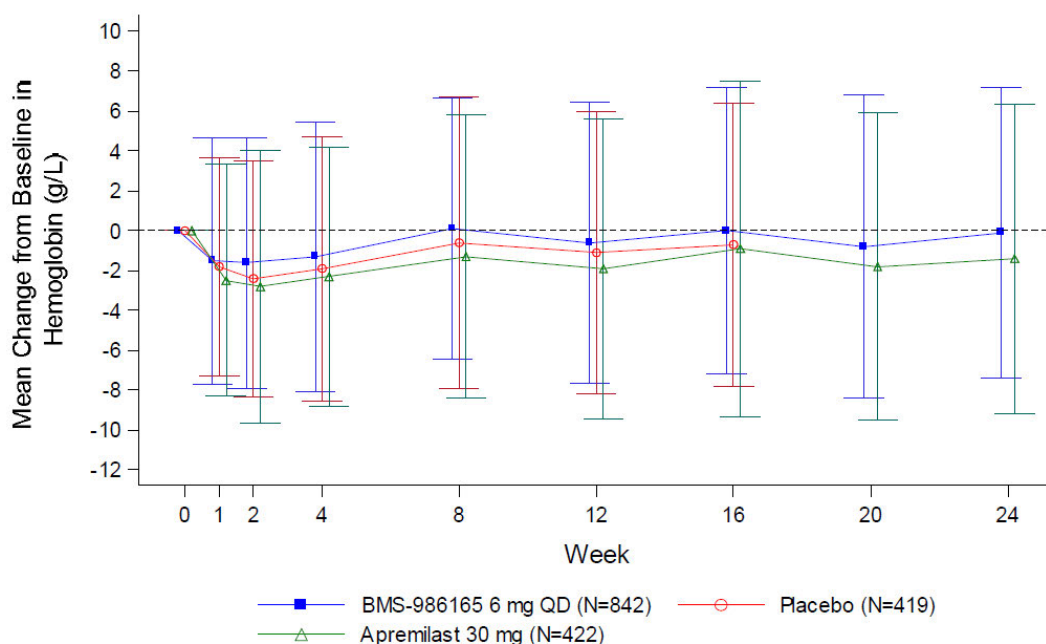
Apremilast-controlled Period, Week 0-24

Through 24 weeks, 3/1152 (0.3%) subjects receiving deucravacitinib and 1/405 (0.2%) receiving apremilast reported hemoglobin shifts ≥ 2 CTCAE grades. Worst toxicity grade assessments

showed that a lower proportion of subjects in the deucravacitinib group (7.1) reported Grade 1 anemia compared to placebo (9.4) and apremilast (10.5) groups. Rates of Grade 2 anemia were comparable among treatment groups.

For subjects in the Controlled Safety Pool who were continuously treated with either deucravacitinib or apremilast through 24 weeks, mean change from baseline in hemoglobin for deucravacitinib was -0.01 and for apremilast -0.14.

Figure 25. Mean Change From Baseline in Hemoglobin (g/L) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 24, Subjects Who Were Randomized to and Remained on the Same Treatment



Source: Applicant response to information request dated 31-May-2022.

From Applicant: Baseline through Week 16 visits include observed records of all subjects treated with BMS-986165 (Deucravacitinib), Placebo, or Apremilast in Period 1. Week 20 through Week 24 visits include observed records of all subjects continuously treated with BMS-986165 or Apremilast in Period 1 and Period 2. Includes data from IM011046 and IM011047.

Error bars represent standard deviation of the mean changes from baseline.

Program Source: /gbs/prod/clin/programs/im/011/ebr16-fda/20220531/rpt

Program Name: rg-lb-mcfb-0-24-v01.sas 02JUN2022:16:46:05

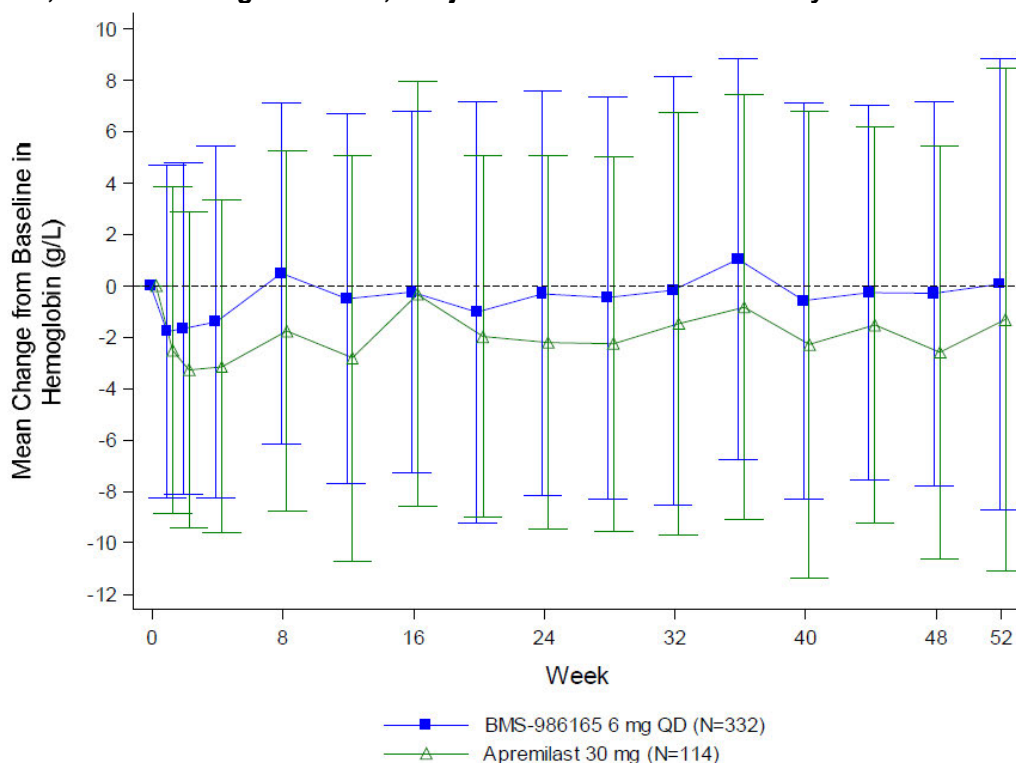
Anemia shifts of ≥ 2 CTCAE grades from baseline were reported in 3/831 (0.4%) subjects in the deucravacitinib group and 1/418 (0.2%) in the apremilast group. Grade 1 anemia was comparable between treatment groups during this period. Decreases in hemoglobin below 10 g/dL (Grade 2) occurred at the same rate in subjects treated with deucravacitinib (6/831, 0.7%) and apremilast (3/418, 0.7%). Note: one subject in each of the treatment groups started at grade 2 at baseline and decreases in hemoglobin below 8 g/dL occurred in 0% of subjects treated with deucravacitinib and 1/418, 0.2% of subjects treated with apremilast. According to the Applicant there were no Grade 4 events of anemia (CTCAE version 5 does not have a corresponding hemoglobin value (i.e., Grade 4 anemia is characterized as "life-threatening consequences; urgent intervention indicated").

No additional subject continuously treated with deucravacitinib (total 2/840, 0.2%) and 1 additional subject continuously treated with apremilast reported an AE of anemia from week 16 to 24 (total 3/422, 0.7%) during the 0-24 week period.

Apremilast-controlled Period, Week 0-52 – Trial IM011046

In the 52-week active-controlled period in Trial IM011046, mean change from baseline in hemoglobin for deucravacitinib was 0.01 and for apremilast -0.13.

Figure 26. Mean Change From Baseline in Hemoglobin (g/L) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 52, Subjects Who Were Continuously Treated in IM011046



Source: Applicant response to information request dated 31-May-2022.

From Applicant: Includes observed records of all subjects continuously treated with BMS-986165 or Apremilast in Period 1, Period 2, and Period 3.

Includes data from IM011046.

Error bars represent standard deviation of the mean changes from baseline.

Program Source: /gbs/prod/clin/programs/im/011/ibr16-fda/20220531/rpt

Program Name: rg-lb-mcfb-0-52-v01.sas 02JUN2022:16:42:50

Anemia shifts of ≥ 2 CTCAE grades from baseline were reported in 5/328 (1.5%) subjects in the deucravacitinib group and 0/111 in the apremilast group. Grade 1 anemia were comparable between treatment groups during this period. Decreases in hemoglobin below 10 g/dL (Grade 2) occurred in 6/328 (1.8%) subjects in the deucravacitinib group and 1/111 (0.9%) subjects in the apremilast group. There was no Grade 3 anemia reported in either treatment group. According to the Applicant there were no Grade 4 events of anemia (CTCAE version 5 does not

have a corresponding hemoglobin value (i.e., Grade 4 anemia is characterized as “life-threatening consequences; urgent intervention indicated”).

In the 52-week active-controlled period of Trial IM011046, anemia was reported in one additional subject (total 2/330 (0.6%)) subjects continuously treated with deucravacitinib and no additional subjects (total 1/114 (0.9%) subjects treated with apremilast. One deucravacitinib-treated subject had severe anemia in the setting of Hodgkin’s lymphoma. The apremilast-treated subjects had mild, non-serious anemia that did not lead to change in study drug dosing.

To also capture events of anemia and decreased hemoglobin levels outside of the periods and pools discussed above, events that occurred through 52-weeks of exposure regardless of whether subjects switched treatment were evaluated. With exposure through 52 weeks, 9/1313 (0.7%) deucravacitinib-treated subjects reported hemoglobin shifts ≥ 2 CTCAE grades and 9 deucravacitinib-treated subjects reported adverse events of *anemia*. Of these 9 subjects, 2 were considered severe--one subject had severe anemia in the setting of Hodgkin’s lymphoma and the other subject was a 47-year-old white male who had received apremilast during Week 0-24 and was diagnosed with symptomatic anemia secondary to Vitamin B12 deficiency after treatment with deucravacitinib for 14 weeks. Following cyanocobalamin administration, his hemoglobin level gradually returned to normal range.

Overall, there was no significant change in mean change in hemoglobin for deucravacitinib. However, there was a greater proportion of subjects treated with deucravacitinib during the 52 week period with grade 2 anemia (hemoglobin below 10 g/dL) compared to subjects treated with apremilast.

Continuous administration of deucravacitinib beyond 52 weeks of exposure was not associated with a significant change in mean hemoglobin levels.

During the LTE trial, 5 subjects reported adverse events of mild anemia that were not considered serious and did not result in drug interruption or discontinuation. None of the shifts were ≥ 2 CTCAE grades.

Between the safety data cut-off date of June 15, 2021 and the 120 day data cut-off date of October 1, 2022, there were 3 new AEs of anemia: 1 subject with a history of iron deficiency anemia had Grade 1 decrease in hemoglobin; 1 subject experienced a reported gradual Grade 1 decrease in hemoglobin attributed to diet according to the investigator; and 1 subject had Grade 3 decrease in hemoglobin that returned to normal range upon repeat testing 7 days later.

8.2.5.6.5. Hemoglobin, Hematocrit, and Erythrocytes

The rates of elevated hemoglobin (g/L) were noted to be comparable across treatment groups (deucravacitinib: 3/840 (0.4%) subjects, placebo: 3/419 (0.7%) subjects, and apremilast: 2/422 (0.5%) subjects for Weeks 0-16 and between deucravacitinib: 3/840 (0.4%) subjects and

apremilast: 3/422 (0.7%) subjects for Weeks 0-24. There was a greater proportion of subjects who had elevated hemoglobin during the 52-week active-controlled period in Trial IM011046 in the deucravacitinib group (15/330, 4.5%) compared to the apremilast group (1/114, 0.9%).

The rates of elevated hematocrit (v/v) were noted to be comparable across treatment groups (deucravacitinib: 4/840 (0.5%), placebo: 5/419 (1.2%) , and apremilast: 6/422 (1.4%)) for Weeks 0-16 and between deucravacitinib: 4/840 (0.5%) and apremilast: 7/422 (1.7%) for Weeks 0-24 and between deucravacitinib: 25/330 (7.6%) and apremilast: 9/114 (7.9%) for Weeks 0-52 for Trial IM011046.

The rates of elevated erythrocytes (/HPF) were comparable across treatment groups (deucravacitinib: 1/840 (0.1%), placebo: 0/419 (0%), and apremilast: 4/422 (0.9%)) for Weeks 0-16 and between deucravacitinib: 2/840 (0.2%) and apremilast: 4/422 (0.9%) for Weeks 0-24 and between deucravacitinib: 28/330 (8.5%) and apremilast: 9/114 (7.9%) for Weeks 0-52 for Trial IM011046.

A search of the ADAE dataset for polycythaemia revealed one subject (IM011047-(b) (6)) who was treated with deucravacitinib, who had an AE of polycythaemia noted 17 days after the start of deucravacitinib.

Based on the available data, there does not appear to be a notable effect of increased erythropoiesis by deucravacitinib.

8.2.5.6.6. Hematologic Parameters Summary

In summary, based on the available data reviewed above, deucravacitinib does not appear to have a significant effect on lymphocyte counts, neutrophil counts, hemoglobin, or platelets.

- Regarding lymphocyte counts, there were no reported AEs >1% of “lymphopenia/decreased lymphocyte count” in deucravacitinib-treated subjects and the rates appear similar to placebo and apremilast groups during the previously discussed respective time periods. There was 1 case of Grade 3 lymphopenia (<500 cells/mm³) in a subject treated with deucravacitinib that occurred in the 0-16 week period that led to treatment discontinuation.
- There were no mean changes in lymphocyte counts noted with deucravacitinib. There were no noted decreases in natural killer (NK) cell counts associated with deucravacitinib during the 0-16 week period.
- Regarding neutrophil counts, there were no reported AEs >1% of “neutropenia/decreased neutrophil count” in deucravacitinib-treated subjects, and the rates appear similar to placebo and apremilast controls during the previously discussed respective time periods. There were no cases of Grade 3 neutropenia (<1000 cells/mm³) in subjects treated with deucravacitinib. There were no mean changes in neutrophil counts noted with deucravacitinib.
- Regarding hemoglobin, there were no reported AEs >1% of anemia in deucravacitinib-treated subjects and the rates appear similar to or less than placebo and/or apremilast

controls during the previously discussed respective time periods. There were no reported cases of Grade 3 anemia (hemoglobin <8 g/dL) in subjects treated with deucravacitinib. There were no mean changes in hemoglobin noted with deucravacitinib.

- Regarding platelets, there were no reported AEs of thrombocytopenia or thrombocytosis in deucravacitinib-treated subjects. There was a small decrease in mean change in platelets noted with deucravacitinib ($-6.6 \times 10^9/L$).

While the current hematologic findings do not warrant labeling, there is concern for possible bone marrow effects with prolonged use based on nonclinical findings and deucravacitinib's pairing with JAK2 (which is essential for normal hematopoiesis), as well as its impact on signaling of IL-6 (which has a key role in hematopoiesis). To address the uncertainty regarding the long-term safety of deucravacitinib and to identify a potential risk for bone marrow effects, hematological parameters will be monitored in the post-marketing setting.

8.2.5.7. Hepatic Events and Assessment

During the review team's analyses, a potential Hy's Law case was identified, therefore an Information Request to provide additional information on subjects whose laboratory assessments can be categorized under Hy's Law and Temple's Corollary was sent to the Applicant. The Agency specifically requested case level data reporting for subjects on investigational product who developed:

- Total bilirubin >2x ULN with ALT or AST >3x ULN
- ALT or AST > 5x ULN
- ALP > 2x ULN
- Liver-related serious adverse events

If baseline values were >ULN then the Applicant was instructed to substitute the baseline values for ULN in (1) through (4). Additionally, if unblinded data were available, then only subjects on study drug needed to be reported.

To assess the criteria defined in the request, the Applicant used the FDA-requested approach where baseline values >ULN were substituted for ULN in the calculations of ratio to ULN. The approach was applied to the Phase 3 Safety Pool which includes data from 1519 subjects treated with deucravacitinib in the 2 controlled Phase 3 psoriasis studies (IM011046

Appears this way on original

and IM011047) and in the open-label long-term extension study (IM011075 through June 15, 2021). Using this method of analysis, a total of 24 subjects in the Phase 3 Safety Pool met the criteria specified in the request and are listed in the table below. No subject met criteria "a" (total bilirubin >2x ULN with ALT or AST >3x ULN), 21 subjects met criterion "b" (ALT or AST >5x ULN), 6 subjects met criterion "c" (ALP >2x ULN), and 2 subjects met criterion "d" [liver-related serious adverse events (SAEs)]. Five subjects met more than one criteria: 4 subjects had both ALT or AST and ALP elevations, and 1 subject had AST elevation and a liver-related SAE.

Table 71. Subjects With Total Bilirubin >2x ULN With ALT or AST >3x ULN, ALT or AST > 5x ULN, ALP> 2x ULN, or Liver-related Serious Adverse Event - Phase 3 Safety Pool (Through 15-Jun-2021)

Count	Parent Study Subject Identifier	IM011075 Subject Identifier	Criteria A: total bilirubin >2x ULN with ALT or AST >3x ULN (N = 0)	Criterion B: ALT or AST > 5x ULN N = 21	Criterion C: ALP> 2x ULN N = 6	Criterion D: Liver Related SAE N = 2
1	(b) (6)	(b) (6)		ALT or AST >5x ULN		
2			ALT or AST >5x ULN			
3			ALT or AST >5x ULN	ALP > 2x ULN		
4				ALP > 2x ULN		
5			ALT or AST >5x ULN			
6			ALT or AST >5x ULN			
7			ALT or AST >5x ULN			Liver function test increased
8			ALT or AST >5x ULN			
9			ALT or AST >5x ULN	ALP > 2x ULN		
10			ALT or AST >5x ULN			
11			ALT or AST >5x ULN	ALP > 2x ULN		
12			ALT or AST >5x ULN			
13			ALT or AST >5x ULN			
14						Hepatitis
15			ALT or AST >5x ULN			
16			ALT or AST >5x ULN	ALP > 2x ULN		
17			ALT or AST >5x ULN			
18			ALT or AST >5x ULN			
19			ALT or AST >5x ULN			
20				ALP > 2x ULN		
21			ALT or AST >5x ULN			
22			ALT or AST >5x ULN			
23			ALT or AST >5x ULN			
24			ALT or AST >5x ULN			

Source: Applicant's table in response to an FDA Information Request dated January 4, 2022.

Upon clinical review of these cases, several (9) subjects with AST and/or ALT >5x ULN or isolated ALP > 2x ULN had concomitant CPK elevations; many others had confounding past and/or concurrent comorbidities as well as concomitant medications that might have contributed to the liver enzyme abnormalities.

The division subsequently consulted the Drug-induced Liver Injury (DILI) Team of the Division of Hepatology and Nutrition to assess the Applicant’s hepatic safety analyses and provide advice on whether labeling or additional data and analyses to better assess hepatic safety is needed. Ling Lan, MD, PhD and Paul H. Hayashi, MD, MPH examined the non-clinical and pharmacokinetic (ADME) data relevant to DILI and comprehensively reviewed study level information as well as performed case level analyses. Refer to their review dated August 2, 2022.

8.2.5.7.1. DILI Team’s Findings, Conclusions, and Recommendations

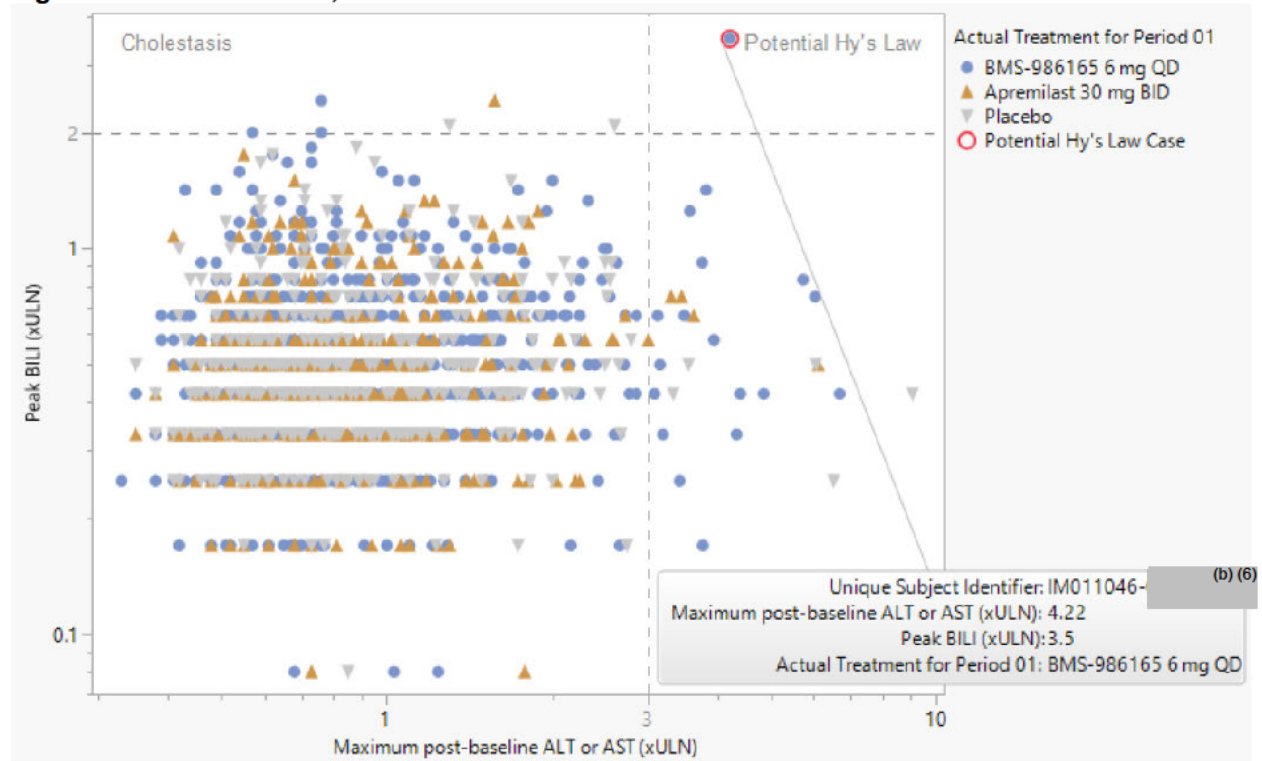
Because Trials IM011046 and IM011047 had identical eligibility criteria, the DILI team considered pooling of the trials acceptable to increase powering for hepatic injury evaluation especially during the first 16- and 24-week periods. The following table summarizes the DILI team’s analyses of liver transaminase and total bilirubin elevations across treatment arms, and the figures provide the graphic categorization of subjects via eDISH plots at Weeks 16 and 24.

Table 72. ISS Liver Biochemistry Results

Variable	ISS: Studies 046 and 047				
	Week 0-16			Week 0-24	
	DEUC N = 842	Apremilast N = 422	Placebo N = 419	DEUC N = 842	Apremilast N = 422
ALT					
≥ 3 x ULN	9 (1.1%)	3 (0.7%)	5 (1.2%)	11 (1.3%)	3 (0.7%)
≥ 5 x ULN	0	0	3 (0.7%)	1 (0.1%)	0
AST					
≥ 3 x ULN	13 (1.5%)	3 (0.7%)	2 (0.5%)	14 (1.7%)	3 (0.7%)
≥ 5 x ULN	3 (0.4%)	0	1 (0.2%)	3 (0.4%)	1 (0.2%)
BILI ≥ 2 x ULN	4 (0.5%)	1 (0.2%)	2 (0.5%)	5 (0.6%)	1 (0.2%)
ALP ≥ 2 x ULN	0	0	0	0	0

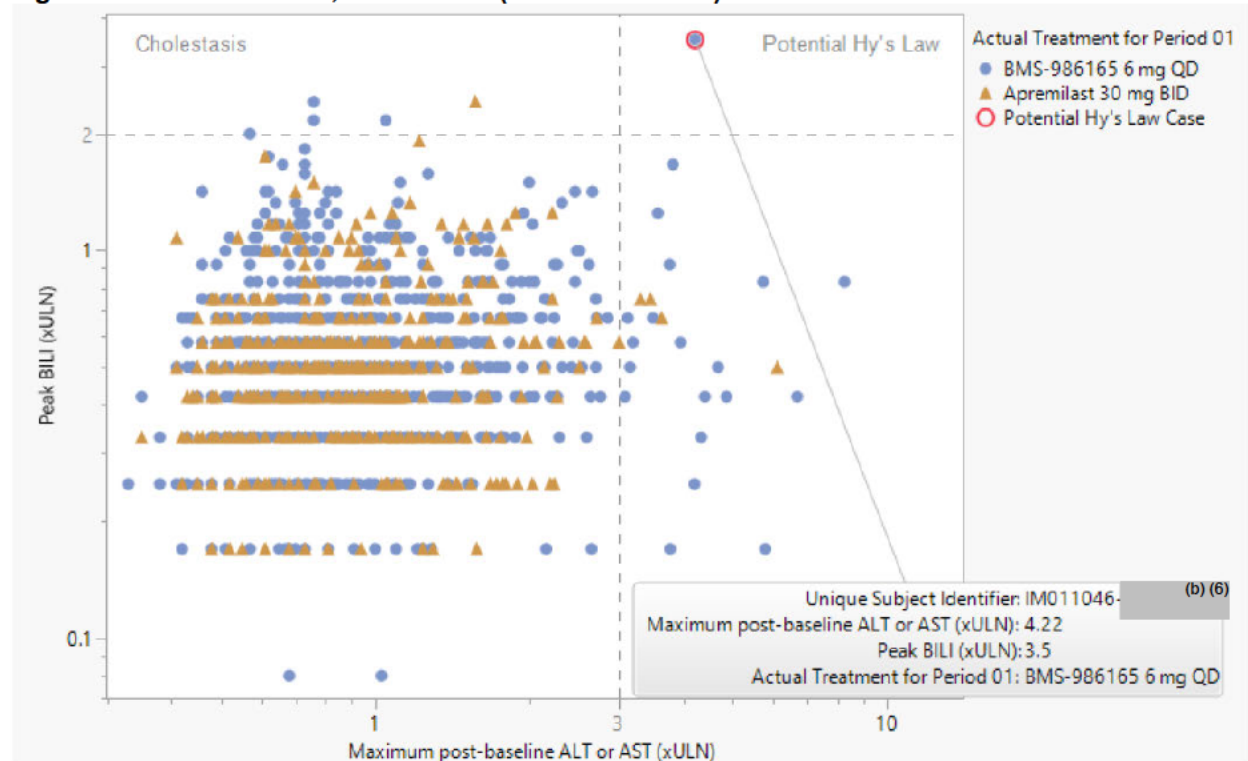
Source: DILI team adaptation based on IR response dated April 28, 2022.
 Abbreviations: DEUC, deucravacitinib

Figure 27. ISS eDISH Plot, Weeks 0-16



Source: DILI team.

Figure 28. ISS eDISH Plot, Weeks 0-24 (No Placebo Arm)



Source: DILI team.

During Week 0-16, subjects in the deucravacitinib group had the highest AST elevation (1.5%, $\geq 3 \times$ ULN) among all subjects. By Week 24, deucravacitinib-treated subjects experienced more ALT, AST and bilirubin elevation compared to apremilast-treated subjects, although, according to the DILI team, the difference for ALT was not sustained at $>5 \times$ ULN. For AST, the differences persisted at $>5 \times$ ULN but more modestly (+0.2% differences) than at $>3 \times$ ULN (data not shown).

The SUR included datasets for all 3 trials (IM011046, IM011047, and IM011075). The DILI team identified a total of 30 subjects who had ALT or AST $\geq 5 \times$ ULN and related AEs and determined that the findings within the SUR were consistent with the overall results by Week 52.

Case level analyses included assessment of 27 subjects with transaminase greater than $5 \times$ ULN or $>3 \times$ ULN with total bilirubin $>2 \times$ ULN or cases identified as having a liver related SAE. Dr. Hayashi determined that "none of the cases were considered probable DILI. One had possible DILI due to deucravacitinib with competing etiologies of non-alcoholic fatty liver (NAFLD) and/or alcoholic fatty liver disease (AFLD). One subject had a rapidly progressive liver cancer, and the rapid progression may have been related to deucravacitinib. The remaining 25 were considered unlikely related to deucravacitinib. Of the 25 unlikely DILI subjects, the most common alternate diagnosis was myopathy or myositis (9 subjects) which is atypical. In the DILI Team's experience, myopathy or myositis are not common competing diagnoses. The next most common was "unknown" (six subjects) which is typical in our experience. There were four subjects with NAFLD and/or AFLD, three with DILI from another agent, two with gallstone disease and one with CMV infection as alternate diagnoses."

As discussed within Section [8.2.5.9](#) of this review, treatment with deucravacitinib was associated with an increased incidence of CPK elevation compared to placebo and apremilast. There was also a higher proportion of Grade 4 CPK elevations ($>10 \times$ ULN) with deucravacitinib treatment throughout the Phase 3 trials. Reports of associated rhabdomyolysis and myopathy (including pain and muscle weakness) occurring with higher grade events was observed. As literature suggests a strong correlation between CPK and serum transaminases (Mathur et al. 2014), the diagnoses of myopathy or myositis identified by the DILI team accounting for the elevated liver enzymes in 9 subjects is understandable.

The DILI team highlighted 3 subjects: 1 subject potentially meeting Hy's Law but liver injury was more likely from alcohol use and underlying Gilbert syndrome; 1 subject with possible DILI due to deucravacitinib, but NAFLD and AFLD were competing diagnoses; and 1 subject with hepatocellular carcinoma (HCC). The former 2 subjects will be discussed below. The subject with HCC was previously discussed in Section [8.2.4.1](#).

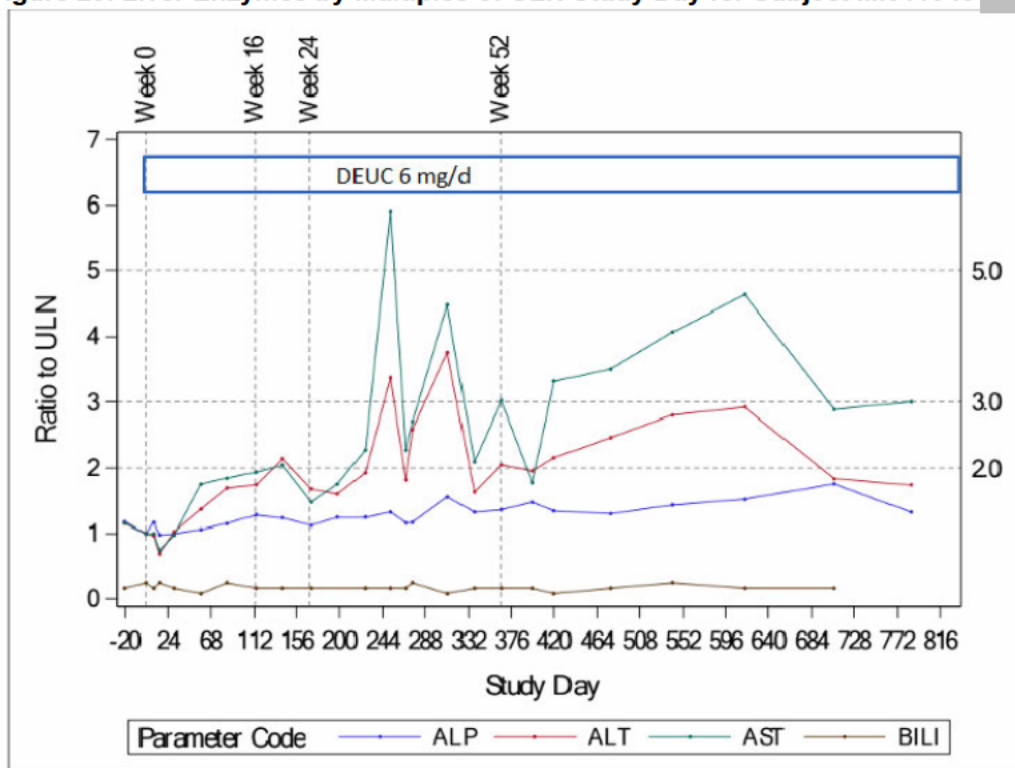
Subject IM011046-^{(b) (6)}: Possible DILI due to Deucravacitinib, but Alcohol and Non-alcoholic Fatty Liver Disease Compete

45-year-old White female with a history of jaundice possibly due to hepatitis A in ^{(b) (6)}, but ALT remained elevated thereafter. Her BMI was 32.3 kg/m² and she was diagnosed with "hepatic steatosis" in ^{(b) (6)}. It is unclear if biopsy was done for diagnosis. The narrative gives no history of alcohol use. She took acetaminophen (APAP) ^{(b) (6)}, but no other concomitant

medications. Her liver biochemistries at baseline: ALT 65 U/L, AST 44, AP 114, total bilirubin (TB) 0.3 mg/dL.

She started deucravacitinib 6 mg/day on [REDACTED] (b) (6). During [REDACTED] (b) (6), she took APAP (500 mg q 6 hours) for an URI. On [REDACTED] (b) (6), her ALT was 219, AST 260, AP 151. No other new medications were taken within 6 months prior to this rise. She had no other symptoms. Her liver enzymes remained modestly elevated over baseline, but TB remained normal. Deucravacitinib continued to censor date of [REDACTED] (b) (6). CPK and LDH were not elevated. No evaluation testing was done. No symptoms mentioned. Deucravacitinib continued without change in dose.

Figure 29. Liver Enzymes by Multiples of ULN Study Day for Subject IM011046- [REDACTED] (b) (6)



DILI Team Case Assessment

“We considered this case as only possible DILI due to deucravacitinib. The overall rise and lack of return to baseline while on deucravacitinib could be a chronic DILI with only partial or stuttering tolerance. Onset could be when initial rise at around day 50, making latency more consistent with DILI. However, worsening NALFD or alcohol liver injury would fit this injury pattern well if weight increased during this time and/or occult alcohol use occurred. Without jaundice and only possible attribution to deucravacitinib, we do not see this case as a significant concern for approval or labeling.”

Subject IM011046- (b) (6) : Liver Injury Likely Secondary to Alcohol Use and Gilbert Syndrome

41-year-old Asian male with a history of "alcohol dependence and "moderate fatty liver by sonogram".

The DILI team's narrative summary describes ALT was 110 U/L, AST 80 U/L, TB 0.9-1.2 mg/dL, AP 88 U/L at baseline. There was no other past medical history given. He started deucravacitinib 6 mg/day on (b) (6). On (b) (6), his liver enzymes and TB rose to ALT 119, AST 119, AP 90, TB 4.2 mg/dL (no bilirubin fractionation). No symptoms are mentioned. The investigator stopped deucravacitinib on (b) (6) (Day 58). On (b) (6), enzymes rose further to peak at ALT 158, AST 156, AP 92, but TB fell to 2.0 mg/dL (no fractionation).

Evaluation testing is unclear. The submission narrative states, "no other immediately apparent possible causes of liver function test elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic", but specific test results are not given. There was still no fractionation of bilirubin. The narrative says the diagnosis was "confounded by alternative etiologies (alcohol dependence, fatty liver, ALT and AST elevated to $\geq 2x$ ULN at screening and baseline, and bilirubin at ULN at screening)." Thereafter his liver tests returned to near his baseline.

Table 73. Subject IM011046- (b) (6) Liver Test Results

LFT-US		ALP	LDH	ALT	AST	BILI
Units	U/L	U/L	U/L	U/L	U/L	mg/dL
Range	40-129	0-250	0-41	0-37	0-1.2	
Day-28	98	284	82	86	1.2	
Day1	88	256	110	80	0.9	
Day8	92	287	82	97	1	
Day15	93	267	101	113	1.9	
Day29	90	278	82	96	2	
Day58	98	292	119	119	4.2	
Day62	92	249	158	156	2.6	
Day92	93	176	101	74	1.5	

DILI Team Case Assessment

"This is unlikely DILI due to deucravacitinib. Latency and modest dechallenge are supportive of DILI, but the level of injury is mild when comparing peak TA levels to the subject's baseline (1.5 to 2 x baseline). The rise in TB is out of proportion (3.5 x ULN) the TA elevations, and inconsistent with acute DILI. There was no fractionation of the TB. This case fits better with alcohol related fatty liver with Gilberts."

Conclusion of the DILI Team

The ISS included 1683 subjects exposed to deucravacitinib across two Phase 3 studies. While there was an increase in subjects with ALT > 3x ULN compared to apremilast (1.3% versus 0.7%) during weeks 0 to 24, we did not see such a difference compared to placebo during weeks 0 to 16. Moreover, there were no significant differences at ALT > 5x ULN. The differences for AST did

persist for AST >5x ULN but this may be due to myopathy rather than DILI. We assessed almost all cases with significant ALT or AST elevation as unlikely DILI, and myopathy was the most common alternate explanation. No case meeting biochemical criteria for Hy's Law (i.e., transaminases > 3x ULN and TB >2 x ULN) was attributable to DILI. Thus, there were no Hy's Law cases.

Subjects with evidence of hepatitis B infection were excluded from the deucravacitinib phase 3 trials, so reactivation risk could not be addressed. However, approved JAK inhibitors have been associated with reactivation.

The only subject of concern was a man who died of rapidly progressive hepatocellular carcinoma (HCC) with significant thromboses of his portal, splenic and mesenteric veins. He likely had cirrhosis from hepatitis C so development of HCC cannot be attributed to deucravacitinib. However, a case of HCC rapid progression has been reported in a patient taking baricitinib followed by tofacitinib for rheumatoid arthritis (Migita et al. 2022). "Lymphoma and other malignancies" and "deep venous thromboses" are boxed warnings for at least three approved JAK inhibitors.

In summary, there is no DILI risk found that would hold up approval. One fatality due to rapidly progressive HCC is noteworthy and may warrant mention in the label. Labeling for hepatitis B reactivation risk similar to other JAK inhibitors may also be warranted.

Recommendations From the DILI Team

- There were no hepatotoxicity risk concerns that would preclude approval.
- Liver enzymes and bilirubin should be checked at baseline, and when clinically indicated thereafter.
- While subjects with positive hepatitis B serologies were excluded in the pivotal trials, consider labeling for hepatitis B reactivation risk, similar to other JAK inhibitors.
- Consider inclusion of a description of the deucravacitinib-treated subject who developed rapidly progressive HCC in the product label as a reminder for physicians to follow hepatocellular carcinoma (HCC) screening guidelines when deucravacitinib is used in patients with cirrhosis or who are otherwise at increased risk for HCC.
- Post-market evaluation should include identification and characterization of any new cases of HCC and portal system thromboses in subjects with cirrhosis, and hepatitis B reactivation.

The review team concurs with the DILI Team's conclusions and recommendations.

- Labeling will incorporate the DILI team's recommendations to evaluate liver enzymes at baseline and as indicated thereafter in Section 5 of the FPI. Clinical trial findings of liver enzymes ≥ 3 times the ULN will be described in Section 6.
- HBV reactivation will be included in Section 5 to inform healthcare providers (1) that subjects with positive screening tests for hepatitis B or C, active acute or chronic hepatitis B, or untreated hepatitis were excluded from clinical trials; (2) to consider viral hepatitis

screening and monitoring for reactivation in accordance with clinical guidelines before starting therapy and during therapy with deucravacitinib; and (3) consult a liver specialist if signs of reactivation exist.

Deucravacitinib is an inhibitor of TYK2, which belongs to the JAK family. JAK inhibitors approved for the treatment of chronic inflammatory conditions have been associated with mild-to-moderate transient serum aminotransferase elevations and hepatitis B reactivation. The labeling for tofacitinib, upadacitinib, and baricitinib include liver enzyme elevations in sections Warnings and Precautions and Adverse Reactions. Based on the submitted data, as outlined above, liver enzyme elevations will similarly be labeled in Sections 5 and 6 as follows:

Section 5 (Warnings and Precautions):

Liver Enzyme Elevations - Treatment with SOTYKTU was associated with an increase in the incidence of liver enzyme elevation compared to treatment with placebo. Liver serum transaminase elevations ≥ 3 times the ULN were reported in subjects treated with SOTYKTU. Evaluate liver enzymes at baseline and thereafter in patients with known or suspected liver disease according to routine patient management. If treatment-related increases in liver enzymes occur and drug-induced liver injury is suspected, interrupt SOTYKTU until a diagnosis of liver injury is excluded [see *Adverse Reactions (6.1)*].

Section 6 (Adverse Reactions):

Liver Enzyme Elevations

Events of increases in liver enzymes ≥ 3 times the ULN were observed in subjects treated with SOTYKTU [see Warnings and Precautions (5.5)]. In the 16-week placebo-controlled period:

- ALT elevations ≥ 3 times the ULN was reported in 9 subjects (3.6 per 100 patient-years) treated with SOTYKTU, and 2 subjects (1.6 per 100 patient-years) treated with placebo.
- AST elevations ≥ 3 times the ULN was reported in 13 subjects (5.2 per 100 patient-years) treated with SOTYKTU, and 2 subjects (1.6 per 100 patient-years) treated with placebo.

Other hepatic related issues generated from a dedicated hepatic impairment (HI) study (IM011062) were discussed among members of the review team. Refer to 6.2.2. General Dosing and Therapeutic Individualization for details. Proposed labeling includes a recommendation that deucravacitinib not be used in patients with severe hepatic impairment (Child-Pugh C). The Applicant's rationale for not recommending the use of deucravacitinib in severe hepatic impairment was based on the observed increase in *unbound* concentrations. Drs. Soo Hyeon Shin and Chinmay Shukla assessed that the increase in *total* concentrations in severe HI is not significant to warrant restriction; however, they determined that due to safety concerns with liver enzyme elevations, this drug should not be administered in subjects with severe HI.

Recommended labeling will therefore include the following language in Section 2.3:

SOTYKTU is not recommended in patients with severe hepatic impairment (Child-Pugh C) [see *Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)*].

Moreover, under Section 8.7 Hepatic Impairment, a cross-reference to Adverse Reactions (6.1) was added due to safety concerns with liver enzyme elevations.

8.2.5.8. Renal Events

Serum creatinine and glomerular filtration rate (GFR) were monitored throughout deucravacitinib's psoriasis program as labeling for apremilast recommends dose reduction when patients have a GFR < 30 mL/min. Therefore, the protocols for Trials IM011046 and IM011047 prespecified that randomized subjects have a baseline GFR $\geq$ 45 mL/min and that study treatment be discontinued if a subject's GFR decreased to < 45 mL/min (confirmed by repeat).

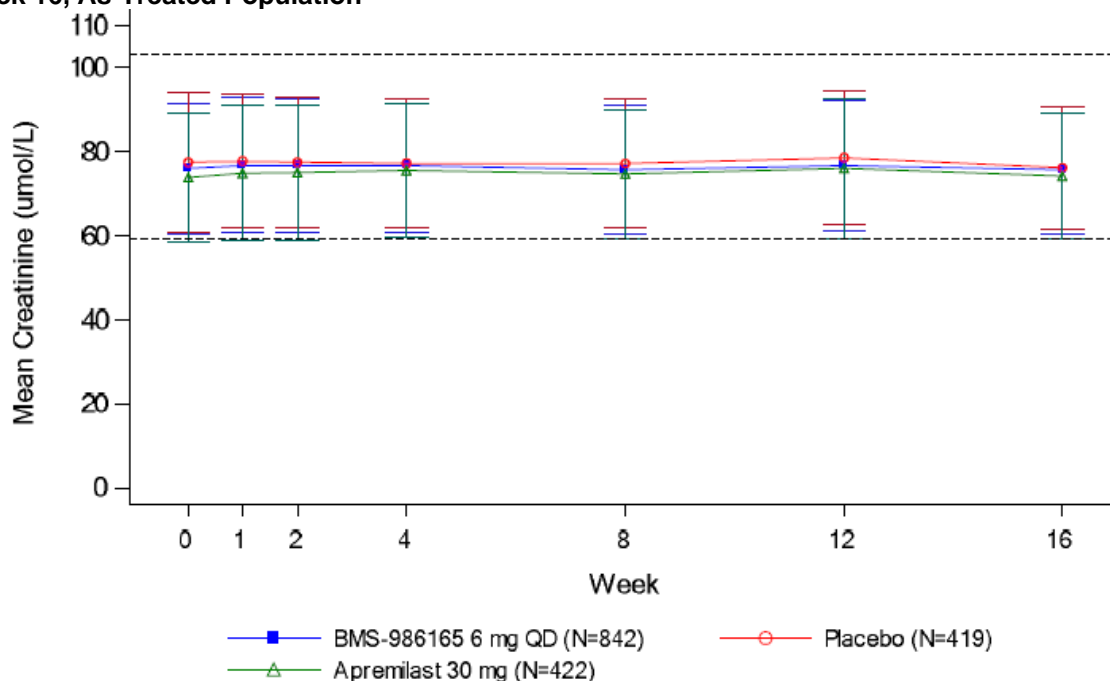
Clinical safety laboratory evaluations were performed in the Phase 3 trials at Baseline, Week 1, Week 2, Week 4, and then every 4 weeks through the end of study in Trials IM011046 and IM011047 and at every visit in IM011075.

Within this section creatinine and GFR, where applicable, will be described in terms of i) mean change from baseline, ii) AEs based on laboratory abnormalities, iii) worst toxicity CTCAE grades, and iv) shifts $\geq$ 2 CTCAE grade from baseline. Comparisons will be made between treatment groups for appropriate pools and periods.

Placebo- and Apremilast-controlled Period, Week 0-16

The mean serum creatinine during the first 16 weeks of treatment was comparable between treatment groups as shown in the figure below.

Figure 30. Mean Creatinine ($\mu\text{mol/L}$) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 16, As-Treated Population



Source: Applicant's Figure S.7.2.5

Error bars represent standard deviation for the mean.

The reference range for males was used because the majority of subjects in the study(ies) were male.

Adverse events of blood creatinine increased occurred in a higher proportion of placebo subjects (2/419, 0.5%) compared to deucravacitinib-treated (1/840, 0.1%) and apremilast-treated (0/422, 0%) subjects. The single event in the deucravacitinib-treated subject was mild, not serious, and didn't alter study treatment dosing. There were no Grade 3 ($>3.0 \times$ Baseline; $>3.0 - 6.0 \times$ ULN) or 4 ($>6.0 \times$ ULN) events of creatinine increased during the first 16 weeks of the study, as well as none reported throughout the entire Phase 3 program. Grade 2 events were reported at a higher rate in deucravacitinib-treated subjects (13/840, 1.5%) compared to placebo (3/419, 0.7%) and apremilast (4/422, 0.9%) subjects. Shifts ≥ 2 CTCAE grades were reported at similar rates in the deucravacitinib and apremilast groups (1.0%) which was higher than that for the placebo group (0.5%).

During this period, 4 (0.5%) deucravacitinib-treated subjects (described below) were discontinued from study treatment because of a reduced GFR while 1 (0.2%) placebo subject (IM011046-^{(b) (6)}) and no apremilast-treated subjects withdrew from the trial due to a reduced GFR. The subject in the placebo group was a 67-year-old White female with a PMH of hypertension and DM Type 2 who had a reduced estimated GFR (eGFR) of 44 mL/min at baseline--her GFR initially increased to 49 mL/min at Week 2, but decreased again to 43 mL/min, at which time study treatment was stopped. No further details were provided.

Subject IM011047-^{(b) (6)}: Discontinued Week 0-16 due to GFR Decrease

65-year-old White male with a PMH of chronic kidney disease (baseline eGFR of 45 mL/min, reference range ≥ 60 mL/min), DM Type 2, hypertension, coronary artery disease, atrial

fibrillation, and dyslipidemia, had a decreased GFR of 36 mL/min at Week 4. Study drug was discontinued 3 weeks later at which time the GFR returned to baseline (44 mL/min) but concomitant proteinuria of 1+ was observed which was worse compared to a trace amount at baseline. Despite discontinuation of study drug, proteinuria worsened further to 2+ at Week 11 during the Safety Follow-up visit. GFR remained unchanged (43 mL/min).

Subject IM011047- (b) (6): Discontinued Week 0-16 due to GFR Decrease

54-year-old White male with a history of DM Type 2, hypertension, and hypercholesterolemia had a screening GFR of 48 mL/min (reference range ≥ 60 mL/min). He developed unexplained diarrhea which persisted from Week 2 to Week 130 requiring chronic loperamide use. Throughout the trial, the subject's GFR ranged from 38 mL/min to 48 mL/min. Study treatment was discontinued at Week 20 (Day 147) due to a decreased GFR of 42 mL/min. Urine protein was 1+ at baseline and at the time of drug discontinuation; however, it increased to 3+ at the Week 25 Safety Follow-up Visit.

Subject IM011047- (b) (6): Discontinued Week 0-16 due to GFR Decrease

65-year-old white female with a PMH of hypertension had a baseline GFR of 50 mL/min (reference range ≥ 60 mL/min). At Week 8, her GFR decreased to 41 mL/min. Six weeks later, study treatment was discontinued. The event was considered ongoing (GFR 45 mL/min) at the time of study discontinuation at Week 18 (Day 130).

These subjects with preexisting low GFRs developed progressive proteinuria and/or further reduction of their GFR despite discontinuation of study drug. It is unclear if these findings are irreversible and whether deucravacitinib hastened these changes.

Subject IM011047- (b) (6): Discontinued Week 0-16 due to GFR Decrease

71-year-old White female with a PMH of hypertension, hypercholesterolemia, and vascular encephalomalacia had a normal GFR at screening and baseline (65 mL/min, reference range ≥ 60 mL/min). At Week 11, her eGFR was 44 mL/min and serum creatinine became elevated (1.21 mg/dL; baseline 0.86; reference range 0.51-0.95 mg/dL). No specific treatment was provided for these adverse events. At Week 16, study treatment was discontinued due to the decreased GFR, which was subsequently considered resolved (GFR 58 mL/min) at the time of study discontinuation (Week 21). The subject's serum creatinine correspondingly returned to normal range (0.95 mg/dL) by Week 21.

Improvement of both GFR and serum creatinine following discontinuation of study drug in this subject with a normal GFR at baseline suggests causality.

Apremilast-controlled Period, Week 0-24

Mean change in serum creatinine from baseline through Week 24 remained stable and comparable between treatment groups. For those who did not switch treatment from Week 16 to 24, 2 (0.2%) additional deucravacitinib-treated subjects and no apremilast-treated subjects reported an AE of *blood creatinine increased*. The events were mild, not considered serious, and did not result in dosing change. Grade 2 events occurred at a higher rate in the apremilast

(2/422, 0.5%) group compared to the deucravacitinib group (2/840, 0.2%). Shifts ≥ 2 CTCAE grades were reported at similar rates in deucravacitinib and apremilast subjects (1.2% and 1.4%, respectively). There were no reported events of decreased GFR for either group.

Apremilast-controlled Period, Week 0-52 – Trial IM011046

Mean change in serum creatinine continued to be stable between treatment groups. The mean increase of 0.008 mg/dL in the 52-week pooled safety analysis for deucravacitinib subjects was not significant. During this period, 2 additional deucravacitinib-treated subjects who did not switch treatment reported an AE of *blood creatinine increased*. The events were mild, non-serious, and did not require change in dosing. Similar to Week 0-24, Grade 2 events occurred at a higher rate in the apremilast group (5/114, 4%) compared to the deucravacitinib group (9/330, 2.7%). Shifts ≥ 2 CTCAE grades were reported at a higher rate in the apremilast group (5.4%) compared to the deucravacitinib group (3.0%).

During Week 24 to 52, no apremilast subjects were reported with a decreased GFR; however, 3 deucravacitinib subjects had reduced GFRs, one of whom (IM011046-^{(b) (6)}) had study drug withdrawn as described below

Subject IM011046-^{(b) (6)}: GFR Decreased, Discontinued Study Drug

80-year-old White female with a PMH of hypertension, DM Type 2, and chronic kidney disease stage 3 had a baseline GFR of 50 mL/min (reference range ≥ 60 mL/min). At Week 28 (Day 198), her GFR was recorded as 44 mL/min, and study drug was discontinued. The subject continued to undergo safety assessments. By Week 36, the event was considered resolved (GFR 48 mL/min).

During the LTE trial, 4 subjects, of which only one received deucravacitinib throughout a controlled trial (IM011046) without switching, reported an AE of *blood creatinine increased*. Grade 2 events were reported in 24 subjects, 10 of whom received deucravacitinib without switching during the controlled trials. Estimated GFR was not measured in Trial IM011075.

In the SUR, 1 new AE of blood creatinine increase (Grade 0 to Grade 1) was reported.

The effect of deucravacitinib on renal function appears inconsistent. The mean change in serum creatinine was stable and comparable across treatment groups throughout Week 52. While there was not a clear imbalance of serum creatinine events upon assessment of TEAEs, Grade 2 toxicity, and shifts ≥ 2 CTCAE grades, more deucravacitinib-treated subjects reported a reduction in GFR and discontinued treatment due to a reduced GFR of < 45 mL/min compared to the apremilast and placebo groups. Furthermore, in deucravacitinib-treated subjects with already reduced GFRs, worsening proteinuria was observed in 2 subjects even after discontinuation of study drug. These observations are recommended to be described in Section 6 of the Full Prescribing Information (FPI) to inform healthcare providers of the potential risks:

Adverse Reactions
Decreased Glomerular Filtration Rate (GFR)

In the 16-week placebo-controlled period in subjects who had moderate renal impairment (eGFR 30-59 mL/min) at baseline, decreased GFR was reported in 4 subjects (1.6 per 100 patient-years) treated with SOTYKTU, and 1 subject (0.8 per 100 patient-years) treated with placebo. Two of the deucravacitinib-treated subjects had worsening of baseline proteinuria.

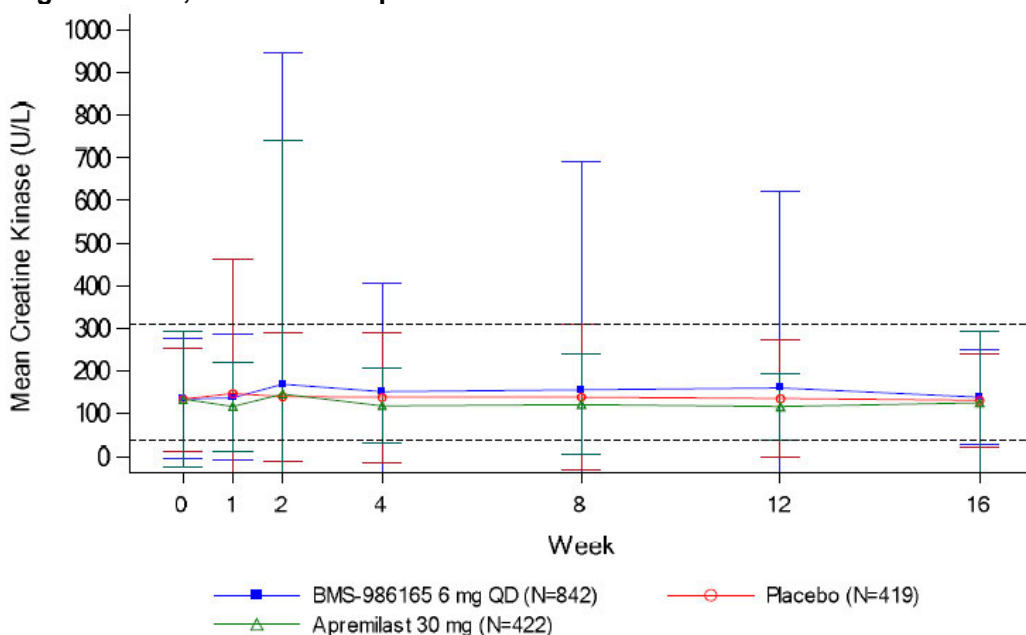
8.2.5.9. Muscular Events,-Increased Creatine Phosphokinase/Myalgia/Rhabdomyolysis

Increased creatine phosphokinase (CPK) has been observed with use of JAK inhibitors. During the Phase 2 dose-finding trial (IM011011) in subjects with moderate to severe psoriasis, several dose-dependent events of increased CPK were reported; therefore, CPK was monitored throughout deucravacitinib's Phase 3 trials.

Placebo- and Apremilast-controlled Period, Week 0-16

The mean CPK levels during the first 16 weeks of treatment were comparable between treatment groups; however, worth noting is that the standard error for the mean was wider for the deucravacitinib group as demonstrated in the figure below.

Figure 31. Mean Creatine Kinase (U/L) by Treatment Group, Controlled Safety Pool, Week 0 Through Week 16, As-Treated Population



Source: Applicant's Figure S.7.2.8.

Error bars represent standard error for the mean.

The reference range for males was used because the majority of subjects in the study(ies) were male.

The incidence of AEs of "CPK increased" was highest in the deucravacitinib group (23/840, 2.7%) compared with 5/419 (1.2%) in the placebo group and 3/422 (0.7%) in the apremilast group. Although none of the AEs in deucravacitinib-treated subjects were reported as serious, there were several Grade 3 (>5 x ULN - 10 x ULN) and Grade 4 (>10 x ULN) events reported, not all of which were considered AEs by investigators. Additionally, during this period, 3/840 (0.4%)

subjects in the deucravacitinib group required dose interruption and 1/422 (0.2%) subject in the apremilast group had study drug withdrawn due to an AE of increased CPK.

The rate of Grade 3 events was generally comparable between treatment groups (5, 0.6%; 3, 0.7%, and 2, 0.5% for deucravacitinib, placebo, and apremilast groups respectively) during this period, but the rate of Grade 4 events was highest for deucravacitinib-treated subjects (6, 0.7%) compared to placebo (1, 0.2%) and apremilast (1, 0.2%). Of the 5 deucravacitinib-treated subjects with Grade 3 CPK elevation, only one (IM011047-^{(b) (6)}) was reported as an AE. Of the 6 deucravacitinib-treated subjects with Grade 4 CPK increases, one subject had associated myalgias, another discontinued study treatment, and one subject had a concurrent AE of rhabdomyolysis. Further details are provided below.

Subject IM011046-^{(b) (6)}: Grade 4 CPK Increase With Myalgias

35-year-old Asian male with no reported PMH developed Grade 4 CPK increase (14,707 U/L, reference range 39-308 U/L) following treatment with deucravacitinib for 8 weeks. The subject reported exercising within the previous 7 days and had associated muscle aches/myalgias. He remained on study treatment and did not receive treatment for this event. Five weeks later, his CPK level returned to normal range. At Week 55, the subject was reported as "lost to follow-up".

Subject IM011046-^{(b) (6)}: Grade 4 CPK Increase, Discontinued Study Treatment

37-year-old White male with no reported PMH, developed Grade 4 elevation of his CPK level (12,270 U/L, reference range 39-308 U/L) following 12 weeks of treatment with deucravacitinib. This event was not considered an AE by the investigator. There were no reports of associated pain, muscle aches, myalgia, weakness, muscle cramps, or muscle swelling. The subject reportedly exercised 3-4 times per week and exercised within 7 days prior to the elevated creatine kinase event. No other details were provided. At Week 17, his CPK level returned to normal range despite continued treatment with study drug. At Week 41, the subject withdrew from the study as he reportedly no longer wanted to participate or take study drug. His last dose was received during Week 24.

Subject IM011046-^{(b) (6)}: Grade 4 CPK Increase, Rhabdomyolysis

31-year-old female was reported with a CPK level of 21,020 U/L (reference range: 26-192 U/L) and rhabdomyolysis associated with muscle aches/myalgia after 2 weeks of deucravacitinib exposure in the setting of increased exercise training. Concurrent elevations of ALT (59 U/L, reference: 0-33 U/L), AST 207 U/L, (reference 0-31 U/L) and LDH 801 U/L (Reference < 250 U/L) were reported. Treatment was not provided for these AEs. Study drug was interrupted for one week and resumed without recurrence of events.

Subject IM011046-^{(b) (6)}: Grade 4 CPK Increase

27-year-old White male had multiple CPK elevations, none of which were considered AEs by the investigator. The subject had *asymptomatic* elevated CPK levels (6468 U/L at Week 5, 1180 U/L at Week 12, 6982 U/L at Week 27 that fluctuated with levels within normal range, 39-308 U/L). He reportedly exercised routinely although did not exercise the 7 days prior to the event during

Week 52 at which time his CPK level peaked at 7514 U/L and he transitioned into the LTE trial. The subject was later reported to have discontinued from the LTE trial for unspecified reasons.

Subject IM011047-^{(b) (6)}: Grade 4 CPK Increase

43-year-old White male with a history of hypertension and remote herpes zoster infection who developed *asymptomatic* Grade 4 CPK increase (5553 U/L; reference range 39-308 U/L) 2 weeks after starting treatment with deucravacitinib. He was reported to be consuming a product that contained caffeine, aspirin, and ephedrine and having exercised within 7 days of the event. Two weeks later his CPK level returned to normal range without treatment intervention or change in study drug.

Subject IM011047-^{(b) (6)}: Grade 4 CPK Increase

47-year-old Asian female with a PMH of migraines and seasonal allergies was reported to have *asymptomatic* Grade 4 CPK increase (1942 U/L; reference range 26-192 U/L) following treatment with deucravacitinib for 7 weeks. She had resolution of a common cold one day prior to the event and reported having exercised within 7 days. By Week 10, the CPK level returned to normal range.

In the setting of exercise and lack of recurrent CPK elevations despite continued deucravacitinib exposure in 5 of these 6 subjects, it is unclear that the events occurred due to study treatment, although a synergistic effect with exercise cannot be excluded.

Apremilast-controlled Period, Week 0-24

Of subjects who were treated with either apremilast or deucravacitinib without switching through 24 weeks, 1 (0.2%) additional subject in the apremilast group had elevated CPK levels that were reported as mild, non-serious AEs. No additional deucravacitinib subjects had an AE of increased CPK levels reported.

From Week 16 to 24, 1 deucravacitinib subject (IM011046-^{(b) (6)}) and 3 apremilast subjects had Grade 3 CPK elevation. There were no additional subjects who reported Grade 4 elevations of CPK during Week 0-24.

Apremilast-controlled Period, Week 0-52 – Trial IM011046

Analyses of subjects who were treated in Trial IM011046 without switching showed a higher rate of increased CPK AEs for deucravacitinib-treated subjects (12/330, 3.6%) compared to apremilast-treated subjects (3/114, 2.6%).

While Grade 3 CPK elevations were reported in a smaller proportion of subjects who were treated with deucravacitinib without switching (5/330, 1.5%) compared to apremilast-treated subjects (4/114, 3.5%), Grade 4 elevated CPK levels occurred more frequently in the deucravacitinib group (5, 1.5%) compared to none in the apremilast group. Of the 5 deucravacitinib subjects with Grade 4 events, 4 were previously described under Week 0-16 (IM011046-^{(b) (6)}, IM011046-^{(b) (6)}, IM011046-^{(b) (6)}, and IM011046-^{(b) (6)}). The fifth subject, IM011046-^{(b) (6)}, is described below.

Subject IM011046- (b) (6): Grade 4 CPK Increase Associated With Muscle Pain and Weakness led to Discontinuation of Study Drug

52-year-old White female with a history of obesity, had CPK levels at screening (264 U/L; reference range 26-192 U/L) and at Baseline (205 U/L) that were above normal range (reference range 26-192 U/L). She developed Grade 4 CPK increase of 2697 U/L after receiving treatment with deucravacitinib for 48 weeks. Prior to this event, she had transient, asymptomatic Grade 3 CPK increase (1735 U/L). She experienced associated myalgias with the Grade 4 event and had not experienced physical trauma or exercised within 7 days of this elevated CPK event. No treatment was given for this event, and no changes were made to study drug. Her CPK level decreased a week later to 338 U/L. This subject transitioned to the LTE trial and was reported to discontinue Study IM011075 due to recurrent CPK elevations associated with pain, muscle aches/myalgia, and weakness.

This subject had baseline elevated CPK levels. Although there were no apparent confounders, it cannot be determined that the fluctuating values in the setting of continuous treatment with deucravacitinib was a result of use of study drug.

To capture events of increased CPK outside of the periods and pools discussed above, events that occurred through 52-weeks of exposure were evaluated including subjects who switched treatment groups. A total of 45/1362 (3.3%, 4.7/100 PY) deucravacitinib-treated subjects in the Controlled Safety Pool had elevated CPK AEs. None of the events were considered serious; however, one was severe (IM011047- (b) (6)) and another was associated with rhabdomyolysis (IM011047- (b) (6)). Two led to study discontinuation (IM011047- (b) (6) and IM011047- (b) (6)), the former of which was previously discussed under Week 0-16. Brief narratives of select subjects are provided below. There was a total of 19/1349 (1.4%) subjects with Grade 3 CPK elevation and 13/1349 (1.0%) with Grade 4 CPK elevation in subjects receiving deucravacitinib through Week 0 to 52.

Subject IM011047- (b) (6) With Rhabdomyolysis

Subject is described within Section [8.2.5.3.3](#). His elevated CPK and muscle injury during the Week 24-52 period occurred in the context of thrombosis of a right popliteal artery aneurysm.

Subject IM011047- (b) (6): Grade 3 CPK Increase, Discontinued due to CPK AE

35-year-old white male with a PMH of hypertension had elevated CPK levels at screening and at baseline [1796 U/L (Grade 3) and 932 U/L (Grade 2), respectively, reference range 39-308 U/L], as well as fluctuating Grade 1-3 levels throughout the study. His elevated CPK values were in the setting of daily exercise and were not associated with muscular pain, swelling, or weakness. After 40 weeks of exposure to deucravacitinib, he withdrew from study treatment at which time his CPK levels had peaked at 2557 U/L. Eight weeks following his last dose, his CPK level decreased to 573.

Given the subject's history of elevated CPK levels prior to study participation and undulating levels throughout the study, attribution to study drug is difficult to determine although a synergistic effect with exercise cannot be excluded.

Subject IM011047- (b) (6): Grade 3 CPK Increased, Discontinued Study Treatment/Lost to Follow-up

59-year-old White male with a history of hypertension had a baseline Grade 2 elevated CPK level of 1503 U/L (reference range: 39-308 U/L). His values throughout study participation ranged from 341 U/L (Grade 1) to 1072 U/L (Grade 2) until Week 40 when Grade 3 elevation was reported (1863 U/L) in conjunction with an elevated CKMB value of 23.9 ug/L (reference range: 0-5 ug/L). The subject had no accompanying symptoms, no changes in his liver enzymes or serum creatinine, and no reports of hemolyzed blood sample, physical trauma, surgery, or intramuscular injections. His CPK level decreased to 1436 U/L at the time of the subject's last study visit at Week 52. He was lost to follow-up and did not return to complete the Safety Follow-up visit.

Similar to the previous subject who had baseline elevated CPK levels and discontinued study treatment, it cannot be determined that the increased CPK was due to study drug.

Subject IM011047- (b) (6): Grade 4 CPK Increase, Discontinued due to Lack of Efficacy

49-year-old White male with a history of being overweight and having hypertension, diabetes, and hyperuricemia, developed Grade 4 CPK increase (3357 U/L; reference range 26-192 U/L) after receiving treatment with deucravacitinib for 31 weeks. He did not experience associated pain, muscle aches, myalgia, weakness, muscle cramps, or muscle swelling, and he reported not exercising within 7 days of the elevated CPK event. No treatment was given for this event and no changes were made to study drug. His CPK level returned to normal range by Week 35. This subject transitioned to the LTE trial and was reported to discontinue Study IM011075 due to lack of efficacy.

In the LTE study, 29 subjects were reported with AEs of increased CPK levels. One subject had an event that was considered severe and one subject discontinued study treatment due to myalgias as described below.

Subject IM011046- (b) (6): CPK Increase, Severe

37-year-old White male with no significant PMH was reported with severe elevation of CPK levels (8211 U/L) up from a Baseline level of 274 U/L (reference range 39-308 U/L) after 23 weeks of exposure to deucravacitinib (he received apremilast throughout Study IM011046). The CPK elevation occurred the day after prolonged physical exercise as the subject participated in a 100 mile obstacle course over 11 hours. Within one week, his CPK level returned to normal range (248 U/L) without treatment intervention.

Subject IM011046- (b) (6): CPK Increase, Discontinued due to Muscle Pain and Weakness

52-year-old White female received deucravacitinib throughout Trial IM011046 was previously described under the Apremilast-controlled Period, Week 0-52 – Trial IM011046 section; she transitioned into the LTE study. After a total of 56 weeks of exposure, a CPK level of 866 U/L (reference range: 26-192 U/L) associated with muscle pain and weakness was reported. After 5 more weeks of treatment and no reported relevant provoking factors, the CPK level increased further to 2287 U/L (Grade 4) and study drug was discontinued. The CPK level declined to a

nadir of 208 U/L. The 120 day SUR did not reflect any further clinical information for this subject.

In the SUR, there was 1 new Grade 3 and 1 new Grade 4 event of increased CPK, neither were serious or led to treatment discontinuation.

Treatment with deucravacitinib was associated with an increased incidence of CPK elevation compared to placebo and apremilast. There was also a higher proportion of Grade 4 CPK elevations (>10 x ULN) with deucravacitinib treatment. Due to this imbalance and reports of associated rhabdomyolysis and myopathy (including pain and muscle weakness) occurring with higher grade events, labeling of rhabdomyolysis, myalgias, and CPK elevation in Sections 5 and 6 of the Full Prescribing Information (FPI) as described below is recommended to inform healthcare providers of these significant safety concerns. A Medication Guide will also adequately communicate the risk of rhabdomyolysis to patients.

Warnings and Precautions

Cases of rhabdomyolysis were reported in subjects treated with SOTYKTU resulting in interruption or discontinuation of SOTYKTU dosing.

Treatment with SOTYKTU was associated with an increased incidence of asymptomatic CPK elevation and rhabdomyolysis compared to treatment with placebo. (b) (4)

(b) (4)
(b) (4)
(b) (4) Discontinue SOTYKTU if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever [see *Adverse Reactions* (6.1)].

Adverse Reactions

Creatine Phosphokinase (CPK)

In the 16-week placebo- and active- controlled period, increased CPK (including Grade 4) was reported in 23 subjects (9.3 per 100 patient-years) treated with [SOTYKTU], and 5 subjects (4.1 per 100 patient-years) treated with placebo.

Increased CPK is also described in labeling for JAK inhibitors (tofacitinib, baricitinib, upadacitinib, and abrocitinib) approved for chronic inflammatory conditions within the Adverse Reactions section. The role of JAK and TYK2 inhibition in these events is not known.

8.2.5.10. Neuropsychiatric Events

Given the epidemiologic association between psoriasis and depression and suicidal ideation and behavior, and the warning regarding psychiatric adverse reactions associated with apremilast (section 5 of the labeling), the Division of Psychiatry (DP) was consulted to assess the psychiatric AEs, including suicide-related AEs, for this NDA application. Refer to the DP clinical consult review by Dr. Roberta Rasetti, dated May 09, 2022. The DP consult review concluded the following:

- (1) The psychiatric safety monitoring for the developmental program of deucravacitinib, while not optimal, appeared adequate overall for assessing SIB.
- (2) Based on the available clinical trial data, there is insufficient evidence of increased risk of suicidal ideation and behavior or other psychiatric adverse reactions with deucravacitinib compared to placebo to recommend specific psychiatric warning language. In addition, the incidence of SIB and depressive symptoms was low and similar across treatment groups and does not appear to meet the typical standard for inclusion in the adverse reactions section of the prescribing information.
- (3) Although the enrollment criteria appeared to be unnecessarily restrictive with respect to neuropsychiatric illness, very few potential subjects were reportedly excluded from study participation based on these criteria, which somewhat allays concerns that the results could have been made significantly more generalizable to the target population by optimizing enrollment criteria. An additional dedicated safety study that optimizes the study population and safety monitoring for evaluating SIB safety does not appear to be warranted.

Based on the DP review of the data, there is insufficient evidence of increased risk of suicidal ideation and behavior or other psychiatric adverse reactions with deucravacitinib compared to placebo to recommend specific psychiatric warning language. The review team agrees with DP's conclusions.

8.2.5.11. Retinal Detachment

In the two Phase 3 controlled trials there were 2 reported cases of retinal detachment related to the study drug treatment. Additional information regarding these cases and any others that may have been identified in other deucravacitinib development programs were requested of the Applicant. There were no additional cases of retinal detachment reported across other deucravacitinib development programs.

Noteworthy is that retinal detachment is labeled for some JAK inhibitors (RINVOQ, NDA 211675 and CIBINQO, NDA 213871) based on adverse events reported in atopic dermatitis trials. The literature suggests that psoriasis is associated with retinal disease (Dai et al. 2021).

The Division (DDD) requested the Division of Ophthalmology review the cases of retinal detachment reported in the development program for Ps and comment on the possible relationship between deucravacitinib and this adverse event. The summary of the consult review by Dr. Wiley Chambers is provided below:

The two cases reported as retinal detachments are distinctly different types of events from each other. One case should more appropriately be labeled a central serous retinal pigment epithelial (RPE) detachment. While some RPE detachments are drug related, the reported features of this event are not consistent with drug related cases. Drug related cases are multifocal and bilateral. This case is unifocal and unilateral.

Rhegmatogenous retinal detachments are commonly associated with high myopia in older individuals. While the refractive error of the individual who had the rhegmatogenous retinal detachment is not known, the likelihood of this case being drug related is very low.

Review of all other ocularly reported adverse events did not suggest a pattern of reported ocular adverse events.

Based on Dr. Wiley's assessment, retinal detachment will not be included in labeling. Retinal detachment will be evaluated postmarketing with routine pharmacovigilance activities.

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

There were no patient-reported outcome assessments that measured safety parameters.

8.2.7. Safety Analyses by Demographic Subgroups

Analyses to evaluate the safety profile of deucravacitinib in different subgroups were conducted for subjects who received deucravacitinib without switching during the controlled trials, IM011046 and IM011047. Four intrinsic factors were analyzed including age (< 40 years, 40-65 years, ≥ 65 years), sex (male, female), race (white, Asian, black or African American, or Other), and body weight (< 90 kg and > 90 kg).

In the safety population, subjects had a mean age of 47 years and were predominantly male (67%) and white (87%). In the Controlled Safety Pool, approximately 32% of the subjects were in the age group < 40 years, approximately 58% were in the age group 40 - < 65 years, and 10% of the subjects were in the age group ≥ 65 years. The proportion of subjects with body weight < 90 kg and > 90 kg were similar across treatment groups (52% and 48%, respectively).

Subjects who were included in deucravacitinib safety data appear generally representative of the population of patients with moderate to severe Ps expected to receive deucravacitinib in the United States.

Age

For subjects who received deucravacitinib without switching during the controlled trials, IM011046 and IM011047, the incidence of AEs was similar across age groups (63.0% for <40 years; 66.0% for 40-65 years, and 71.3% for >65%). In all age groups, the most common SOC was Infections and Infestations and the most common AEs were generally similar across age groups.

SAEs occurred at a higher rate in subjects >65 years (7, 8.8%) compared to the other two cohorts (6, 2.2% for <40 years and 20, 4.1% for 40-<65years); however due to the small number of subjects >65 year, meaningful conclusions regarding the differences in SAEs between the oldest and younger groups is difficult to make. The proportion of subjects who discontinued

treatment due to AEs was similarly highest for those >65 years (7, 8.8%) relative to the other groups (7, 2.6% for <40 years and 20, 4.1% for 40-<65years), but again, it is challenging to draw meaningful conclusions due to the large difference in the number of subjects in the younger groups compared to the group representing >65 years of age. Nonetheless, the Applicant's proposed labeling for Geriatric use will be modified to exclude the following sentence: (b) (4)

(b) (4). Further, the language below is recommended.

"For those subjects (68 subjects $\geq$ 65 years old and 12 subjects $\geq$ 75 years old) who received [SOTYKTU] without switching treatment arms, there was a higher rate of overall serious adverse events, including serious infections, and discontinuations due to adverse events."

Sex

The overall incidence of TEAEs, SAES, and AEs leading to discontinuation were comparable between females (65.9%, 3.6%, and 3.6%) and males (64.0%, 4.1%, and 3.9%) who received deucravacitinib without switching during the controlled trials. In both groups, Infections and Infestations was the most common SOC. While the proportion of males (79.7%) who reported infections was greater than the proportion of females (51.1%), the most types of infections were generally similar. Increased creatine phosphokinase occurred more frequently in males (4.6%) compared to females (2.5%); however, none of the cases were reported as serious and the majority of cases did not result in withdrawal of study drug.

Race

The majority of subjects who received deucravacitinib without switching during trials IM011046 and IM011047 were White (740, 88%). The Asian subgroup comprised the next largest number of subjects (83) followed by the Black or African American (10) and Other groups (9). The incidence of TEAEs, SAES, and AEs leading to discontinuation was highest in the Asian subgroup (78.3%, 9.6%, and 4.8%) compared to the white group (63.4%, 3.2%, and 3.8%), Black or African American group (40%, 10%, 0%), and Other group (44%, 0%, 0%). Even with these differences, race-dependent safety signals were not evident during the safety analysis of deucravacitinib but most importantly, due to the comparatively small number of non-white subjects, no meaningful conclusion could be drawn with regard to AEs and race.

Weight

The incidence of TEAEs, SAES, and AEs leading to discontinuation were comparable between subjects who weighed <90kg (56.5%, 2.9%, and 3.2%) and those with a weight >90kg (65.6%, 4.0%, and 4.0%). The Applicant's population PK analysis indicated that subjects with body weight > 90 kg had a lower deucravacitinib $C_{max,SS}$ (24.8%) and $C_{avg,SS}$ (19.3%); however, this difference in exposure did not appear to correlate with the overall rate of AEs in subjects who received deucravacitinib without switching during trials IM011046 and IM011047 .

Overall, there are no substantial differences in the risk of ARs in demographic subgroups to warrant restricted use. However, because the trials were not powered for these analyses, the data must be interpreted with caution.

8.2.8. Specific Safety Studies/Clinical Trials

Ongoing, blinded trials in deucravacitinib's development programs are not included in the pooled safety analyses; however, the 120-day Safety Update included additional safety data through the cut-off date of October 1, 2021 which contained updated safety narratives for deaths, suspected unexpected adverse reactions (SUSARs), and pregnancies in ongoing, blinded studies: IM011065 (psoriasis; regional study conducted in China, Taiwan, and South Korea), IM011021 (systemic lupus erythematosus), IM011023 (Crohn's disease), IM011024 (ulcerative colitis), IM011073 (lupus nephritis), and IM011074 (systemic lupus erythematosus).

Also, Trial IM011066, a single-arm, open-label study in patients with psoriasis conducted in Japan, and Trial IM011084, a randomized, double-blind, placebo-controlled study in subjects with psoriatic arthritis, were completed after the submission of NDA 214958 (September 10, 2021).

With additional safety data as of this SUR data cutoff, no new safety signals have been identified compared with the initial submission. Relevant information from the SUR are discussed within the review sections that pertain to the safety issue. The additional data provided in the SUR supports the conclusions from the integrated safety.

8.2.9. Additional Safety Explorations

8.2.9.1. Human Carcinogenicity or Tumor Development

There is a theoretical risk of increased malignancy for any product that causes immunosuppression and is chronically administered. In patients with psoriasis, this risk may be potentiated by prior exposure to other immunosuppressive agents or other therapies that may enhance tumor development such as phototherapy.

Deucravacitinib was not carcinogenic in the 6-month oral carcinogenicity study in CByB6F1/Tg rasH2 hemizygous mice or the 2-year oral carcinogenicity study in rats.

The limited duration of treatment during the psoriasis development program is unlikely to allow for the detection of rare events with a long latency period such as malignancy. Therefore, postmarketing data are needed to evaluate the long-term risk of malignancy in patients with psoriasis receiving deucravacitinib.

8.2.9.2. Human Reproduction and Pregnancy

In animal reproduction studies, no effects on embryo-fetal development were observed with oral administration of deucravacitinib to rats and rabbits during organogenesis at doses that were at least 91 times the maximum recommended human dose (MRHD) of 6 mg once daily. The protocols for clinical trials excluded pregnant females and required use of contraception by females of reproductive potential, as well as males with partners who are of reproductive potential while in the study. All female subjects promptly discontinued the study medication at the time of discovery of a positive pregnancy test.

The Applicant identified 24 pregnancies (13 maternal exposures and 11 paternal exposures) across clinical trials for all indications. Exposures occurred before conception and/or in the first trimester.

Jean Limpert, MD, Division of Pediatric and Maternal Health, reviewed the pregnancy data and provided recommendations for labeling. Dr. Limpert identified the outcomes below. While the Applicant provided pregnancy outcome information for cases with reported paternal exposure, deucravacitinib is not considered genotoxic and paternal exposure would not be expected to impact pregnancy outcomes.

Pregnancy Outcomes for Maternal Exposure (n=13):

- 3 live births (all reported as full-term infants; two cases reported first trimester exposure; one case reported pregnancy 14-16 days after last dose of deucravacitinib)
- 4 elective terminations (first trimester exposure in all cases; unwanted pregnancy in one case; reasons not provided for other cases)
- 2 spontaneous abortions (first trimester exposure in one case; unclear timing in second case)
- 1 ectopic pregnancy (first trimester exposure)
- 2 ongoing cases (one case still blinded to study drug)
- 1 unknown outcome (exposure before conception; pregnancy reported "within a few weeks after completing the study")

No congenital malformations were reported. No perinatal complications were reported. Review of the literature by the Applicant and DPMH did not identify relevant publications regarding pregnancy and females and males of reproductive potential.

Regarding pregnancy, Dr. Limpert proposed labeling and made the following conclusions and recommendations for post-marketing assessments:

8.1 Pregnancy

(b) (4)

Risk Summary

Available data from case reports on SOTYKTU use during pregnancy are insufficient to evaluate for a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, no effects on embryo-fetal

development were observed with oral administration of deucravacitinib to rats and rabbits during organogenesis at dose exposures that were at least 91 times the exposure at the maximum recommended human dose (MRHD) of 6 mg once daily (see *Data*).

The (b) (4) background risk of major birth defects and miscarriage for the indicated population(s) is unknown. (b) (4)

(b) (4) In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Deucravacitinib was administered orally during the period of organogenesis at doses of 5, 15, or 75 mg/kg/day in rats and 1, 3, or 10 mg/kg/day in rabbits. Deucravacitinib was not associated with embryofetal lethality or fetal malformations in either species. These doses resulted in maternal exposures (AUC) that were 266 times (rat) or 91 times (rabbit) the exposure at the MRHD.

In a pre- and post-natal development study in rats, deucravacitinib was administered orally from gestation day 6 through lactation day 20, at doses of 5, 15, or 50 mg/kg/day. At 50 mg/kg/day, F1 offspring had reduced body weight gains during the pre-weaning period. After weaning, body weights of affected F1 offspring gradually normalized to control levels. No maternal effects were observed at 50 mg/kg/day (110 times the MRHD based on AUC comparison). No deucravacitinib-related effects on postnatal developmental, neurobehavioral, or reproductive performance of offspring were noted at doses up to 15 mg/kg/day (19 times the MRHD based on AUC comparison).

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise patients to report their pregnancy to Bristol Meyers Squibb Company at XXX-XXXXXXX [see *Use in Specific Populations* (8.1)].

The Applicant proposes to perform a medical record claims database study to evaluate the safety of deucravacitinib exposure during pregnancy. DPMH agrees with a claims database study as a complementary study but also recommends a pregnancy exposure registry to evaluate the safety of deucravacitinib during pregnancy. DPMH recommends both safety studies are issued as postmarketing (PMR) requirements.

The following PMR language is suggested:

- A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to SOTYKTU during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective

terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

- An additional pregnancy study that uses a different design from the pregnancy registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to SOTYKTU during pregnancy compared to an unexposed control population.

Regarding Females and Males of Reproductive Potential, Dr. Limpert concluded and made the following recommendation:

- “There are no clinical data regarding fertility in females and males of reproductive potential. Deucravacitinib was not mutagenic in nonclinical studies. No adverse effects on fertility were observed in animal reproductive studies. DPMH recommends omitting subsection 8.3 in labeling.”

8.2.9.3. Pediatrics and Assessment of Effects on Growth

The Applicant has not conducted an evaluation of the safety and efficacy of deucravacitinib in the pediatric population. Because the proposed product is a new active ingredient, approval of deucravacitinib for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy triggers the Pediatric Research Equity Act (PREA)(21 U.S.C. 355c). Per the Food and Drug Administration Safety and Innovation Act (FDASIA), the Applicant submitted an amended Agreed Initial Pediatric Study Plan (iPSP) on October 30, 2018. The Agency agreed with the iPSP (Agreement Letter dated December 3, 2018).

In this submission, the Applicant requested a partial waiver for studies in the pediatric population from birth to less than 4 years of age as “Necessary studies are impossible or highly impracticable due to the extremely low prevalence of moderate to severe psoriasis in this population.” (Section 505B (a)(4)(B)(i) of the Act). Although the epidemiologic data are limited regarding the pediatric population with moderate to severe plaque psoriasis, in general the prevalence of plaque psoriasis increases with age. In addition, the Applicant requested a deferral of studies in the pediatric population from age 4 years to <18 years “until safety and efficacy in the adult indication has been demonstrated in Phase 3 studies” (Section 505B (a)(3)(A)(ii) of the Act).

The Division presented the pediatric study plan to the Pediatric Review Committee (PeRC) on July 19, 2022, who agreed with the partial waiver for studies in the pediatric population from birth to less than 4 years of age and deferral of studies in the pediatric population from age 4 years to <18 years.

Pediatric PMR # 4336-5: Conduct a randomized, controlled trial to evaluate the safety, efficacy, and pharmacokinetics of deucravacitinib in the adolescent population (12 years to less than 18 years) with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy. Evaluate at least 300 subjects exposed to deucravacitinib at the highest proposed dosage for a minimum of 52 weeks.

Final Protocol Submission: May 2023
Study Completion: (b) (4)
Final Report Submission: (b) (4)

Pediatric PMR # 4336-6: Conduct a clinical trial to evaluate the safety, efficacy, and pharmacokinetics of deucravacitinib in pediatric subjects 4 years to less than 12 years of age with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy. Evaluate at least 150 subjects exposed to deucravacitinib at the highest proposed dosage for a minimum of 52 weeks.

The trial should not be initiated until results from PMR 4336-5 for pediatric subjects 12 to less than 18 years of age are reviewed by the Agency. Based on the review, the Agency will determine the type of data and the trial design that would be required to evaluate the pediatric population age 4 years to less than 12 years.

Final Protocol Submission: (b) (4)
Study Completion: (b) (4)
Final Report Submission: (b) (4)



8.2.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

In trials IM011046, IM011047, or IM011075, overdose was defined in the protocol as taking more than 2 days' worth of study treatment within a 24-hour time period. No cases of deucravacitinib overdose has been reported.

Based on the lack of cases and results from an open-label, single-dose study (IM011061) for the evaluation of PK and safety of deucravacitinib (12 mg) in subjects with varying degrees of renal

impairment, and in subjects with end-stage renal disease on hemodialysis the following language is recommended for section 10 OVERDOSAGE of the labeling:

- There is no experience regarding human overdosage with [SOTYKTU]. In case of overdose, (b) (4) (b) (4) (4)
- The extent of deucravacitinib elimination by hemodialysis was small (5.4% of dose per dialysis treatment), and thus hemodialysis for treatment of overdose with [SOTYKTU] is limited.

Drug Abuse Potential

Deucravacitinib does not cross the blood brain barrier and is not expected to lead to drug abuse. There is no available data on the potential for drug abuse; the Applicant did not conduct dedicated trials in animals or humans to evaluate drug dependence or abuse.

Withdrawal and Rebound

The safety of deucravacitinib in subjects who had treatment withdrawn and restarted was assessed in Trial IM011047. From the available data in this trial, no clinically meaningful changes in or pattern of AEs were observed with subsequent retreatment. There were also no cases of rebound which was pre-defined as worsening of psoriasis over baseline (measured as a PASI score > 125% over baseline PASI score) or new pustular, erythrodermic or more inflammatory psoriasis occurring within 2 months of stopping therapy in subjects re-randomized to placebo.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

To date deucravacitinib has not been approved in any country and no postmarketing information is available.

Expectations on Safety in the Postmarket Setting

Quantitative assessment of the relative risk of deucravacitinib was limited to assessment of safety data from the controlled periods of the 2 Phase 3 randomized clinical trials (IM011046 and IM011047). To fully characterize deucravacitinib's safety profile and address uncertainties regarding the long-term safety of deucravacitinib, a long-term trial with an active comparator will be required. This trial will serve to assess the safety for major AEs of interest that may manifest after prolonged exposure to deucravacitinib, such as cardiovascular adverse events (MACE and thrombosis), opportunistic infections, and overall malignancies.

Furthermore, additional data are needed to characterize the safety profile of deucravacitinib in special populations (pregnant and lactating females and the pediatric population age $\geq$ 4 years). Refer to Section [13](#) of this review for the postmarketing requirements.

8.2.11. Integrated Assessment of Safety

The safety of deucravacitinib for the treatment of adults with moderate to severe plaque

psoriasis who are candidates for systemic therapy and phototherapy was assessed primarily using data from two Phase 3 trials (IM011046 and IM011047) and an ongoing open-label long-term extension trial (IM011075) in which all subjects who completed trials IM011046 and IM011047 could enroll to receive deucravacitinib. The size of the overall safety database was consistent with ICH E1. The database includes 1519 subjects exposed to at least 1 dose of deucravacitinib and a total of 1179 subjects who received deucravacitinib without switching treatment for at least 1 year, as well as 584 who received deucravacitinib without switching treatment for at least 2 years. The clinical trial experience is sufficient to support approval in adults with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy. However, uncertainties pertaining to long-latency and rare adverse events remain. Potential ARs of concern include major adverse cardiovascular events (MACE), malignancy, and opportunistic infections. These ARs have been identified in long-term studies as risks associated with use of JAK inhibitors indicated for the treatment of chronic inflammatory conditions. Because it is unknown if TYK2 inhibition could also be associated with similar ARs, a randomized long-term trial with an active comparator will be required. The Medical Policy and Program Review Council (MPPRC) concurs with requiring the Applicant to conduct a post marketing randomized long-term trial.

The safety database is insufficient to assess the risks of deucravacitinib use in specific populations. Pregnant and lactating females and children were excluded from the clinical trials. Evaluation of drug-associated risks for major maternal or fetal outcomes, impact on lactation, and benefit-risk in the pediatric population, will be required as postmarketing assessments for pregnant, lactating and pediatric populations.

Common adverse reactions identified include upper respiratory infections, blood creatine phosphokinase increased, herpes simplex, mouth ulcers, folliculitis, and acne and will be included labeling.

Treatment with deucravacitinib did not appear to increase the risk of mortality as compared to placebo through 16 weeks of randomized, blinded treatment. A total of 12 deaths were reported in the deucravacitinib psoriasis development program. Of these, 10 occurred in the deucravacitinib group and one each occurred in the placebo and apremilast groups. Six of the deaths reported in the deucravacitinib group were due to COVID-19 and were reported during the long-term extension (LTE) trial that coincided with the pandemic.

The most common serious infections (requiring inpatient care and intervention) associated with deucravacitinib use included pneumonia and COVID-19 infection. A single case of active TB was reported in a subject receiving deucravacitinib. Serious infections reported in deucravacitinib-treated subjects were limited in number and the types reported in the psoriasis population were not consistent with those reported in trials evaluating tofacitinib in the treatment of psoriasis or described in labeling for other JAK inhibitors. Several opportunistic infections including listeria encephalitis, fungal pneumonia, herpes simplex meningitis and cryptococcal pneumonia were identified in a pooled analysis across six clinical trials assessing tofacitinib's benefit-risk profile in moderate to severe psoriasis (Strober et al. 2019). Similarly,

serious and opportunistic infections for JAK inhibitors (tofacitinib, baricitinib, upadacitinib, and abrocitinib) are described in a Boxed Warning and include BK virus encephalitis, esophageal candidiasis, cryptococcus, acute histoplasmosis, and pneumocystis jirovecii pneumonia. Given the absence of cases of invasive fungal infections in the deucravacitinib development program which included a 52-week controlled period, a Boxed Warning for serious infections is not justified at this time. Findings of infections will be communicated in Section 5 (Warnings and Precautions) and Section 6 (Adverse Reactions) of the full prescribing information, as well as in a Medication Guide. To address uncertainties of whether long-term exposure and/or real world use of a TYK-2 inhibitor could contribute to development of OIs, additional postmarketing assessments will be conducted via pharmacovigilance and as an endpoint in a required long-term controlled safety trial.

An assessment of viral reactivation identified probable cases of herpes simplex and herpes zoster reactivation. No reactivation of viral hepatitis was reported, however, subjects with HBV and HCV were excluded from the clinical trials. Regarding deucravacitinib-associated herpes zoster, notable cases included a single, 37-year-old immunocompetent subject with multiple dermatomal disease and 10 of the 15 subjects who reported AEs of herpes zoster were under 50 years of age.

Regarding malignancies, a possible signal for lymphoma was identified. Three subjects developed lymphoma after 25, 77, and 98 weeks of treatment with deucravacitinib. While the number of cases was low, the exposure-adjusted incidence rate of lymphoma observed in deucravacitinib-treated subjects during the Phase 3 clinical trials (0.1/100 PY) is higher than the rate (0.04-0.06/100 PY) observed in patients with psoriasis (Gelfand et al. 2006) and 5-fold higher than the rate of lymphoma expected in the general U.S. population based on the 5-Year Age-Adjusted Incidence Rates, 2015-2019 Surveillance, Epidemiology, and End Results (SEER) Database. The risk of lymphoma based on these potential cases will be communicated in the Warnings & Precautions and Adverse Reactions sections of the FPI. A Medication Guide will inform patients of this potential risk.

An increase in overall malignancy was not observed in deucravacitinib-treated subjects. However, because these are long-latency events, the duration of deucravacitinib's trials would not likely allow detection of malignancy. Long-term data are needed to identify whether there is a potential serious risk of malignancy as has been identified and labeled for the JAK inhibitors. A postmarketing, active-controlled randomized trial will be required to assess the risk of malignancy.

Treatment with deucravacitinib was associated with the following laboratory abnormalities:

- During the placebo- and active controlled period (Week 0 to 16), more deucravacitinib-treated subjects reported a reduction in GFR and discontinued treatment due to a protocol-specified GFR of less than 45 mL/min relative to the comparator groups. Furthermore, in 2 deucravacitinib-treated subjects with already reduced GFRs, worsening proteinuria was observed. These observations are recommended to be described in Section 6 of the Full Prescribing Information (FPI).

- During the placebo- and active controlled period (Week 0 to 16), treatment with deucravacitinib was associated with an increased incidence of reported adverse events of CPK elevation compared to placebo and apremilast. There was also a higher proportion of Grade 4 CPK elevations ($>10 \times \text{ULN}$) with deucravacitinib treatment [6, (0.7%) subjects compared to 1 (0.2%) each for placebo and apremilast groups]. Reports of associated adverse events of rhabdomyolysis and muscle pain occurred with higher grade events in the deucravacitinib group but neither subject in the placebo or apremilast groups who had Grade 4 CPK elevation experienced these muscle-related AEs. Labeling of rhabdomyolysis, myalgias, and CPK elevation will be included in Section 5 of the FPI.
- During Week 0 to 52, a 9% increase in mean triglyceride levels, as well as higher rates of AEs of hypertriglyceridemia, hypertriglyceridemia of higher toxicity grade, and shifts ≥ 2 CTCAE grades were reported in deucravacitinib-treated subjects.

After 52 weeks of treatment, TEAEs of *blood triglycerides increased* and *hypertriglyceridemia* occurred in 6 (1.8%, 2.0/100 PY) subjects who received deucravacitinib but not in any apremilast subjects. Hypertriglyceridemia of higher toxicity grade was reported at an increased incidence in the deucravacitinib group relative to the comparator group. During Trial IM011046, the total number of subjects with Grade 3 and Grade 4 hypertriglyceridemia from Week 0 to 52 were greater in the deucravacitinib group [13 (3.9%) and 3 (0.9%), respectively] compared to the apremilast group [4 (3.5%) and 0, respectively]. Furthermore, in the both Trials IM011046 and IM011047, 5 deucravacitinib-treated subjects reported Grade 4 hypertriglyceridemia (0.8 per 100 PY) compared to 0 in the apremilast group. The proportion of subjects with ≥ 2 CTCAE grade increases was greater for those who received deucravacitinib (6.5%) compared to those who received apremilast (2.8%).

Literature shows that mild to moderate hypertriglyceridemia is an independent risk factor for cardiovascular disease (Harchaoui, K E L et al. 2009; Tsion Aberra, et al. 2020; Berglund et. al, 2013). Therefore, the aforementioned imbalances observed with longer term exposure warrants evaluation of serum triglycerides according to clinical guidelines for hyperlipidemia. The specific findings of increased triglycerides observed in deucravacitinib-treated subjects with moderate to severe psoriasis who are candidates for systemic therapy and phototherapy will be communicated to healthcare providers in Section 5 (Warnings and Precautions) of the FPI in order to mitigate potential CV risk.

Labeling for JAK inhibitors (tofacitinib, baricitinib, upadacitinib, and abrocitinib) includes adverse reactions of all-cause mortality, MACE, thrombosis, gastrointestinal (GI) perforation, and cytopenias. Because the mechanism for these adverse reactions is not understood and it is unknown whether TYK-2 inhibition is contributory, these ARs were evaluated. The findings from the deucravacitinib trials are as follows: :

- An increased risk of all-cause mortality was not observed with deucravacitinib.
- The incidence rates of MACE and thrombosis associated with deucravacitinib treatment were low. Cardiovascular and thrombotic risk was evaluated by subject-matter experts and it is determined that based on the data submitted, such risk was not demonstrated.
- An impact on hematological parameters was not observed for treatment with

deucravacitinib. Analysis of AEs, laboratory grade shifts, and mean change did not demonstrate an effect on lymphocytes, neutrophils, hemoglobin, and platelets. Thus, monitoring for cytopenias will not be included in deucravacitinib labeling.

- There were no reported cases of GI perforation in deucravacitinib-treated subjects.

Although deucravacitinib targets JAK/STAT (Signal Transducers and Activators of Transcription) pathways, the data submitted in this application demonstrates notable differences between deucravacitinib and other approved JAK inhibitors. In vitro data support the determination that deucravacitinib has a different binding domain, distinct mechanism of inhibition, and induces a set of cytokines that is different from those mediated by JAK inhibitors. Furthermore, the clinical trial safety profile of deucravacitinib appears different than the safety labeling of JAK inhibitors.

Due to these notable differences and because the development program did not demonstrate an increased risk of serious and opportunistic infections or higher rates of mortality, overall malignancies, or cardiovascular events, deucravacitinib will not carry JAKi class labeling. It will not receive a boxed warning for serious and opportunistic infections, all-cause mortality, malignancies, MACE, or thrombosis.

Deucravacitinib labeling will communicate the adverse reactions found in the deucravacitinib program. However, because uncertainty remains as to whether the sample size and duration of treatment is sufficient to fully inform risks identified in long-term clinical trials conducted with tofacitinib, deucravacitinib labeling will inform prescribers and patients of the potential risks related to JAK inhibition. Furthermore, given that the safety information reflects potential and not established risks and the efficacy profile of deucravacitinib has been demonstrated, deucravacitinib will not be restricted to patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy and whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable.

To address uncertainties regarding the long-term safety of deucravacitinib, a long-term trial of deucravacitinib along with an active comparator will be required.

8.3. Summary and Conclusions

8.3.1. Statistical Issues

There were no major statistical issues affecting overall conclusions. The treatment effects for deucravacitinib were large and consistent across trials and endpoints. There were no substantial differences in efficacy among subgroups. The amount of missing data was relatively small (< 11%) at Week 16 (i.e., the primary efficacy timepoint). For the handling of missing data, the statistical reviewer conducted an additional sensitivity analysis under the worst-case scenario (i.e., missing data for deucravacitinib was imputed as non-responders and missing data for placebo was imputed as responders). In this extreme case, deucravacitinib remained statistically superior to placebo (p-values < 0.001) for both co-primary efficacy endpoints in both pivotal trials (Trials IM011046 and IM011047).

8.3.2. Conclusions and Recommendations

To establish the effectiveness of deucravacitinib, the Applicant submitted results from two, randomized, multicenter, placebo- and apremilast-controlled, Phase 3 trials (Trials IM011046 and IM011047). The trials enrolled subjects at least 18 years of age with moderate to severe psoriasis [i.e., sPGA score of at least 3 (moderate), PASI ≥ 12 , and BSA $\geq 10\%$]. The co-primary efficacy endpoints were the proportion of subjects achieving an sPGA score of 0 or 1, with at least 2-grade improvement from baseline, at Week 16, and the proportion of subjects achieving PASI 75 at Week 16. In both trials, deucravacitinib was statistically superior to placebo (p-values < 0.001) for both co-primary efficacy endpoints at Week 16. In addition, deucravacitinib was statistically superior to apremilast (p-values < 0.001) for both co-primary efficacy endpoints at Week 16 and Week 24 in both trials.

In both trials, deucravacitinib was statistically superior to placebo for pre-specified secondary endpoints: sPGA of 0, PASI 90, PASI 100, Scalp Specific Physician's Global Assessment (ss-PGA) 0/1 and patient-reported outcomes based on the Psoriasis Symptoms and Signs Diary (PSSD). Maintenance and durability of response was also demonstrated. In Trial IM011046, among Week 24 responders who received deucravacitinib, the response rates at Week 52 were 78% for sPGA 0/1 and 82% for PASI-75. In Trial IM011047, as a greater proportion of Week 24 responders who were re-randomized to deucravacitinib (70%), maintained their response at Week 52 compared to subjects who were re-randomized to placebo (24%). For responders at Week 24 who were re-randomized to treatment withdrawal (i.e., placebo), the median time to loss of sPGA score of 0 or 1 was approximately 8 weeks and the median time to loss of PASI 75 was approximately 12 weeks.

The Applicant provided substantial evidence of effectiveness in the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

To support the safety of deucravacitinib, the Applicant submitted data from trials IM011046 and IM011047, as well as data from an open-label extension trial (IM011075) in which subjects who completed trials IM011046 and IM011047 could enroll. Controlled safety comparisons were conducted between deucravacitinib and placebo with up to 16 weeks of treatment and between deucravacitinib and apremilast with up to 52 weeks of treatment. A total of 1179 subjects who received deucravacitinib without switching treatment for at least 1 year, as well as 584 who received deucravacitinib without switching treatment for at least 2 years.

Limitations of the controlled trial(s) included treatment switching, randomized withdrawal, and a small number of subjects in the active control arm. Limitations of open-label design of extension trial IM011075, include ascertainment of causality of reported adverse events.

The Applicant conducted an adequate safety assessment of deucravacitinib in the target population. The sample size and the duration of treatment informing the deucravacitinib safety database is similar in both size and duration of treatment to the safety databases which have been used to support products approved for the systemic treatment of moderate to severe psoriasis. Frequently occurring adverse reactions were detected and will inform labeling. However, the size and scope of deucravacitinib's safety database is not sufficient to

characterize the safety of long-term TYK2 inhibition with deucravacitinib nor long latency or low frequency adverse reactions, which may include risks such as those identified to be associated with long term use of other products that target the JAK-STAT pathway.

Safety issues identified include serious infections, viral reactivation, lymphoma, hypersensitivity, and laboratory abnormalities (increased CPK, lipid elevations, liver enzymes ≥ 3 times the upper limit of normal, and decreased GFR). Consistent with the in vitro data demonstrating a different mechanism of action and based on the clinical safety data to date, the safety profile of deucravacitinib appears different from the adverse reactions described in labeling for JAK inhibitors used in the treatment of inflammatory conditions. The deucravacitinib safety profile also appears different from the safety reported in published clinical trial data of a JAK inhibitor used in the treatment of psoriasis (Strober et al 2019). The types of serious infections reported in deucravacitinib-treated subjects did not include invasive fungal infections or other infections due to opportunistic pathogens. Additionally, cytopenias were rare, there was no mean change for serum creatinine or total cholesterol, and GI perforation was not observed.

The differences in clinical safety outcomes and how to reflect them in labeling were discussed broadly across the Agency including with the Medical Policy and Program Review Council (MPPRC) on July 6, 2022. The MPPRC acknowledged that there are limitations in the safety assessment as it pertains to characterization of long-term safety, long latency ARs and low frequency ARs. Thus, uncertainties remain and given deucravacitinib's targeted JAK/STAT pathway, additional characterization of its safety profile is warranted. However, because of mechanistic differences, differences in non-clinical outcomes and differences in clinical safety outcomes (adverse event profile and laboratory parameters), the committee found it reasonable for deucravacitinib to carry labeling that is different from the JAKi class. Deucravacitinib labeling will communicate the scientific information and adverse reactions from the deucravacitinib development program, along with the potential serious risks related to JAK inhibition. This advice was provided by the committee.

Deucravacitinib is an NME and with an approval in psoriasis will be the first approval for this product and the first TYK2 inhibitor for the treatment of patients with moderate to severe plaque psoriasis. As an oral agent, deucravacitinib would provide potential dosing advantages over existing injectable biologic agents for some patients. Based on the available safety and efficacy data, the overall risk-benefit profile is favorable and supports the approval of deucravacitinib 6 mg for oral use in the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy; a restricted indication is not warranted. Limitations of use specifying that deucravacitinib is not recommended in combination with [REDACTED] (b) (4) other potent immunosuppressants will be described in labeling.

The Applicant will be required to conduct a post marketing randomized long-term trial to assess safety (e.g., opportunistic infections, overall malignancies, and MACE) and conduct

postmarketing assessments for pregnant, lactating and pediatric populations. Details on these trials and studies are described in Section [13](#).

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting or other external consultations were not solicited. However, a discussion with the Medical Policy and Program Review Council (MPPRC) took place on July 6, 2022. Refer to Section [1.3](#) and Section [8.2.11](#).

10. Pediatrics

Pediatric labeling will be informed by studies conducted under PREA post marketing requirements.

Refer to the following sections of this review for the proposed development program for deucravacitinib in the pediatric population:

- Section [8.2.9.3](#) for a discussion regarding the Pediatric Study Plan.
- Section [13](#) for the deferred pediatric studies, which are required under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)).

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

Table 74. High Level Summary of Significant Labeling Changes

Section	Location of Reviewer Comments on Proposed Labeling	Additional Comments
1 INDICATIONS AND USAGE	1.1, 1.3, 8.3.2	Recommend addition of Limitations of Use: Not recommended for use in combination with other potent immunosuppressants.
2 DOSAGE AND ADMINISTRATION	1.1, 6.2.2	Subjects with active TB were excluded and those with latent TB were required to start treatment prophylaxis prior to starting on deucravacitinib. Tuberculosis assessment prior to initiation is recommended.
4 CONTRAINDICATIONS	8.2.4	Hypersensitivity (angioedema) language recommended
5 WARNINGS AND PRECAUTIONS	1.3, 8.2.5, 8.2.11, 8.3	-Recommend adding additional language to clarify patient population regarding infection status/history. -Recommend addition of hypersensitivity, viral reactivation, malignancies, laboratory abnormalities. -Potential risks related to JAK inhibition specified under separate subsection.
6 ADVERSE REACTIONS	8.2.4, 8.2.5	Specific Adverse Reactions including Infections, Malignancies, and laboratory abnormalities recommended.
7 DRUG INTERACTIONS	6.2.1	
8 USE IN SPECIFIC POPULATIONS	8.2.7, 10	
12 CLINICAL	6.1	

PHARMACOLOGY	
14 CLINICAL STUDIES	7.1, 8.1.1
17 PATIENT COUNSELING INFORMATION	Reflects the data in other sections of labeling, Sections 5, 8

11.2. Patient Labeling

The Applicant submitted a Medication Guide (MG) for deucravacitinib. The Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments on the Medication Guide for deucravacitinib.

The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Shawna Hutchins, MPH, BSN, RN and Laurie Buonaccorsi, PharmD dated August 9, 2022.

12. Risk Evaluation and Mitigation Strategies (REMS)

Risk mitigation measures beyond professional labeling including a Medication Guide are not warranted at this time. A Risk Evaluation and Mitigation Strategy (REMS) would not reduce the known risks associated with treatment with JAK inhibitors. Potential risks in the target population and subgroups will continue to be evaluated using standard surveillance tools and required postmarketing assessments.

13. Postmarketing Requirements and Commitment

Clinical post-marketing requirements are intended to characterize the risks of deucravacitinib use in special populations (pregnancy and pediatrics) and address the long-term safety of this product in the target population with moderate to severe psoriasis. Development of final pharmacovigilance plans is ongoing.

13.1. Postmarketing Requirements Under 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) 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. Clinical postmarketing requirements are intended to characterize the risks of deucravacitinib use in special populations (pregnancy) and address the long-term safety of this novel drug product in the target population. Development of final pharmacovigilance plans is ongoing.

The available safety data regarding deucravacitinib use during pregnancy are limited. The study population as defined by the entry criteria excluded pregnant and breastfeeding females, and females planning to become pregnant or breastfeed during the trials. Because exposures to deucravacitinib during pregnancy are likely to occur and the available data are insufficient to characterize the associated risk in pregnant women, the Agency will require the Applicant to conduct post-marketing assessments to characterize the risk of adverse maternal, fetal, and infant outcomes of women exposed to deucravacitinib during pregnancy.

Analysis of expected adverse reactions based on biologic plausibility and potential class effects did not identify a definitive safety signal of all-cause mortality, including sudden cardiovascular death, major adverse cardiovascular events, overall thrombosis, deep venous thrombosis, pulmonary embolism, and overall malignancies (excluding non-melanoma skin cancer). However, because deucravacitinib inhibits TYK2, which is a member of the Janus Kinase (JAK) family and TYK2 pairs with JAK1 or JAK2 to regulate downstream signaling of type I interferons, as well as Interleukins 10, 6, 12, and 23, the Agency will require post-marketing safety studies to assess the risk of malignancy and other serious adverse events which may not be identified during clinical trials due to a long latency period or low incidence rate.

Therefore, based on appropriate scientific data, FDA has determined that the Applicant is required to conduct PMR trials and studies as listed in Sections 13.1.1, 13.1.2, 13.1.3 and 13.1.4. At the time of review closure, the timelines for the PMRs remain under negotiation.

13.1.1. Long Term Safety PMR

PMR # 4336-1: Conduct a randomized, active-controlled clinical trial to evaluate the long-term safety of deucravacitinib in patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The trial should be of sufficient size and

duration to characterize safety events of interest, including cardiovascular adverse events, opportunistic infections, and malignancy.

- Draft Protocol Submission: February 2023
- Final Protocol Submission: May 2023
- Study Completion: June 2028
- Final Report Submission: December 2028

13.1.2. Pregnancy PMR 1

PMR # 4336-2: Conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to SOTYKTU during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

For more information, see the May 2019 FDA draft Guidance for Industry "*Post approval Pregnancy Safety Studies*," (May 2019).

- Draft Protocol Submission February 2023
- Final Protocol Submission October 2023
- Interim Report July 2026
- Study/Trial Completion July 2028
- Final Report Submission February 2029

13.1.3. Pregnancy PMR 2

PMR # 4336-3: Conduct an additional pregnancy study that uses a different design from the pregnancy registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to SOTYKTU during pregnancy compared to an unexposed control population.

- Draft Protocol Submission February 2023
- Final Protocol Submission October 2023
- Study/Trial Completion July 2028
- Final Report Submission February 2029

13.1.4. Lactation PMR

PMR # 4336-4: Perform a lactation study (milk only) in lactating women who have received SOTYKTU to assess concentrations of deucravacitinib in breastmilk using a validated assay.

- Draft Protocol Submission February 2023
- Final Protocol Submission September 2023
- Study/Trial Completion March 2025
- Final Report Submission September 2025

13.2. Required Pediatric Assessments: Pediatric Research Equity Act (PREA) (21 U.S.C. 355c)

We are waiving the pediatric study requirement for ages 0 to less than 4 years because the studies are impossible or highly impractical due to insufficient numbers of pediatric patients with moderate to severe psoriasis who are candidates for systemic therapy and phototherapy in this age group.

We are deferring the evaluation of deucravacitinib in US adolescents (12 to less than 18 years) with moderate to severe psoriasis because this product is ready for approval for use in adults and additional safety and effectiveness data is needed.

In addition, we are deferring the evaluation of deucravacitinib in US children (4 to less than 12 years) with moderate to severe psoriasis. The trial in this younger cohort should not be initiated until results from the adolescent trial are reviewed by the Agency. Based on the review, the Agency will determine the type of data and the trial design that would be required to evaluate the pediatric population age 4 years to less than 12 years.

(b) (4)

13.2.1. Pediatric PMR

PMR # 4336-5: Conduct a randomized, controlled trial to evaluate the safety, efficacy, and pharmacokinetics of deucravacitinib in the adolescent population (12 years to less than 18 years) with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy. Evaluate at least 300 subjects exposed to deucravacitinib at the highest proposed dosage for a minimum of 52 weeks.

- Final Protocol Submission: May 2023
- Study Completion: (b) (4)
- Final Report Submission: (b) (4)

13.2.2. Pediatric PMR

APPEARS THIS WAY ON
ORIGINAL

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

PMR # 4336-6: Conduct a clinical trial to evaluate the safety, efficacy, and pharmacokinetics of deucravacitinib in pediatric subjects 4 years to less than 12 years of age with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy. Evaluate at least 150 subjects exposed to deucravacitinib at the highest proposed dosage for a minimum of 52 weeks.

The trial should not be initiated until results from PMR 4336-5 for pediatric subjects 12 to less than 18 years of age are reviewed by the Agency. Based on the review, the Agency will determine the type of data and the trial design that would be required to evaluate the pediatric population age 4 years to less than 12 years.

- Final Protocol Submission: September 2030
- Study Completion: (b) (4)
- Final Report Submission: March 2036

14. Division Director (DPT-II) Comments

Not applicable.

15. Division Director (OCP) Comments

Not applicable.

16. Division Director (OB) Comments

Not applicable.

17. Division Director (Clinical)/Division Associate Director for Therapeutics Review (DDD) Comments

I concur with the review team's recommendation for approval of SOTYKTU (deucravacitinib) tablets, 6 mg for oral use for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Recommended dosage is 6 mg orally once daily, with or without food. Before initiation of treatment, the patient should be evaluated for active and latent tuberculosis (TB) infection, and immunizations should be updated according to current immunization guidelines.

Psoriasis is a chronic, inflammatory disease that primarily affects the skin and is characterized by erythematous, scaly plaques and substantial impairment of quality of life. For the treatment of moderate to severe plaque psoriasis, current therapeutic options include phototherapy and photochemotherapy with methoxsalen, systemic small molecule drugs (acitretin, apremilast, cyclosporine, methotrexate), and biologic products (adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, and risankizumab).

Deucravacitinib is a new-molecular-entity and is an inhibitor of tyrosine kinase 2 (TYK2), which belongs to the Janus kinase (JAK) family. Deucravacitinib binds to the regulatory domain of TYK2, stabilizing an inhibitory interaction between the regulatory and the catalytic domains of the enzyme. This results in allosteric inhibition of receptor-mediated activation of TYK2 and its downstream activation of Signal Transducers and Activators of Transcription (STATs) as shown in cell-based assays. JAK kinases, including TYK2, function as pairs of homo- or heterodimers in the JAK-STAT pathways. TYK2 pairs with JAK1 to mediate multiple cytokine pathways and also pairs with JAK2 to transmit signals as shown in cell-based assays. The precise mechanism linking inhibition of TYK2 enzyme to therapeutic effectiveness in the treatment of adults with moderate-to-severe plaque psoriasis is not currently known.

The efficacy and safety of deucravacitinib were evaluated in two 52-week, multicenter, randomized, double-blind, placebo- and active-controlled clinical trials, POETYK PSO-1 (NCT03624127) and POETYK PSO-2 (NCT03611751) which enrolled subjects 18 years of age and older with moderate-to-severe plaque psoriasis who were eligible for systemic therapy or phototherapy. Subjects had a body surface area (BSA) involvement of $\geq 10\%$, a Psoriasis Area and Severity Index (PASI) score ≥ 12 , and a static Physician's Global Assessment (sPGA) ≥ 3 (moderate or severe). Trial POETYK PSO-2 additionally had a randomized withdrawal and maintenance period.

Both trials assessed the responses at Week 16 compared to placebo for the two co-primary endpoints: the proportion of subjects achieving an sPGA score of 0 (clear) or 1 (almost clear), with at least 2-grade improvement from baseline, at Week 16, and the proportion of subjects achieving PASI 75 at Week 16. Deucravacitinib was statistically superior to placebo for both co-primary efficacy endpoints in both trials.

Other comparisons between deucravacitinib and placebo were made for the following secondary endpoints at Week 16: proportion of subjects who achieved PASI 90, PASI 100, sPGA 0, Scalp Specific Physician's Global Assessment (ss-PGA) score of 0/1 with at least 2-grade improvement, and Psoriasis Symptoms and Signs Diary (PSSD) Symptom Score of 0 (symptom-free). In both trials, deucravacitinib was statistically superior to placebo for secondary endpoints based in sPGA and PASI at Week 16. In both trials, treatment with deucravacitinib was statistically superior to placebo among subjects with scalp involvement. Also, a greater proportion of subjects treated with deucravacitinib compared to placebo achieved PSSD symptom score of 0 (absence of itch, pain, burning, stinging, and skin tightness). Additionally, efficacy of deucravacitinib was evaluated compared to apremilast. In both trials, deucravacitinib was statistically superior to apremilast for all pre-specified investigator-reported efficacy endpoints at Week 16.

Maintenance and durability of response of deucravacitinib were also assessed. In Trial POETYK PSO-1, among Week 24 responders who received deucravacitinib, the response rates at Week 52 were 78% for sPGA 0/1, 82% for PASI-75 and 74% (103/140) for PASI-90. In Trial POETYK PSO-2, subjects originally randomized to deucravacitinib at baseline and who were PASI 75 responders at Week 24 were re-randomized to either continue treatment with deucravacitinib or to be withdrawn from therapy (i.e., placebo). The response at Week 52 among Week 24 responders for sPGA was 70% for subjects who were re-randomized to deucravacitinib, and 24% for subjects who were re-randomized to treatment withdrawal. For responders at Week 24 who were re-randomized to treatment withdrawal, the median time to loss of sPGA 0/1 response was approximately 57 days, and the median time to loss of PASI-75 response was approximately 85 days.

The safety database includes a total of 1,519 subjects who received deucravacitinib 6 mg orally once daily. Of these, 1,141 subjects were exposed to deucravacitinib for at least one year. The most common adverse reactions were infection (including herpes simplex), increased creatine

phosphokinase, mouth ulcers, folliculitis and acne. The majority of infections were non-serious and mild to moderate in severity and did not lead to discontinuation of deucravacitinib. The most common serious infections reported were pneumonia and COVID-19. Adverse reactions that occurred in < 1% of subjects in the deucravacitinib group were herpes zoster, rhabdomyolysis, angioedema, and urticaria. Malignancies, including lymphomas, were observed in clinical trials with deucravacitinib. Three subjects developed lymphoma while receiving deucravacitinib after 25, 77, and 98 weeks of treatment. Treatment with deucravacitinib was associated with an increased incidence of CPK elevation (including both asymptomatic and rhabdomyolysis cases) compared to treatment with placebo. In addition, treatment with deucravacitinib was associated with increases in triglyceride levels and liver enzyme elevation (≥ 3 times the ULN) compared to treatment with placebo.

The risks for hypersensitivity, infection including viral reactivation, malignancy including lymphomas, rhabdomyolysis and laboratory abnormalities (including increased CPK, triglyceride elevation and liver enzymes elevation) will be included in deucravacitinib labeling (Contraindications and Warnings and Precautions sections). Based on data submitted by the Applicant, no dose adjustment of deucravacitinib is recommended for patients with renal impairment. However, deucravacitinib is not recommended for use in patients with severe hepatic impairment.

Although deucravacitinib is an inhibitor of tyrosine kinase 2 (TYK2), it belongs to the Janus kinase (JAK) family. It is not known whether TYK2 inhibition may be associated with the observed or potential adverse reactions of JAK inhibition. Given the size of safety database and duration of treatment with deucravacitinib during clinical trials, potential risks related to JAK inhibition can't be excluded. Therefore, deucravacitinib labeling (Warning and Precaution section) will include information of potential risks related to JAK inhibition.

Approval of deucravacitinib will include post-marketing requirements for long-term safety obtaining the data from a randomized, active-controlled clinical trial in patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The trial should be of sufficient size and duration to evaluate safety events of interest, including cardiovascular adverse events and thrombosis. In addition, post-marketing requirements will include studies/trials in specific population (e.g., pregnancy and pediatrics).

18. Office Director Comments

I concur with the recommendation of the Division of Dermatology and Dentistry to approve NDA 214958 for deucravacitinib for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Deucravacitinib is a tyrosine kinase 2 inhibitor and a new molecular entity. Deucravacitinib is administered orally daily at a dose of 6 mg.

The efficacy of deucravacitinib was evaluated in two 52-week randomized, placebo- and apremilast-controlled trials. One trial included assessment of efficacy following a randomized withdrawal of active treatment. In both trials, treatment with deucravacitinib was statistically superior to placebo at Week 16 in the co-primary endpoints of: 1) static Physician's Global Assessment (sPGA) scores of 0/1 [the proportion of subjects who achieve sPGA scores of 0 (clear) or 1 (minimal) with at least a 2-point improvement from baseline] and, 2) PASI 75 [the proportion of subjects who achieve at least a 75% reduction in PASI score from baseline]. In both trials, treatment with deucravacitinib was statistically superior to placebo among subjects with scalp involvement, defined as having a baseline Scalp-specific Physician's Global Assessment (ss-PGA) score of > 3. Improvement in scalp involvement was defined as the proportion of subjects who achieve ss-PGA of 0 (clear) or 1 (minimal) with at least a 2-point improvement from baseline.

In both trials, deucravacitinib was also statistically superior to apremilast for all pre-specified investigator-reported secondary efficacy endpoints at Week 16. For deucravacitinib responders at Week 24 who were re-randomized to treatment withdrawal, the median time to loss of sPGA 0/1 response was approximately 57 days and the median time to loss of PASI 75 response was approximately 85 days.

Treatment with deucravacitinib was generally well tolerated. Commonly reported adverse events included upper respiratory infections, herpes simplex infection, folliculitis, acne, and mucosal ulceration. Hypersensitivity reactions were infrequent; a single case of drug-induced angioedema led to discontinuation of treatment. Cytopenias and opportunistic infections were rarely reported. Non-serious fungal infections were observed but none led to treatment discontinuation. Elevations of triglycerides were observed; the clinical significance of these is unclear. Based on available data, deucravacitinib is not recommended for individuals with severe hepatic impairment. Treatment with deucravacitinib was associated with rare reports of reduced GFR < 45 mL/min and proteinuria, and CPK elevations that may be accompanied by myalgias or rhabdomyolysis. Product labeling will communicate the adverse reactions identified in deucravacitinib clinical trials; the potential serious risks related to JAK inhibition will also be labeled although the full spectrum of risks related to JAK inhibition have not been observed to date with deucravacitinib exposure.

Given the association of psoriasis with cardiovascular disease, the Applicant will be required to conduct a postmarketing randomized long-term trial to further characterize the risk of MACE and thrombosis in psoriasis subjects. Additional postmarketing study requirements will focus on the collection of safety data in populations that have not yet been studied (e.g., pregnant and lactating females, and pediatric subjects age ≥ 12 years).

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19. Appendices

19.1. References

Literature

- Armstrong, AW, MD Mehta, CW Schupp, GC Gondo, SJ Bell, and CEM Griffiths, 2021, Psoriasis Prevalence in Adults in the United States, *JAMA Dermatol*, 157(8):940-946.
- Baris, D and SH Zahm, 2000, Epidemiology of Lymphomas, *Curr Opin Oncol*, 12(5):383-394.
- Bekal, S, C Gaudreau, RA Laurence, E Simoneau, and L Raynal, 2006, *Streptococcus pseudoporcinus* sp. nov., a Novel Species Isolated From the Genitourinary Tract of Women, *J Clin Microbiol*, 44(7):2584-2586.
- Catlett, IM, Y Hu, L Gao, S Banerjee, K Gordon, and JG Krueger, 2022, Molecular and Clinical Effects of Selective Tyrosine Kinase 2 Inhibition With Deucravacitinib in Psoriasis, *J Allergy Clin Immunol*, 149(6):2010-2020 e2018.
- Dai, YX, YH Tai, DD Lee, YT Chang, TJ Chen, and MH Chen, 2021, Risk of Retinal Diseases in Patients With Psoriasis: A Population-based Cohort Study in Taiwan, *J Dermatol*, 48(10):1550-1556.
- Dobry, AS, CP Quesenberry, GT Ray, JL Geier, and MM Asgari, 2017, Serious Infections Among a Large Cohort of Subjects With Systemically Treated Psoriasis, *J Am Acad Dermatol*, 77(5):838-844.
- Facklam, R, J Elliott, N Pigott, and AR Franklin, 1995, Identification of *Streptococcus porcinus* From Human Sources, *J Clin Microbiol*, 33(2):385-388.
- Florentino, D, V Ho, MG Lebwohl, L Leite, L Hopkins, C Galindo, K Goyal, W Langholff, S Fakharzadeh, B Srivastava, and RG Langley, 2017, Risk of Malignancy With Systemic Psoriasis Treatment in the Psoriasis Longitudinal Assessment Registry, *J Am Acad Dermatol*, 77(5):845-854 e845.
- Gelfand, JM, DB Shin, AL Neimann, X Wang, DJ Margolis, and AB Troxel, 2006, The Risk of Lymphoma in Patients With Psoriasis, *J Invest Dermatol*, 126(10):2194-2201.
- Hagg, D, A Sundstrom, M Eriksson, and M Schmitt-Egenolf, 2017, Severity of Psoriasis Differs Between Men and Women: A Study of the Clinical Outcome Measure Psoriasis Area and Severity Index (PASI) in 5438 Swedish Register Patients, *Am J Clin Dermatol*, 18(4):583-590.
- Harpaz, R and JW Leung, 2019, The Epidemiology of Herpes Zoster in the United States During the Era of Varicella and Herpes Zoster Vaccines: Changing Patterns Among Older Adults, *Clin Infect Dis*, 69(2):341-344.
- Kimball, AB, J Schenfeld, NA Accortt, MS Anthony, KJ Rothman, and D Pariser, 2015, Cohort Study of Malignancies and Hospitalized Infectious Events in Treated and Untreated Patients With Psoriasis and a General Population in the United States, *Br J Dermatol*, 173(5):1183-1190.

- Kumar, N, S Kumar, A Kumar, T Shakoor, and A Rizwan, 2019, Lipid Profile of Patients with Acute Myocardial Infarction (AMI), *Cureus*, 11(3):e4265.
- Martinez, SR, KL Barr, and RJ Canter, 2011, Rare Tumors Through the Looking Glass: an Examination of Malignant Cutaneous Adnexal Tumors, *Arch Dermatol*, 147(9):1058-1062.
- Mathur, T, AM Manadan, S Thiagarajan, B Hota, and JA Block, 2014, Serum Transaminases are Frequently Elevated at Time of Diagnosis of Idiopathic Inflammatory Myopathy and Normalize With Creatine Kinase, *J Clin Rheumatol*, 20(3):130-132.
- McNab, F, K Mayer-Barber, A Sher, A Wack, and A O'Garra, 2015, Type I Interferons in Infectious Disease, *Nat Rev Immunol*, 15(2):87-103.
- Migita, R, Y Kimoto, J Hiura, Y Okumura, and T Horiuchi, 2022, A Case of Rapidly Progressing Hepatocellular Carcinoma after Administration of JAK Inhibitors to Treat Rheumatoid Arthritis, *Case Rep Rheumatol*, 2022:6852189.
- Oliveira Mde, F, O Rocha Bde, and GV Duarte, 2015, Psoriasis: Classical and Emerging Comorbidities, *An Bras Dermatol*, 90(1):9-20.
- Papp, KA, JG Krueger, SR Feldman, RG Langley, D Thaci, H Torii, S Tyring, R Wolk, A Gardner, C Mebus, H Tan, Y Luo, P Gupta, L Mallbris, and S Tatulych, 2016, Tofacitinib, an Oral Janus Kinase Inhibitor, for the Treatment of Chronic Plaque Psoriasis: Long-term Efficacy and Safety Results From 2 Randomized Phase-III Studies and 1 Open-label Long-term Extension Study, *J Am Acad Dermatol*, 74(5):841-850.
- Penn, I, 1997, Skin Disorders in Organ Transplant Recipients. External Anogenital Lesions, *Arch Dermatol*, 133(2):221-223.
- Plewa, MC and K Chatterjee, 2022, Aphthous Stomatitis, *StatPearls*, Treasure Island (FL).
- Queeney, K, W Housley, J Sokolov, and A Long, 2019, FRI0131 Elucidating the Mechanism Underlying Creatine Phosphokinase Upregulation With Upadacitinib, *Annals of the Rheumatic Diseases*, 78(Suppl 2):734-735.
- Strober, B E et al. "Benefit-risk profile of tofacitinib in patients with moderate-to-severe chronic plaque psoriasis: pooled analysis across six clinical trials." *The British journal of dermatology* vol. 180,1 (2019): 67-75.
- Teng, MW, EP Bowman, JJ McElwee, MJ Smyth, JL Casanova, AM Cooper, and DJ Cua, 2015, IL-12 and IL-23 Cytokines: From Discovery to Targeted Therapies for Immune-mediated Inflammatory Diseases, *Nat Med*, 21(7):719-729.
- Valenzuela, F, KA Papp, D Pariser, SK Tyring, R Wolk, M Buonanno, J Wang, H Tan, and H Valdez, 2015, Effects of Tofacitinib on Lymphocyte Sub-populations, CMV and EBV Viral Load in Patients With Plaque Psoriasis, *BMC Dermatol*, 15:8.
- Wu, JJ, BE Strober, PR Hansen, O Ahlehoff, A Egeberg, AA Qureshi, D Robertson, H Valdez, H Tan, and R Wolk, 2016, Effects of Tofacitinib on Cardiovascular Risk Factors and Cardiovascular Outcomes Based on Phase III and Long-term Extension Data in Patients With Plaque Psoriasis, *J Am Acad Dermatol*, 75(5):897-905.

Yawn, BP, P Saddier, PC Wollan, JL St Sauver, MJ Kurland, and LS Sy, 2007, A Population-based Study of the Incidence and Complication Rates of Herpes Zoster Before Zoster Vaccine Introduction, *Mayo Clin Proc*, 82(11):1341-1349.

Guidances for Industry

Guidance for Industry *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020)

Guidance for Industry *Bioanalytical Method Validation* (May 2018)

Draft Guidance for Industry *Postapproval Pregnancy Safety Studies* (May 2019)

Prescribing Information

Pfizer, I, 2021, Xeljanz (tofacitinib), accessed August 18, 2022, www.accessdata.fda.gov/drugsatfda_docs/label/2021/203214s028,208246s013,213082s003lbl.pdf.

Other

FDA, 2022, Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, accessed, 2022, <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>.

The Voice of the Patient *Psoriasis* (November 2016)

19.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies for deucravacitinib. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

On February 24, 2022, the Applicant informed the Agency that they received updated financial disclosure information after the data cutoff (February 24, 2021) used for the purpose of submission preparation. The updated information was provided post study close-out by a Principal Investigator from a single site in Study IM011046 and was not originally included in the September 10, 2021 NDA. This updated information is reflected below and an attachment is provided with details of the disclosable financial interests/arrangements.

The covered clinical studies as defined in 21 CFR 54.2(e) were studies IM011046 and IM011047, which provided the primary data to establish effectiveness and safety of this product. Refer to Sections 7.1 and 8.1 for the trial designs. The Applicant adequately disclosed financial interests involving clinical investigators. Because the number of investigators with financial disclosures was limited and assessments were blinded, the strategies employed by the Applicant to

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

minimize potential bias arising from investigator financial interests/arrangements appear reasonable.

Covered Clinical Study (Name and/or Number): IM011046

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>721 investigators/subinvestigators</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
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: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator of covered study: <u>1</u>		
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) <u>0</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): IM011047

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>812 investigators/subinvestigators</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotykto (deucravacitinib) tablets, 6 mg

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
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: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in covered study: <u>0</u>		
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) <u>2</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): IM011075

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>993 investigators/subinvestigators</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
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: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u>		

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Significant equity interest held by investigator in covered study: <u>0</u>		
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) <u>0</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Table 75. List of Investigators and Sub investigators With Information to Disclose

Protocol/ Site Number	Investigator Name (Principal Investigator name bolded)	Financial Interests or Arrangements	Bias Statement	Principal Investigator Office Address Phone Fax Email	Enrolled	Randomized
(b) (6)					4	1
					7	7

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

(b) (6)



Table 76. List of Investigators and Sub-investigators Due Diligence

Protocol/Site Number	Investigator Name (Principal Investigator name bolded)	Reason/Due Diligence	Principal Investigator Office Address Phone, Fax and Email	Enrolled	Randomized
(b) (6)	(b) (6)	Note to file states that several attempts were made to collect the Financial Disclosure form with no success. COVID-19 circumstances restricted site contact and traceable mail was not an option.	(b) (6)	7	6
		Note to file states that several attempts were made to collect the Financial Disclosure form with no success. COVID-19 circumstances restricted site contact and traceable mail was not an option.		1	0

* Non-IND Sites

19.3. Nonclinical Pharmacology/Toxicology

19.3.1. Calculations for Multiples of Exposure

At the recommended human dose (6 mg/day) in adult subjects, AUC_{0-24h} and C_{max} were 0.473 $\mu\text{g}\cdot\text{hr}/\text{mL}$ and 0.045 $\mu\text{g}/\text{mL}$, respectively (study # 930166658). The following table summarizes the multiples of exposure based on AUC comparisons between the MRHD and AUC values from nonclinical studies referenced in the label.

Table 77. Multiples of Exposure

Study Type	Dose of Interest (NOAEL or Dose That Resulted in Toxicity as Described in Label)	Estimated AUC_{0-24h} ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	Multiples of Exposure
Fertility	Male and female NOAEL for mating, fertility, and early embryonic development: 50 mg/kg/day	Male: 106 Female: 81.1	224 171
Embryofetal development (Female Rats)	NOAEL for fetal effects: 75 mg/kg/day	126	266
Embryofetal development (Female Rabbits)	NOAEL for fetal effects: 10 mg/kg/day	43.2	91
Prenatal and postnatal development (Dams plus pups)	NOAEL for maternal effects: 50 mg/kg/day NOAEL for F1 Generational effects: 15 mg/kg/day	51.9	110
		9.2	19
Carcinogenicity (Rats)	NOAEL: 15 mg/kg/day	24.6 (male)	52
		23.5 (female)	50

19.3.2. Review of Carcinogenicity Studies Conducted With Deucravacitinib

Study Title: BMS-986165, Six-Month Oral Carcinogenicity Study in CByB6F1/Tg rasH2 Hemizygous Mice

Study no.: DN18025, study report No. 930140831 1.0

Study report location: SDN 1, Module 4.2.3.4.1

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes
Drug, lot #, and % purity: Deucravacitinib (BMS-986165), batch # AAJ6215, purity 90.2%
Prior Exec CAC Dose Concurrency: Y
Basis for Dose Selection: Severe immunosuppression was seen at the dose of 100 mg/kg/day in a 28-day dose range-finding study in CByB6F1 wild type mice. The dose of 60 mg/kg/day was then selected as the high dose to avoid potentially excessive immunosuppression and subsequent clinical/pathologic adversity in the 6-month study.

Reviewer Carcinogenicity Conclusion: Negative
ECAC Carcinogenicity Conclusion: Negative

Tumor Findings:

No statistically significant differences in deucravacitinib-related tumor incidence were observed in mice of either sex in this study, according to the statistical criteria used by the Executive Carcinogenicity Assessment Committee (ECAC). The NOAEL was the highest dose 60 mg/kg/day.

Methods

Doses: 0 (water control), 0 (vehicle control), 10, 30, and 60 mg/kg/day
Frequency of dosing: Once daily
Number/Sex/Group: 25
Dose volume: 10 mL/kg
Formulation/Vehicle: (b) (4)
Route of administration: ORAL GAVAGE
Species: MOUSE
Strain: CB6F1-TgN (RasH2)
Age: Approx. 8 weeks at initiation of treatment.
Comment on Study Design and Conduct: The main study was conducted in hemizygous Tg.rasH2 mice; however, the TK study was conducted in wild-type homozygous Tg.rasH2 mice. The study design is summarized below:

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Group Number	Test Material	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Adjusted Dose Concentration (mg/mL)	Number of Animals (Animal Numbers)	
					Carcinogenicity Phase	Toxicokinetic Phase ^e
1	Water Control ^b	0	10	0	25 M (33-57)	12 M (313-324)
					25 F (58-82)	12 F (325-336)
2	Control Article ^c	0	10	0	25 M (83-107)	12 M (337-348)
					25 F (108-132)	12 F (349-360)
3	BMS-986165	10	10	1 ^d	25 M (133-157)	34 M (361-394)
					25 F (158-182)	34 F (395-428)
4	BMS-986165	30	10	3 ^d	25 M (572, 184-193, 573, 195-206, 574)	34 M (429-443, 571, 445-459, 575, 461-462)
					25 F (208-215, 565, 217-221, 570, 223-232)	34 F (463-484, 576, 486-496)
5	BMS-986165	60	10	6 ^d	25 M (233-250, 567, 252-257)	34 M (497-530)
					25 F (258, 568, 260-282)	34 F (531-564)
6	NMU (Positive Control)	75 ^e	10	7.5	15 M (283-286, 569, 288-297)	-
					15 F (298-312)	-
7	Health Screen/Sentinel	-	-	-	11 M (1-11)	5 M ^f (23-27)
					11 F (12-22)	5 F ^f (28-32)

Dosing Comments (Dose Adjustments or Early Termination): None

Dosing Solution Analysis: Adequate. The concentrations of all doses were within $\pm 4\%$ of their nominal values.

Observations and Results

Mortality

There were no deucravacitinib-related deaths observed.

Clinical Signs

There were no deucravacitinib-related clinical signs observed.

Body Weights

There were no deucravacitinib-related effects on body weights or body-weight gains.

Feed Consumption

There were no deucravacitinib-related effects on food consumption.

Gross Pathology

There were no deucravacitinib-related macroscopic findings at unscheduled or scheduled necropsies.

Histopathology

- Peer Review Conducted: Yes
- Historical Control Provided for Tumor Incidence: Yes

Histopathology was performed on a standard list of tissues, plus any gross lesions, from all animals including both premature decedents and animals killed at terminal sacrifice.

Neoplastic

There were no statistically significant differences in deucravacitinib-related tumor incidences observed in mice of either sex in this study, according to the statistical criteria used by the ECAC. In contrast, the positive control N-Nitrosomethylurea (NMU) at a single dose of 75 mg/kg (intraperitoneal injection on Day 1) caused statistically significant increases in incidences of systemic malignant lymphomas (60% males, 73% females), squamous cell carcinoma and/or papilloma in the stomach (73% males, 80% females), skin, esophagus, and tongue.

Non-Neoplastic

There were no statistically significant differences in deucravacitinib-related non-neoplastic microscopic findings observed in mice of either sex in this study. The positive control NMU caused expected non-neoplastic changes such as retinal degeneration (100% in both sexes).

Toxicokinetics

Blood samples were collected on Days 1 and 180 for toxicokinetic analysis of deucravacitinib and its metabolites BMT-153261 (pharmacologically active) and BMT-158170 (pharmacologically inactive). Day 180 data are summarized in the following table. T_{max} of deucravacitinib was 1-4 hours post-dose. Systemic deucravacitinib exposures, as indicated by C_{max} and AUC_{0-24h} values, increased more than dose proportionally in both sexes. Deucravacitinib exposure was slightly higher in females than in males at all doses. The mouse TK parameters are summarized in the table below.

Table 78. Toxicokinetics Analysis in the 6-Month Carcinogenicity Study in rasH2 Transgenic Mice

Parameter	BMS-986165 (mg/kg/day)		
	10	30	60
BMS-986165			
Males			
AUC(0-24h); µg·h/mL	3.93	18.8	74.1
Cmax; µg/mL	0.717	3.81	10.3
Tmax; h	1.0	1.0	2.0
Females			
AUC(0-24h); µg·h/mL	6.89	25.9	101
Cmax; µg/mL	1.18	4.92	11.6
Tmax; h	1.0	2.0	4.0
Sexes Combined			
AUC(0-24h); µg·h/mL	5.41	22.4	87.5
Cmax; µg/mL	0.948	4.28	10.3
Tmax; h	1.0	1.0	1.0
BMT-153261			
Males			
AUC(0-24h); µg·h/mL	0.124 ^a	1.17	2.83
Cmax; µg/mL	0.0291	0.476	0.383
Tmax; h	1.0	1.0	1.0
Females			
AUC(0-24h); µg·h/mL	0.333	0.751 ^a	2.30
Cmax; µg/mL	0.0276	0.347	0.307
Tmax; h	1.0	1.0	4.0
Sexes Combined			
AUC(0-24h); µg·h/mL	0.269	1.06	2.57
Cmax; µg/mL	0.0284	0.411	0.290
Tmax; h	1.0	1.0	1.0
BMT-158170			
Males			
AUC(0-T); µg·h/mL	0.0742 ^b	1.18 ^a	3.45 ^a
Cmax; µg/mL	0.0291	0.274	0.647
Tmax; h	2.0	1.0	1.0
Females			
AUC(0-T); µg·h/mL	0.146 ^b	1.78 ^a	3.42 ^a
Cmax; µg/mL	0.0621	0.406	0.678
Tmax; h	2.0	2.0	1.0
Sexes Combined			
AUC(0-T); µg·h/mL	0.109 ^b	1.48 ^a	3.41 ^a
Cmax; µg/mL	0.0456	0.316	0.662
Tmax; h	2.0	2.0	1.0

^a Mean systemic exposure is AUC(0-8h) due to unmeasurable concentrations at 24 hours post dose.

^b Mean systemic exposure is AUC(0-4h) due to unmeasurable concentrations at 8 and 24 hours post dose.

Study Title: BMS-986165, Two-Year Oral Gavage Carcinogenicity Study in Rats

Study no.: DN17062
Study report location: SDN 1, Module 4.2.3.4.1
Conducting laboratory and location: (b) (4)
GLP compliance: Yes
Drug, lot #, and % purity: Deucravacitinib, batch # AAR7019, purity 91.1%
Prior Exec CAC Dose Concurrence: Y
Mortality and a significant decrease in body weight were seen at the dose of 50 mg/kg/day in the 6-month rat oral toxicity study. The high dose of 15 mg/kg/day was then selected to ensure
Basis for Dose Selection: long-term survival in the 2-year study.

- Reviewer Carcinogenicity Conclusion: Negative
- ECAC Carcinogenicity Conclusion: Negative

Tumor Findings

In male rats, there were no statistically significant differences in deucravacitinib-related tumor incidences observed. In female rats, however, there was a statistically significant dose-dependent increase in the incidence of hepatocellular adenoma in the liver. The trend P value was 0.0057 compared to water control and 0.0095 compared to vehicle control. At the high dose of 15 mg/kg/day in female rats, the incidence of hepatocellular adenoma was 11.43% with a pairwise P value of 0.02 compared to water control and 0.04 compared to vehicle control. These pairwise P values were lower than 0.05 but did not reach statistical significance ($P > 0.01$) for a common tumor. Therefore, deucravacitinib is considered to be noncarcinogenic in the 2-year oral carcinogenicity study in rats.

Methods

Doses: 0 (water control), 0 (vehicle control), 3, 8, and 15 mg/kg/day
Frequency of dosing: Once daily
Number/Sex/Group: 90
Dose volume: 5 mL/kg/day
Formulation/Vehicle: (b) (4)

Route of administration: ORAL GAVAGE
 Species: RAT
 Strain: SPRAGUE-DAWLEY
 Age: Approximately 6 weeks old at initiation of treatment
 Comment on Study Design and Conduct: The study design is summarized below:

Group Number	BMS-986165			Number of Animals ^c
	Dose (mg/kg)	Volume (mL/kg)	Concentration (mg/mL)	
1/Water Control ^a	0	5	0	90 M, 90 F
2/Vehicle control ^b	0	5	0	90 M, 90 F
3/BMS-986165	3	5	0.6	90 M, 90 F
4/BMS-986165	8	5	1.6	90 M, 90 F
5/BMS-986165	15	5	3	90 M, 90 F
6/Health Screen ^d	-	-	-	10 M, 10 F
7/Sentinel ^e	-	-	-	30 M, 30 F

Dosing Comments (Dose Adjustments or Early Termination): Due to decreased survival across all groups, all surviving males in Groups 1-5 and Group 5 females were euthanized starting at Week 90. All surviving females in Groups 1-4 were euthanized starting at Week 99.

Dosing Solution Analysis: Adequate. The concentrations of all doses were within $\pm 6\%$ of their nominal values.

Observations and Results

Mortality

Males in Groups 1-5 and females in Group 5 were euthanized starting at Week 90, because the survival in Group 1 males and Group 5 females reached prescribed limits for group termination (20 rats in Group 1 males and 15 rats in Group 5 females) during Week 90. Females in Groups 1-4 were euthanized starting at Week 99, because Group 4 females reached a limit for early group termination (15 rats) during Week 99. The mortality findings are summarized in [Table 79](#).

Table 79. Summary of Mortality Ratios With % Survival

Group	Males		Females	
	Mortality	Survival	Mortality	Survival
1	50/70	29%	46/70	34%
2	49/70	30%	49/70	30%
3	54/70	23%	55/70	21%
4	52/70	26%	55/70	21%
5	52/70	26%	55/70	21%

There were no deucravacitinib-related effects on survival in males. For female rats, the survival rates in treated groups and the vehicle control group were all below the lower limit of the historical range (32.3-75.8%). The survival analyses showed a statistically significant dose response relationship in mortality across the vehicle/water control groups and treated groups. The pairwise comparisons showed a statistically significant difference in mortality between the

vehicle control group and the high dose group, and between the water control group and each of the treated groups.

Clinical Signs

There were no deucravacitinib-related clinical signs observed.

Body Weights

There were no deucravacitinib-related effects on body weights or body-weight gains.

Feed Consumption

There were no deucravacitinib-related effects on food consumption.

Gross Pathology

There were no deucravacitinib-related macroscopic findings at unscheduled or scheduled necropsies.

Histopathology

- Peer Review Conducted: Yes
- Historical Control Provided for Tumor Incidence: Not complete

Histopathology was performed on a standard list of tissues, plus any gross lesions, from all animals including both premature decedents and animals killed at terminal sacrifice.

Neoplastic

In male rats, there were no deucravacitinib-related tumor findings noted. In female rats, there was a statistically significant dose-dependent increase in the incidence of hepatocellular adenoma in the liver. However, none of the incidences reached statistical significance during pairwise analysis when compared to the vehicle/water control groups. Therefore, deucravacitinib was not carcinogenic in the 2-year carcinogenicity study in rats.

Non-Neoplastic

Deucravacitinib-related non-neoplastic microscopic findings were observed in the liver. There was an increased incidence of minimal to mild brown pigment accumulation in the Kupffer cells in both sexes at all deucravacitinib dose levels with no dose relationship. The amount of brown pigment was minor in affected cells and the difference in severity was attributed to the number of affected Kupffer cells. The pigment was not associated with any other microscopic findings such as hepatocellular degeneration/necrosis and/or inflammation.

Toxicokinetics

Blood samples were collected on Weeks 1, 13, and 26 for toxicokinetic analysis of deucravacitinib and its metabolites BMT-153261 and BMT-158170. Week 26 data are summarized in the following table ([Table 80](#)). T_{max} of deucravacitinib was 2-4 hours post-dose. C_{max} increased more than dose proportionally in both sexes across all doses. AUC_{0-24h} values increased more than dose proportionally in males across all doses and in females from 3 to 8 mg/kg/day; and increased dose proportionally from 8 to 15 mg/kg/day in females. Deucravacitinib exposure was similar in two sexes at all doses.

Table 80. Toxicokinetics Analysis of Deucravacitinib and Metabolites in Rats

Parameter	BMS-986165 (mg/kg/day)		
	3	8	15
BMS-986165			
Males			
AUC(0-24h); µg·h/mL	2.37	9.41	24.6
Cmax; µg/mL	0.213	1.05	2.58
Tmax; h	4.0	4.0	4.0
Females			
AUC(0-24h); µg·h/mL	2.18	13.8	23.5
Cmax; µg/mL	0.295	1.17	3.02
Tmax; h	2.0	4.0	2.0
Sexes Combined			
AUC(0-24h); µg·h/mL	2.28	11.3	24.2
Cmax; µg/mL	0.247	1.11	2.70
Tmax; h	2.0	4.0	2.0
BMT-153261			
Males			
AUC(0-T); µg·h/mL	0.0615 ^a	0.244 ^a	0.527 ^a
Cmax; µg/mL	0.0107	0.0483	0.0976
Tmax; h	4.0	4.0	2.0
Females			
AUC(0-T); µg·h/mL	N/A	0.101 ^a	0.152 ^a
Cmax; µg/mL	N/A	0.0263	0.0273
Tmax; h	N/A	8.0	4.0
BMT-158170			
Males			
AUC(0-T); µg·h/mL	0.0675 ^a	0.487 ^a	1.38 ^a
Cmax; µg/mL	0.0123	0.0875	0.242
Tmax; h	4.0	4.0	4.0
Females			
AUC(0-T); µg·h/mL	0.0368 ^b	0.593 ^a	1.61 ^a
Cmax; µg/mL	0.0131	0.0984	0.304
Sexes Combined			
AUC(0-T); µg·h/mL	0.0703 ^a	0.531 ^a	1.49 ^a
Cmax; µg/mL	0.0126	0.0929	0.262
Tmax; h	4.0	4.0	2.0
N/A = Not applicable			
^a Mean systemic exposure is AUC(0-8h).			
^b Mean systemic exposure is AUC(0-4h).			

Overall, deucravacitinib was not carcinogenic in the 6-month oral carcinogenicity study in CByB6F1/Tg rasH2 hemizygous mice or the 2-year oral carcinogenicity study in rats.

19.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

19.4.1. Population PK Analysis

19.4.1.1. Executive Summary

The FDA's Assessment

- Dose adjustment is not suggested based PPK analysis for specific populations.
- PK profiles of healthy adults and plaque psoriasis (PsO) patients are adequately described by the PPK model except for the absorption phase. Further characterization is needed to improve the fitting of concentrations around T_{max} .
- PPK modeling is applicable to produce individual Empirical Bayesian Estimate (EBE) estimates for exposure prediction and covariate identification. The C_{max} prediction could be inaccurate due to high eta-shrinkage in V2 and bioavailability. The E-R analysis with C_{max} should be interpreted with caution.

19.4.1.2. PPK Review Summary

Table 81. PPK Review Summary

General Information	
Goal of PPK Analysis: ▪ Characterize the PK profile of deucravacitinib and its active metabolite BMT-153261 ▪ Explore the source of PK variability for the potential need of individualized dosing ▪ Predict individual exposure for E-R assessment	
Study Included	Phase I: IM011002, IM011031, IM011045, IM011048, IM011061, IM011062, IM011067, IM011071, IM011090, IM011119 Phase II: IM011011 (ITT) Phase III: IM011046, IM011047 (ITT)
Dose(s) Included	<u>Single dose:</u> 1-40 mg <u>Multiple doses:</u> 3 mg QOD 3, 6 (label dose, n=856), 12 mg QD 2, 3, 4, 6, 12 mg BID
Dosage Form Included	Solution, capsule, tablet
Population Included	Healthy adults, adults with hepatic and renal impairment, patients with moderate-to-severe plaque psoriasis
Population Characteristics (Median/Range, n%) (Table 82)	General
	Organ Impairment
Age: 43 yr (18-84 yr), 100 (7%) ≥ 65 yr, 13 (1%) ≥ 75 yr Weight: 85.5 kg (36-180 kg) Sex: 944 (68%) male Race: 1149 (83%) White, 61 (4%) Black, 153 (11%) Asian, 25 (2%) Other Hepatic (NCI): 136 (10%) mild, 8 (0.6%) moderate, 3 (0.2%) severe Renal (MDRD): 530 (38%) mild, 40 (3%) moderate, 8 (0.6%) severe, 8 (0.6%) end stage	

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

No. of Patients, PK Samples, BLQ	1388 subjects, 18781 PK samples exclusive of 3293 BLQ (1390 prior to first dose) for PPK analysis	
Sampling Schedule	Rich Sampling	Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 10, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192 h
	In ITT Population	Week 0/16: Pre-dose, 0.5h, 2h (Week 0) / 3h (Week 16) Week 1/2/4/8/12/36/52: Pre-dose
Covariates Evaluated	Baseline demographics (age, sex, race, ethnicity, country, and smoking status), baseline disease (BSA involved with PsO, baseline PASI), body metrics, subject type (healthy, PsO), eGFR, NCI liver function group, Child-Pugh, albumin, ALT, AST, bilirubin, formulation, pH-modifying agent, food	
Final Model	Summary	Acceptability/Comment
Software (Version)	NONMEM software (Ver 7.4.3)	Yes
Estimation Algorithm	first-order conditional estimation with INTERACTION	Yes
Model Structure	2-compartment model with sequential zero input and first order absorption with a lag time, and linear elimination. BMT-153261 PPK model was developed in a sequential manner. The EBE parameter values obtained from the deucravacitinib PPK model were used to drive the deucravacitinib part of the BMT-153261 model.	Acceptable. The absorption profile could be improved, see comment below.
Model Parameter Estimates	Table 83 (parent drug), Table 84 (active metabolite BMT-153261)	N/A
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	- For the parent drug, key parameters were estimated with good precision ($ \%RSE < 30\%$). The magnitude of the IIV was moderate for CL (39% CV-psoriasis patients) but high for KA (118% CV) and bioavailability (130% CV). IIV for Q and V3 were fixed to 0%. Residual variability was small for additive error, and moderate (49%-phase 2&3) for proportional error. Eta and epsilon shrinkages were reasonable (<30%) for diagnostics and EBE estimation except for CL (50%) of non-PsO subjects, V2(53%), and bioavailability (52%). - For the active metabolite BMT-153261, only race effect on V4 was estimated with poor precision (RSE of 46%). The magnitude of the IIV was moderate for CLM (37% CV) but higher	Acceptable. Steady-state exposures were derived from individual EBE estimates for E-R analysis of PsO patients. The large eta-shrinkage of V2 and bioavailability will impact the accuracy of predicting peak deucravacitinib concentrations. Due to the complex absorption process, observed concentrations around T_{max} is also inaccurate and some unexpected low concentrations around T_{max} were observed. Together, neither predicted nor

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

	for V4 (84%). Shrinkages are reasonable.	observed steady-state C_{max} is ideal for E-R analysis.
BLQ for Parameter Accuracy	BLQ excluded in PPK analysis.	Yes. Post infusion BLQ is ~8% and has minor impact on PK parameter estimates using M3 method.
Goodness of Fit (GOF) and Visual Predicted Check (VPC)	Figure 32 , Figure 33 & Figure 34 GOF plots showed overall agreement between observed and model-predicted concentrations. VPC showed an underpredicted C_{max} of the parent drug.	Acceptable. The underprediction of concentrations around T_{max} is about 20-30% for the parent drug, indicating the absorption profile needs be further characterized.
Significant Covariates and Clinical Relevance	Figure 35 <u>CL of the parent drug:</u> - Positive factors: weight, healthy adults, eGFR - Negative factors: age, female <u>V2 of the parent drug:</u> - Positive factors: weight - Negative factors: female, healthy adults, baseline disease duration <u>KA of the parent drug:</u> - Positive factors: capsule, liquid - Negative factors: fed	Yes. None are likely to have clinically meaningful impact on exposure, and no evident age/race effect is observed. <u>Note:</u> The significant covariates of the active metabolite were not reported in the review as the metabolite only has minor contribution to the overall activity.
Labeling language	Description	Acceptability/Action
12.3 Pharmacokinetics	Specific population information was based on the impact of covariates assessed in PPK or results from dedicated studies. No dose adjustment is suggested.	Yes

Table 82. Summary of Baseline Characteristics and Laboratory Values in the PPK Dataset.

Characteristics	Level	Phase 1 Studies	Phase 2/3 studies (PsO)	Total
N		328	1060	1388
Dosing regimen, n (%)	Single: 1-40 mg	220 (67.1%)	0 (0%)	220 (15.9%)
	Multiple: 2 mg BID	15 (4.6%)	0 (0%)	15 (1.1%)
	Multiple: 3 mg QOD	0 (0%)	44 (4.2%)	44 (3.2%)
	Multiple: 3 mg QD	0 (0%)	44 (4.2%)	44 (3.2%)
	Multiple: 3 mg BID	0 (0%)	45 (4.2%)	45 (3.2%)
	Multiple: 4 mg BID	9 (2.7%)	0 (0%)	9 (0.6%)
	Multiple: 6 mg QD	18 (5.5%)	838 (79.1%)	856 (61.7%)

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Characteristics	Level	Phase 1 Studies	Phase 2/3 studies (PsO)	Total
	Multiple: 6 mg BID	15 (4.6%)	45 (4.2%)	60 (4.3%)
	Multiple: 12 mg QD	36 (11.0%)	44 (4.2%)	80 (5.8%)
	Multiple: 12 mg BID	15 (4.6%)	0 (0%)	15 (1.1%)
Current smoking status, n (%)	Non-smoker	0 (0%)	416 (39.2%)	416 (30.0%)
	Current smoker	0 (0%)	231 (21.8%)	231 (16.6%)
	Prior smoker	0 (0%)	191 (18.0%)	191 (13.8%)
	Missing	328 (100%)	222 (20.9%)	550 (39.6%)
Region, n (%)	US	121 (36.9%)	301 (28.4%)	422 (30.4%)
	EU	69 (21.0%)	510 (48.1%)	579 (41.7%)
	Rest of the world	138 (42.1%)	249 (23.5%)	387 (27.9%)
Race, n (%)	White	228 (69.5%)	921 (86.9%)	1,149 (82.8%)
	Black	50 (15.2%)	11 (1.0%)	61 (4.4%)
	Asian	38 (11.6%)	115 (10.8%)	153 (11.0%)
	Other	12 (3.7%)	13 (1.2%)	25 (1.8%)
Sex, n (%)	Male	224 (68.3%)	720 (67.9%)	944 (68.0%)
	Female	104 (31.7%)	340 (32.1%)	444 (32.0%)
NCI-ODWG hepatic impairment category ^a , n (%)	Normal	301 (91.8%)	940 (88.7%)	1,241 (89.4%)
	Mild	21 (6.4%)	115 (10.8%)	136 (9.8%)
	Moderate	3 (0.9%)	5 (0.5%)	8 (0.6%)
	Severe	3 (0.9%)	0 (0%)	3 (0.2%)
Renal impairment classification by MDRD, n (%)	Normal	230 (70.1%)	572 (54.0%)	802 (57.8%)
	Mild	73 (22.3%)	457 (43.1%)	530 (38.2%)
	Moderate	9 (2.7%)	31 (2.9%)	40 (2.9%)
	Severe	8 (2.4%)	0 (0%)	8 (0.6%)
	End stage	8 (2.4%)	0 (0%)	8 (0.6%)
Biologic treatment use, n (%)	No	0 (0%)	676 (63.8%)	676 (48.7%)
	Yes	0 (0%)	384 (36.2%)	384 (27.7%)
	Missing	328 (100%)	0 (0%)	328 (23.6%)
Food status, n (%)	Fasted	229 (69.8%)	820 (77.4%)	1049 (75.6%)
	Fed	82 (25%)	15 (1.4%)	97 (7%)
	Unknown	99 (30.2%)	1,060 (100%)	1,159 (83.5%)
Age (yr), mean (sd)		34.6 (13.3)	46.0 (13.4)	43.3 (14.3)
Weight (kg), mean (sd)		78.9 (15.0)	78.9 (15.0)	78.9 (15.0)
PASI score, mean (sd)		NA (NA)	20.4 (7.69)	20.4 (7.69)
BSA involvement (%), mean (sd)		NA (NA)	25.6 (15.4)	25.6 (15.4)
Disease duration (years), mean (sd)		NA (NA)	18.4 (12.6)	18.4 (12.6)
C-reactive protein (mg/L), mean (sd)		NA (NA)	4.78 (9.58)	4.78 (9.58)

Source: Reviewer's summary.

^aNCI-ODWG category defined by baseline labs of bilirubin and AST: bilirubin ≤ ULN and AST ≤ ULN – normal, bilirubin ≤ ULN and AST > ULN – mild B1, ULN < bilirubin ≤ 1.5X ULN – mild B2, 1.5X ULN < bilirubin ≤ 3X ULN – moderate, bilirubin >3X ULN – severe.

Table 83. Parameter Estimates and SE From Final Population PK Model: Deucravacitinib Parent Drug

Parameter	Parameter Estimate	RSE	Shrinkage	1000 Bootstrap (83.7% Success rate)
				Median [95% CI]
Fixed Effects				
CL (L/h)	10.7	3.4%	--	10.7 [9.42, 11.3]
V2 (L)	104	3.9%	--	104 [90.9, 111]
V3 (L)	42.5	4.5%	--	42.1 [37.8, 46.4]
Q (L/h)	3.15	7.4%	--	3.12 [2.64, 3.59]
KA (1/h)	2.35	7%	--	2.41 [2.09, 2.86]
Logit of F1	2.53	17.5%	--	2.47 [1.53, 3.87]
ED50 on F1 (mg)	0.713	19.8%	--	0.698 [0.488, 0.997]
Tlag (h)	0.112	22.6%	--	0.115 [0.0591, 0.216]
D1 (h)	0.573	8.1%	--	0.571 [0.373, 0.674]
CLBBWT: Baseline BW on CL	0.502	11.4%	--	0.493 [0.387, 0.599]
CLAGE: Age on CL	-0.154	21%	--	-0.154 [-0.223, -0.0858]
CLBGFRM: Baseline eGFR on CL	0.124	25.9%	--	0.126 [0.065, 0.192]
CLPOP: Subject Type on CL	0.153	17.1%	--	0.149 [0.0969, 0.203]
CLSEXN: Sex on CL (Female vs Male)	-0.177	13.3%	--	-0.179 [-0.226, -0.137]
V2BBWT: Baseline BW on V2	0.859	5.4%	--	0.863 [0.766, 0.959]
V2POP: Subject Type on V2	-0.0758	30.8%	--	-0.0762 [-0.127, -0.0324]
V2SEXN: Sex on V2 (Female vs Male)	-0.119	15.3%	--	-0.118 [-0.151, -0.0805]
V2DISDUR	-0.0471	28.7%	--	-0.0467 [-0.0723, -0.0237]
KAFED: Food on KA (High-fat Meal vs Fasted)	-1.46	10.3%	--	-1.44 [-1.81, -1.2]
KAFORMN1: Formulation on KA (Tablet vs Solution)	0.858	12.5%	--	0.858 [0.368, 1.24]
KAFORMN2: Formulation on KA (Tablet vs Capsule)	0.337	37.5%	--	0.353 [0.0833, 0.616]
IIV				
CL	0.0762	11.1%	49%	0.0755 [0.0601, 0.095]
CL-V2	0.0291	19.8%	--	0.0279 [0.0174, 0.0409]
V2	0.0225	21.7%	53%	0.0211 [0.0116, 0.0319]
KA	1.4	9.3%	17%	1.43 [1.19, 1.84]
LF	1.68	38.4%	52%	1.66 [0.466, 3.94]
CL-PsO	0.152	5.8%	19%	0.152 [0.135, 0.17]
Residual Error				
Proportional Error (Phase 1) (%)	0.269	3.2%	5%	0.268 [0.25, 0.286]
Additive Error (Phase 1) (ng/mL)	0.291	14.9%	5%	0.286 [0.189, 0.38]
Proportional Error (Phases 2 and 3) (%)	0.492	1.6%	5%	0.49 [0.472, 0.507]
Additive Error (Phases 2 and 3) (ng/mL)	0.158	29.7%	5%	0.155 [0.0254, 0.406]

Source: EDR 5.3.3.5 Population PK report Table 5.1.1.3-1 & Table 5.2.1.3-1).

Abbreviations: BBWT: baseline body weight; BGFRM: baseline eGFR by MDRD method; CI: confidence interval; CL: clearance of deucravacitinib; CLM: BMT-153261 clearance; D1: zero order absorption time; ED50: deucravacitinib dose to achieve half maximal F1; F1: bioavailability of deucravacitinib; IIV: interindividual variability; Fraction: deucravacitinib to the active metabolite BMT-153261 conversion fraction; HEPAN: hepatic impairment groups; IIV: Inter-individual variability; KA: absorption rate constant; LF: logit transformation of F1; Q: intercompartmental clearance of deucravacitinib; QM: inter-compartmental clearance of BMT-153261; PsO: psoriasis; RSE: relative standard error; Tlag: absorption lag time; V2: central volume of distribution of deucravacitinib; V3: peripheral volume of distribution of deucravacitinib; V4: central volume of distribution of BMT-153261; V5: peripheral volume of distribution of BMT-153261.

Table 84. Parameter Estimates and SE From Final Population PK Model Deucravacitinib Active Metabolite BMT-153261

Parameter	Parameter Estimate	RSE	Shrinkage	Sampling Importance Resampling Median [95% CI]
Fixed effects				
CLM (L/h)	9.6	1.4%	--	9.6 [9.33, 9.89]
QM (L/h)	16.4	2.9%	--	16.4 [15.4, 17.3]
V4 (L)	14.1	6.4%	--	14.1 [12.6, 16]
V5 (L)	54.3	1.4%	--	54.3 [52.8, 55.7]
Fraction Conversion (Parent to Metabolite)	0.22 FIX	0%	--	--
CLMAGE: AGE on CLM	0.228	16.1%	--	0.227 [0.162, 0.296]
CLMHEPAN: HEPAN on CLM	0.228	17.1%	--	0.231 [0.15, 0.31]
CLMBBWT: BBWT on CLM	0.786	5.9%	--	0.789 [0.696, 0.877]
CLMBGFRM: BGFRM on CLM	0.275	12.7%	--	0.276 [0.209, 0.343]
CLMRACE1: RACE1 on CLM (Asian vs White)	0.16	26.6%	--	0.16 [0.0782, 0.24]
CLMRACE2: RACE2 on CLM (Other vs White)	-0.0368	126%	--	-0.0383 [-0.125, 0.0547]
V4BBWT: BBWT on V4	0.993	6.6%	--	0.992 [0.862, 1.11]
V4AGE: AGE on V4	0.585	19.5%	--	0.579 [0.388, 0.794]
V4POP: Subject Type on V4	0.365	24.5%	--	0.366 [0.186, 0.527]
V4RACE1: RACE1 on V4 (Asian vs White)	0.479	29.6%	--	0.486 [0.214, 0.742]
V4RACE2: RACE2 on V4 (Other vs White)	-0.285	45.9%	--	-0.276 [-0.518, -0.0215]
V4HEPAN: HEPAN on V4	0.599	20.1%	--	0.597 [0.366, 0.824]
IIV				
CLM	0.139	4.9%	8.8%	0.139 [0.127, 0.154]
V4	0.704	8%	29.3%	0.706 [0.607, 0.823]
Residual Error				
Proportional Error (Phase 1) (%)	0.185	1.4%	--	0.185 [0.18, 0.19]
Additive Error (Phase 1) (ng/mL)	0.5 FIX	--	--	--
Proportional Error (Phases 2 and 3) (%)	0.343	1.2%	--	0.343 [0.336, 0.351]
Additive Error (Phases 2 and 3) (ng/mL)	0.5 FIX	--	--	--

Source: EDR 5.3.3.5 Population PK report Table 5.1.1.3-1 & Table 5.2.1.3-1).

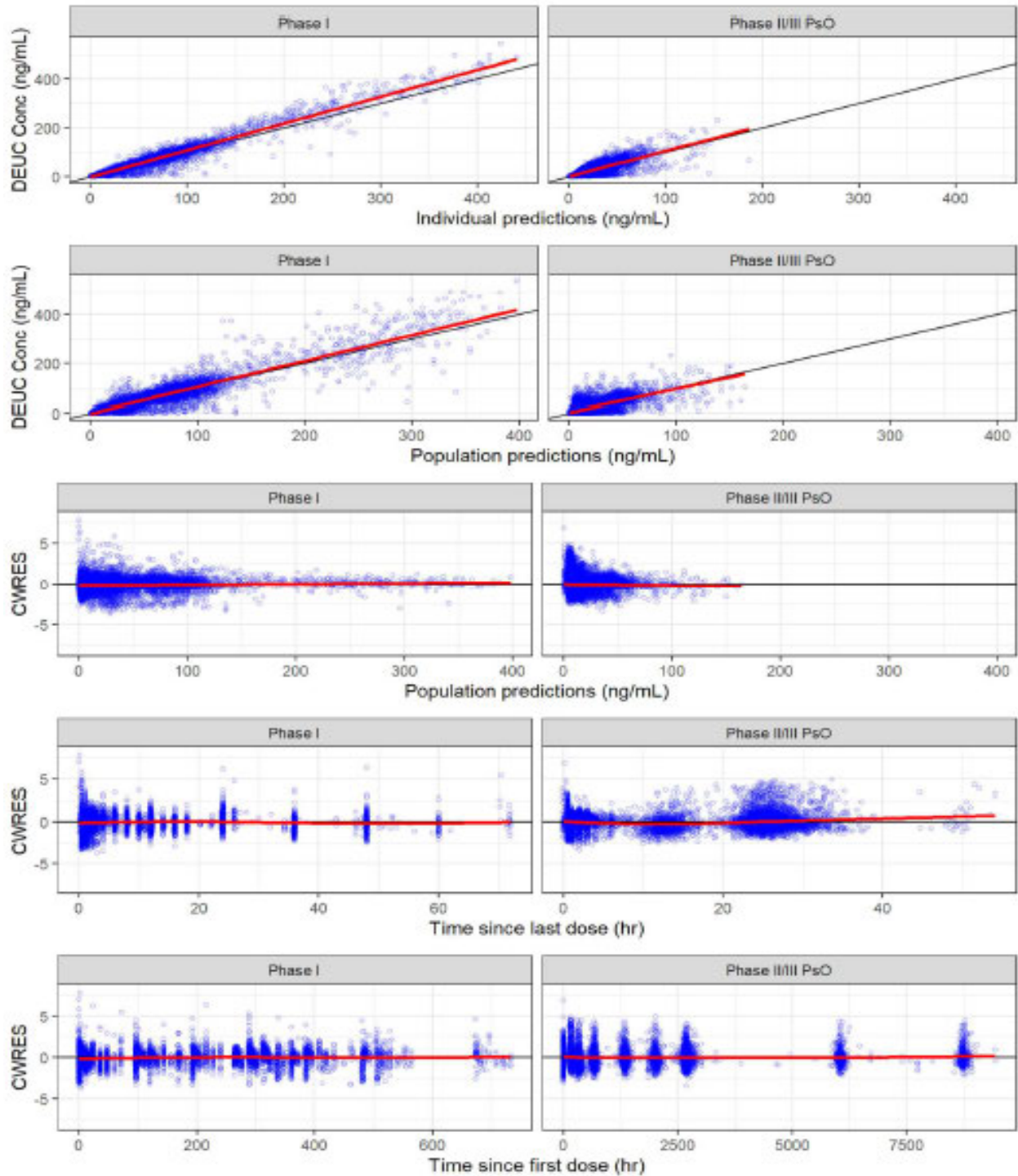
Abbreviations: BBWT: baseline body weight; BGFRM: baseline eGFR by MDRD method; CI: confidence interval; CL: clearance of deucravacitinib; CLM: BMT-153261 clearance; D1: zero order absorption time; ED50: deucravacitinib dose to achieve half maximal F1; F1: bioavailability of deucravacitinib; IIV: interindividual variability; Fraction: deucravacitinib to the active metabolite BMT-153261 conversion fraction; HEPAN: hepatic impairment groups; IIV: Inter-individual variability; KA: absorption rate constant; LF: logit transformation of F1; Q: intercompartmental clearance of deucravacitinib; QM: inter-compartmental clearance of BMT-153261; PsO: psoriasis; RSE: relative standard error; Tlag: absorption lag time; V2: central volume of distribution of deucravacitinib; V3: peripheral volume of distribution of deucravacitinib; V4: central volume of distribution of BMT-153261; V5: peripheral volume of distribution of BMT-153261.

The effect of covariates was parameterized as the following:

$$TVP_{ind} = TVP \cdot \prod_{i=1}^m \left(\frac{COV_i}{COV_{ref}} \right)^{THETA_i} \cdot \prod_{j=m}^p \exp(THETA_j)$$

In this equation, *i* describes the effect of the continuous variable and *j* describes the effect of the categorical variable that differs from the reference group. The reference is male PsO patient of 40 years old, weighs 85.5 kg, with eGFR of 90 mL/min/1.73m², disease duration of 15 months.

Figure 32. Goodness-of-Fit Plots for the Final Population PK Models: Deucravacitinib Parent Drug

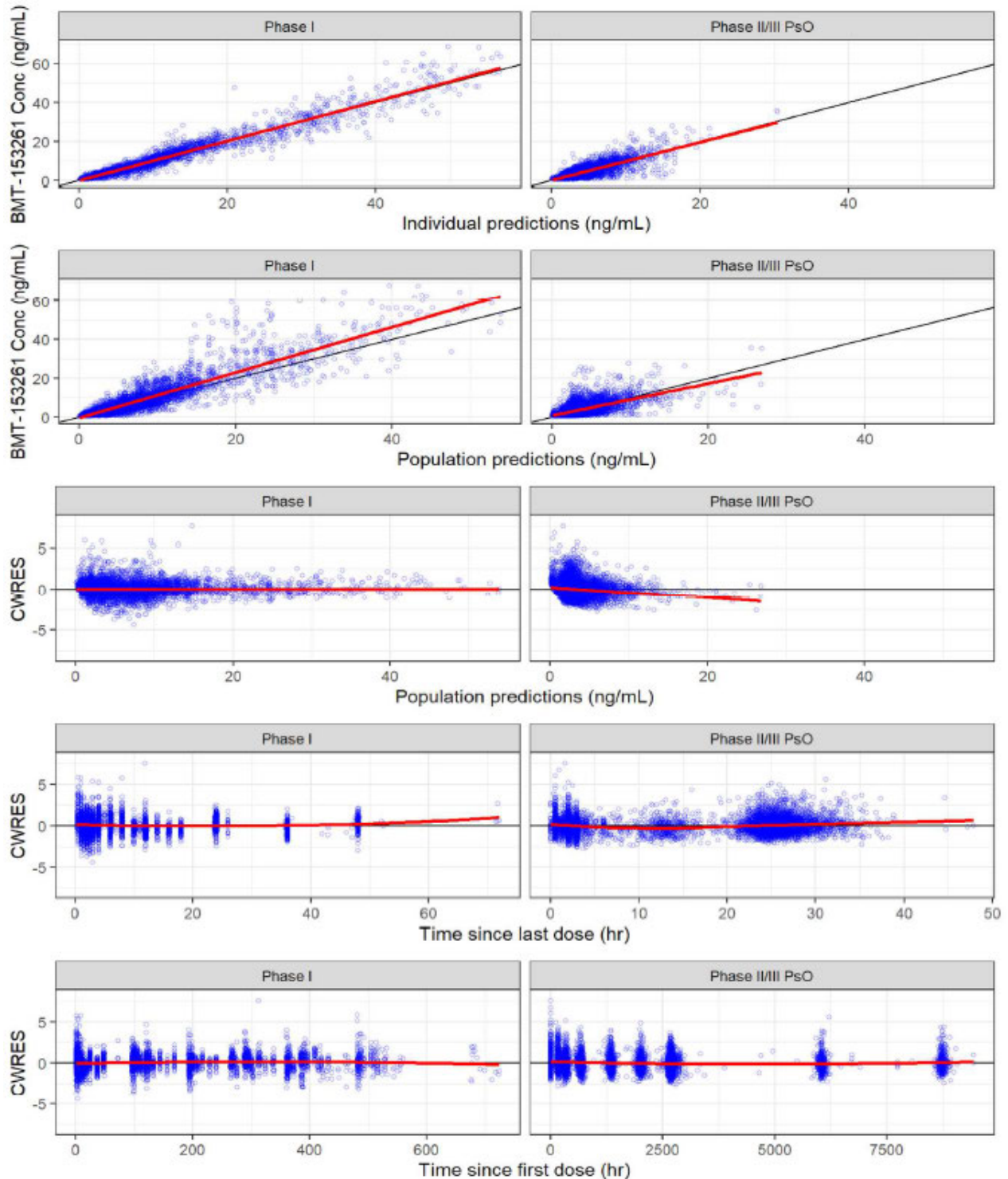


Source: EDR 5.3.3.5 Population PK report Figure 5.1.1.3-1 & Figure 5.2.1.3-1.

Blue dots represent data, and red line represents the smoothed conditional mean. Plots of CWRES versus time after previous dose were adjusted to focus on the period with the most available concentrations.

Abbreviations: CWRES: conditional weighted residuals; DEUC: Deucravacitinib; PsO: psoriasis.

Figure 33. Goodness-of-Fit Plots for the Final Population PK Models: Deucravacitinib Active Metabolite BMT-153261



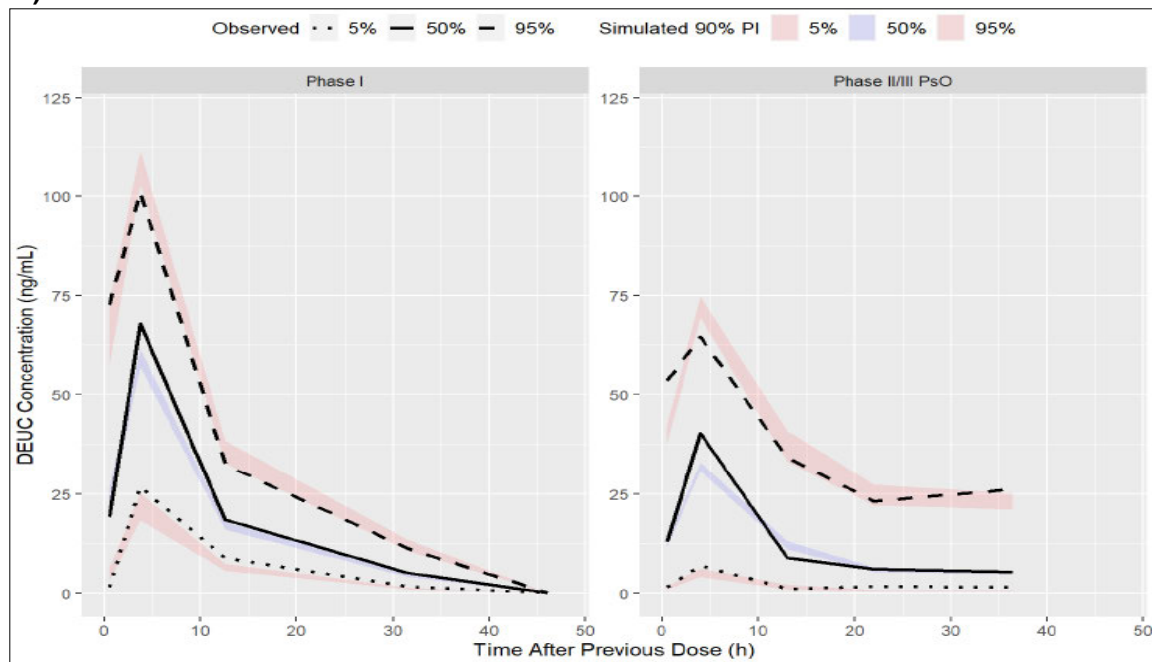
Source: EDR 5.3.3.5 Population PK report Figure 5.1.1.3-1 & Figure 5.2.1.3-1.

Blue dots represent data, and red line represents the smoothed conditional mean. Plots of CWRES versus time after previous dose were adjusted to focus on the period with the most available concentrations.

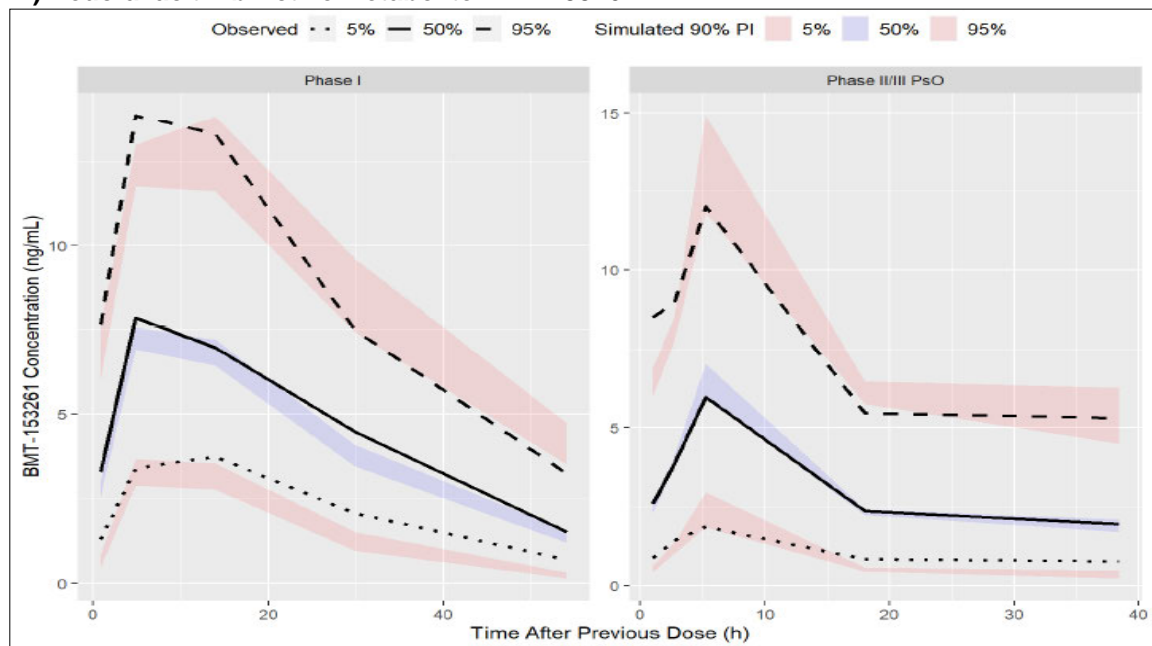
Abbreviations: CWRES: conditional weighted residuals; DEUC: Deucravacitinib; PsO: psoriasis.

Figure 34. VPC for Deucravacitinib PPK Model.

A.) Deucravacitinib



B.) Deucravacitinib Active Metabolite BMT-153261

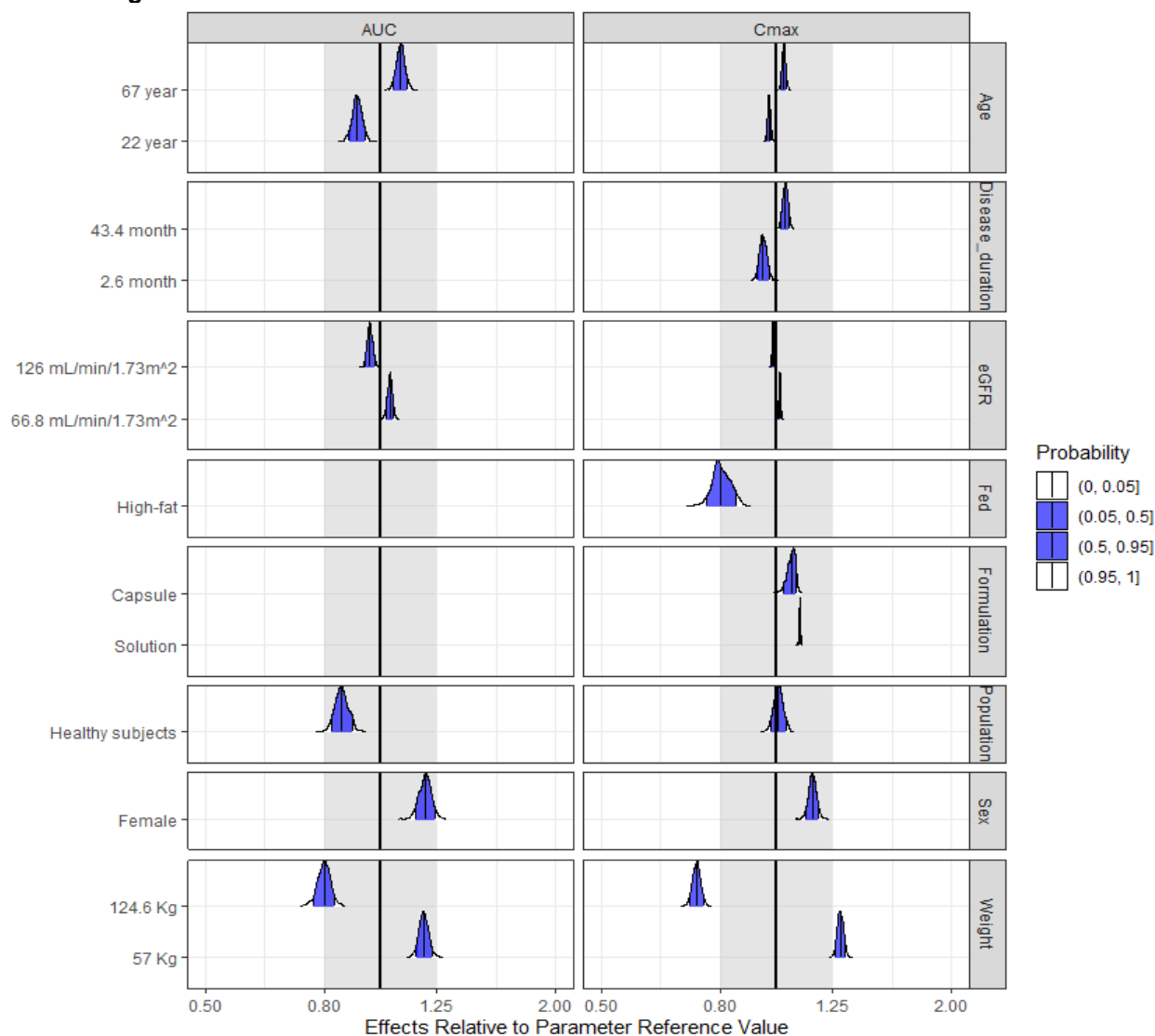


Source: EDR 5.3.3.5 Population PK report Figure 5.1.2-1 & Figure 5.2.2-1.

Dotted, solid, and dashed black lines: 5th, 50th, and 95th percentiles of the observed data; shaded area: 90% prediction interval (PI).

Independent variable: time (h) after last dose. Dependent variable: deucravacitinib (A) or BMT-153261 (B) concentrations ($\mu\text{g/mL}$). PsO: psoriasis

Figure 35. Influence of Covariates in the Final Model on Steady-State $AUC_{0-\tau}$ and C_{max} of the Parent Drug.



Source: Reviewer's analysis.

Density plot for each covariate reflects the uncertainty of Applicant's PPK model parameter estimates. The vertical line represents the predicted steady-state $AUC_{0-\tau}$ and C_{max} in the typical subject receiving 6 mg QD deucravacitinib tablet on empty stomach (male PsO patient of 40 years old, weighs 85.5 kg, with eGFR of 90 mL/min/1.73m², disease duration of 15 months). The points show the median ratio in the modeled $AUC_{0-\tau}$ or C_{max} as covariates are changed one at a time to indicated values. For continuous variables, the selected values are the 5th and 95th percentiles of the population.

19.4.1.3. Review Issues and Reviewer's Independent Analysis

19.4.1.3.1. Influence of Smoking Status on PK

Current smokers and prior smokers together consisted of ~40% of the PsO subjects in the PPK dataset. Given that smoking is known as a potent inducer of CYP1A2 enzyme activity, it may result in a reduction of deucravacitinib exposure as the drug is primarily metabolized via CYP1A2. The effect of smoking was evaluated as a categorical covariate in population PK analysis. Despite that the smoking status was only collected in PsO subjects, the effect is estimable as the CL in PsO subjects is shifted from other subject types. With covariate analysis,

the effect of smoking was found to be insignificant ($p > 0.05$). In a post-hoc analysis, a modest reduction in the exposure of the parent drug was observed in current smokers compared to non-smokers: 6% and 15% in all current smokers, 13% and 20% in current heavy smokers (≥ 20 cigarettes per day) for C_{max} and $C_{avg,ss}$, respectively. Based on the E-R relationship for efficacy (see Section 19.4.2), this magnitude of decrease in exposure is unlikely to result in clinically meaningful impact on response.

The active metabolite BMT-153261 is the product of CYP1A2 metabolism, thus the exposure was correspondingly increased in current smokers, which was also modest ($\leq 20\%$). As the active metabolite has minor contribution to the overall activity, and the change in exposure is in the opposite direction to the parent drug, the net change of the overall activity is smaller than that of the parent drug.

19.4.2. Exposure-Response Analysis

19.4.2.1. Executive Summary

The FDA's Assessment

- Dose adjustment is not suggested based on E-R models of efficacy and safety for specific populations.
- E-R models adequately describe dose/exposure-dependent change in efficacy endpoints (PASI and sPGA) and safety endpoint (infection/infestation adverse events).
 - For PASI and sPGA, $C_{avg,ss}$ of the parent drug best correlated with the response. A 50% lower exposure is predicted to result in a modest decrease in response (~9% in PASI75, ~6% in sPGA0/1 response) relative to that achieved at the median 6 mg QD dose exposures.
 - For infections/infestations, $C_{min,ss}$ of the parent drug best correlated with the event rate. A 100% higher exposure is predicted to result in a modest increase in infections/infestations (~3%) to that achieved at the median 6 mg QD dose exposures.
- Positive E-R relationship was identified for Gr3+ creatine phosphokinase (CK) elevation. Under 6mg QD, event rate is low (1.4%) and not apparently associated with an increase in exposure. A 50% reduction in exposure is expected to minimally impact the rate of this AE event, thus dose modification is unlikely to provide meaningful clinical benefit.
- Exploratory E-R analysis for lab abnormality observed in other JAK inhibitors do not show prominent trend at the therapeutic concentrations.

19.4.2.2. E-R Review Summary

Table 85. Exposure-Response Review Summary

Goal of E-R analysis: Evaluate/explore the E-R relationship for efficacy and safety for potential dose optimization.
General Information

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Study Included	Phase II: IM011011 (ITT) Phase III: IM011046, IM011047 (ITT)		
Exposure Variable	C_{minSS} , C_{maxSS} , C_{avgSS} of the parent drug		
Endpoint	Efficacy: PASI, sPGA Safety: infections/infestations at Week 12/16		
No. of Patients in Treatment Arm	1524		
Population Characteristics (Median/Range, n/%) (Table 82)	Age: 46 yr (18-84 yr), 149 (10%) ≥ 65 yr, 19 (1%) ≥ 75 yr Weight: 88.6 kg (36-182 kg) Sex: 1049 (69%) male Race: 1364 (90%) White, 160 (10%) Asian		
Dose(s) Included	Placebo 3 mg QOD 3, 6 (label dose, n=838), 12 mg QD 3, 6, 12 mg BID		
Exposure Explored (Min/Ref - Max/Ref, Ref: Median Exposure Under 6 mg QD)	The parent drug (excluding placebo): C_{minSS} (0.025-3.9), C_{maxSS} (0.0028-16), C_{avgSS} (0.015-6.2)		
Covariates Evaluated	Weight, BMI, sex, age, smoking status, country/region, race, baseline PASI/sPGA, baseline BSA involvement, baseline disease duration, native vs previous biologic use		
E-R Model			
	Summary	Acceptability/Comments	
Efficacy	Estimation Algorithm	Laplace method	Yes
	Model Structure	Longitudinal multilevel logistic regression model. The placebo effect and drug effect composed of concentration (C_{avgSS}) and time as E_{max} functions were parameterized as a linear combination on log-odds	Yes. Active metabolite has minor contribution to the overall activity. ER Analysis with the exposure of the total active moieties does not differ from that with the exposure of the parent drug.
	Model Parameter Estimates	Table 86 (PASI), Table 87 (sPGA)	N/A
	Significant Covariates for PASI E-R Model	<u>B_{max} (placebo effect):</u> - Negative factors: biologic use, male, weight <u>ET50 (time to achieve 50% E_{max}):</u> - Positive factors: age - Negative factors: baseline PASI, current/previous smoker	Yes. Factors affecting B_{max} or E_{max} are anticipated to have a reduced response at week 16/24. No covariates were found to have an added effect on EC50.
	Significant Covariates for sPGA E-R Model	<u>B_{max} (placebo effect):</u> - Negative factors: weight <u>E_{max} (drug effect):</u> - Negative factors: US/Rest of the world (EU as reference) <u>ET50 (time to achieve 50% E_{max}):</u> - Positive factors: weight	Benefit of dose increase is unsubstantiated given the exposures at 6 mg QD are in the plateau region of the E-R curve irrespective of the values of the significant covariates.

Multi-disciplinary Review and Evaluation
 NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

	Visualization of E-R	Figure 36, Figure 38 (PASI) Figure 37, Figure 39 (sPGA)	Yes. The trajectory of PASI score and sPGA over time is adequately described by the model.
Safety	Model Structure	Logistic regression with the effect of $C_{min,ss}$ parameterized using an E_{max} function	Yes.
	Significant Covariates	<u>RPCB (placebo effect):</u> - Negative factors: age <u>E_{max} (drug effect):</u> - Negative factors: biologic experience, baseline BSA involvement	Yes. The E-R curve is shallow at the therapeutic concentrations, and the risk is nominally increased at extreme values of the covariates thus no dose adjustment is warranted.
	Visualization of E-R	Figure 40, Figure 41	Acceptable. The trajectory of infections/infestations across exposure range generally aligns with the model prediction.

Table 86. Parameter Estimates and SE From Final Efficacy E-R Model: PASI

Parameter	Parameter estimate	RSE	Shrinkage	Median [95% CI]
B10: Baseline log-odds of placebo PASI 50 response	-3.4	3.5%	--	-3.41 [-3.65, -3.19]
B2: Difference in log-odds between PASI 50 and PASI 75	2.56	2.8%	--	2.56 [2.43, 2.72]
B3: Difference in log-odds between PASI 50 and PASI 75	2.57	3.1%	--	2.57 [2.43, 2.73]
B4: Difference in log-odds between PASI 50 and PASI 75	2.92	4.3%	--	2.93 [2.72, 3.19]
E _{max} : Maximal DEUC effect in log-odds	14	8.6%	--	14 [11.8, 16.1]
Ln(EC ₅₀): C _{avg} of the parent drug achieving half of the maximal effect on log-odds (ng/mL) at log scale	1.05	22.9%	--	1.05 [0.477, 1.53]
GAM: Hill coefficient on DEUC effect	1 FIX	--	--	--
B _{max} : Maximum log-odds of placebo PASI 50 response	-1.59	70.1%	--	-1.55 [-3.58, 0.555]
Ln(ET ₅₀): Time achieving half of the maximal effect on log-odds (ng/mL) at log scale	3.93	2%	--	3.93 [3.78, 4.08]
DELTA (1/s): Steepness parameter on sigmoidal time term	1 FIX	--	--	--
Scaling factor for placebo IIV	8.05	13.8%	--	8.01 [6.24, 10.4]
Scaling factor for DEUC IIV	4.3	4.4%	--	4.3 [3.94, 4.67]
Biologic use on B _{max}	-1.05	27.5%	--	-1.07 [-1.6, -0.514]
Female vs male on B _{max}	1.06	30.5%	--	1.07 [0.492, 1.69]
Body weight on E _{max}	-0.0517	16.2%	--	-0.0525 [-0.0681, -0.0364]
Age on ET ₅₀	0.0071	35.1%	--	0.00707 [0.0028, 0.0116]
Baseline PASI on ET ₅₀	-0.0178	28.5%	--	-0.0172 [-0.0283, -0.00787]
Current smoker on ET ₅₀	-0.195	47.3%	--	-0.193 [-0.383, -0.0266]
Previous smoker on ET ₅₀	-0.364	31.6%	--	-0.366 [-0.563, -0.141]
Missing smoking status on ET ₅₀	-0.366	24.5%	--	-0.354 [-0.524, -0.182]
IIV of baseline log-odds of placebo PASI 50 response*	1 FIX	--	16%	--

Source: EDR 5.3.3.5 Population ER report Table 5.1.1.3-1 & Table 5.2.1.3-1).

Abbreviations: B_{max}: maximal placebo effect; CI = confidence interval; DEUC: deucravacitinib; EC₅₀: concentration corresponding to half of the maximal drug effect; E_{max}: maximal drug effect; ET₅₀: time to achieve half of the maximal drug effect; IIV: inter-individual variability; PASI: Psoriasis Area and Severity Index; PASI 50/75/90/100: reductions in PASI score from baseline of 50%, 75%, 90%, and 100%, respectively; RSE: relative standard error. The effect of covariates was parameterized as $TVP_{ind} = TVP + \sum_{i=1}^m THETA_i * (COV_i - COV_{ref}) + \sum_{j=m}^p THETA_j$ where i describes the effect of continuous variable and j describes the effect of categorical variable that differs from the reference group. The reference is male PsO patient in EU of 40 years old, weighs 80 kg, non-smoker, no naive to prior biologic use, and baseline PASI score of 20.

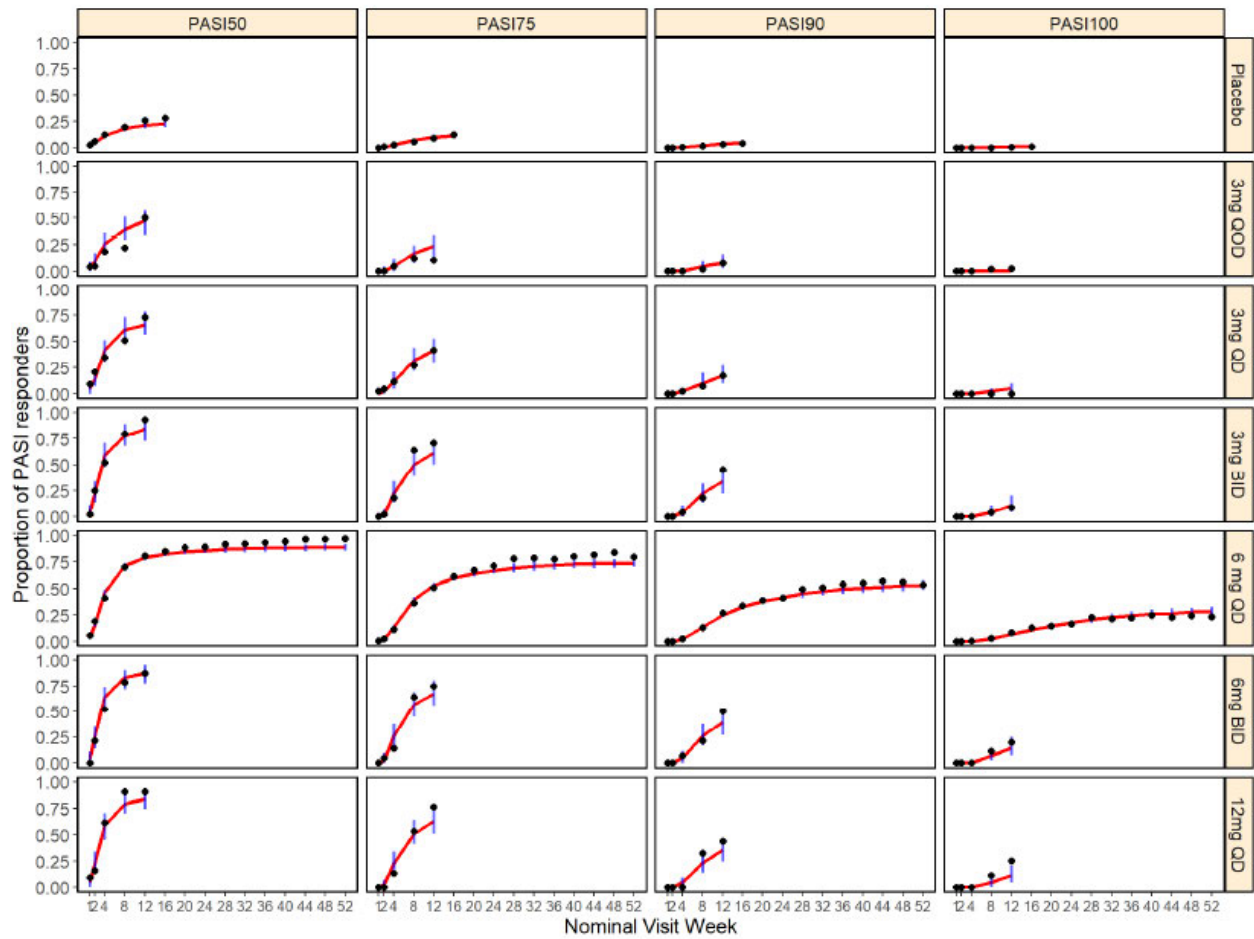
Table 87. Parameter Estimates and SE From Final Efficacy E-R Model: sPGA

Parameter	Parameter Estimate	RSE	Shrinkage	Median [95% CI]
B10: Baseline log-odds of placebo sPGA response	-4.54	4.2%	--	-4.55 [-4.94, -4.2]
B2: Difference in log-odds between sPGA0 and sPGA1	3.85	3.1%	--	3.84 [3.61, 4.11]
E _{max} : Maximal DEUC effect in log-odds	13.7	6.4%	--	13.9 [12.1, 15.5]
Ln(EC ₅₀): C _{avg} of the parent drug achieving half of the maximal effect on log-odds (ng/mL) at log scale	0.565	73.6%	--	0.581 [-0.838, 1.2]
GAM: Hill coefficient on DEUC effect	1 FIX	--	--	--
B _{max} : Maximum log-odds of placebo PASI 50 response	-4.77	16.6%	--	-4.84 [-6.38, -3.41]
Ln(ET ₅₀): Time achieving half of the maximal effect on log-odds (ng/mL) at log scale	3.56	2.9%	--	3.56 [3.34, 3.76]
DELTA (1/s): Steepness parameter on sigmoidal time term	1 FIX	--	--	--
Scaling factor for placebo IIV	10.3	9.8%	--	10.4 [8.29, 12.4]
Scaling factor for DEUC IIV	3.9	5.6%	--	3.87 [3.48, 4.32]
Body weight on B _{max}	-0.0316	28.5%	--	-0.0326 [-0.0518, -0.015]
Region (US vs EU) on E _{max}	-2.05	19.9%	--	-2.07 [-2.9, -1.31]
Region (Rest of world vs EU) on E _{max}	-0.483	76.6%	--	-0.497 [-1.16, 0.21]
WT on ET ₅₀	0.00605	41.8%	--	0.00587 [0.000105, 0.11]
IIV of baseline log-odds of placebo PASI 50 response	1 FIX	--	28%	--

Source: EDR 5.3.3.5 Population ER report Table 5.1.1.3-1 & Table 5.2.1.3-1).

Abbreviations: B_{max}: maximal placebo effect; CI = confidence interval; DEUC: deucravacitinib; EC₅₀: concentration corresponding to half of the maximal drug effect; E_{max}: maximal drug effect; ET₅₀: time to achieve half of the maximal drug effect; IIV: inter-individual variability; PASI: Psoriasis Area and Severity Index; PASI 50/75/90/100: reductions in PASI score from baseline of 50%, 75%, 90%, and 100%, respectively; RSE: relative standard error. The effect of covariates was parameterized as $TVP_{ind} = TVP + \sum_{i=1}^m THETA_i * (COVi - COVref) + \sum_{j=m}^p THETA_j$ where i describes the effect of continuous variable and j describes the effect of categorical variable that differs from the reference group. The reference is male PsO patient in EU of 40 years old, weighs 80 kg, non-smoker, no naive to prior biologic use, and baseline PASI score of 20.

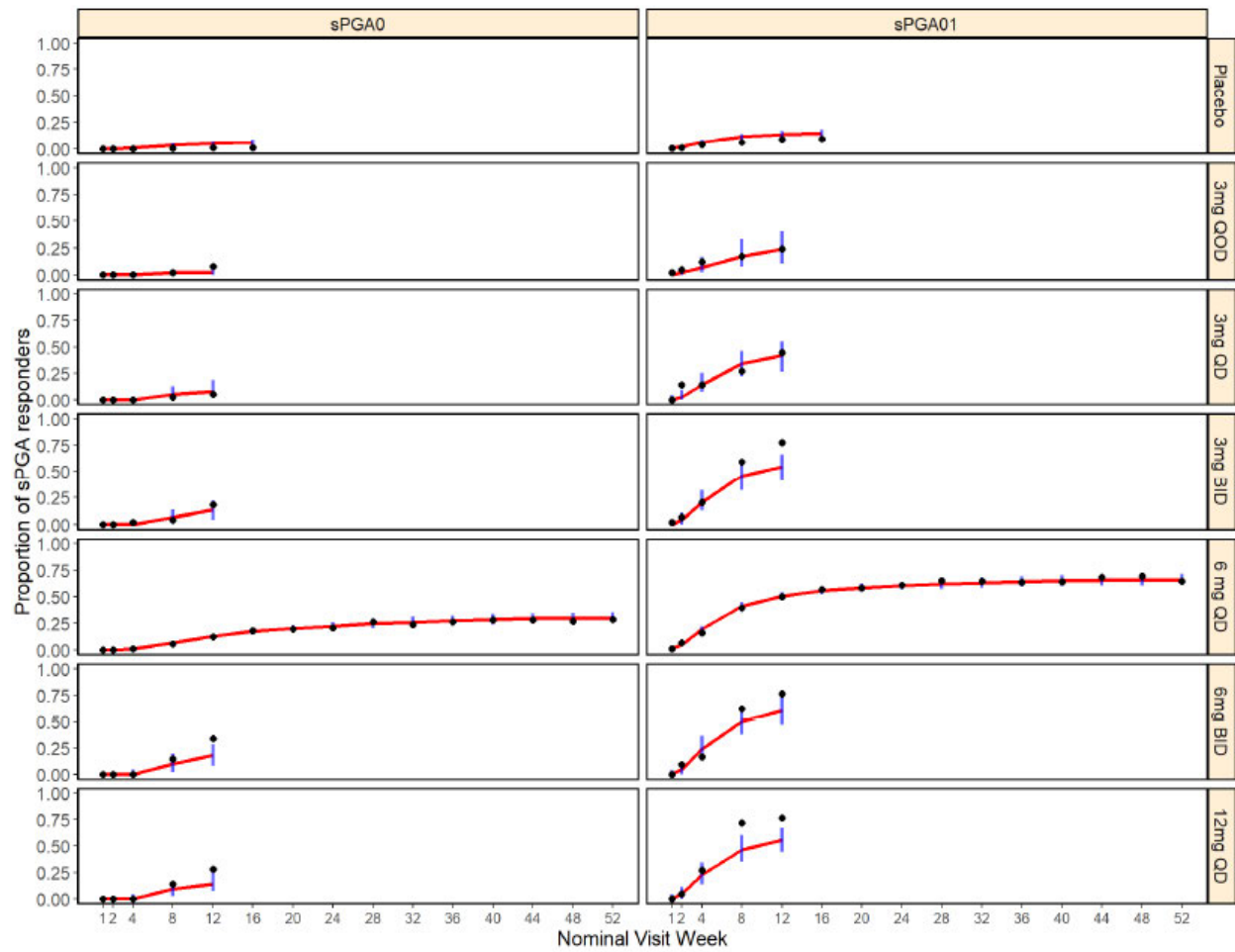
Figure 36. VPC of Final PASI E-R Model



Source: EDR 5.3.3.5 Population ER report Figure 5.1.2-1.

Black dots represent the observed response rate at a specific nominal visit week, red lines represent the median model predicted response rate, and the blue vertical lines represent the 90% PI for a specific visit week. PASI 50/75/90/100 = reductions in PASI score from baseline of 50%, 75%, 90%, and 100%, respectively.

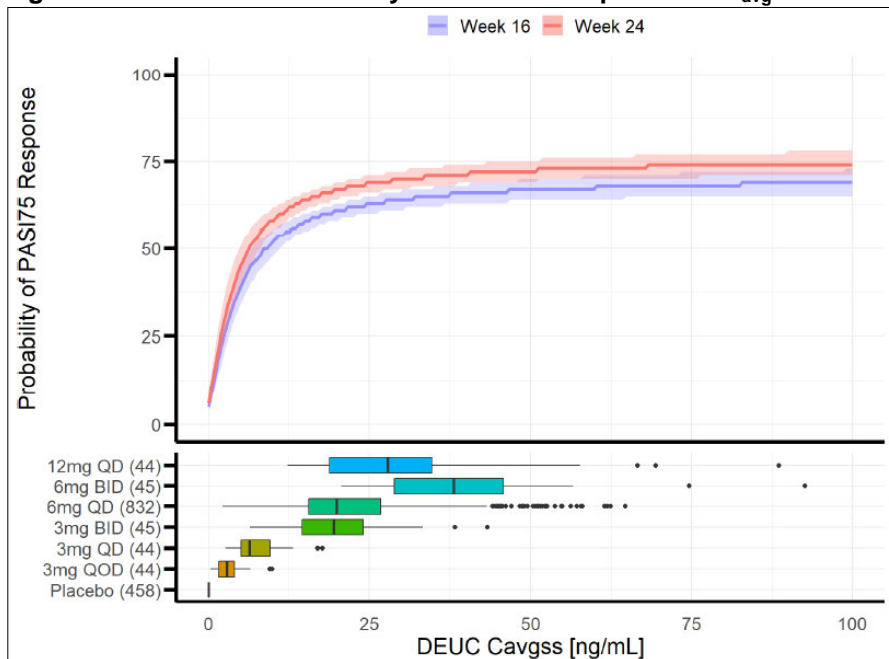
Figure 37. VPC of Final sPGA E-R Model



Source: EDR 5.3.3.5 Population ER report Figure 5.2.2-1.

Black dots show the response rate at a specific nominal visit week, the red line shows the VPC prediction with 90% confidence interval (blue vertical line).

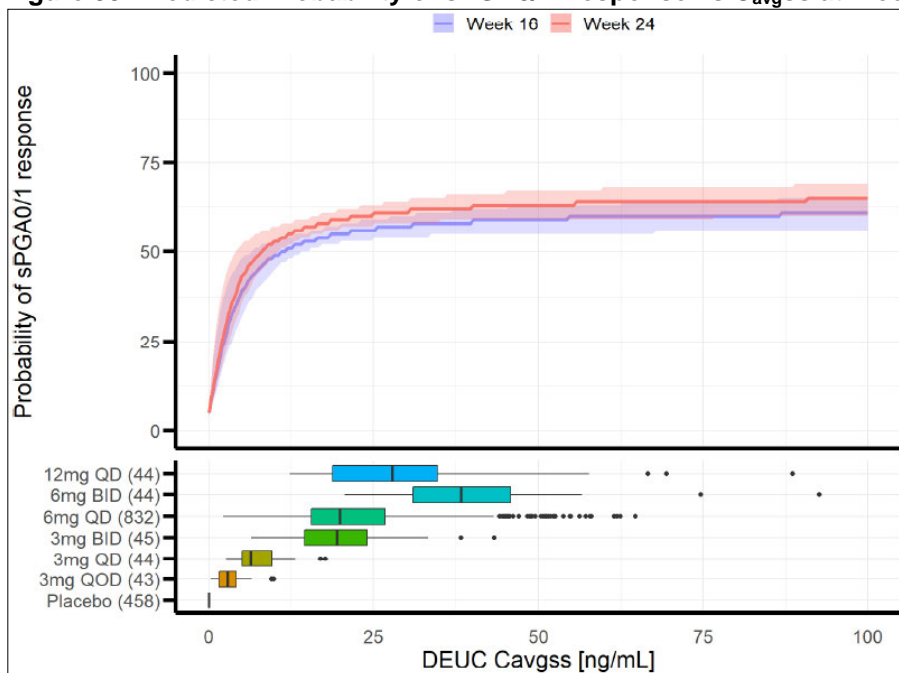
Figure 38. Predicted Probability of PASI 75 Response vs $C_{avg,ss}$ at Weeks 16 and 24



Source: EDR 5.3.3.5 Population ER report Figure 5.1.3-1.

Solid curve on upper panel gives the median PASI 75 probability for Week 16 or 24 with a ribbon showing the corresponding 90% prediction interval. PASI 75 = 75% reductions in PASI score from baseline.

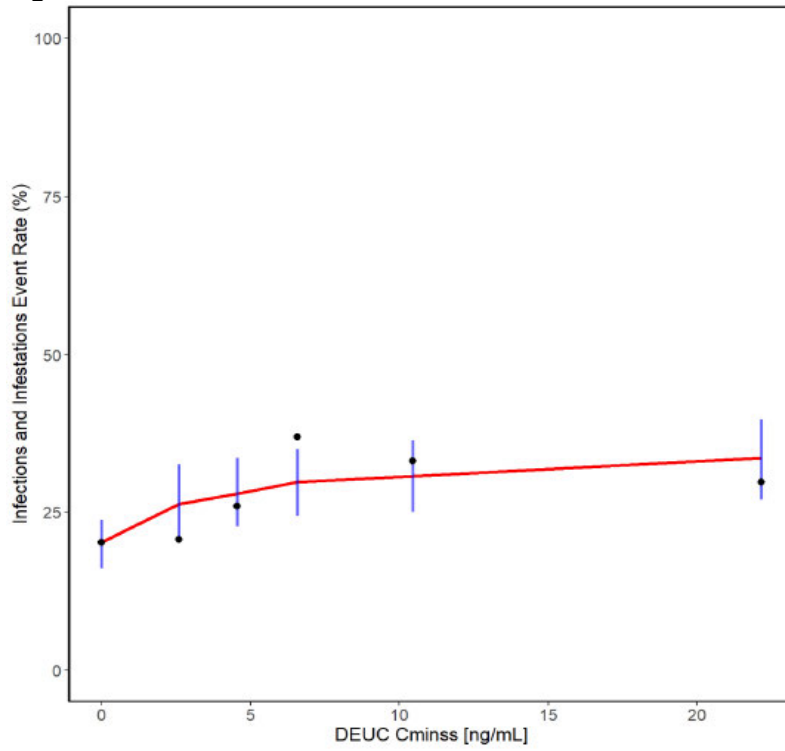
Figure 39. Predicted Probability of sPGA0/1 Response vs $C_{avg,ss}$ at Weeks 16 and 24



Source: EDR 5.3.3.5 Population ER report Figure 5.1.3-1.

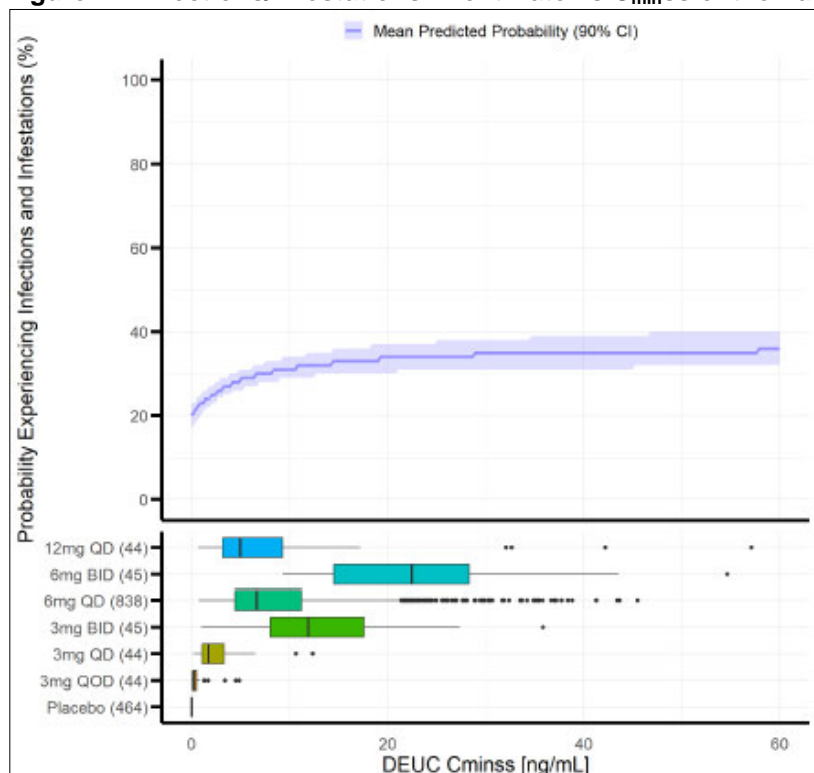
Solid curve on upper panel gives the median sPGA0/1 probability for Week 16 or 24 with a ribbon showing the corresponding 90% prediction interval. The boxplots at the bottom represent the exposure range achieved by each dosing regimen.

Figure 40. VPC of Final Infections/Infestations E-R Model



Source: EDR 5.3.3.5 Population ER report Figure 5.3.2-1.
Black dots show event rate for placebo + exposure quantiles of 0.2, 0.4, 0.6, 0.8, and 1, the red line shows the VPC prediction with 90% confidence interval (blue vertical line).

Figure 41. Infections/Infestations Event Rate vs $C_{min,ss}$ of the Parent Drug



Source: EDR 5.3.3.5 Population ER report Figure 5.1.3-1.

Solid curve on upper panel gives the median sPGA01 probability for Week 16 or 24 with a ribbon showing the corresponding 90% prediction interval. The boxplots at the bottom represent the exposure range achieved by each dosing regimen.

19.4.2.3. Review Issues and Reviewer's Independent Analysis

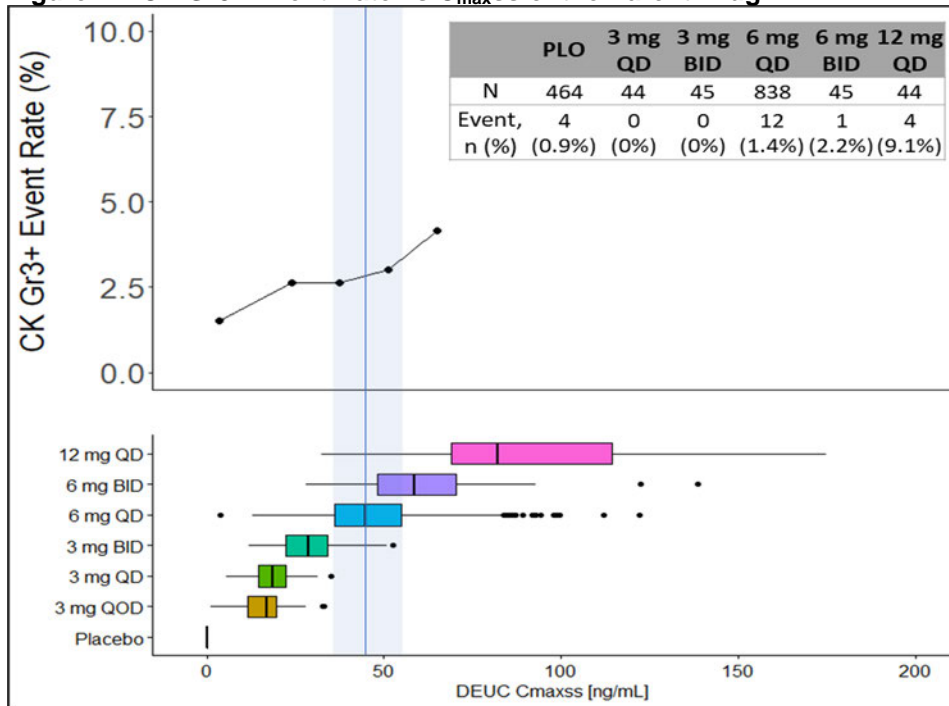
19.4.2.3.1. Dose-dependent Elevation in Creatine Phosphokinase (CK) Gr3+ Event Rate

A dose/exposure-dependent elevation in CK Gr3+ event rate was observed (Figure 42); the event rate in 12 mg QD is about 9-fold of that in placebo, and 6-fold of that in 6 mg QD. It was found to significantly correlate with C_{max} ($p < 0.05$).

Under the proposed dose of 6 mg QD, this particular AE occurs at a low rate, and it is generally not accompanied by muscle pathology and rarely leads to dose interruption/treatment discontinuation (dose interrupted in 4 subjects; treatment discontinued in 2 subjects). Dose reduction is not likely to reduce this AE as 1) the exposure in subjects with CK Gr3+ event greatly overlaps with that in subjects without CK Gr3+ event, and 2) 50% reduction in $C_{max,ss}$ is associated with a minimal reduction in the event rate.

CK AE appears to be a class effect for JAK inhibitors that may represent restoration of myoblast differentiation for muscle development (Queeney et al. 2019). Subjects with CK Gr2+ or Gr3+ has a right-skewed distribution for age but not weight (Figure 43), suggesting this elevation may be related to an advantage of young age in restoring muscle damage with chronic inflammatory disorders.

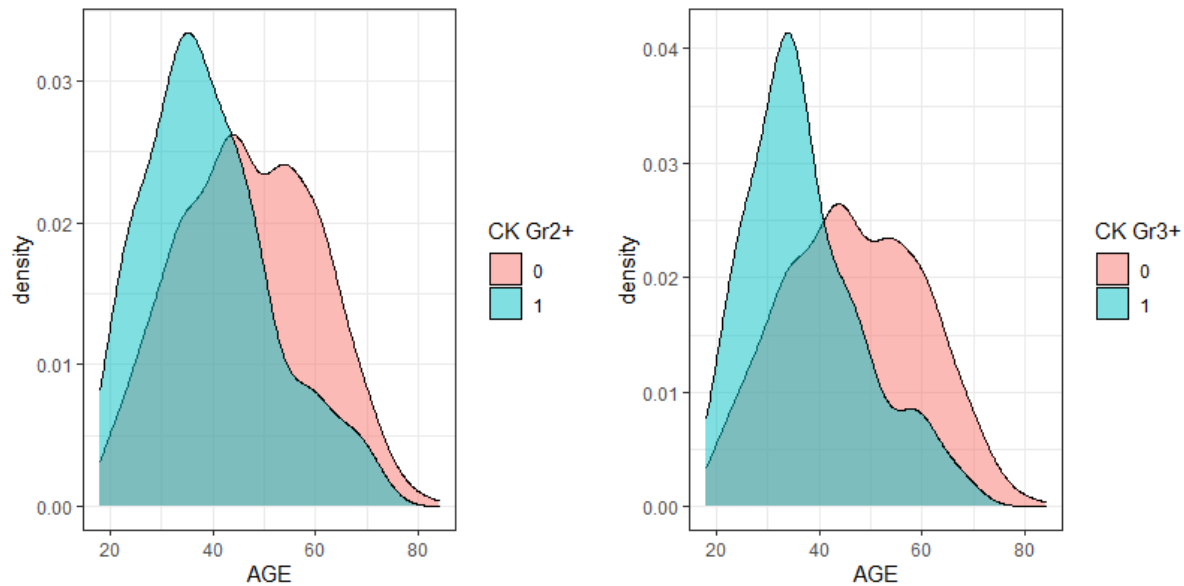
Figure 42. CK Gr3+ Event Rate vs C_{max}ss of the Parent Drug



Source: Reviewer analysis.

CK Gr3+ events up to Week 52 from Ph2/3 studies were included in the analysis. Black dots show event rate for placebo and exposure quantiles of 0.25, 0.5, 0.75, and 1.

Figure 43. Age Distribution of Subjects With or Without CK Event.



Source: Reviewer analysis

CK Gr2+ or Gr3+ events up to Week 52 from Ph2/3 studies were included in the analysis.

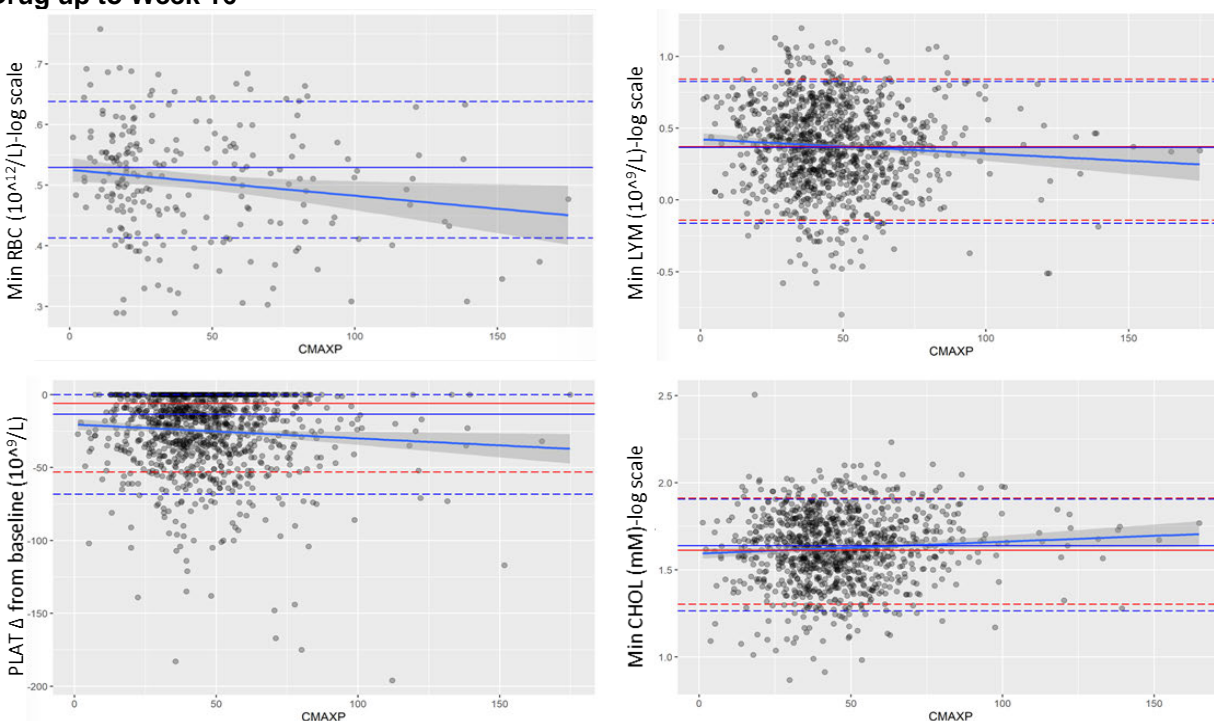
19.4.2.3.2. Evaluation of Exposure-dependent Effect on Lab Abnormalities Identified for Other JAK Inhibitors

To examine if dose dependent lab abnormalities due to class effect of JAK inhibitors are present in TYK2 inhibitor deucravacitinib at the therapeutic concentrations, univariate analysis and graphical exploration were performed. The lab measures include red blood cell count (RBC), neutrophil count (NEUT), lymphocyte count (LYM), platelets (PLAT) which are found to increase, and creatine kinase (CK), cholesterol (CHOL), low density lipoprotein (LDL), creatinine (CREAT) which are found to decrease, when treated with JAK inhibitors. The maximal values and the maximal change from baseline were evaluated as response variables, and all exposure measures on linear scale including $C_{max,ss}$, $C_{min,ss}$, $C_{avg,ss}$ of the parent, active metabolite, and total active species were evaluated as the independent variables. Two time points were used as the cutoff: Week 16 for Phase 2/3 studies, and Week 52 for Phase 3 studies. The response variables of placebo (Week 16 only) and apremilast (Weeks 16 and 52) were used as reference. Linear regression was applied to screen for significant univariate relationship ($p < 0.05$) between exposure and lab measures.

The following labs (up to Week 16) was found to have a statistically significant relationship with exposure: the minimal values of RBC and LYM are negatively associated with exposure, the maximal value of CHOL is positively associated with exposure, and the reduction of PLAT from baseline is positively associated with exposure ([Figure 44](#)). Similar observations were made for Study 46 and 47 up to Week 52. All of the significant relationships had a shallow slope, and none of the regression lines crossed the 5th or 95th of the reference, indicating no obvious exposure-dependent lab abnormalities tested. Extreme lab values defined by those situated outside of the 5th or 95th of the reference were observed in some subjects. Given the corresponding concentrations are generally in the low to middle range, the abnormalities were unlikely to be related to overexposure.

Overall, no exposure-dependent lab abnormality observed in JAK family inhibitors was identified for deucravacitinib at the therapeutic concentrations.

Figure 44. Maximal/Minimal Laboratory Values or Change From Baseline vs C_{max} SS of the Parent Drug up to Week 16



Reference lines of 5th, 50th, 95th lab values (red-apremilast, blue-placebo). Data included Study 11, 46, 47 up to week 16.

19.4.3. Summary of Bioanalytical Method Validation and Performance

19.4.3.1. Bioanalytical Methods for Deucravacitinib and Its Metabolites in Plasma

The concentrations of deucravacitinib, its metabolites BMT-153261, BMT-158170, BMT-334616 and stable-label microdose of deucravacitinib, (¹³C₂, ¹⁵N₃) BMS-986165 (BMT-409408-02) in human plasma were quantified using validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) methods. Several methods were used for bioanalysis. The validation of a method for quantification of deucravacitinib is summarized in [Table 88](#) and the cross-validation and partial validation of this method are summarized in [Table 89](#). The validation for a method developed for simultaneous analysis of deucravacitinib and BMT-153261 is summarized in [Table 90](#), and the cross-validation of this method is summarized in [Table 91](#). The validation of a method for quantification of BMT-158170 is summarized in [Table 92](#), and the cross-validation of this method is summarized in [Table 93](#). The validation of a method for quantification of BMT-334616 is summarized in [Table 94](#). The validation of a method for quantification of deucravacitinib and BMT-409408-02 is summarized in [Table 95](#). The bioanalytical method was adequately validated and met the acceptance criteria suggested in the FDA Bioanalytical Method Validation Guidance (May 2018).

The method performances for plasma sample quantification were acceptable.

Incurring sample reanalysis (ISR) for plasma samples were acceptable in terms of both sample size (at least 10% of the first 1000 samples and 5% of the remaining samples) and the results (>67% of the study samples evaluated within $\pm 20\%$ of the original sample concentrations) for all studies, except for IM011011 and IM011084. The number of samples analyzed from these studies were slightly lower than the recommended; 165 (of 2485 total samples) compared to the recommended 175 and 130 (of 1662 total samples) compared to the recommended 134 for studies IM011011 and IM011084, respectively.

All samples were analyzed within the established long-term stability window.

The results of the method validation and method performance for quantification of plasma samples are acceptable. The slightly lower number of samples analyzed in the two studies (IM011011 and IM011084) does not significantly affect the conclusions of these studies.

Table 88. Summary of LC-MS/MS Bioanalytical Method Validation for Determination of Deucravacitinib in Plasma

Parameter	Study Information					
Method ID	BAS RPT 1566					
Matrix	Human plasma					
Anticoagulant	Dipotassium ethylenediaminetetraacetic acid (K ₂ EDTA)					
Extraction method	Liquid-liquid extraction					
Analyte	Deucravacitinib					
Internal standard (IS)	(b) (4)					
Calibration curve range	0.200 to 500 ng/mL					
QC levels (ng/mL)	0.200 (LLOQ), 0.600 (LQC), 10.0 (GMQC), 200 (MQC), 350 (HQC), 10000 (dilution QC)					
Precision	LLOQ	LQLC	GM QC	Mid QC	High QC	Dilution QC
Between run (% CV)	0.0	3.2	4.8	0.0	2.8	3.6
Within run (% CV)	7.3	4.9	2.7	5.3	2.8	3.3
Total variation (% CV)	6.9	5.8	5.5	5.1	3.9	4.9
Accuracy	LLOQ	LQLC	GM QC	Mid QC	High QC	Dilution QC
% Deviation	3.5	0.2	2.4	-0.9	-2.4	4.0
Selectivity	blank: $\leq 1.5\%$ of LLOQ response 0.200 ng/mL : within $\pm 6.5\%$ bias					
Matrix effect	Mean Matrix Factor: 1.00 - 1.06					
Carry over	0.0007%					
Freeze/Thaw stability	3 cycles -20°C and -70°C					
Room temperature stability	24 hours					
Long-term stability	451 days at -20 °C					
Processed sample stability	48 hours at 5 °C					
Autosampler stability/ rejection integrity	72 hours at 5 °C					
Studies supported	IM011-002					

Table 89. Summary of Method BAS RPT 1566 Cross Validation and Partial Validation

Cross Validation	
Parameter	Study Information
Method ID	160394VPEJ_BPN
Matrix	Human plasma

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Anticoagulant	Dipotassium ethylenediaminetetraacetic acid (K ₂ EDTA)				
Extraction method	Liquid-liquid extraction				
Analyte	Deucravacitinib				
Internal standard (IS)	(b) (4)				
Calibration curve range	0.200 to 500 ng/mL				
QC Levels (ng/mL)	LLOQ QC: 0.200 QC1: 0.600 QC2: 15.0 QC3: 200 QC4: 350				
Precision	LLOQ QC	QC1	QC2	QC3	QC4
Between run (% CV)	6.5	3.8	2.2	2.1	2.4
Within run (% CV)	≤4.7%	≤3.6	≤1.4	≤1.6	≤1.9
Accuracy	LLOQ QC	QC1	QC2	QC3	QC4
Between run (% bias)	1.0	1.5	2.7	1.5	-0.3
Within run (% bias)	-6.0 to 6.5	-1.8 to 4.2	0.7 to 5.3	-0.5 to 3.5	2.3 to 2.0
Selectivity	blank: no peaks observed 0.200 ng/mL: -6.0 to 0.0% mean bias 500 ng/mL: -1.0 to 0.4% mean bias				
Matrix effect	Mean Normalized Matrix Factor 1.00				
Carry over	<20% of LLOQ response				
Freeze/thaw stability	5 cycles at -20 °C and -70 °C				
Room temperature stability	24 hours				
Long-term stability	392 days at -20 °C and -70 °C				
Studies supported	IM011-015, IM011-016, IM011-031, IM011-039				
Partial Validation					
Parameter	Study Information				
Method ID	170152VPEJ_BPN				
Matrix	Human plasma				
Anticoagulant	Dipotassium ethylenediaminetetraacetic acid (K ₂ EDTA)				
Extraction method	Liquid-liquid extraction				
Analyte	Deucravacitinib				
Internal standard (IS)	(b) (4)				
Calibration curve range	0.0500 to 50.0 ng/mL				
QC Levels (ng/mL)	LLOQ QC: 0.0500 QC1: 0.150 QC2: 1.50 QC3: 15.0 QC4: 37.5				
Precision	LLOQ QC	QC1	QC2	QC3	QC4
Between run (% CV)	4.3	3.0	1.1	1.1	1.8
Within run (% CV)	≤5.7%	≤3.2	≤1.3	≤1.0	≤2.6
Accuracy	LLOQ QC	QC1	QC2	QC3	QC4
Between run (% bias)	-8.2	-4.0	-3.3	-5.3	-7.7
Within run (% bias)	-11.0 to -6.0	-6.7 to -2.7	-4.0 to -2.7	-4.0 to -2.7	-8.8 to -6.9
Selectivity	blank: ≤2.9% of LLOQ peak area 0.0500 ng/mL: -10.8 to -4.6% bias				
Matrix effect	Mean Normalized Matrix Factor 1.01				
Carry over	<20% of LLOQ response				
Freeze/thaw stability	5 cycles at -20 °C and -70 °C				
Room temperature stability	24 hours				
Long-term stability	363 days at -20 °C and -70 °C				

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Studies supported	IM011-011

Table 90. Summary of LC-MS/MS Bioanalytical Method Validation for Determination of Deucravacitinib and BMT-153261 in Plasma

Parameter	Study Information				
Method ID	171731VRM_BPN				
Matrix	Human plasma				
Anticoagulant	Dipotassium ethylenediaminetetraacetic acid (K ₂ EDTA)				
Extraction method	Liquid-liquid extraction				
Analyte	Deucravacitinib, BMT-153261				
Internal standard (IS)	(b) (4) (IS deucravacitinib), (b) (4) (IS for BMT-153261)				
Calibration curve range	0.500 to 500 ng/mL				
QC levels (ng/mL)	LLOQ QC: 0.500 QC1: 1.50 QC2 (GM QC): 15.0 QC3: 150 QC4: 375 Dilution QC: 5000				
Precision					
Drug	LLOQ	QC1	QC3	QC4	
Deucravacitinib					
Between run (% CV)	8.4	6.4	4.0	7.0	
Within run (% CV)	≤11.1	≤9.2	≤4.9	≤9.4	
BMT-153261					
Between run (% CV)	6.4	3.9	3.4	4.8	
Within run (% CV)	≤7.4	≤4.6	≤4.3	≤6.8	
Accuracy					
Drug	LLOQ	QC1	QC3	QC4	
Deucravacitinib					
Between Run (% bias)	3.0	4.0	3.3	1.6	
Within Run (% bias)	-1.0 to 5.4	3.3 to 4.7	2.7 to 4.0	-3.5 to 4.3	
BMT-153261					
Between run (% bias)	3.6	2.7	2.7	-1.1	
Within run (% bias)	1.0 to 7.2	0.0 to 4.7	2.0 to 2.7	-4.0 to 1.3	
Selectivity	Deucravacitinib: LLOQ -8.0% to 19.2%; QC4 -13.6% to 0.8%. BMT-153261: LLOQ -16.4% to 6.8%; QC4 -15.2% to -3.7%.				
Matrix effect	Deucravacitinib Mean Matrix Factor: 1.01 – 1.02 BMT-153261 Mean Matrix Factor: 1.01				
Carry over	<20% of LLOQ response				
Freeze/Thaw stability	5 cycles -20°C and -70°C				
Room temperature stability	48 hours				
Long-term stability	1064 days at -20 °C and -70 °C				
Studies supported	IM011-011, IM011-025, IM011-031, IM011-039, IM011-045, IM011-046, IM011-047, IM011-048, IM011-061, IM011-062, IM011-071, IM011-084, IM011-087, IM011-088, IM011-090, IM011-100, IM011-101, IM011-119				

Table 91. Cross Validation Summary of Method 171731VRM_BPN

Parameter	Study Information
Method ID	400040-181206-PMV
Matrix	Human plasma

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Anticoagulant	Dipotassium ethylenediaminetetraacetic acid (K ₂ EDTA)	
Extraction method	Liquid-liquid extraction	
Analyte	Deucravacitinib, BMT-153261	
Internal standard (IS)	(b) (4) (IS deucravacitinib), (b) (4) (IS for BMT-153261)	
Calibration curve range	0.500 to 500 ng/mL	
QC Levels (ng/mL)	LLOQ QC: 0.500 LQC: 1.50 GMQC: 15.0 MQC: 150 HQC: 375 Dilution QC: 5000	
Precision (% CV)		
Precision Parameter	Deucravacitinib	BMT-153261
Intra-batch (All QC except LLOQ)	≤3.6	3.6
Intra-batch (LLOQ)	≤5.7	7.5
Inter-batch (All QC except LLOQ)	≤5.2	4.0
Inter-batch (LLOQ)	≤8.7	7.9
Accuracy (% bias)		
Accuracy Parameter	Deucravacitinib	BMT-153261
Intra-batch (All QC except LLOQ)	-3.2 to 12.7	-2.1 to 7.3
Intra-batch (LLOQ)	-7.2 to 9.4	-6.4 to 6.4
Inter-batch (All QC except LLOQ)	0.3 to 6.7	0.0 to 4.0
Inter-batch (LLOQ)	0.8	-0.6
Selectivity	No interference observed	
Matrix effect	Deucravacitinib: Matrix Factor (Normalized) 0.98 - 0.99 BMT-153261 : Matrix Factor(Normalized) 0.95 - 0.99	
Carry over	No carryover >20% of LLOQ observed	
Freeze/thaw stability	5 cycles at -20 °C and -70 °C	
Room temperature stability	27 hours	
Long-term stability	357 days at -20 °C and -70 °C	
Studies supported	IM011-046	

Table 92. Summary of LC-MS/MS Bioanalytical Method Validation for Determination of BMT-158170 in Plasma

Parameter	Study Information
Method ID	171775VWBA_BPN
Matrix	Human plasma
Anticoagulant	Dipotassium ethylenediaminetetraacetic acid (K ₂ EDTA)
Extraction method	Liquid-liquid extraction
Analyte	BMT-158170
Internal standard (IS)	(b) (4)
Calibration curve range	0.500 to 500 ng/mL
QC levels (ng/mL)	0.500 (LLOQ), 1.50 (LQC), 150 (MQC), 375 (HQC)
Precision (%CV)	Intra-assay: ≤4.4% Inter-assay: ≤6.7%
Accuracy (%Bias)	Intra-assay: -3.4% to 11.0% Inter-assay: 2.1% to 5.0%
Selectivity	LLOQ -5.0% to 11.8% HQC -5.3% to 3.7%.
Matrix effect	No matrix effect observed
Carry over	No carryover >20% of LLOQ observed

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Freeze/Thaw stability	5 cycles -20°C and -70°C
Room temperature stability	24 hours
Long-term stability	593 days at -20 °C and -70°C
Processed sample stability	125 hours at 4 °C
Studies supported	IM011-045, IM011-046, IM011-047, IM011-048, IM011-061, IM011-062, IM011-071, IM011-084, IM011-087, IM011-088, IM011-090, IM011-100, IM011-101

Table 93. Cross Validation Summary of Method 171775VWBA_BPN

Parameter	Study Information
Method ID	400040-181576-PMV
Matrix	Human plasma
Anticoagulant	Dipotassium ethylenediaminetetraacetic acid (K ₂ EDTA)
Extraction method	Liquid-liquid extraction
Analyte	BMT-158170
Internal standard (IS)	(b) (4)
Calibration curve range	0.500 to 500 ng/mL
QC levels (ng/mL)	0.500 (LLOQ), 1.50 (LQC), 150 (MQC), 375 (HQC)
Precision (%CV)	Intra-assay (all QC except LLOQ): ≤5.1 Intra-assay (LLOQ): ≤9.5 Inter-assay (all QC except LLOQ): ≤10.1 Inter-assay (LLOQ): ≤10.2
Accuracy (%Bias)	Intra-assay (all QC except LLOQ): -6.9 to 14.1 Intra-assay (LLOQ): -3.6 to 17.4 Inter-assay (all QC except LLOQ): 0.5 to 5.3 Inter-assay (LLOQ): 7.6
Selectivity	LLOQ -5.0% to 11.8% HQC -5.3% to 3.7%.
Matrix effect	Matrix factor bias: LQC: ≤ -5.9 %; HQC: ≤ -2.0%
Carry over	No carryover >20% of LLOQ observed
Freeze/Thaw stability	5 cycles -20°C and -70°C
Room temperature stability	27.5 hours
Long-term stability	506 days at -20 °C and -70°C
Studies supported	IM011-046

Table 94. Summary of LC-MS/MS Bioanalytical Method Validation for Determination of BMT-334616 in Plasma

Parameter	Study Information
Method ID	191060VRM_BPN
Matrix	Human plasma
Anticoagulant	Dipotassium ethylenediaminetetraacetic acid (K ₂ EDTA)
Extraction method	Protein precipitation
Analyte	BMT-334616
Internal standard (IS)	(b) (4)
Calibration curve range	0.100 to 100 ng/mL
QC levels (ng/mL)	0.100 (LLOQ), 0.300 (LQC), 30.0 (MQC), 75.0 (HQC)
Precision (%CV)	Intra-assay: ≤14.5 Inter-assay: ≤9.1
Accuracy (%Bias)	Intra-assay: -7.8 to 2.0 Inter-assay: -2.7 to -0.8
Selectivity	No interference

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Matrix effect	Mean normalized matrix factor: 0.98 – 1.03
Carry over	No carryover >20% of LLOQ observed
Freeze/Thaw stability	5 cycles -20°C and -70°C
Room temperature stability	24 hours
Long-term stability	202 days at -20 °C and -70°C
Studies supported	IM011-100, IM011-101

Table 95. Summary of LC-MS/MS Bioanalytical Method Validation for Determination of Deucravacitinib and BMT-409408-02 in Plasma

Parameter	Study Information
Method ID	181653VRM_BPN
Matrix	Human plasma
Anticoagulant	Dipotassium ethylenediaminetetraacetic acid (K ₂ EDTA)
Extraction method	Liquid-liquid extraction
Analytes	Deucravacitinib, BMT-409408-02 ([¹³ C ₂ , ¹⁵ N ₃] Deucravacitinib)
Internal standard (IS)	(b) (4)
Calibration curve range	50.0 to 50000 pg/mL for Deucravacitinib 2.00 to 2000 pg/mL for BMT-409408-02
QC levels (pg/mL)	<u>Deucravacitinib:</u> 50.0 (LLOQ), 150 (LQC), 15000 (MQC), 37500 (HQC) <u>BMT-409408-02:</u> 2.00 (LLOQ), 6.00 (LQC), 600 (MQC), 1500 (HQC)
Precision (%CV)	<u>Deucravacitinib:</u> Intra-assay: ≤6.3 Inter-assay: ≤5.7 <u>BMT-409408-02:</u> Intra-assay: ≤11.2 Inter-assay: ≤11.2
Accuracy (%Bias)	<u>Deucravacitinib:</u> Intra-assay: -4.8 to 8.7% Inter-assay: -3.7 to 6.7% <u>BMT-409408-02:</u> Intra-assay: -5.5 to 12.5% Inter-assay: -4.0 to 7.5%
Selectivity	Overall acceptance criteria was met : At least 80% of the lots within RE 15.0% (LOQ ±20.0%) for two-thirds of the replicates
Matrix effect	Mean normalized matrix factor: 1.01-1.03 for deucravacitinib; 0.97-1.01 for BMT-409408-02
Carry over	No carryover >20% of LLOQ observed
Freeze/Thaw stability	5 cycles -20°C and -70°C
Room temperature stability	24 hours
Long-term stability	105 days at -20 °C and -70°C
Studies supported	IM011-067

19.4.3.2. Bioanalytical Methods for Deucravacitinib and Its Metabolites in Urine

The concentrations of deucravacitinib, its metabolites BMT-153261, BMT-158170 and BMT-334616 in urine were quantified using validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) methods. Several methods were used. The validation of a method used for quantification of deucravacitinib is summarized in [Table 96](#), and the cross-validation of this method is summarized in [Table 97](#). The validation of a method used for

quantification of BMT-153261 and BMT-158170 is summarized in [Table 98](#). The validation of a method used for quantification of BMT-334616 is summarized in [Table 99](#). The bioanalytical method was adequately validated and met the acceptance criteria suggested in the FDA Bioanalytical Method Validation Guidance (May 2018).

All samples were analyzed within the established long-term stability window.

Table 96. Summary of LC-MS/MS Bioanalytical Method Validation for Determination of Deucravacitinib in Urine

Parameter	Study Information
Method ID	BAS RPT 1567
Matrix	0.2% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonic (CHAPS) human urine
Extraction method	Liquid-liquid extraction
Analyte	Deucravacitinib
Internal standard (IS)	(b) (4)
Calibration curve range	0.200 to 500 ng/mL
Accuracy and Precision	LLOQ QC (0.200 ng/mL) Low QC (0.600 ng/mL) GM QC (10.0 ng/mL) Mid QC (200 ng/mL) High QC (350 ng/mL) Dilution QC (10000 ng/mL)
Mean Conc.	0.206 0.590 9.976 198.973 320.957 10442.646
% Dev	3.0 -1.7 -0.2 -0.5 -8.3 4.4
Between Run (%CV)	0.0 2.5 3.8 0.0 2.0 0.0
Within Run (%CV)	4.5 4.8 8.0 4.6 3.7 5.2
Total Variation (%CV)	4.2 5.4 8.9 4.5 4.2 4.8
Selectivity	No interference
Matrix effect	No matrix effect
Carry over	No carryover >20% of LLOQ observed
Freeze/Thaw stability	4 cycles -20°C
Room temperature stability	27 hours
Long-term stability	188 days at -20 °C
Studies supported	IM011002

Table 97. Cross Validation Summary of Method BAS RPT 1567

Parameter	Study Information
Method ID	170147VPEJ_BPN
Matrix	0.2% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonic (CHAPS) human urine
Extraction method	Liquid-liquid extraction
Analyte	Deucravacitinib
Internal standard (IS)	(b) (4)
Calibration curve range	0.200 to 500 ng/mL
Precision (%CV)	
QC Level	Conc. Intra-run Inter-run
LLOQQC	0.200 ng/mL ≤6.0% 7.2%
LQC	0.600 ng/mL ≤4.0% 4.0%
MQC	200 ng/mL ≤1.2% 2.2%
HQC	350 ng/mL ≤1.0% 2.7%
Accuracy (%Bias)	
QC Level	Conc. Intra-run Inter-run
LLOQQC	0.200 ng/mL -14.5 to -3.5% -7.5%
LQC	0.600 ng/mL -5.7 to 1.0% -2.3%

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

MQC	200 ng/mL	-6.0 to -2.0%	-4.5%
HQC	350 ng/mL	-8.9 to -3.1%	-6.6%
Selectivity	No interference		
Matrix effect	Mean matrix factor: 1.00-1.02		
Carry over	No carryover >20% of LLOQ observed		
Freeze/Thaw stability	5 cycles -20°C and -70 °C		
Room temperature stability	25 hours		
Long-term stability	398 days at -20 °C and -70 °C		
Studies supported	IM011-016, IM011-061, IM011-071, IM011-100, IM011-101		

Table 98. Summary of LC-MS/MS Bioanalytical Method Validation for Determination of BMT-153261 and BMT-158170 in Urine

Parameter	Study Information				
Method ID	181324VRM_BPN				
Matrix	0.2% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonic (CHAPS) human urine				
Extraction method	Liquid-liquid extraction				
Analytes	BMT-153261 and BMT-158170				
Internal standard (IS)	(b) (4) (IS for BMT-153261), (b) (4) (IS for BMT-158170)				
Calibration curve range	0.200 to 500 ng/mL				
Precision (%CV)	BMT-153261				
	QC Level	Conc.	Intra-run	Inter-run	
	LLOQQC	0.200 ng/mL	≤9.2%	9.6%	
	LQC	0.600 ng/mL	≤5.8%	4.5%	
	MQC	150 ng/mL	≤5.4%	3.9%	
	HQC	375 ng/mL	≤5.1%	4.9%	
	BMT-158170 in Urine				
	QC Level	Conc.	Intra-run	Inter-run	
	LLOQQC	0.200 ng/mL	≤9.7%	11.4%	
	LQC	0.600 ng/mL	≤8.0%	7.0%	
	MQC	150 ng/mL	≤4.5%	5.0%	
	HQC	375 ng/mL	≤4.3%	4.4%	
	Accuracy (%Bias)	BMT-153261			
		QC Level	Conc.	Intra-run	Inter-run
LLOQQC		0.200 ng/mL	2.0 to 15.5%	8.5%	
LQC		0.600 ng/mL	6.0 to 8.7%	7.0%	
MQC		150 ng/mL	0.7 to 2.7%	1.3%	
HQC		375 ng/mL	-8.0 to -1.9%	-5.6%	
BMT-158170					
QC Level		Conc.	Intra-run	Inter-run	
LLOQQC		0.200 ng/mL	-11.0 to 6.5%	-2.5%	
LQC		0.600 ng/mL	-3.0 to 7.2%	1.3%	
MQC		150 ng/mL	-2.7 to 6.7%	1.3%	
HQC		375 ng/mL	-6.9 to -0.3%	-2.9%	
Selectivity		No issues with interference			
Matrix effect		Mean matrix factor: 1.07-1.14 for BMT-153261; 1.03-1.05 for BMT-158170			
Carry over	No carryover >20% of LLOQ observed				

Multi-disciplinary Review and Evaluation
NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg

Freeze/Thaw stability	5 cycles -20°C and -70 °C
Room temperature stability	24 hours
Long-term stability	405 days and 357 days for BMT-153261 and BMT-158170398, respectively at -20 °C 409 days for BMT-153261 and BMT-158170398 at -70 °C
Studies supported	IM011-061, IM011-071, IM011-100, IM011-101

Table 99. Summary of LC-MS/MS Bioanalytical Method Validation for Determination of BMT-334616 in Urine

Parameter	Study Information
Method ID	191057VRM_BPN
Matrix	0.2% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonic (CHAPS) human urine
Sample Isolation	Dilution
Analytes	BMT-334616
Internal standard (IS)	(b) (4)
Calibration curve range	50.0 to 1000 ng/mL
QC Levels (ng/mL)	50.0 (LLOQ), 150 (LQC), 300 (MQC), 750 (HQC)
Precision (%CV)	Intra-run: ≤3.5% Inter-run: ≤3.0%
Accuracy (%Bias)	Intra-run: 2.7 to 6.8% Inter-run: 3.7 to 5.0%
Selectivity	No issues with interference
Matrix effect	Mean normalized matrix factor: 0.99 to 1.01
Carry over	No carryover >20% of LLOQ observed
Freeze/Thaw stability	5 cycles -20°C and -70 °C
Room temperature stability	24 hours
Long-term stability	231 days at -20 °C and -70 °C
Studies supported	IM011-100, IM011-101

19.4.3.3. Bioanalytical Methods for Coadministered Drugs

The bioanalytical methods and method performance for the coadministered drugs used in the clinical studies are summarized below. The bioanalytical method was adequately validated and met the acceptance criteria suggested in the FDA Bioanalytical Method Validation Guidance (May 2018).

All samples were analyzed within the established long-term stability window.

Cyclosporine

Samples were prepared using a liquid-liquid extraction method and a validated LC-MS/MS method was used for quantification of cyclosporine in human whole blood. The assay is validated over the range of 2.00 to 2000 ng/mL. The inter-run accuracy and precision demonstrated during validation is ± 4.16% and ≤ 10.0%, respectively. Stability of cyclosporine in human whole **APPEARS THIS WAY ON ORIGINAL** blood was demonstrated at room temperature for 24 hr, during freeze/thaw for 5 cycles at -20°C and -70°C and during long-term storage at -20°C for 616 days and at -70°C for 37 days.

Diflunisal

Samples were prepared using a protein precipitation extraction method and a validated LC-MS/MS method was used for quantification of diflunisal in human plasma. The assay is validated over the range 400 to 200,000 ng/mL. The inter-run accuracy and precision demonstrated during validation is $\pm 4.19\%$ and $\leq 7.55\%$, respectively. Stability of diflunisal in human plasma was demonstrated at room temperature for 4 hr, at 4°C for 21 hr, during freeze/thaw for 4 cycles at -20°C and -80°C and during long-term storage at -20°C and -80°C for 665 days.

Ethinyl Estradiol/Norethindrone

Samples were prepared using a liquid-liquid extraction method and a validated LC-MS/MS method was used for quantification of ethinyl estradiol and norethindrone in human plasma. The assay is validated over the range 0.002 to 0.500 ng/mL for ethinyl estradiol and 0.050 to 25.0 ng/mL for norethindrone. The inter-run accuracy and precision demonstrated during validation for ethinyl estradiol is $\pm 4.68\%$ and $\leq 8.15\%$ and for norethindrone is $\pm 4.00\%$ and $\leq 11.6\%$, respectively. Stability of ethinyl estradiol and norethindrone in human plasma was demonstrated at room temperature for 24 hr, during freeze/thaw for at least 5 cycles at -20°C and during long-term storage at -20°C for 490 days.

Fluvoxamine

Samples were prepared using a dilution procedure and a validated LC-MS/MS method was used for quantification of fluvoxamine in human plasma. The assay is validated over the range 1.00 to 400 ng/mL. The inter-run accuracy and precision demonstrated during validation is $\pm 6.5\%$ and $\leq 6.80\%$, respectively. Stability of fluvoxamine in human plasma was demonstrated at room temperature for 27 hr, during freeze/thaw for 4 cycles at -20°C and -80°C and during long-term storage at -20°C and -80°C for 1.3 days.

Methotrexate/7-Hydroxymethotrexate

Samples were prepared using a solid phase extraction and a validated LC-MS/MS method was used for quantification of methotrexate and 7-Hydroxymethotrexate in human plasma. The assay is validated over the range 0.250 to 200 ng/mL for methotrexate and 1.00 to 120 ng/mL for 7-Hydroxymethotrexate. The inter-run accuracy and precision demonstrated during validation for methotrexate is $\pm 3.7\%$ and $\leq 11.1\%$ and for 7-Hydroxymethotrexate is $\pm 5.6\%$ and $\leq 5.6\%$, respectively. Stability of methotrexate and 7-Hydroxymethotrexate in human plasma was demonstrated at room temperature for 24 hr, during freeze/thaw for 5 cycles at -20°C and -70°C and during long-term storage at -20°C and -70°C for 90 days.

Moxifloxacin

Samples were prepared using a protein precipitation extraction and a validated LC-MS/MS method was used for quantification of moxifloxacin in human plasma. The assay is validated over the range 25.0 to 5000 ng/mL. The inter-run accuracy and precision demonstrated during validation is $\pm 6.4\%$ and $\leq 2.5\%$, respectively. Stability of moxifloxacin in human plasma was demonstrated at room temperature for 24 hr, during freeze/thaw for 5 cycles at -20°C and -70°C and during long-term storage at -20°C and -70°C for 685 days.

Mycophenolic Acid

Samples were prepared using a liquid-liquid extraction and a validated LC-MS/MS method was used for quantification of mycophenolic acid in human plasma. The assay is validated over the range 50.0 to 40,000 ng/mL. The inter-run accuracy and precision demonstrated during validation is $\pm 2.00\%$ and $\leq 8.13\%$, respectively. Stability of mycophenolic acid in human plasma was demonstrated in an ice bath for 23 hr, during freeze/thaw for at least 5 cycles at -80°C and during long-term storage at -20°C and -80°C for 403 days.

Mycophenolic Acid Glucuronide

Samples were prepared using a liquid-liquid extraction and a validated LC-MS/MS method was used for quantification of mycophenolic acid glucuronide in human plasma. The assay is validated over the range 500 to 200,000 ng/mL. The inter-run accuracy and precision demonstrated during validation is $\pm 4.00\%$ and $\leq 5.97\%$, respectively. Stability of mycophenolic acid glucuronide in human plasma was demonstrated in an ice bath for 23 hr, during freeze/thaw for at least 5 cycles at -80°C and during long-term storage at -20°C and -80°C for 394 days.

Pyrimethamine

Samples were prepared using a protein precipitation and a validated LC-MS/MS method was used for quantification of pyrimethamine in human plasma. The assay is validated over the range 0.250 to 250 ng/mL. The inter-run accuracy and precision demonstrated during validation is $\pm 4.4\%$ and $\leq 6.2\%$, respectively. Stability of pyrimethamine in human plasma was demonstrated at room temperature for 24 hr, during freeze/thaw for 5 cycles at -20°C and -70°C and during long-term storage at -20°C and -70°C for 166 days.

Rabeprazole

Samples were prepared using a protein precipitation and a validated LC-MS/MS method was used for quantification of rabeprazole in human plasma. The assay is validated over the range 0.50 to 1000 ng/mL. The inter-run accuracy and precision demonstrated during validation is $\pm 3.78\%$ and $\leq 4.39\%$, respectively. Stability of rabeprazole in human plasma was demonstrated at room temperature for 23 hr, during freeze/thaw for 4 cycles at -20°C and -80°C and during long-term storage at -20°C and -80°C for 227 days.

Ritonavir

Samples were prepared using a protein precipitation and a validated LC-MS/MS method was used for quantification of ritonavir in human plasma. The assay is validated over the range 10.0 to 5000 ng/mL. The inter-run accuracy and precision demonstrated during validation is $\pm 7.3\%$ and $\leq 4.8\%$, respectively. Stability of ritonavir in human plasma was demonstrated at room temperature for 24 hr, during freeze/thaw for 3 cycles at -20°C and during long-term storage at -20°C for 98 days.

Rosuvastatin

Samples were prepared using a protein precipitation and a validated LC-MS/MS method was used for quantification of rosuvastatin in human plasma. The assay is validated over the range

0.100 to 100 ng/mL. The inter-run accuracy and precision demonstrated during validation is $\pm 3.0\%$ and $\leq 5.9\%$, respectively. Stability of rosuvastatin in human plasma was demonstrated on ice for 8 hr, during freeze/thaw for 5 cycles at -20°C and -70°C and during long-term storage at -20°C for 48 days and at -70°C for 422 days.

19.5. Clinical/Biostatistics

19.5.1. Scales Assessing Efficacy

19.5.1.1. Static Physician's Global Assessment

The static PGA is used to determine the subject's psoriasis lesions overall at a given time point. Overall lesions are graded for erythema, induration, and scaling based on the scales below. The average of the 3 scales, which is rounded to the nearest whole number, is the final sPGA score.

Figure 45. Static Physician's Global Assessment (sPGA)

Characteristics	Score	Rating Score
Erythema (E) (averaged over the whole body)		0 = No evidence of erythema, but post inflammatory hyper/hypopigmentation changes may be present 1 = Faint erythema 2 = Light red coloration 3 = Moderate red coloration 4 = Bright red coloration
Induration (I) (averaged over the whole body)		0 = No evidence of plaque elevation 1 = Minimal plaque elevation, barely palpable, = 0.25 mm 2 = Mild plaque elevation, slight but definite elevation, indistinct edge, = 0.5 mm 3 = Moderate plaque elevation, elevated with distinct edges, = 0.75 mm 4 = Severe plaque elevation, hard/sharp borders, ≥1 mm
Scaling (S) (averaged over the whole body)		0 = No evidence of scaling 1 = Minimal; occasional fine scaling 2 = Mild; fine scale predominates 3 = Moderate; coarse scale predominates 4 = Severe; thick scale predominates

Source: Protocol Version 6 for Trial IM011046; Appendix 5, page 113

The following equation is utilized based on the 3 rating scores in the assessment from [Figure 45](#):

$$\frac{(E + I + S)}{3} = Total\ Average$$

The output from the equation above has the following definitions:

- 0 = Clear, except for residual discoloration.
- 1 = Almost clear – majority of lesions have individual scores for E + I + S / 3 that averages 1.
- 2 = Mild – majority of lesions have individual scores for E + I + S / 3 that averages 2.
- 3 = Moderate – majority of lesions have individual scores for E + I + S / 3 that averages 3.
- 4 = Severe – majority of lesions have individual scores for E + I + S / 3 that averages 4.

One important note, scores should be rounded to the nearest whole number. If the average total score ≤ 1.49 , score = 1; if total ≥ 1.50 , score = 2.

19.5.1.2. Psoriasis Area and Severity Index

The information contained in this section is an excerpt from Protocol Version 6 for Trial IM011046; Appendix 6, page 114.

The Psoriasis Area and Severity Index (PASI) is a weighted sum score endpoint that typically ranges from 0 to 72. The body is divided into four sections:

- Head (h), accounting for 10% of total body surface area
- Arms (a), accounting for 20% of total body surface area
- Trunk (t), accounting for 30% of total body surface area
- Legs (l), accounting for 40% of total body surface area

The extent of psoriatic involvement for each of the four areas was determined using the following scale:

- 0 = 0% of involved area
- 1 = 1-9% of involved area
- 2 = 10-29% of involved area
- 3 = 30-49% of involved area
- 4 = 50-69% of involved area
- 5 = 70-89% of involved area
- 6 = 90-100% of involved area

Within each area, the severity is estimated by three clinical signs:

- Erythema ('E'; redness),
- Induration ('T'; thickness)
- Desquamation ('S'; scaling)

Severity parameters are measured on a scale of 0 to 4, from none to maximum severity possible. To calculate the PASI, the sum of the severity rating for the three main signs are multiplied with the numerical value of the area affected (i.e. [0]-[6] from [above](#)) and with the various percentages of the four body areas (i.e. 0.1, 0.2, 0.3, 0.4). These values are then added to complete the formula as follows:

$$\text{PASI} = [0.1(\text{Eh} + \text{Th} + \text{Sh})\text{Ah}] + [0.2(\text{Ea} + \text{Ta} + \text{Sa})\text{Aa}] + [0.3(\text{Et} + \text{Tt} + \text{St})\text{At}] + [0.4(\text{El} + \text{Tl} + \text{Sl})\text{Al}]$$

19.5.1.3. Psoriasis Symptoms and Signs Diary

Figure 46. Psoriasis Symptoms and Signs Diary (PSSD)

1. Rate the severity of <u>itch</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
2. Rate the severity of <u>dryness</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
3. Rate the severity of <u>cracking</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
4. Rate the severity of <u>skin tightness</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
5. Rate the severity of <u>scaling (build-up of skin)</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
6. Rate the severity of <u>shedding or flaking</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
7. Rate the severity of <u>redness</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
8. Rate the severity of <u>bleeding</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
9. Rate the severity of <u>burning</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
10. Rate the severity of <u>stinging</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
11. Rate the severity of <u>pain from your psoriasis lesions</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable

Source: Protocol Version 6 for Trial IM011046; Appendix 13, page 122

19.5.2. Sensitivity Analysis for Site 0092 in Trial IM011046

Table 100. Results for the Co-Primary Endpoints at Week 16 in Trial IM011046 With and Without Site 0092 (FAS; NRI)

Endpoint	Including Site 0092		Excluding Site 0092	
	DEUC (N=332)	PBO (N=166)	DEUC (N=330)	PBO (N=166)
sPGA 0/1	178 (53.6%)	12 (7.2%)	178 (53.9%)	12 (7.2%)
Difference (95% CI) ²	46.7% (40.2%, 53.2%)		46.96% (40.49%, 53.4%)	
P-Value ²	<0.001		<0.001	
PASI-75	194 (58.4%)	21 (12.7%)	193 (58.5%)	21 (12.65%)
Difference (95% CI) ²	46.09% (38.9%, 53.25%)		46.08% (38.9%, 53.25%)	
P-Value ²	<0.001		<0.001	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSPGA.xpt, ADPASBSA.xpt

¹ Full Analysis Set (FAS): all randomized subjects; missing data are imputed using non-responder imputation (NRI).

² Estimate, 95% CI and p-value for the difference are based on CMH test stratified for region, body weight and prior biologic use; Note: body weight stratum not applied in Japan or China.

Abbreviations: DEUC, deucravacitinib; PBO, placebo; CI, Confidence Interval

19.5.3. Endpoints at Week 24 - Sensitivity Analysis for Missing Data Due to COVID-19

Table 101. Results for the Investigator-Reported Secondary Endpoints at Weeks 24 Against Apremilast – Trial IM011047 (FAS; NRI)

Endpoint	DEUC (N=511)	APR (N=254)	Difference (P-value) ²
sPGA 0/1 at Week 24			
Including COVID-19 Missing Data	251/511 (49.1%)	75/254 (29.5%)	19.7% (<0.001)
Excluding COVID-19 Missing Data	251/504 (49.8%)	75/254 (29.5%)	20.45% (<0.001)
PASI-75 at Week 24			
Including COVID-19 Missing Data	296/511 (57.9%)	96/254 (37.8%)	20.2% (<0.001)
Excluding COVID-19 Missing Data	296/504 (58.7%)	96/254 (37.8%)	21.1% (<0.001)
PASI-90 at Week 24			
Including COVID-19 Missing Data	164/511 (32.1%)	50/254 (19.7%)	15.6% (<0.001)
Excluding COVID-19 Missing Data	164/504 (32.5%)	50/254 (19.7%)	13.0% (<0.001)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSPGA.xpt, ADPASBSA.xpt

¹ Full Analysis Set (FAS): all randomized subjects; missing data for reasons other than COVID-19 are imputed using non-responder imputation (NRI)

² Estimate and p-value for the difference are based on CMH test stratified for region, body weight and prior biologic use; Note: body weight stratum not applied in Japan or China.

Abbreviations: DEUC, deucravacitinib; APR, apremilast; CI, Confidence Interval

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/

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09/08/2022 11:48:46 PM

Signing on behalf of clinical reviewer Mary Kim, MD and as the Clinical TL and CDTL

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YE XIONG

09/09/2022 09:33:44 AM

YOUWEI N BI

09/09/2022 09:36:01 AM

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Correction for Signatures - page (p17): Instead of “ Division Director (clinical)”,
should be “ Associate Director for Therapeutic Review”

JULIE G BEITZ
09/09/2022 10:40:01 AM



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Translational Science

Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number: NDA 214958

Drug Name: Deucravacitinib

Indication: Treatment of Moderate-to-Severe Plaque Psoriasis

Applicant: Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543

Test Facility for Rats Study: [REDACTED] (b) (4)

[REDACTED] (b) (4)

Documents Reviewed: Study reports (Rat Study BMS-986165 and Mouse Study BMS-986165) and electronic data submitted on September 10, 2021 via NDA214958/0001

Biometrics Division: Division of Biometrics -6

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Keywords: Carcinogenicity, Dose response

Table of Contents

1. Summary5

2. Background7

3. Rat Study7

 Table 1: Study Design in Rat Study 7

 3.1. Sponsor's analyses 7

 3.1.1. Survival analysis 7

 Sponsor's findings 7

 3.1.2. Tumor data analysis 8

 Sponsor's findings 8

 3.2. Reviewer's analyses 8

 3.2.1. Survival analysis 8

 Reviewer's findings 8

 3.2.2. Tumor data analysis 9

 Adjustment for multiple testing.....9

 Reviewer's findings 10

 Table 2: Tumor Types with P-Values ≤ 0.05 for Comparisons between Water Control and Treated Groups-Male Rats 10

 Table 3: Tumor Types with P-Values ≤ 0.05 for Comparisons between Water Control and Treated Groups-Female Rats.....10

 Table 4: Tumor Types with P-Values ≤ 0.05 for Comparisons between Vehicle Control and Treated Groups-Female Rats.....11

4. Mouse Study 12

 Table 5: Study Design in Mouse Study.....12

 4.1. Sponsor's analyses 12

 4.1.1. Survival analysis 12

 4.1.2. Tumor data analysis 12

 Sponsor's findings 12

 4.2. Reviewer's analyses 12

 4.2.1. Survival analysis 13

 Reviewer's findings 13

 4.2.2. Tumor data analysis 13

 Adjustment for multiple testing.....13

 Reviewer's findings 14

 Reviewer's findings 14

 Table 6: Tumor Types with P-Values ≤ 0.05 for Comparisons between Vehicle Control and Positive Control-Male Mice 14

 Table 7: Tumor Types with P-Values ≤ 0.05 for Comparisons between Water Control and Positive Control-Male Mice 15

 Table 8: Tumor Types with P-Values ≤ 0.05 for Comparisons between Vehicle Control

and Positive Control-Female Mice	15
Table 9: Tumor Types with P-Values ≤ 0.05 for Comparisons between Water Control and Positive Control-Female Mice	16
5	Appendix
Table 10: Intercurrent Mortality Rate -Male Rats.....	17
Table 11: Intercurrent Mortality Rate -Female Rats	17
Table 12: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control -Male Rats.....	17
Table 13: Intercurrent Mortality Comparison between Treated Groups and Water Control -Male Rats.....	17
Table 14: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control -Female Rats	18
Table 15: Intercurrent Mortality Comparison between Treated Groups and Water Control -Female Rats	18
Table 16: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between the Vehicle Controls and the Treated Groups-Male Rats.....	19
Table 17: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between the Water Controls and the Treated Groups-Male Rats	22
Table 18: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between the Vehicle Controls and the Treated Groups-Female Rats	26
Table 19: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between the Water Controls and the Treated Groups-Female Rats.....	30
Table 20: Intercurrent Mortality Rate -Male Mice.....	34
Table 21: Intercurrent Mortality Rate -Female Mice	34
Table 22: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control-Male Mice.....	34
Table 23: Intercurrent Mortality Comparison between Treated Groups and Water Control-Male Mice.....	34
Table 24: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control-Female Mice.....	35
Table 25: Intercurrent Mortality Comparison between Treated Groups and Water Control-Female Mice.....	35
Table 26: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups-Male Mice	36
Table 27: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Water Control and the Treated Groups-Male Mice.....	37
Table 28: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups-Female Mice	38
Table 29: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Water Control and the Treated Groups-Female Mice	39
Table 30: Tumor Rates and P-Values for Comparisons between Vehicle Control and Positive Control- Male Mice.....	40
Table 31: Tumor Rates and P-Values for Comparisons between Water Control and Positive Control- Male Mice.....	41
Table 32: Tumor Rates and P-Values for Comparisons between Vehicle Control and Positive Control- Female Mice	42
Table 33: Tumor Rates and P-Values for Comparisons between Water Control and Positive Control- Female Mice	43
Figure 1: Kaplan-Meier Survival Functions for Male Rats.....	44
Figure 2: Kaplan-Meier Survival Functions for Female Rats	45
Figure 3: Kaplan-Meier Survival Functions for Male Mice	46
Figure 4: Kaplan-Meier Survival Functions for Female Mice.....	47

6. References48

1. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in Sprague Dawley rats and one in CByB6F1/Tg rasH2 Hemizygous mice. These studies were intended to assess the carcinogenic potential of BMS-986165, when administered by oral gavage at appropriate drug levels for 104 weeks in rats and 26 weeks in mice.

Rat Study: The survival analyses didn't show any statistically significant dose response relationship in mortality across the vehicle/water control group and treated groups in male rats. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle/water control group and each of the treated groups in male rats.

For female rats, the survival analyses showed a statistically significant dose response relationship in mortality across the vehicle/water control group and treated groups (Vehicle vs treated: P-value=0.0171 for likelihood ratio test; Water vs treated: P-value=0.0023 for likelihood ratio test and P-value=0.008 for log-rank test). The pairwise comparisons showed a statistically significant difference in mortality between the vehicle control group and the high dose group (P-value=0.0114 for likelihood ratio test and P-value=0.0104 for log-rank test). The pairwise comparisons showed statistically significant differences in mortality between the water control group and the low dose group (P-value=0.0352 for likelihood ratio test and P-value=0.0323 for log-rank test), the water control group and the medium dose group (P-value=0.0446 for likelihood ratio test and P-value=0.0415 for log-rank test), and the vehicle/water control group and the high dose group (vehicle vs high: P-value=0.0114 for likelihood ratio test and P-value=0.0104 for log-rank test; water vs high: P-value=0.0013 for likelihood ratio test and P-value=0.001 for log-rank test).

Tumor analysis:

1. There were no significant differences when comparing vehicle control to water control for male or female rats.
2. For male rats, the pairwise comparisons between the water control and the 8 mg/kg/day group showed statistically significant increase in incidence of adenoma, gland parathyroid (p-value=0.0438<0.05) and c-cell adenoma, gland thyroid (p-value=0.0098<0.01).

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	3 mg/kg/day Low (N=70) P-value - Water vs. Low	8 mg/kg/day Med (N=70) P-value - Water vs. Med	15 mg/kg/day High (N=70) P-value - Water vs. High
Male					
GLAND, PARATHYROID	ADENOMA	0/70 (29) 0.1097	4/68 (28) 0.0518	4/67 (26) 0.0438	4/70 (31) 0.0645
GLAND, THYROID	C-CELL ADENOMA	3/70 (31) 0.5923	6/70 (29) 0.2032	12/70 (32) 0.0098	2/70 (30) 0.8128

Mouse Study: For male mice, the survival analyses didn't show any statistically significant dose response relationship in mortality across the vehicle/water control group and treated groups. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle control group and each of the treated groups. The pairwise comparisons showed a statistically significant difference in mortality between the water control group and the low dose group (p-value=0.0066 for likelihood ratio test and p-value=0.0196 for log-rank test)

For female mice, the survival analyses didn't show any statistically significant dose response relationship in mortality across the vehicle/water control group and treated groups. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle/water control group and each of the treated groups.

The pairwise comparison between the vehicle/water control group and positive control group showed statistically significant increases in mortality in male and female mice.

Tumor analysis:

1. For male mice, the pairwise comparisons between the vehicle control and the positive control group showed statistically significant increase in incidence of adenoma, gland harderian (p-value=0.0086), combined tumors of adenoma and adenocarcinoma, gland harderian (p-value=0.0022), lymphoma, hemolymphoreticula (p-value<0.001), combined tumors of bronchioloalveolar adenoma and carcinoma (p-value=0.00169), papilloma, skin(p-value<0.001) and papilloma, stomach (p-value<0.001).
2. For male mice, the pairwise comparisons between the water control and the positive control group showed statistically significant increase in incidence of adenoma,

gland harderian (p-value=0.0253), combined tumors of adenoma and adenocarcinoma, gland harderian (p-value=0.0076), lymphoma, hemolymphoreticula (p-value<0.001), combined tumors of bronchioloalveolar adenoma and carcinoma (p-value=0.014), papilloma, skin(p-value<0.001) and papilloma, stomach (p-value<0.001).

3. For female mice, the pairwise comparisons between the vehicle control and the positive control group showed statistically significant increase in incidence of adenoma, gland harderian (p-value=0.0258), lymphoma, hemolymphoreticula (p-value<0.001), papilloma, skin(p-value<0.001) and papilloma, stomach (p-value<0.001).
4. For female mice, the pairwise comparisons between the water control and the positive control group showed statistically significant increase in incidence of adenoma, gland harderian (p-value=0.0211), lymphoma, hemolymphoreticula (p-value<0.001), combined tumors of bronchioloalveolar adenoma and carcinoma (p-value=0.0471), papilloma, skin(p-value<0.001) and papilloma, stomach (p-value<0.001).

2. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in Sprague Dawley rats and one in CByB6F1/Tg rasH2 Hemizygous mice. These studies were intended to assess the carcinogenic potential of BMS-986165, when administered by oral gavage at appropriate drug levels for 104 weeks in rats and 26 weeks in mice. Results of this review have been discussed with the reviewing pharmacologist Dr. Yongcheng Huang. This review analyzed the SAS data sets of these studies received from the sponsor on September 10, 2021 via NDA214958/0001.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as the dose increases.

3. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one water control group and one vehicle control group. Three hundred and fifty Sprague Dawley rats of each sex were randomly assigned to the five groups in equal size of 70 rats per group. The dose levels for treated groups were 3, 8 and 15 mg/kg/day. The rats in the vehicle control group received the vehicle ((b) (4) (w/w/w)). The rats in the water control group received the Ultra Pure Water. The study for the rats was designed to continue for up to 104 weeks. In accordance with study termination criteria, all surviving male rats were sacrificed during Week 105.

Table 1: Study Design in Rat Study

Protocol Group No.	Dose Levels (mg/kg/day)	Identification	Number of Animals Enrolled	
			Males	Females
1	0	water	70	70
2	0	vehicle	70	70
3	3	BMS-986165	70	70
4	8	BMS-986165	70	70
5	15	BMS-986165	70	70

3.1. Sponsor's analyses

3.1.1. Survival analysis

The survival data for the BMS-986165-treated groups and vehicle-control groups are displayed as Kaplan-Meier product-limit curves, separately by sex. Dose-related trends in survival were tested with life table trend (log-rank) tests that are sensitive to both increasing and decreasing trends. These tests included the vehicle-control groups and were evaluated at the 0.05 level of significance. Within each sex, the vehicle-control and water-control groups were also tested for differences in survival; the survival data for these groups are also displayed as Kaplan-Meier product-limit curves. In addition, within each sex, the number of animals surviving in each group was tabulated at 10-week intervals.

Sponsor's findings: Sponsor's analysis showed the numbers (percents) of survival were 20 (29%), 21 (30%), 16 (23%), 18 (26%) and 18 (26%) in water control, vehicle control, 3 mg/kg/day, 8 mg/kg/day, and 15 mg/kg/day dose groups, respectively in males and 24 (34%), 21 (30%), 15 (21%), 15 (21%) and 15 (21%) in water control, vehicle control, 3 mg/kg/day, 8 mg/kg/day, and 15 mg/kg/day dose groups, respectively in females. The sponsor concluded that based on the trend test that evaluated overall survival, there were no significant doserelated trends in survival for the vehicle- and BMS-986165-treated males; there was a significant decreasing trend in survival for the vehicle-control and all BMS-986165-treated dose groups.

3.1.2. Tumor data analysis

Tumor data were analyzed using the poly-k trend test, using suggested methodology and following the FDA Draft Guidance⁵. Tumor incidences in the vehicle-control and BMS-986165-treated groups were evaluated separately by sex. The value of 'k' selected was '3', as recommended in Bieler and Williams. In calculating the weights for the individual animals for use in the test, the first day of the terminal sacrifice (Day 625 for males and Day 688 for females) was used. The trend test was followed by pairwise Fisher Exact tests (FET) for BMS-986165-treated groups versus the vehicle-control group. The trend tests and pairwise tests were one-sided, each assessed at the 0.05 significance level. For the FET, the test was performed only when the tumor incidence in the BMS-986165-treated group was

greater than the tumor incidence in the vehicle-control group. These analyses were applied to all tumor types found on protocol-specified tissues. At the recommendation of the study pathologist and confirmed by the peer review pathologist, no tumor combinations were evaluated.

Sponsor's findings: The sponsor concluded that for males, there was a significant increasing trend ($P = 0.0164$) in sebaceous cell adenomas in skin. For females, there was an increasing trend ($P = 0.0158$) in incidences of granulocytic leukemia in hemolymphoreticular tissue. There was a significant increasing trend in hepatocellular adenomas in liver ($P = 0.0079$). There was a significant increasing trend in benign thymomas in thymus ($P = 0.0166$).

3.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses.

3.2.1. Survival analysis

The survival distributions of animals in four groups were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested for the vehicle controls, low, medium and high dose groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 10 and 11 in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1 and 2 in the appendix for males and females, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 12, 13, 14 and 15 in the appendix for males and females, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percents) of survival were 20 (29%), 21 (30%), 16 (23%), 18 (26%) and 18 (26%) in water control, vehicle control, 3 mg/kg/day, 8 mg/kg/day, and 15 mg/kg/day dose groups, respectively in males and 24 (34%), 21 (30%), 15 (21%), 15 (21%) and 15 (21%) in water control, vehicle control, 3 mg/kg/day, 8 mg/kg/day and 15 mg/kg/day dose groups, respectively in females.

The survival analyses didn't show any statistically significant dose response relationship in mortality across the vehicle/water control group and treated groups in male rats. The pairwise

comparisons did not show any statistically significant differences in mortality between the vehicle/water control group and each of the treated groups in male rats.

For female rats, the survival analyses showed a statistically significant dose response relationship in mortality across the vehicle/water control group and treated groups (Vehicle vs treated: P-value=0.0171 for likelihood ratio test; Water vs treated: P-value=0.0023 for likelihood ratio test and P-value=0.008 for log-rank test). The pairwise comparisons showed a statistically significant difference in mortality between the vehicle control group and the high dose group (P-value=0.0114 for likelihood ratio test and P-value=0.0104 for log-rank test). The pairwise comparisons showed statistically significant differences in mortality between the water control group and the low dose group (P-value=0.0352 for likelihood ratio test and P-value=0.0323 for log-rank test), the water control group and the medium dose group (P-value=0.0446 for likelihood ratio test and P-value=0.0415 for log-rank test), and the water control group and the high dose group (P-value=0.0013 for likelihood ratio test and P-value=0.001 for log-rank test).

3.2.2. Tumor data analysis

The tumor data were analyzed for the positive dose response relationships and the positive pairwise comparison increases between each of the treated groups with control group. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-K method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of $s_h = 1$. An animal that dies at week w_h without a tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}} \right)^k < 1$. The adjusted group size is defined as $\sum s_h$. As an interpretation, an animal with score $s_h = 1$ can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size $\sum s_h$ is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes were then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value

of k , which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of $k=3$ is suggested in the literature. Hence, this reviewer used $k=3$ for the analysis of this data. For the calculation of p -values the exact permutation method was used. The tumor rates and the p -values for the positive dose response relationship tests and pairwise comparisons are listed in Tables 16, 17, 18 and 19 in the appendix for male and female rats, respectively.

Adjustment for multiple testing: For the chronic study in rats, the adjustment of multiple testing of the dose response relationship for a submission with one chronic rat study and one transgenic mouse study, the more recently revised draft (January, 2013) FDA guidance for the carcinogenicity studies suggests the use of test levels $\alpha = 0.005$ for common tumors and $\alpha = 0.025$ for rare tumors for the chronic rat study. For pairwise comparisons for the chronic rat study in the above type of submission with one chronic rat study and one transgenic mouse study, the same guidance document suggests the use of test levels $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors for the chronic rat study.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: The tumor types in Tables 2, 3, and 4 below showed p -values less than or equal to 0.05 in the trend tests and the tests for pairwise comparisons between the vehicle/water and the treated groups for male and female rats. Based on the above criterion for multiple testing adjustment, we make the following conclusions:

1. There were no significant differences when comparing vehicle control to water control for male or female rats.
2. For male rats, the pairwise comparisons between the water control and the 8 mg/kg/day group showed statistically significant increase in incidence of adenoma, gland parathyroid (p -value=0.0438<0.05) and c-cell adenoma, gland thyroid (p -value=0.0098<0.01).

Table 2: Tumor Types with P -Values ≤ 0.05 for Comparisons between Water

Control and Treated Groups-Male Rats

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	3 mg/kg/day Low (N=70) P-value - Water vs. Low	8 mg/kg/day Med (N=70) P-value - Water vs. Med	15 mg/kg/day High (N=70) P-value - Water vs. High
GLAND THYROID	C_c-cell adenoma+carcinoma	4/70 (32) 0.7477	8/70 (30) 0.1380	12/70 (32) 0.0207	2/70 (30) 0.8870
GLAND, PARATHYROID	ADENOMA	0/70 (29) 0.1097	4/68 (28) 0.0518	4/67 (26) 0.0438	4/70 (31) 0.0645
GLAND, THYROID	C-CELL ADENOMA	3/70 (31) 0.5923	6/70 (29) 0.2032	12/70 (32) 0.0098	2/70 (30) 0.8128

Table 3: Tumor Types with P-Values ≤ 0.05 for Comparisons between Water
Control and Treated Groups-Female Rats

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	3 mg/kg/day Low (N=70) P-value - Water vs. Low	8 mg/kg/day Med (N=70) P-value - Water vs. Med	15 mg/kg/day High (N=70) P-value - Water vs. High
GLAND, MAMMARY	ADENOCARCINOMA	18/70 (51) 0.3521	25/70 (45) 0.0368	20/70 (43) 0.1859	15/70 (34) 0.2768
HEMOLYMPHORETICULA	LYMPHOMA, MALIGNANT	0/70 (43) 0.0370	0/70 (34) NC	0/70 (34) NC	2/70 (27) 0.1453
LIVER	HEPATOCELLULAR ADENOMA	3/70 (44) 0.0057	3/70 (35) 0.5473	6/70 (37) 0.1623	8/70 (30) 0.0221

Table 4: Tumor Types with P-Values ≤ 0.05 for Comparisons between Vehicle
Control and Treated Groups-Female Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-value - Trend	3 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	8 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	15 mg/kg/day High (N=70) P-value - Vehicle vs. High
HEMOLYMPHORETICULA	LEUKEMIA, GRANULOCYTIC	0/70 (38) 0.0424	0/70 (34) NC	0/71 (34) NC	2/70 (28) 0.1762
LIVER	HEPATOCELLULAR ADENOMA	3/70 (38) 0.0095	3/70 (35) 0.6226	6/71 (37) 0.2264	8/70 (30) 0.0395
THYMUS	THYMOMA, BENIGN	0/68 (37) 0.0419	0/70 (33) NC	0/70 (33) NC	2/70 (27) 0.1741

4. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one vehicle control group, one water control group and one positive control group. One hundred and twenty five mice of each sex were randomly assigned to the treated water control and vehicle control group in equal size of 25 mice per group. The dose levels for treated groups were 10, 30 and 60 mg/kg/day for males and females. The mice in the vehicle control group received the vehicle (b) (4)

The mice in the water control group received the Milli-Q Gradient A10 water. The mice in the positive control group received 7.5 mg/mL N-Nitrosomethylurea (NMU) in citrate-buffered saline (pH 4.5) only once on Day 1 via intraperitoneal injection.

Table 5: Study Design in Mouse Study

Protocol Group No.	Dose Levels (mg/kg/day)	Identification	Number of Animals Enrolled	
			Males	Females
1	0	water	25	25
2	0	vehicle	25	25
3	10	BMS-986165	25	25
4	30	BMS-986165	25	25
5	60	BMS-986165	25	25
6	75	Positive	15	15

4.1. Sponsor's analyses

4.1.1. Survival analysis

The sponsor used the same survival analysis methods used for the rats study in this mouse study.

Sponsor's findings: The sponsor's analysis showed that the numbers (percents) of survival were 25 (100%), 23 (92%), 20 (80%), 23 (92%), 23 (92%) and 2 (13%) in male mice, and 24 (96%), 24 (96%), 25 (100%), 22 (88%), 24 (96%) and 2 (13%) in female mice in water control, vehicol control, low, medium, high and positive dose groups, respectively.

The sponsor concluded that, there were no statistically significant differences in survival for any BMS-986165-treated groups in either sex relative to control groups.

4.1.2. Tumor data analysis

The sponsor used the same tumor data analysis methods used for the rat study in this mouse study

Sponsor's findings: The sponsor concluded that there were no statistically significant tumor findings in the test article groups when compared to the vehicle control group.

4.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses.

4.2.1. Survival analysis

The survival distributions of three treated groups, one vehical control group, and one positive control group were estimated using the Kaplan-Meier product limit method. The dose response relationship in survival was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 3 and 4 in the appendix for male and female mice, respectively. The intercurrent mortality data are given in Tables 20 and 21 in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals among the vehicle control and three treated groups are given in Tables 22, 23, 24, and 25 in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed that the numbers (percents) of survival were 25 (100%), 23 (92%), 20 (80%), 23 (92%), 23 (92%) and 2 (13%) in male mice, and 24 (96%), 24 (96%), 25 (100%), 22 (88%), 24 (96%) and 2 (13%) in female mice in water control, vehicol control, low, medium, high and positive dose groups, respectively.

For male mice, the survival analyses didn't show any statistically significant dose response relationship in mortality across the vehicle/water control group and treated groups. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle control group and each of the treated groups. The pairwise comparisons showed a statistically significant difference in mortality between the water control group and the low dose group (p-value=0.0066 for likelihood ratio test and p-value=0.0196 for log-rank test)

For female mice, the survival analyses didn't show any statistically significant dose response relationship in mortality across the vehicle/water control group and treated groups. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle/water control group and each of the treated groups.

The pairwise comparison between the vehicle/water control group and positive control group showed statistically significant increases in mortality in male and female mice.

4.2.2. Tumor data analysis

The reviewer used the same tumor data analysis methods for the rat study in this mouse study.

The tumor rates and the p-values for the positive dose response relationship tests and pairwise comparisons between vehicle control and three treated groups, and between vehicle/water control and positive control are listed in Tables 26, 27, 28, 29, 30, 31, 32, and 33 in the appendix for male and female mice, respectively.

Adjustment for multiple testing: For the chronic study in rats, the adjustment of multiple testing of the dose response relationship for a submission with one chronic rat study and one transgenic mouse study, the more recently revised draft (January, 2013) FDA guidance for the carcinogenicity studies suggests the use of test levels $\alpha = 0.05$ for both common tumors and rare tumors for the mouse study. For pairwise, the same guidance document suggests the use of test levels $\alpha = 0.05$ for both common tumors and rare tumors for the mouse study.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: The tumor types in Tables 6, 7, 8, and 9 below showed p-values less than or equal to 0.05 in the tests for pairwise comparisons between vehicle and positive control groups for male mice and female mice, respectively.

Reviewer's findings: Based on the criteria of adjustment for multiple testing discussed in the mouse data analysis section, we make the following statistical conclusions:

1. For male mice, the pairwise comparisons between the vehicle control and the positive control group showed statistically significant increase in incidence of adenoma, gland harderian (p-value=0.0086), combined tumors of adenoma and adenocarcinoma, gland harderian (p-value=0.0022), lymphoma, hemolymphoreticula (p-value<0.001), combined tumors of bronchioloalveolar adenoma and carcinoma (p-value=0.00169), papilloma, skin(p-value<0.001) and papilloma, stomach (p-value<0.001).
2. For male mice, the pairwise comparisons between the water control and the positive control group showed statistically significant increase in incidence of adenoma, gland harderian (p-value=0.0253), combined tumors of adenoma and adenocarcinoma, gland harderian (p-value=0.0076), lymphoma, hemolymphoreticula (p-value<0.001), combined tumors of bronchioloalveolar adenoma and carcinoma (p-value=0.014), papilloma, skin(p-value<0.001) and papilloma, stomach (p-value<0.001).
3. For female mice, the pairwise comparisons between the vehicle control and the positive control group showed statistically significant increase in incidence of adenoma, gland harderian (p-value=0.0258), lymphoma, hemolymphoreticula (p-value<0.001), papilloma, skin(p-value<0.001) and papilloma, stomach (p-value<0.001).
4. For female mice, the pairwise comparisons between the water control and the positive control group showed statistically significant increase in incidence of adenoma, gland harderian (p-value=0.0211), lymphoma, hemolymphoreticula (p-value<0.001), combined tumors of bronchioloalveolar adenoma and carcinoma (p-

value=0.0471), papilloma, skin(p-value<0.001) and papilloma, stomach (p-value<0.001).

Table 6: Tumor Types with P-Values $\leq$ 0.05 for Comparisons between Vehicle Control and Positive Control-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=15) P-value - Vehicle vs. Positive
GLAND, HARDERIAN	ADENOMA	0/25 (23)	3/15 (7) 0.0086
Gland Harderian	C_adenoma+adenocarcinoma	0/25 (23)	4/15 (8) 0.0022
HEMOLYMPHORETICULA	LYMPHOMA, MALIGNANT	0/25 (23)	9/15 (12) <0.001
Lung	C_bronchioloalveolar adenoma+carcinoma	0/25 (23)	3/15 (9) 0.0169
SKIN	PAPILLOMA	0/25 (23)	8/15 (11) <0.001
STOMACH	PAPILLOMA	0/25 (23)	9/15 (12) <0.001

Table 7: Tumor Types with P-Values $\leq$ 0.05 for Comparisons between Water Control and Positive Control-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25)	Positive (N=15) P-value - Water vs. Positive
GLAND, HARDERIAN	ADENOMA	1/25 (25)	3/15 (7) 0.0253
Gland Harderian	C_adenoma+adenocarcinoma	1/25 (25)	4/15 (8) 0.0076
HEMOLYMPHORETICULA	LYMPHOMA, MALIGNANT	0/25 (25)	9/15 (12) <0.001
Lung	C_bronchioloalveolar adenoma+carcinoma	0/25 (25)	3/15 (9) 0.0140
SKIN	PAPILLOMA	1/25 (25)	8/15 (11) <0.001
STOMACH	PAPILLOMA	0/25 (25)	9/15 (12) <0.001

Table 8: Tumor Types with P-Values ≤ 0.05 for Comparisons between Vehicle Control and Positive Control-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=15) P-value - Vehicle vs. Positive
GLAND, HARDERIAN	ADENOMA	1/25 (24)	3/16 (7) 0.0258
HEMOLYMPHORETICULA	LYMPHOMA, MALIGNANT	0/25 (24)	11/16 (13) <0.001
SKIN	PAPILLOMA	0/25 (24)	6/16 (9) <0.001
STOMACH	PAPILLOMA	0/25 (24)	12/16 (13) <0.001

Table 9: Tumor Types with P-Values ≤ 0.05 for Comparisons between Water Control and Positive Control-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25)	Positive (N=15) P-value - Water vs. Positive
GLAND, HARDERIAN	ADENOMA	1/25 (25)	3/16 (7) 0.0211
HEMOLYMPHORETICULA	LYMPHOMA, MALIGNANT	0/25 (25)	11/16 (13) <0.001
Lung	C_bronchioloalveolar adenoma+carcinoma	0/25 (25)	2/16 (8) 0.0471
SKIN	PAPILLOMA	0/25 (25)	6/16 (9) <0.001
STOMACH	PAPILLOMA	0/25 (25)	12/16 (13) <0.001

Zhuang Miao, Ph.D.
Mathematical

Statistician

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Karl Lin, Ph.D.

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Page 21 of 52

Mathematical Statistician, Team Leader, Biometrics-6

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5. Appendix

Table 10: Intercurrent Mortality Rate -Male Rats

Week	Water 0 mg/kg/day (N=60)		Vehicle 0 mg/kg/day (N=60)		3 mg/kg/day (N=60)		8 mg/kg/day (N=60)		15 mg/kg/day (N=60)	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	7	10.00	13	18.57	12	17.14	12	17.14	8	11.43
53 - 78	29	51.43	28	58.57	28	57.14	31	61.43	27	50.00
79 - 91	14	71.43	8	70.00	14	77.14	9	74.29	17	74.29
Ter. Sac.	20	28.57	21	30.00	16	22.86	18	25.71	18	25.71

Cum. %: Cumulative percentage except for Ter. Sac.

Table 11: Intercurrent Mortality Rate -Female Rats

Week	Water 0 mg/kg/day (N=60)		Vehicle 0 mg/kg/day (N=60)		3 mg/kg/day (N=60)		8 mg/kg/day (N=60)		15 mg/kg/day (N=60)	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	5	7.14	8	11.43	8	11.43	9	12.86	13	18.57
53 - 78	17	31.43	21	41.43	27	50.00	27	51.43	28	58.57
79 - 91	19	58.57	12	58.57	15	71.43	9	64.29	14	78.57
92 - 105	5	65.71	8	70.00	5	78.57	10	78.57	.	.
Ter. Sac.	24	34.29	21	30.00	15	21.43	15	21.43	15	21.43

Cum. %: Cumulative percentage except for Ter. Sac.

Table 12: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control -Male Rats

Test	Statistic	P_Value Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Medium	P_Value Vehicle vs. High
Dose-Response	Likelihood Ratio	0.8996	0.6751	0.5050	0.8896
Homogeneity	Log-Rank	0.8190	0.6709	0.5003	0.8881

Table 13: Intercurrent Mortality Comparison between Treated Groups and Water Control -Male Rats

Test	Statistic	P_Value Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Medium	P_Value Vehicle vs. High
Dose-Response	Likelihood Ratio	0.8896	0.4318	0.3011	0.8278

Test	Statistic	P_Value Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Medium	P_Value Vehicle vs. High
Homogeneity	Log-Rank	0.8881	0.4246	0.2946	0.8254

Table 14: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control -Female Rats

Test	Statistic	P_Value Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Medium	P_Value Vehicle vs. High
Dose-Response	Likelihood Ratio	0.0171	0.1981	0.2276	0.0114
Homogeneity	Log-Rank	0.0670	0.1921	0.2210	0.0104

Table 15: Intercurrent Mortality Comparison between Treated Groups and Water Control -Female Rats

Test	Statistic	P_Value Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Medium	P_Value Vehicle vs. High
Dose-Response	Likelihood Ratio	0.0023	0.0352	0.0446	0.0013
Homogeneity	Log-Rank	0.0080	0.0323	0.0415	0.0010

Table 16: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between the Vehicle Controls and the Treated Groups-Male Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-value - Trend	3 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	8 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	15 mg/kg/day High (N=70) P-value - Vehicle vs. High
ADIPOSE TISSUE	HEMANGIOMA	0/1 (1) 0.8000	1/2 (1) 0.5000	1/1 (1) 0.5000	0/5 (2) NC
	HEMANGIOSARCOMA	0/1 (1) 0.8000	1/2 (1) 0.5000	0/1 (1) NC	0/5 (2) NC
BODY CAVITY, NASAL	SQUAMOUS CELL CARCINOMA	0/70 (27) 0.2027	0/70 (27) NC	1/70 (26) 0.4906	1/70 (30) 0.5263
BONE, FEMUR	OSTEOMA	1/70 (27) 1.0000	0/70 (27) 1.0000	0/70 (25) 1.0000	0/70 (29) 1.0000
BRAIN	ASTROCYTOMA, MALIGNANT	0/70 (27) 0.6352	1/70 (28) 0.5091	1/70 (26) 0.4906	0/70 (29) NC
	GRANULAR CELL TUMOR, BENIGN	1/70 (27) 0.9449	3/70 (29) 0.3333	0/70 (25) 1.0000	0/70 (29) 1.0000
GLAND THYROID	C_c-cell adenoma+carcinoma	6/70 (30) 0.8969	8/70 (30) 0.3805	12/70 (32) 0.1077	2/70 (30) 0.9738
GLAND, ADRENAL	CORTICAL ADENOMA	0/70 (27) 0.2679	1/70 (27) 0.5000	2/70 (26) 0.2358	1/70 (29) 0.5179
	PHEOCHROMOCYTOMA, BENIGN	6/70 (30) 0.7590	4/70 (29) 0.8367	3/70 (26) 0.8907	4/70 (31) 0.8631
	PHEOCHROMOCYTOMA, MALIGNANT	0/70 (27) 0.5000	0/70 (27) NC	1/70 (25) 0.4808	0/70 (29) NC
GLAND, MAMMARY	ADENOCARCINOMA	0/3 (2) 0.1282	0/4 (2) NC	0/9 (4) NC	2/8 (5) 0.4762
	ADENOMA	0/3 (2) 0.2947	1/4 (2) 0.5000	1/9 (5) 0.7143	2/8 (5) 0.4762
	FIBROADENOMA	1/3 (2) 0.9434	2/4 (3) 0.7000	4/9 (6) 0.6429	0/8 (4) 1.0000
GLAND, PARATHYROID	ADENOMA	4/67 (28) 0.5638	4/68 (28) 0.6476	4/67 (26) 0.6042	4/70 (31) 0.7038
GLAND, PITUITARY	ADENOMA, PARS DISTALIS	21/70 (40) 0.2586	31/70 (44) 0.0710	29/70 (43) 0.1219	29/70 (45) 0.1851
GLAND, THYROID	C-CELL ADENOMA	6/70 (30) 0.8524	6/70 (29) 0.6008	12/70 (32) 0.1077	2/70 (30) 0.9738
	C-CELL CARCINOMA	0/70 (27) 0.7432	2/70 (28) 0.2545	1/70 (25) 0.4808	0/70 (29) NC
	FOLLICULAR CELL ADENOMA	2/70 (28) 0.7332	2/70 (28) 0.6945	2/70 (26) 0.6659	1/70 (29) 0.8880
HEART	HEMANGIOSARCOMA	0/70 (27) 0.5046	0/70 (27) NC	1/70 (26) 0.4906	0/70 (29) NC

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-value - Trend	3 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	8 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	15 mg/kg/day High (N=70) P-value - Vehicle vs. High
HEMOLYMPHORETIC ICULA	HISTIOCYTIC SARCOMA	2/70 (29) 1.0000	0/70 (27) 1.0000	0/70 (25) 1.0000	0/70 (29) 1.0000
	LEUKEMIA, GRANULOCYTIC	1/70 (28) 0.5511	1/70 (28) 0.7545	1/70 (26) 0.7358	1/70 (30) 0.7713
	LEUKEMIA, LARGE GRANULAR LYMPHOCYTIC	0/70 (27) 0.7523	1/70 (28) 0.5091	0/70 (25) NC	0/70 (29) NC
	LYMPHOMA, MALIGNANT	1/70 (27) 0.6010	2/70 (28) 0.5139	2/70 (27) 0.5000	1/70 (30) 0.7801
KIDNEY	AMPHOPHILIC VACUOLAR TUBULAR ADENOMA	0/70 (27) 0.7500	1/70 (27) 0.5000	0/70 (25) NC	0/70 (29) NC
	AMPHOPHILIC VACUOLAR TUBULAR CARCINOMA	0/70 (27) 0.2752	0/70 (27) NC	0/70 (25) NC	1/70 (30) 0.5263
	LIPOMA	1/70 (27) 1.0000	0/70 (27) 1.0000	0/70 (25) 1.0000	0/70 (29) 1.0000
LARGE INTESTINE, C	ADENOCARCINOMA	1/70 (27) 1.0000	0/70 (27) 1.0000	0/70 (25) 1.0000	0/70 (29) 1.0000
LIVER	HEPATOCELLULAR ADENOMA	0/70 (27) 0.3140	1/70 (27) 0.5000	1/70 (26) 0.4906	1/70 (29) 0.5179
LUNG	BRONCHIOLOALVEOLAR ADENOMA	1/70 (27) 0.7523	0/70 (27) 1.0000	1/70 (25) 0.7353	0/70 (29) 1.0000
LYMPH NODE, MESENT	HEMANGIOMA	2/68 (27) 0.7052	1/70 (28) 0.8885	1/70 (25) 0.8676	1/69 (29) 0.8945
	HEMANGIOSARCOMA	0/68 (27) 0.7523	1/70 (28) 0.5091	0/70 (25) NC	0/69 (29) NC
MUSCLE, SKELETAL	SCHWANNOMA, MALIGNANT	0/70 (27) 0.5093	0/68 (26) NC	1/70 (26) 0.4906	0/70 (29) NC
PANCREAS	ACINAR ADENOMA	3/70 (29) 0.5008	7/70 (30) 0.1633	2/70 (26) 0.7883	5/70 (31) 0.3924
	ACINAR CARCINOMA	1/70 (28) 0.5141	0/70 (27) 1.0000	0/69 (25) 1.0000	1/70 (29) 0.7632
	C_isLET CELL adenoma+acinar adenoma	9/70 (31) 0.8185	13/70 (33) 0.2718	6/69 (28) 0.8336	8/70 (32) 0.7401
	ISLET CELL ADENOMA	6/70 (30) 0.8465	7/70 (30) 0.5000	4/69 (27) 0.8049	4/70 (31) 0.8631
	ISLET CELL CARCINOMA	3/70 (28) 0.8409	0/70 (27) 1.0000	4/69 (27) 0.4789	0/70 (29) 1.0000
SKIN	BASAL CELL TUMOR, BENIGN	1/70 (28) 0.1829	0/70 (27) 1.0000	2/70 (27) 0.4861	2/70 (30) 0.5263
	C_papillomas+squamous cell carcinomas	0/70 (27) 0.4761	2/70 (28) 0.2545	0/69 (25) NC	1/70 (30) 0.5263
	FIBROMA	1/70 (28) 0.1303	1/70 (27) 0.7455	3/69 (26) 0.2775	3/70 (30) 0.3325
	FIBROSARCOMA	1/70 (28) 1.0000	0/70 (27) 1.0000	0/69 (25) 1.0000	0/70 (29) 1.0000

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-value - Trend	3 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	8 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	15 mg/kg/day High (N=70) P-value - Vehicle vs. High
	KERATOACANTHOMA	4/70 (29) 0.3517	7/70 (31) 0.2942	2/69 (27) 0.8866	7/70 (32) 0.3152
	PAPILLOMA	0/70 (27) 0.8119	2/70 (28) 0.2545	0/69 (25) NC	0/70 (29) NC
	SCHWANNOMA, MALIGNANT	0/70 (27) 0.7500	1/70 (27) 0.5000	0/69 (25) NC	0/70 (29) NC
	SEBACEOUS CELL ADENOMA	0/70 (27) 0.0739	0/70 (27) NC	0/69 (25) NC	2/70 (30) 0.2706
	SEBACEOUS CELL CARCINOMA	0/70 (27) 0.7523	1/70 (28) 0.5091	0/69 (25) NC	0/70 (29) NC
	SQUAMOUS CELL CARCINOMA	0/70 (27) 0.2752	0/70 (27) NC	0/69 (25) NC	1/70 (30) 0.5263
SPINAL CORD, CERVI	ASTROCYTOMA, MALIGNANT	0/70 (27) 0.2685	0/70 (27) NC	0/70 (25) NC	1/69 (29) 0.5179
SUBCUTIS	FIBROMA	0/6 (3) 0.1878	2/5 (4) 0.2857	3/9 (6) 0.2381	2/5 (4) 0.2857
	HEMANGIOMA	0/6 (3) 0.1978	0/5 (3) NC	1/9 (5) 0.6250	1/5 (3) 0.5000
	LEIOMYOMA	0/6 (3) 0.5385	0/5 (3) NC	1/9 (4) 0.5714	0/5 (3) NC
	LIPOMA	2/6 (4) 0.5974	0/5 (3) 1.0000	1/9 (4) 0.9286	1/5 (3) 0.8857
	OSTEOSARCOMA	1/6 (3) 1.0000	0/5 (3) 1.0000	0/9 (4) 1.0000	0/5 (3) 1.0000
	SCHWANNOMA, MALIGNANT	2/6 (4) 0.9511	1/5 (4) 0.9286	1/9 (5) 0.9524	0/5 (3) 1.0000
TESTIS	HEMANGIOMA	0/70 (27) 0.5046	0/70 (27) NC	1/70 (26) 0.4906	0/70 (29) NC
	INTERSTITIAL (LEYDIG) CELL ADENOMA	2/70 (28) 0.4811	1/70 (28) 0.8818	1/70 (25) 0.8602	2/70 (30) 0.7001
	SCHWANNOMA, MALIGNANT	1/70 (28) 1.0000	0/70 (27) 1.0000	0/70 (25) 1.0000	0/70 (29) 1.0000
THYMUS	THYMOMA, MALIGNANT	0/70 (27) 0.5047	0/66 (26) NC	1/68 (25) 0.4808	0/70 (29) NC
Whold Body	C_Hemangiosarcoma	0/70 (27) 0.7451	2/70 (28) 0.2545	1/70 (26) 0.4906	0/70 (29) NC

Table 17: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between the Water Controls and the Treated Groups-Male Rats

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	3 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	8 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	15 mg/kg/day High (N=70) P-value - Vehicle vs. High
ADIPOSE TISSUE	HEMANGIOMA	0/4 (1) 0.8000	1/2 (1) 0.5000	1/1 (1) 0.5000	0/5 (2) NC
	HEMANGIOSARCOMA	0/4 (1) 0.8000	1/2 (1) 0.5000	0/1 (1) NC	0/5 (2) NC
BODY CAVITY, NASAL	SQUAMOUS CELL CARCINOMA	0/70 (29) 0.1955	0/70 (27) NC	1/70 (26) 0.4707	1/70 (30) 0.5085
BRAIN	ASTROCYTOMA, MALIGNANT	1/70 (30) 0.8199	1/70 (28) 0.7368	1/70 (26) 0.7175	0/70 (29) 1.0000
	GRANULAR CELL TUMOR, BENIGN	1/70 (30) 0.9343	3/70 (29) 0.2930	0/70 (25) 1.0000	0/70 (29) 1.0000
	MENINGIOMA, MALIGNANT	1/70 (30) 1.0000	0/70 (27) 1.0000	0/70 (25) 1.0000	0/70 (29) 1.0000
GLAND THYROID	C_c-cell adenoma+carcinoma	4/70 (32) 0.7477	8/70 (30) 0.1380	12/70 (32) 0.0207	2/70 (30) 0.8870
GLAND, ADRENAL	CORTICAL ADENOMA	3/70 (31) 0.7712	1/70 (27) 0.9258	2/70 (26) 0.7640	1/70 (29) 0.9355
	PHEOCHROMOCYTOMA, BENIGN	7/70 (32) 0.8120	4/70 (29) 0.8761	3/70 (26) 0.9193	4/70 (31) 0.8986
	PHEOCHROMOCYTOMA, MALIGNANT	1/70 (30) 0.7386	0/70 (27) 1.0000	1/70 (25) 0.7071	0/70 (29) 1.0000
GLAND, MAMMARY	ADENOCARCINOMA	0/3 (2) 0.1282	0/4 (2) NC	0/9 (4) NC	2/8 (5) 0.4762
	ADENOMA	0/3 (2) 0.2947	1/4 (2) 0.5000	1/9 (5) 0.7143	2/8 (5) 0.4762
	FIBROADENOMA	2/3 (3) 0.9702	2/4 (3) 0.8000	4/9 (6) 0.7619	0/8 (4) 1.0000
GLAND, PARATHYROID	ADENOMA	0/70 (29) 0.1097	4/68 (28) 0.0518	4/67 (26) 0.0438	4/70 (31) 0.0645
GLAND, PITUITARY	ADENOMA, PARS DISTALIS	29/70 (46) 0.5401	31/70 (44) 0.3012	29/70 (43) 0.4162	29/70 (45) 0.5316
GLAND, PROSTATE	TRANSITIONAL CELL CARCINOMA	1/70 (30) 1.0000	0/70 (27) 1.0000	0/70 (25) 1.0000	0/70 (29) 1.0000
GLAND, THYROID	C-CELL ADENOMA	3/70 (31) 0.5923	6/70 (29) 0.2032	12/70 (32) 0.0098	2/70 (30) 0.8128
	C-CELL CARCINOMA	1/70 (30) 0.8663	2/70 (28) 0.4737	1/70 (25) 0.7071	0/70 (29) 1.0000
	FOLLICULAR CELL ADENOMA	0/70 (29) 0.3700	2/70 (28) 0.2368	2/70 (26) 0.2189	1/70 (29) 0.5000

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	3 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	8 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	15 mg/kg/day High (N=70) P-value - Vehicle vs. High
	FOLLICULAR CELL CARCINOMA	2/70 (30) 1.0000	0/70 (27) 1.0000	0/70 (25) 1.0000	0/70 (29) 1.0000
HEART	HEMANGIOSARCOMA	0/69 (29) 0.4955	0/70 (27) NC	1/70 (26) 0.4707	0/70 (29) NC
HEMOLYMPHORET ICULA	LEUKEMIA, GRANULOCYTIC	2/70 (30) 0.7135	1/70 (28) 0.8684	1/70 (26) 0.8535	1/70 (30) 0.8814
	LEUKEMIA, LARGE GRANULAR LYMPHOCYTIC	0/70 (29) 0.7387	1/70 (28) 0.4912	0/70 (25) NC	0/70 (29) NC
	LYMPHOMA, MALIGNANT	1/70 (30) 0.5697	2/70 (28) 0.4737	2/70 (27) 0.4598	1/70 (30) 0.7542
KIDNEY	AMPHOPHILIC VACUOLAR TUBULAR ADENOMA	1/70 (30) 0.9287	1/70 (27) 0.7074	0/70 (25) 1.0000	0/70 (29) 1.0000
	AMPHOPHILIC VACUOLAR TUBULAR CARCINOMA	0/70 (29) 0.2703	0/70 (27) NC	0/70 (25) NC	1/70 (30) 0.5085
	LIPOSARCOMA	1/70 (30) 1.0000	0/70 (27) 1.0000	0/70 (25) 1.0000	0/70 (29) 1.0000
LIVER	HEPATOCELLULAR ADENOMA	2/70 (30) 0.7085	1/70 (27) 0.8612	1/70 (26) 0.8535	1/70 (29) 0.8751
LUNG	BRONCHIOLOALVEOLAR ADENOMA	1/70 (30) 0.7386	0/70 (27) 1.0000	1/70 (25) 0.7071	0/70 (29) 1.0000
LYMPH NODE, MESENT	HEMANGIOMA	3/70 (31) 0.8188	1/70 (28) 0.9309	1/70 (25) 0.9143	1/69 (29) 0.9355
	HEMANGIOSARCOMA	0/70 (29) 0.7387	1/70 (28) 0.4912	0/70 (25) NC	0/69 (29) NC
MUSCLE, SKELETAL	SCHWANNOMA, MALIGNANT	0/70 (29) 0.5000	0/68 (26) NC	1/70 (26) 0.4707	0/70 (29) NC
PANCREAS	ACINAR ADENOMA	4/70 (31) 0.5798	7/70 (30) 0.2344	2/70 (26) 0.8580	5/70 (31) 0.5000
	ACINAR CARCINOMA	0/70 (29) 0.2636	0/70 (27) NC	0/69 (25) NC	1/70 (29) 0.5000
	C_isLET CELL adenoma+acinar adenoma	6/70 (32) 0.5734	13/70 (33) 0.0591	6/69 (28) 0.5239	8/70 (32) 0.3816
	ISLET CELL ADENOMA	3/70 (31) 0.5655	7/70 (30) 0.1369	4/69 (27) 0.4207	4/70 (31) 0.5000
	ISLET CELL CARCINOMA	2/70 (30) 0.6969	0/70 (27) 1.0000	4/69 (27) 0.2853	0/70 (29) 1.0000
SKIN	BASAL CELL TUMOR, BENIGN	2/70 (30) 0.3260	0/70 (27) 1.0000	2/70 (27) 0.6531	2/70 (30) 0.6940
	C_papillomas+squamous cell carcinomas	1/70 (30) 0.6792	2/70 (28) 0.4737	0/69 (25) 1.0000	1/70 (30) 0.7542
	FIBROMA	4/70 (31) 0.4877	1/70 (27) 0.9629	3/69 (26) 0.7088	3/70 (30) 0.7739
	KERATOACANTHOMA	7/70 (33) 0.5897	7/70 (31) 0.5666	2/69 (27) 0.9700	7/70 (32) 0.5929

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	3 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	8 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	15 mg/kg/day High (N=70) P-value - Vehicle vs. High
	PAPILLOMA	1/70 (30) 0.9287	2/70 (28) 0.4737	0/69 (25) 1.0000	0/70 (29) 1.0000
	SCHWANNOMA, MALIGNANT	0/70 (29) 0.7364	1/70 (27) 0.4821	0/69 (25) NC	0/70 (29) NC
	SEBACEOUS CELL ADENOMA	0/70 (29) 0.0713	0/70 (27) NC	0/69 (25) NC	2/70 (30) 0.2542
	SEBACEOUS CELL CARCINOMA	0/70 (29) 0.7387	1/70 (28) 0.4912	0/69 (25) NC	0/70 (29) NC
	SQUAMOUS CELL CARCINOMA	0/70 (29) 0.2703	0/70 (27) NC	0/69 (25) NC	1/70 (30) 0.5085
SPINAL CORD, CERVI	ASTROCYTOMA, MALIGNANT	0/70 (29) 0.2636	0/70 (27) NC	0/70 (25) NC	1/69 (29) 0.5000
SPINAL CORD, THORA	ASTROCYTOMA, MALIGNANT	1/70 (30) 1.0000	0/70 (27) 1.0000	0/70 (25) 1.0000	0/70 (29) 1.0000
SPLEEN	HEMANGIOSARCOMA	1/70 (30) 1.0000	0/70 (27) 1.0000	0/69 (25) 1.0000	0/70 (29) 1.0000
	LIPOMA	1/70 (30) 1.0000	0/70 (27) 1.0000	0/69 (25) 1.0000	0/70 (29) 1.0000
SUBCUTIS	FIBROMA	2/5 (3) 0.6688	2/5 (4) 0.8857	3/9 (6) 0.8810	2/5 (4) 0.8857
	HEMANGIOMA	0/5 (3) 0.1978	0/5 (3) NC	1/9 (5) 0.6250	1/5 (3) 0.5000
	LEIOMYOMA	0/5 (3) 0.5385	0/5 (3) NC	1/9 (4) 0.5714	0/5 (3) NC
	LIPOMA	2/5 (4) 0.5974	0/5 (3) 1.0000	1/9 (4) 0.9286	1/5 (3) 0.8857
	SCHWANNOMA, MALIGNANT	1/5 (3) 0.8901	1/5 (4) 0.8571	1/9 (5) 0.8929	0/5 (3) 1.0000
TESTIS	HEMANGIOMA	0/70 (29) 0.4955	0/70 (27) NC	1/70 (26) 0.4707	0/70 (29) NC
	INTERSTITIAL (LEYDIG) CELL ADENOMA	3/70 (30) 0.6224	1/70 (28) 0.9354	1/70 (25) 0.9196	2/70 (30) 0.8234
THYMUS	THYMOMA, BENIGN	1/69 (30) 1.0000	0/66 (26) 1.0000	0/68 (24) 1.0000	0/70 (29) 1.0000
	THYMOMA, MALIGNANT	0/69 (29) 0.4954	0/66 (26) NC	1/68 (25) 0.4630	0/70 (29) NC
URINARY BLADDER	TRANSITIONAL CELL CARCINOMA	1/69 (29) 1.0000	0/70 (27) 1.0000	0/70 (25) 1.0000	0/69 (28) 1.0000
Whold Body	C_Hemangiosarcoma	2/70 (30) 0.9419	2/70 (28) 0.6675	1/70 (26) 0.8535	0/70 (29) 1.0000

Table 18: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between the Vehicle Controls and the Treated Groups- Female Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-value - Trend	3 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	8 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	15 mg/kg/day High (N=70) P-value - Vehicle vs. High
BONE, FEMUR	OSTEOMA	1/70 (38) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/69 (26) 1.0000
	OSTEOSARCOMA	0/70 (38) 0.7043	1/70 (35) 0.4795	0/70 (34) NC	0/69 (26) NC
BRAIN	ASTROCYTOMA, MALIGNANT	0/69 (37) 0.2522	1/70 (35) 0.4861	0/70 (34) NC	1/70 (27) 0.4219
	GRANULAR CELL TUMOR, BENIGN	0/69 (37) 0.0766	1/70 (34) 0.4789	1/70 (35) 0.4861	2/70 (27) 0.1741
CERVIX	ENDOMETRIAL STROMAL POLYP	1/69 (37) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/70 (27) 1.0000
	GRANULAR CELL TUMOR, BENIGN	3/69 (38) 0.9941	1/70 (34) 0.9283	0/70 (34) 1.0000	0/70 (27) 1.0000
GLAND, ADRENAL	CORTICAL ADENOMA	5/70 (39) 0.2819	0/70 (34) 1.0000	2/70 (35) 0.9280	4/70 (29) 0.5909
	PHEOCHROMOCYTOMA, BENIGN	2/70 (38) 0.9780	1/70 (34) 0.8586	0/70 (34) 1.0000	0/70 (27) 1.0000
	PHEOCHROMOCYTOMA, COMPLEX, BENIGN	0/70 (38) 0.4586	0/70 (34) NC	1/70 (34) 0.4702	0/70 (27) NC
GLAND, CLITORAL	ADENOCARCINOMA	0/1 (1) 0.5333	1/3 (2) 0.6667	1/5 (4) 0.8000	1/5 (3) 0.7500
GLAND, MAMMARY	ADENOCARCINOMA	17/70 (46) 0.4299	25/70 (45) 0.0581	20/70 (43) 0.2424	15/70 (34) 0.3384
	ADENOMA	5/70 (40) 0.2157	2/70 (34) 0.9170	9/70 (39) 0.1748	4/70 (29) 0.5748
	FIBROADENOMA	48/70 (56) 0.3379	34/70 (46) 0.9594	42/70 (51) 0.7703	41/70 (48) 0.6279
GLAND, PARATHYROID	ADENOMA	3/68 (37) 0.5973	0/67 (31) 1.0000	2/68 (33) 0.7839	1/62 (24) 0.8734
GLAND, PITUITARY	ADENOMA, PARS DISTALIS	39/69 (54) 0.4061	38/70 (53) 0.6085	38/70 (52) 0.5476	37/70 (50) 0.5073
	CARCINOMA, PARS DISTALIS	1/69 (38) 0.2695	0/70 (34) 1.0000	2/70 (35) 0.4688	1/70 (27) 0.6620
	PITUICYTOMA	0/69 (37) 0.7018	1/70 (35) 0.4861	0/70 (34) NC	0/70 (27) NC
GLAND, THYROID	C-CELL ADENOMA	9/70 (41) 0.5498	9/70 (37) 0.5070	6/70 (37) 0.8233	7/70 (30) 0.5561
	C-CELL CARCINOMA	1/70 (39) 0.4360	1/70 (34) 0.7080	1/70 (35) 0.7057	1/70 (27) 0.6545

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-value - Trend	3 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	8 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	15 mg/kg/day High (N=70) P-value - Vehicle vs. High
	FOLLICULAR CELL ADENOMA	2/70 (38) 0.8523	2/70 (34) 0.6495	2/70 (35) 0.6609	0/70 (27) 1.0000
	FOLLICULAR CELL CARCINOMA	0/70 (38) 0.2030	0/70 (34) NC	0/70 (34) NC	1/70 (27) 0.4154
Gland Thyroid	C cell Adenoma+Carcinoma	10/70 (42) 0.5256	10/70 (37) 0.4705	7/70 (37) 0.7880	8/70 (31) 0.5285
	follicular cell Adenoma+Carcinoma	2/70 (38) 0.6238	2/70 (34) 0.6495	2/70 (35) 0.6609	1/70 (27) 0.8069
HEMOLYMPHORETIC ICULA	HISTIOCYTIC SARCOMA	1/70 (38) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/70 (27) 1.0000
	LEUKEMIA, GRANULOCYTIC	0/70 (38) 0.0424	0/70 (34) NC	0/70 (34) NC	2/70 (28) 0.1762
	LEUKEMIA, LARGE GRANULAR LYMPHOCYTIC	0/70 (38) 0.7064	1/70 (35) 0.4795	0/70 (34) NC	0/70 (27) NC
	LYMPHOMA, MALIGNANT	2/70 (38) 0.2873	0/70 (34) 1.0000	0/70 (34) 1.0000	2/70 (27) 0.5546
KIDNEY	AMPHOPHILIC VACUOLAR TUBULAR ADENOMA	0/70 (38) 0.0779	1/70 (35) 0.4795	1/70 (35) 0.4795	2/70 (28) 0.1762
	AMPHOPHILIC VACUOLAR TUBULAR CARCINOMA	0/70 (38) 0.7064	1/70 (35) 0.4795	0/70 (34) NC	0/70 (27) NC
	LIPOMA	0/70 (38) 0.3690	2/70 (35) 0.2264	0/70 (34) NC	1/70 (27) 0.4154
LARGE INTESTINE, C	ADENOMA	0/70 (38) 0.7043	1/70 (34) 0.4702	0/70 (34) NC	0/70 (27) NC
LIVER	CHOLANGIOMA	1/70 (38) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/70 (27) 1.0000
	HEPATOCELLULAR ADENOMA	3/70 (38) 0.0095	3/70 (35) 0.6226	6/70 (37) 0.2264	8/70 (30) 0.0395
LUNG	BRONCHIOLOALVEOLAR ADENOMA	1/70 (38) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/70 (27) 1.0000
LYMPH NODE, MESENT	HEMANGIOMA	0/70 (38) 0.4586	0/70 (34) NC	1/70 (34) 0.4702	0/70 (27) NC
	HEMANGIOSARCOMA	0/70 (38) 0.4627	0/70 (34) NC	1/70 (35) 0.4795	0/70 (27) NC
MUSCLE, SKELETAL	HEMANGIOMA	1/70 (38) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/69 (26) 1.0000
OVARY	ADENOMA	1/70 (38) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/69 (26) 1.0000
PANCREAS	ISLET CELL ADENOMA	2/70 (38) 0.0532	1/70 (34) 0.8586	4/70 (35) 0.2982	4/70 (28) 0.2037
	ISLET CELL CARCINOMA	3/70 (39) 0.9936	1/70 (34) 0.9244	0/70 (34) 1.0000	0/70 (27) 1.0000
SKIN	KERATOACANTHOMA	2/70 (38) 0.9701	2/70 (34) 0.6495	0/70 (34) 1.0000	0/70 (27) 1.0000

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-value - Trend	3 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	8 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	15 mg/kg/day High (N=70) P-value - Vehicle vs. High
	PAPILLOMA	2/70 (38) 0.8600	0/70 (34) 1.0000	1/70 (34) 0.8586	0/70 (27) 1.0000
	SQUAMOUS CELL CARCINOMA	0/70 (38) 0.2238	1/70 (35) 0.4795	1/70 (34) 0.4702	1/70 (27) 0.4154
SUBCUTIS	FIBROMA	0/9 (7) 0.2000	0/8 (5) NC	0/7 (4) NC	1/7 (4) 0.3636
	FIBROSARCOMA	1/9 (7) 1.0000	0/8 (5) 1.0000	0/7 (4) 1.0000	0/7 (3) 1.0000
	HEMANGIOSARCOMA	0/9 (7) 0.6316	1/8 (5) 0.4167	0/7 (4) NC	0/7 (3) NC
	LIPOMA	4/9 (8) 0.5357	3/8 (6) 0.7040	2/7 (4) 0.7073	2/7 (4) 0.7073
	SCHWANNOMA, BENIGN	2/9 (7) 1.0000	0/8 (5) 1.0000	0/7 (4) 1.0000	0/7 (3) 1.0000
	SCHWANNOMA, MALIGNANT	2/9 (8) 0.5228	1/8 (5) 0.8042	1/7 (4) 0.7455	1/7 (4) 0.7455
Skin	C_Papilloma+squamous cell Carcinoma+keratoacanthoma	4/70 (38) 0.8764	3/70 (35) 0.7497	2/70 (35) 0.8806	1/70 (27) 0.9392
THYMUS	THYMOMA, BENIGN	0/68 (37) 0.0419	0/70 (33) NC	0/70 (33) NC	2/70 (27) 0.1741
	THYMOMA, MALIGNANT	0/68 (37) 0.7054	1/70 (33) 0.4704	0/70 (33) NC	0/70 (27) NC
UTERUS	ENDOMETRIAL ADENOCARCINOMA	1/70 (38) 0.9211	1/70 (35) 0.7325	0/70 (34) 1.0000	0/70 (27) 1.0000
	ENDOMETRIAL ADENOMA	0/70 (38) 0.2030	0/70 (34) NC	0/70 (34) NC	1/70 (27) 0.4154
	ENDOMETRIAL STROMAL POLYP	3/70 (39) 0.7600	1/70 (34) 0.9244	1/70 (35) 0.9285	1/70 (27) 0.8859
	HEMANGIOMA	0/70 (38) 0.2030	0/70 (34) NC	0/70 (34) NC	1/70 (27) 0.4154
Uterus	endometrial adenoma+adenocarcinoma	1/70 (38) 0.5107	1/70 (35) 0.7325	0/70 (34) 1.0000	1/70 (27) 0.6620
VAGINA	ENDOMETRIAL STROMAL POLYP	1/70 (38) 1.0000	0/70 (34) 1.0000	0/70 (33) 1.0000	0/70 (27) 1.0000
	SCHWANNOMA, MALIGNANT	0/70 (38) 0.4545	0/70 (34) NC	1/70 (33) 0.4648	0/70 (27) NC
Whold Body	C_Hemangiosarcoma	0/70 (38) 0.6674	2/70 (35) 0.2264	1/70 (35) 0.4795	0/70 (27) NC

Table 19: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between the Water Controls and the Treated Groups- Female Rats

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	3 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	8 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	15 mg/kg/day High (N=70) P-value - Vehicle vs. High
BONE, FEMUR	OSTEOSARCOMA	0/70 (43) 0.6884	1/70 (35) 0.4487	0/70 (34) NC	0/69 (26) NC
BRAIN	ASTROCYTOMA, MALIGNANT	0/70 (43) 0.2308	1/70 (35) 0.4487	0/70 (34) NC	1/70 (27) 0.3857
	GRANULAR CELL TUMOR, BENIGN	1/70 (43) 0.1763	1/70 (34) 0.6914	1/70 (35) 0.6993	2/70 (27) 0.3292
CERVIX	GRANULAR CELL TUMOR, BENIGN	0/70 (43) 0.6884	1/70 (34) 0.4416	0/70 (34) NC	0/70 (27) NC
GLAND, ADRENAL	CORTICAL ADENOMA	10/70 (46) 0.7616	0/70 (34) 1.0000	2/70 (35) 0.9928	4/70 (29) 0.8792
	PHEOCHROMOCYTOMA, BENIGN	1/70 (43) 0.9045	1/70 (34) 0.6914	0/70 (34) 1.0000	0/70 (27) 1.0000
	PHEOCHROMOCYTOMA, COMPLEX, BENIGN	0/70 (43) 0.4420	0/70 (34) NC	1/70 (34) 0.4416	0/70 (27) NC
GLAND, CLITORAL	ADENOCARCINOMA	0/5 (3) 0.3182	1/3 (2) 0.4000	1/5 (4) 0.5704	1/5 (3) 0.5000
GLAND, MAMMARY	ADENOCARCINOMA	18/70 (51) 0.3521	25/70 (45) 0.0368	20/70 (43) 0.1859	15/70 (34) 0.2768
	ADENOMA	8/70 (45) 0.4191	2/70 (34) 0.9769	9/70 (39) 0.3695	4/70 (29) 0.7787
	FIBROADENOMA	53/70 (61) 0.4058	34/70 (46) 0.9744	42/70 (51) 0.8239	41/70 (48) 0.6934
GLAND, PARATHYROID	ADENOMA	1/67 (40) 0.2396	0/67 (31) 1.0000	2/68 (33) 0.4273	1/62 (24) 0.6131
GLAND, PITUITARY	ADENOMA, PARS DISTALIS	47/70 (60) 0.6470	38/70 (53) 0.8493	38/70 (52) 0.8079	37/70 (50) 0.7760
	CARCINOMA, PARS DISTALIS	7/70 (47) 0.9311	0/70 (34) 1.0000	2/70 (35) 0.9578	1/70 (27) 0.9791
	PITUICYTOMA	0/70 (43) 0.6906	1/70 (35) 0.4487	0/70 (34) NC	0/70 (27) NC
GLAND, SALIVARY, M	ADENOCARCINOMA	1/70 (43) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/70 (27) 1.0000
GLAND, THYROID	C-CELL ADENOMA	12/70 (46) 0.6949	9/70 (37) 0.6674	6/70 (37) 0.9131	7/70 (30) 0.7032
	C-CELL CARCINOMA	1/70 (43) 0.4115	1/70 (34) 0.6914	1/70 (35) 0.6993	1/70 (27) 0.6261
	FOLLICULAR CELL ADENOMA	1/70 (43) 0.6989	2/70 (34) 0.4116	2/70 (35) 0.4223	0/70 (27) 1.0000

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	3 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	8 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	15 mg/kg/day High (N=70) P-value - Vehicle vs. High
	FOLLICULAR CELL CARCINOMA	0/70 (43) 0.1957	0/70 (34) NC	0/70 (34) NC	1/70 (27) 0.3857
Gland Thyroid	C cell Adenoma+Carcinoma	13/70 (46) 0.6775	10/70 (37) 0.6433	7/70 (37) 0.8946	8/70 (31) 0.6883
	follicular cell Adenoma+Carcinoma	1/70 (43) 0.4200	2/70 (34) 0.4116	2/70 (35) 0.4223	1/70 (27) 0.6261
HEART	HEMANGIOSARCOMA	1/70 (44) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/70 (27) 1.0000
HEMOLYMPHORET ICULA	HISTIOCYTIC SARCOMA	3/70 (45) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/70 (27) 1.0000
	LEUKEMIA, GRANULOCYTIC	1/70 (43) 0.1391	0/70 (34) 1.0000	0/70 (34) 1.0000	2/70 (28) 0.3417
	LEUKEMIA, LARGE GRANULAR LYMPHOCYTIC	0/70 (43) 0.6906	1/70 (35) 0.4487	0/70 (34) NC	0/70 (27) NC
	LYMPHOMA, MALIGNANT	0/70 (43) 0.0370	0/70 (34) NC	0/70 (34) NC	2/70 (27) 0.1453
KIDNEY	AMPHOPHILIC VACUOLAR TUBULAR ADENOMA	1/70 (43) 0.1823	1/70 (35) 0.6993	1/70 (35) 0.6993	2/70 (28) 0.3417
	AMPHOPHILIC VACUOLAR TUBULAR CARCINOMA	0/70 (43) 0.6906	1/70 (35) 0.4487	0/70 (34) NC	0/70 (27) NC
	HEMANGIOSARCOMA	1/70 (44) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/70 (27) 1.0000
	LIPOMA	0/70 (43) 0.3448	2/70 (35) 0.1981	0/70 (34) NC	1/70 (27) 0.3857
LARGE INTESTINE, C	ADENOMA	0/70 (43) 0.6884	1/70 (34) 0.4416	0/70 (34) NC	0/70 (27) NC
LIVER	HEMANGIOSARCOMA	1/70 (43) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/70 (27) 1.0000
	HEPATOCELLULAR ADENOMA	3/70 (44) 0.0057	3/70 (35) 0.5473	6/70 (37) 0.1623	8/70 (30) 0.0221
LUNG	BRONCHIOLOALVEOLAR ADENOMA	1/70 (43) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/70 (27) 1.0000
	HEMANGIOSARCOMA	1/70 (44) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/70 (27) 1.0000
LYMPH NODE, MESENT	HEMANGIOMA	0/70 (43) 0.4420	0/70 (34) NC	1/70 (34) 0.4416	0/70 (27) NC
	HEMANGIOSARCOMA	0/70 (43) 0.4460	0/70 (34) NC	1/70 (35) 0.4487	0/70 (27) NC
MUSCLE, DIAPHRAGM	HEMANGIOSARCOMA	1/70 (44) 1.0000	0/70 (34) 1.0000	0/70 (33) 1.0000	0/70 (27) 1.0000
OVARY	ADENOMA	1/70 (43) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/69 (26) 1.0000
	HEMANGIOSARCOMA	1/70 (44) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/69 (26) 1.0000

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	3 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	8 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	15 mg/kg/day High (N=70) P-value - Vehicle vs. High
PANCREAS	ACINAR ADENOMA	2/70 (43) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/70 (27) 1.0000
	ISLET CELL ADENOMA	6/70 (44) 0.3191	1/70 (34) 0.9855	4/70 (35) 0.7338	4/70 (28) 0.5993
	ISLET CELL CARCINOMA	4/70 (43) 0.9975	1/70 (34) 0.9513	0/70 (34) 1.0000	0/70 (27) 1.0000
SKIN	HEMANGIOSARCOMA	1/70 (44) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/70 (27) 1.0000
	KERATOACANTHOMA	0/70 (43) 0.7498	2/70 (34) 0.1917	0/70 (34) NC	0/70 (27) NC
	PAPILLOMA	2/70 (43) 0.8433	0/70 (34) 1.0000	1/70 (34) 0.8313	0/70 (27) 1.0000
	SQUAMOUS CELL CARCINOMA	0/70 (43) 0.2044	1/70 (35) 0.4487	1/70 (34) 0.4416	1/70 (27) 0.3857
SPLEEN	HEMANGIOSARCOMA	1/70 (43) 1.0000	0/70 (34) 1.0000	0/70 (34) 1.0000	0/70 (27) 1.0000
SUBCUTIS	FIBROMA	3/11 (8) 0.6961	0/8 (5) 1.0000	0/7 (4) 1.0000	1/7 (4) 0.8586
	HEMANGIOSARCOMA	0/11 (7) 0.6316	1/8 (5) 0.4167	0/7 (4) NC	0/7 (3) NC
	LIPOMA	4/11 (8) 0.5357	3/8 (6) 0.7040	2/7 (4) 0.7073	2/7 (4) 0.7073
	SCHWANNOMA, MALIGNANT	2/11 (9) 0.4812	1/8 (5) 0.7692	1/7 (4) 0.7063	1/7 (4) 0.7063
Skin	C_Papilloma+squamous cell Carcinoma+keratoacanthoma	2/70 (43) 0.6379	3/70 (35) 0.4020	2/70 (35) 0.6107	1/70 (27) 0.7746
THYMUS	THYMOMA, BENIGN	2/70 (43) 0.2695	0/70 (33) 1.0000	0/70 (33) 1.0000	2/70 (27) 0.5020
	THYMOMA, MALIGNANT	0/70 (42) 0.6889	1/70 (33) 0.4400	0/70 (33) NC	0/70 (27) NC
UTERUS	ENDOMETRIAL ADENOCARCINOMA	0/70 (43) 0.6906	1/70 (35) 0.4487	0/70 (34) NC	0/70 (27) NC
	ENDOMETRIAL ADENOMA	0/70 (43) 0.1957	0/70 (34) NC	0/70 (34) NC	1/70 (27) 0.3857
	ENDOMETRIAL STROMAL POLYP	6/70 (45) 0.9432	1/70 (34) 0.9843	1/70 (35) 0.9857	1/70 (27) 0.9692
	HEMANGIOMA	0/70 (43) 0.1957	0/70 (34) NC	0/70 (34) NC	1/70 (27) 0.3857
Uterus	endometrial adenoma+adenocarcinoma	0/70 (43) 0.2308	1/70 (35) 0.4487	0/70 (34) NC	1/70 (27) 0.3857
VAGINA	SCHWANNOMA, MALIGNANT	0/70 (43) 0.4380	0/70 (34) NC	1/70 (33) 0.4342	0/70 (27) NC
Whold Body	C_Hemangiosarcoma	2/70 (43) 0.9035	2/70 (35) 0.6107	1/70 (35) 0.8378	0/70 (27) 1.0000

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Table 20: Intercurrent Mortality Rate -Male Mice

Week	Water 0 mg/kg/day (N=25)		Vehicle 0 mg/kg/day (N=25)		10 mg/kg/day (N=25)		30 mg/kg/day (N=25)		60 mg/kg/day (N=25)		Positive 75 mg/kg/day (N=15)	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 13	.	.	2	8.00	1	4.00	.	.	2	8.00	1	6.67
14 - 26	.	.	.	.	4	20.00	2	8.00	.	.	12	86.67
Ter. Sac.	25	100.00	23	92.00	20	80.00	23	92.00	23	92.00	2	13.33

Cum. %: Cumulative percentage except for Ter. Sac.

Table 21: Intercurrent Mortality Rate -Female Mice

Week	Water 0 mg/kg/day (N=25)		Vehicle 0 mg/kg/day (N=25)		10 mg/kg/day (N=25)		30 mg/kg/day (N=25)		60 mg/kg/day (N=25)		Positive 75 mg/kg/day (N=15)	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 13	.	.	1	4.00	.	.	1	4.00	.	.	4	26.67
14 - 26	1	4.00	.	.	.	.	2	12.00	1	4.00	9	86.67
Ter. Sac.	24	96.00	24	96.00	25	100.00	22	88.00	24	96.00	2	13.33

Cum. %: Cumulative percentage except for Ter. Sac.

Table 22: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control-Male Mice

Test	Statistic	P_Value				
		Vehicle vs Treated Groups Dose Response	Vehicle vs. Low	Vehicle vs. Med	Vehicle vs. High	Vehicle vs. Positive
Dose-Response	Likelihood Ratio	0.5122	0.2482	0.9749	0.9749	<0.001
Homogeneity	Log-Rank	0.4517	0.2545	0.9748	0.9748	<0.001

Table 23: Intercurrent Mortality Comparison between Treated Groups and Water Control-Male Mice

Test	Statistic	P_Value				
		Vehicle vs Treated Groups Dose Response	Vehicle vs. Low	Vehicle vs. Med	Vehicle vs. High	Vehicle vs. Positive
Dose-Response	Likelihood Ratio	0.9144	0.0066	0.0935	0.0935	<0.001

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High	P_Value Vehicle vs. Positive
Homogeneity	Log-Rank	0.1015	0.0196	0.1531	0.1531	<0.001

Table 24: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control-Female Mice

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High	P_Value Vehicle vs. Positive
Dose-Response	Likelihood Ratio	0.6316	0.2390	0.3061	0.9885	<0.001
Homogeneity	Log-Rank	0.2707	0.3173	0.3170	0.9885	<0.001

Table 25: Intercurrent Mortality Comparison between Treated Groups and Water Control-Female Mice

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High	P_Value Vehicle vs. Positive
Dose-Response	Likelihood Ratio	0.6125	0.2390	0.2780	0.9885	<0.001
Homogeneity	Log-Rank	0.2544	0.3173	0.2874	0.9885	<0.001

Table 26: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	10 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	30 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	60 mg/kg/day High (N=25) P-value - Vehicle vs. High
GLAND, HARDERIAN	ADENOMA	0/25 (23) 0.7527	1/25 (22) 0.4889	0/25 (25) NC	0/25 (23) NC
Gland Harderian	C_adenoma+adenocarcinoma	0/25 (23) 0.7527	1/25 (22) 0.4889	0/25 (25) NC	0/25 (23) NC
HEMOLYMPHORET ICULA	LYMPHOMA, MALIGNANT	0/25 (23) 0.7553	1/25 (23) 0.5000	0/25 (25) NC	0/25 (23) NC
LUNG	BRONCHIOLOALVEOLAR ADENOMA	0/25 (23) 0.3008	1/25 (22) 0.4889	1/25 (25) 0.5208	1/25 (23) 0.5000
	BRONCHIOLOALVEOLAR CARCINOMA	0/25 (23) 0.7527	1/25 (22) 0.4889	0/25 (25) NC	0/25 (23) NC
Lung	C_bronchioloalveolar adenoma+carcinoma	0/25 (23) 0.4290	2/25 (22) 0.2333	1/25 (25) 0.5208	1/25 (23) 0.5000
SPLEEN	HEMANGIOSARCOMA	0/25 (23) 0.4236	2/25 (23) 0.2444	1/25 (25) 0.5208	1/25 (23) 0.5000
TESTIS	HEMANGIOSARCOMA	0/25 (23) 0.3118	1/25 (22) 0.4889	0/25 (25) NC	1/25 (23) 0.5000
Whold Body	C_Hemangiosarcoma	0/25 (23) 0.1563	3/25 (23) 0.1167	1/25 (25) 0.5208	3/25 (23) 0.1167

Table 27: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Water Control and the Treated Groups-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25) P-value - Trend	10 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	30 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	60 mg/kg/day High (N=25) P-value - Vehicle vs. High
GLAND, HARDERIAN	ADENOMA	1/25 (25) 0.9328	1/25 (22) 0.7025	0/25 (25) 1.0000	0/25 (23) 1.0000
Gland Harderian	C_adenoma+adenocarcinoma	1/25 (25) 0.9328	1/25 (22) 0.7025	0/25 (25) 1.0000	0/25 (23) 1.0000
HEMOLYMPHORET ICULA	LYMPHOMA, MALIGNANT	0/25 (25) 0.7396	1/25 (23) 0.4792	0/25 (25) NC	0/25 (23) NC
LUNG	BRONCHIOLOALVEOLAR ADENOMA	0/25 (25) 0.2856	1/25 (22) 0.4681	1/25 (25) 0.5000	1/25 (23) 0.4792
	BRONCHIOLOALVEOLAR CARCINOMA	0/25 (25) 0.7368	1/25 (22) 0.4681	0/25 (25) NC	0/25 (23) NC
Lung	C_bronchioloalveolar adenoma+carcinoma	0/25 (25) 0.4101	2/25 (22) 0.2137	1/25 (25) 0.5000	1/25 (23) 0.4792
SKIN	PAPILLOMA	1/25 (25) 1.0000	0/25 (22) 1.0000	0/25 (25) 1.0000	0/25 (23) 1.0000
SPLEEN	HEMANGIOSARCOMA	1/25 (25) 0.6148	2/25 (23) 0.4681	1/25 (25) 0.7551	1/25 (23) 0.7340
TESTIS	HEMANGIOSARCOMA	1/25 (25) 0.5836	1/25 (22) 0.7025	0/25 (25) 1.0000	1/25 (23) 0.7340
Whold Body	C_Hemangiosarcoma	2/25 (25) 0.4061	3/25 (23) 0.4592	1/25 (25) 0.8827	3/25 (23) 0.4592

Table 28: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	10 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	30 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	60 mg/kg/day High (N=25) P-value - Vehicle vs. High
GLAND, HARDERIAN	ADENOMA	1/25 (24) 0.5549	1/25 (25) 0.7835	1/25 (24) 0.7553	1/25 (25) 0.7835
LUNG	BRONCHIOLOALVEOLAR ADENOMA	1/25 (24) 0.1925	0/25 (25) 1.0000	1/25 (24) 0.7553	2/25 (25) 0.5450
	BRONCHIOLOALVEOLAR CARCINOMA	0/25 (24) 0.5049	0/25 (25) NC	1/25 (25) 0.5102	0/25 (25) NC
Lung	C_bronchioloalveolar adenoma+carcinoma	1/25 (24) 0.1859	0/25 (25) 1.0000	2/25 (25) 0.5156	2/25 (25) 0.5450
SKIN	HEMANGIOSARCOMA	1/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000
	PAPILLOMA	0/25 (24) 0.1953	0/25 (25) NC	1/25 (25) 0.5102	1/25 (25) 0.5294
SPLEEN	HEMANGIOSARCOMA	2/25 (24) 0.7005	0/25 (25) 1.0000	0/25 (24) 1.0000	1/25 (25) 0.9025
UTERUS	ENDOMETRIAL STROMAL POLYP	1/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000
Whold Body	C_Hemangiosarcoma	0/25 (24) 0.1685	3/25 (25) 0.1482	1/25 (24) 0.5000	3/25 (25) 0.1405

Table 29: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Water Control and the Treated Groups-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25) P-value - Trend	10 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	30 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	60 mg/kg/day High (N=25) P-value - Vehicle vs. High
GLAND, HARDERIAN	ADENOMA	1/27 (27) 0.5276	1/28 (27) 0.7547	1/26 (24) 0.7047	1/28 (27) 0.7547
LUNG	BRONCHIOLOALVEOLAR ADENOMA	0/27 (27) 0.0605	0/28 (27) NC	1/26 (24) 0.4706	2/28 (27) 0.2453
	BRONCHIOLOALVEOLAR CARCINOMA	0/27 (27) 0.4906	0/28 (27) NC	1/26 (25) 0.4808	0/28 (27) NC
Lung	C_bronchioloalveolar adenoma+carcinoma	0/27 (27) 0.0712	0/28 (27) NC	2/26 (25) 0.2262	2/28 (27) 0.2453
SKIN	PAPILLOMA	0/27 (27) 0.1844	0/28 (27) NC	1/26 (25) 0.4808	1/28 (27) 0.5000
SPLEEN	HEMANGIOSARCOMA	1/27 (27) 0.5005	0/28 (27) 1.0000	0/26 (24) 1.0000	1/28 (27) 0.7547
STOMACH	SARCOMA	1/27 (27) 1.0000	0/28 (27) 1.0000	0/26 (24) 1.0000	0/28 (27) 1.0000
Whold Body	C_Hemangiosarcoma	2/27 (27) 0.4155	3/28 (28) 0.5177	1/26 (24) 0.8595	3/28 (27) 0.5000

Table 30: Tumor Rates and P-Values for Comparisons between Vehicle Control and Positive Control- Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=15) P-value - Vehicle vs. Positive
GLAND, HARDERIAN	ADENOCARCINOMA	0/25 (23)	1/15 (8) 0.2581
	ADENOMA	0/25 (23)	3/15 (7) 0.0086
Gland Harderian	C_adenoma+adenocarcinoma	0/25 (23)	4/15 (8) 0.0022
HEMOLYMPHORETICULA	LYMPHOMA, MALIGNANT	0/25 (23)	9/15 (12) <0.001
LARGE INTESTINE, C	ADENOCARCINOMA	0/25 (23)	1/15 (7) 0.2333
LUNG	BRONCHIOLOALVEOLAR ADENOMA	0/25 (23)	2/15 (8) 0.0602
	BRONCHIOLOALVEOLAR CARCINOMA	0/25 (23)	1/15 (8) 0.2581
Lung	C_bronchioloalveolar adenoma+carcinoma	0/25 (23)	3/15 (9) 0.0169
SKIN	PAPILLOMA	0/25 (23)	8/15 (11) <0.001
SMALL INTESTINE, I	ADENOCARCINOMA	0/25 (23)	1/13 (8) 0.2581
SMALL INTESTINE, J	ADENOCARCINOMA	0/25 (23)	1/12 (7) 0.2333
SPLEEN	HEMANGIOSARCOMA	0/25 (23)	1/15 (8) 0.2581
STOMACH	PAPILLOMA	0/25 (23)	9/15 (12) <0.001
	SQUAMOUS CELL CARCINOMA	0/25 (23)	2/15 (8) 0.0602
TONGUE	PAPILLOMA	0/25 (23)	1/15 (7) 0.2333
Whold Body	C_Hemangiosarcoma	0/25 (23)	1/15 (8) 0.2581

Table 31: Tumor Rates and P-Values for Comparisons between Water Control and Positive Control- Male Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25)	Positive (N=15) P-value - Water vs. Positive
GLAND, HARDERIAN	ADENOCARCINOMA	0/25 (25)	1/15 (8) 0.2424
	ADENOMA	1/25 (25)	3/15 (7) 0.0253
Gland Harderian	C_adenoma+adenocarcinoma	1/25 (25)	4/15 (8) 0.0076
HEMOLYMPHORETICULA	LYMPHOMA, MALIGNANT	0/25 (25)	9/15 (12) <0.001
LARGE INTESTINE, C	ADENOCARCINOMA	0/25 (25)	1/15 (7) 0.2188
LUNG	BRONCHIOLOALVEOLAR ADENOMA	0/25 (25)	2/15 (8) 0.0530
	BRONCHIOLOALVEOLAR CARCINOMA	0/25 (25)	1/15 (8) 0.2424
Lung	C_bronchioloalveolar adenoma+carcinoma	0/25 (25)	3/15 (9) 0.0140
SKIN	PAPILLOMA	1/25 (25)	8/15 (11) <0.001
SMALL INTESTINE, I	ADENOCARCINOMA	0/25 (25)	1/13 (8) 0.2424
SMALL INTESTINE, J	ADENOCARCINOMA	0/25 (25)	1/12 (7) 0.2188
SPLEEN	HEMANGIOSARCOMA	1/25 (25)	1/15 (8) 0.4318
STOMACH	PAPILLOMA	0/25 (25)	9/15 (12) <0.001
	SQUAMOUS CELL CARCINOMA	0/25 (25)	2/15 (8) 0.0530
TONGUE	PAPILLOMA	0/25 (25)	1/15 (7) 0.2188
Whold Body	C_Hemangiosarcoma	2/25 (25)	1/15 (8) 0.5784

Table 32: Tumor Rates and P-Values for Comparisons between Vehicle Control and Positive Control- Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=15) P-value - Vehicle vs. Positive
ESOPHAGUS	PAPILLOMA	0/25 (24)	1/16 (6)
GLAND, HARDERIAN	ADENOMA	1/25 (24)	3/16 (7) 0.0258
HEMOLYMPHORET ICULA	LYMPHOMA, MALIGNANT	0/25 (24)	11/16 (13) <0.001
LUNG	BRONCHIOLOALVEOLAR ADENOMA	1/25 (24)	1/16 (7) 0.4065
	BRONCHIOLOALVEOLAR CARCINOMA	0/25 (24)	1/16 (7) 0.2258
Lung	C_bronchioloalveolar adenoma+carcinoma	1/25 (24)	2/16 (8) 0.1468
SKIN	PAPILLOMA	0/25 (24)	6/16 (9) <0.001
STOMACH	PAPILLOMA	0/25 (24)	12/16 (13) <0.001
TONGUE	PAPILLOMA	0/25 (24)	1/16 (7) 0.2258
UTERUS	ENDOMETRIAL STROMAL POLYP	1/25 (24)	1/16 (6) 0.3655
	HEMANGIOMA	0/25 (24)	1/16 (7) 0.2258
Whold Body	C_Hemangiosarcoma	0/25 (24)	1/16 (7) 0.2258

Table 33: Tumor Rates and P-Values for Comparisons between Water Control and Positive Control- Female Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25)	Positive (N=15) P-value - Water vs. Positive
ESOPHAGUS	PAPILLOMA	0/25 (25)	1/16 (6) 0.1875
GLAND, HARDERIAN	ADENOMA	1/25 (25)	3/16 (7) 0.0211
HEMOLYMPHORETICULA	LYMPHOMA, MALIGNANT	0/25 (25)	11/16 (13) <0.001
LUNG	BRONCHIOLOALVEOLAR ADENOMA	0/25 (25)	1/16 (7) 0.2059
	BRONCHIOLOALVEOLAR CARCINOMA	0/25 (25)	1/16 (7) 0.2059
Lung	C_bronchioloalveolar adenoma+carcinoma	0/25 (25)	2/16 (8) 0.0471
SKIN	PAPILLOMA	0/25 (25)	6/16 (9) <0.001
STOMACH	PAPILLOMA	0/25 (25)	12/16 (13) <0.001
	SARCOMA	1/25 (25)	0/16 (6) 1.0000
TONGUE	PAPILLOMA	0/25 (25)	1/16 (7) 0.2059
UTERUS	ENDOMETRIAL STROMAL POLYP	0/25 (25)	1/16 (6) 0.1818
	HEMANGIOMA	0/25 (25)	1/16 (7) 0.2059
Whold Body	C_Hemangiosarcoma	2/25 (25)	1/16 (7) 0.5112

Figure 1: Kaplan-Meier Survival Functions for Male Rats

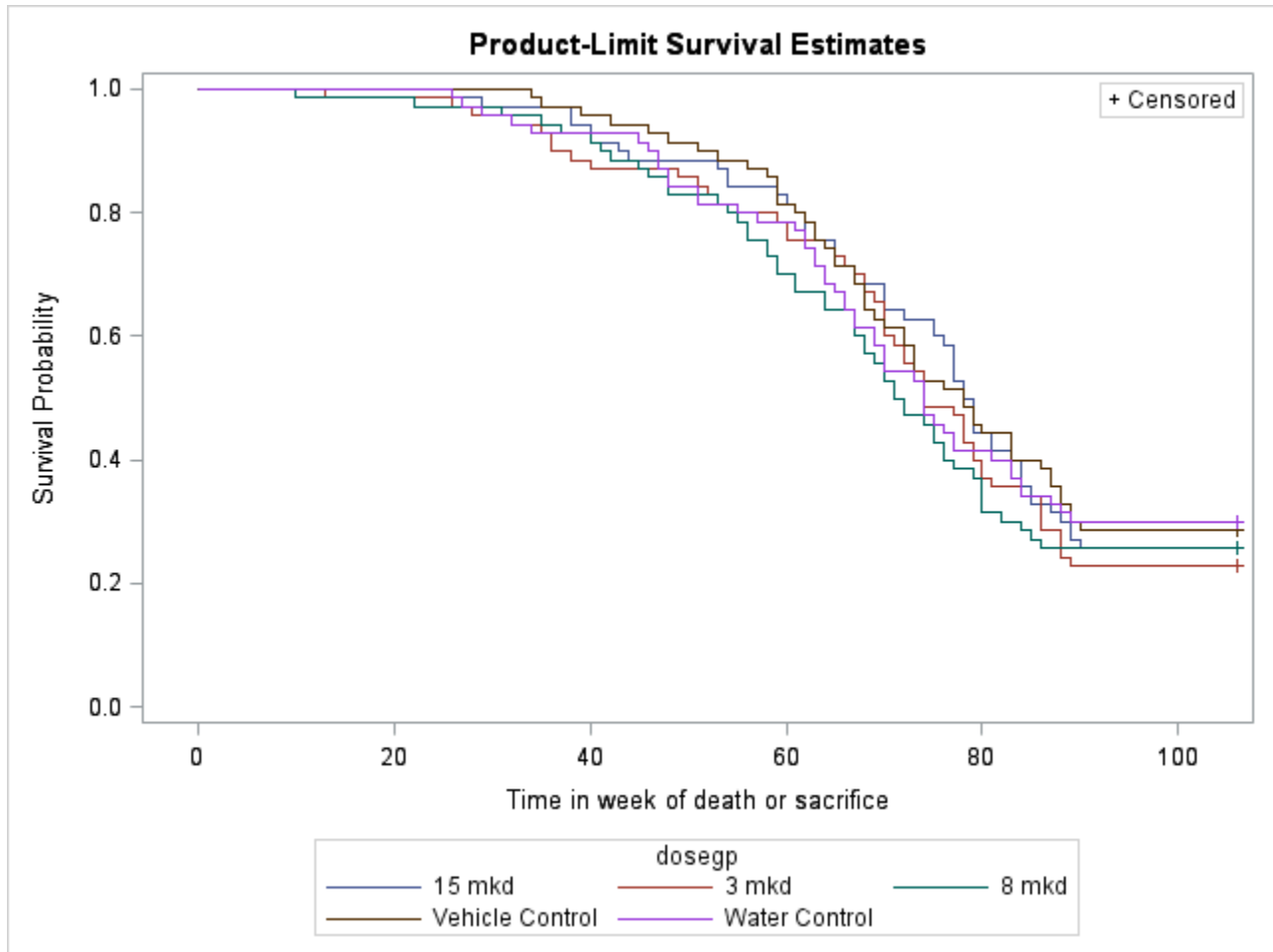


Figure 2: Kaplan-Meier Survival Functions for Female Rats

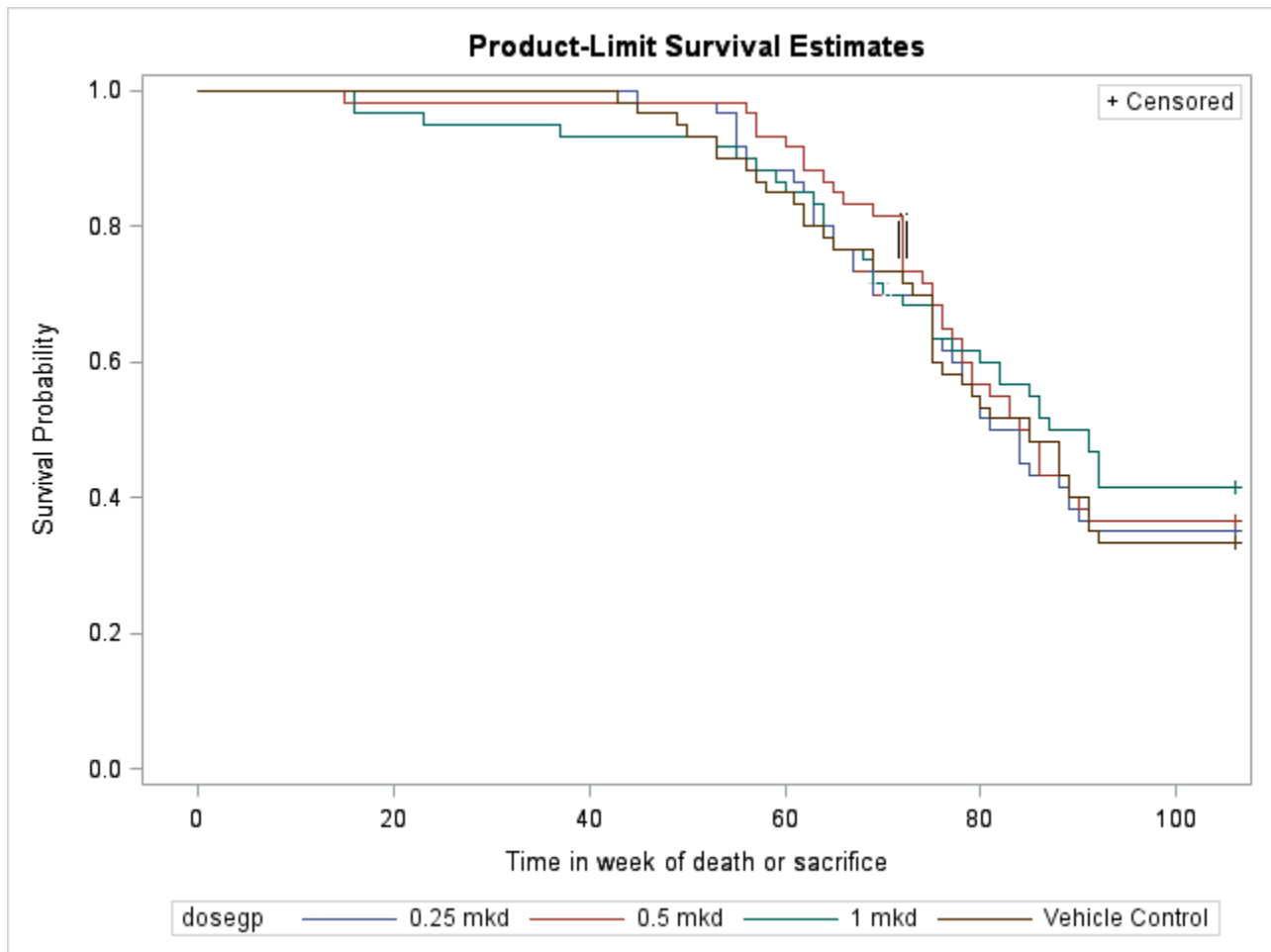


Figure 3: Kaplan-Meier Survival Functions for Male Mice

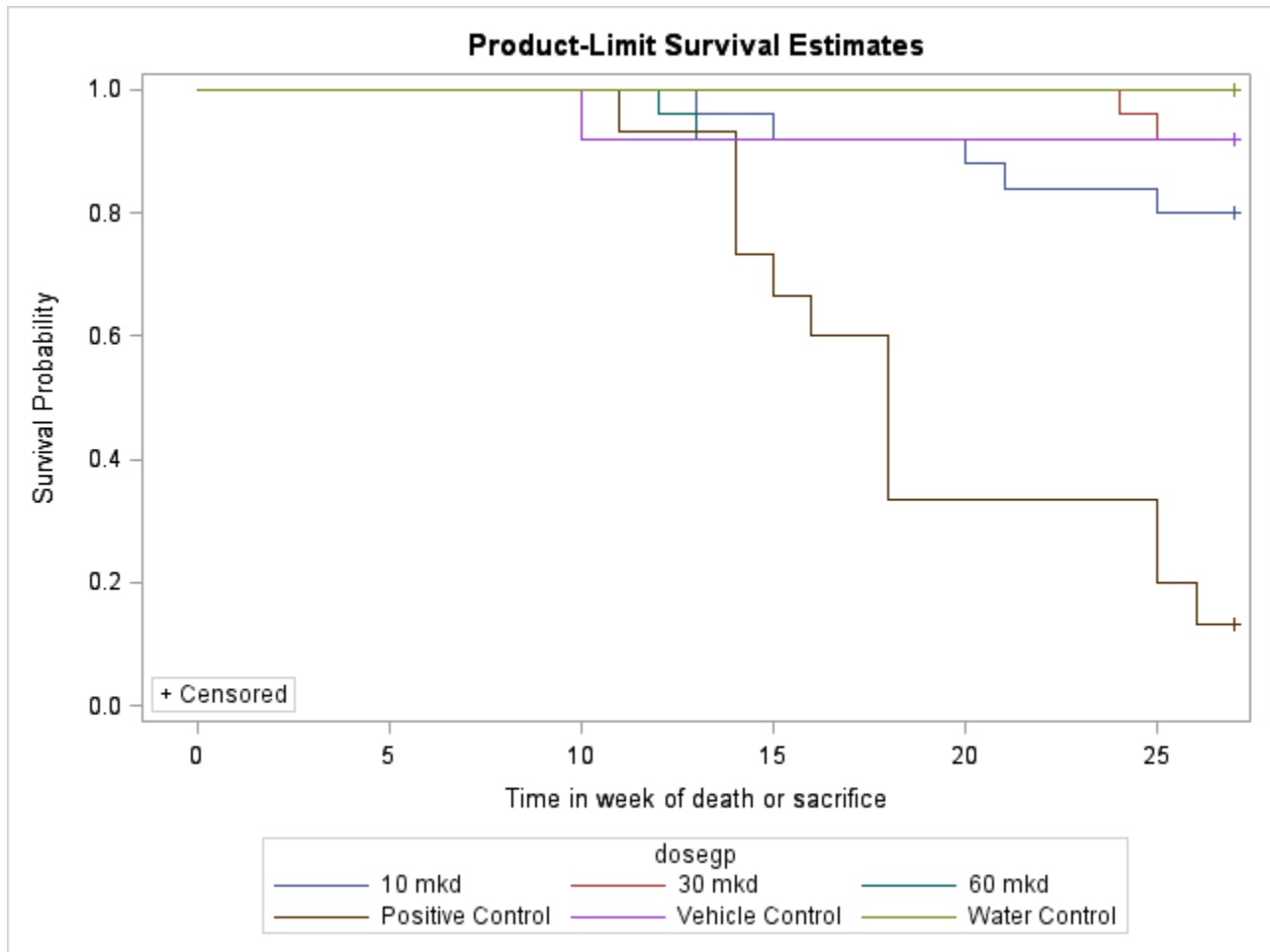
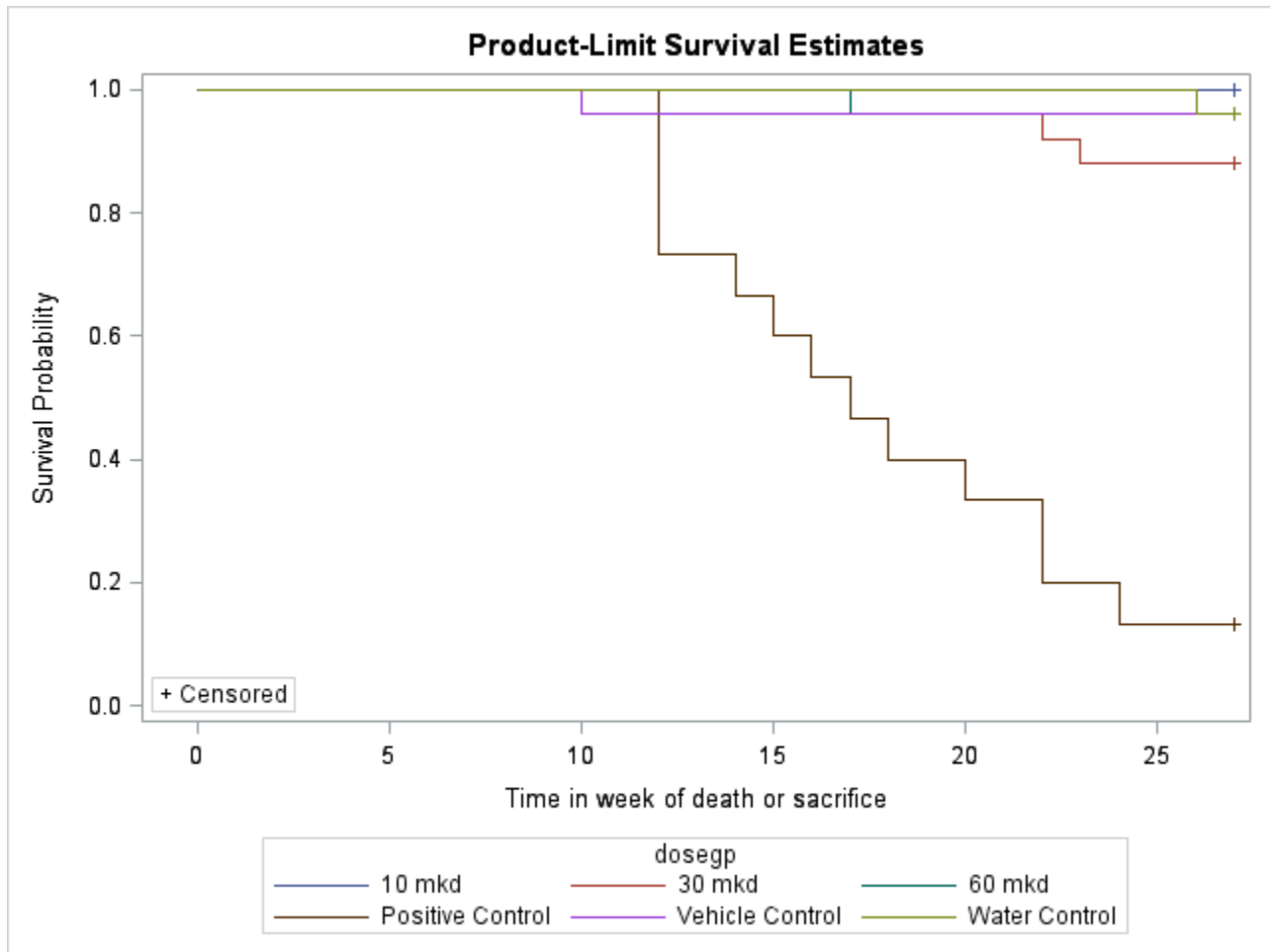


Figure 4: Kaplan-Meier Survival Functions for Female Mice



6. References

- Kaplan EL and Meier P (1958) Nonparametric estimation from incomplete observations. *J. Am. Statist. Assoc.*, 53, 457-481.
- Mantel N (1966) Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy Reports*, 50, 163-170.
- Peto R (1974) Guidelines on the analysis of tumour rates and death rates in experimental animals. *British J. Cancer*, 29, 101-105.
- Lin KK (2000) Carcinogenicity Studies of Pharmaceuticals. In: *Encyclopedia of Biopharmaceutical Statistics*, ed. Shein-Chung Chow, Marcel Dekker, New York.
- Peto R et al. (1980) Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. In: *Long term and Short term Screen Assays for Carcinogens: A Critical Appraisal*. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 2, pp.311-426. WHO International Agency for Research on Cancer, Lyon.
- SAS Institute (2002) SAS OnlineDoc® Version Nine. SAS Institute Inc., Cary, NC, USA.
- Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, Richards, and J.Wahrendorf, "Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments", Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, *Annex to supplement, World Health Organization, Geneva*, 311-426, 1980.
- Bailer AJ, Portier CJ (1988). "Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples." *Biometrics*, 44, 417-431.
- Bieler, G. S. and Williams, R. L. (1993). "Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity". *Biometrics* 49, 793-801.
- Tarone RE, "Test for trend in life table analysis", *Biometrika* 1975, 62: 679-82
- Lin K.K. and Rahman M.A., "Overall false positive rates in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs", *Journal of Biopharmaceutical Statistics*, 8(1), 1-15, 1998.

- Rahman, A.M., and K.K. Lin (2008), "A Comparison of False Positive Rates of Peto and Poly-3 methods for Long-Term Carcinogenicity Data Analysis Using Multiple Comparison Adjustment Method Suggested by Lin and Rahman", *Journal of Biopharmaceutical Statistics*, 18:5, 849-858.
- Haseman, J, "A re-examination of false-positive rates for carcinogenesis studies", *Fundamental and Applied Toxicology*, 3: 334-339, 1983.
- Guidance for Industry. Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (Draft Guidance). U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), May 2001.
- Lin, KK, and MA Rahman (2019), Comparisons of False Negative Rates from a Trend Test Alone and from a Trend Test Jointly with a Control-High Groups Pairwise Test in the Determination of the Carcinogenicity of New Drugs, *Journal of Biopharmaceutical Statistics*, 29(1):128-142.
- Lin, K.K., M.A. Rahman (2018), "Chapter 8: Expanded Statistical Decision Rules for Interpretations of Results of Rodent Carcinogenicity Studies of Pharmaceuticals", IN *Biopharmaceutical Applied Statistics Symposium, Volume 3: Pharmaceutical Applications*, Editors: Peace, Karl E., Chen, Ding-Geng, Menon, Sandeep (Eds.), recently published by Springer in August 2018, Pages 151-183.

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