CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215206Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	215206
Priority or standard	Priority
Submit date(s)	1/28/2021
Received date(s)	1/28/2021
PDUFA goal date	9/28/2021
Division	Division of Neurology II (DNII)
Review completion date	9/28/2021
Established/proper name	Atogepant
(Proposed) proprietary name	Qulipta
Pharmacologic class	Calcitonin gene-related peptide receptor antagonist.
Code names	AGN-241689, MK-8031, L-004880174-008A, L-004880174, C11051808-H
Applicant	Abbvie, Inc
Dosage form(s)/formulation(s)	10 mg, 30 mg, and 60 mg
Dosing regimen	One tablet daily
Applicant proposed indication(s)/ population(s)	(b) (4)
Proposed SNOMED indication	Click or tap here to enter text.
Regulatory action	Approval
Approved dosage (if applicable)	10 mg, 30 mg, 60 mg
Approved indication(s)/ population(s) (if applicable)	The preventive treatment of episodic migraine in adults.
Approved SNOMED term for indication (if applicable)	Click or tap here to enter text.

Reference ID: 4864103

Table of Contents

Table of Tables vii
Table of Figures xii
Glossary 1
I. Executive Summary 3
1. Summary of Regulatory Action 3
2. Benefit-Risk Assessment 5
2.1. Benefit-Risk Framework 5
2.2. Conclusions Regarding Benefit-Risk 8
II. Interdisciplinary Assessment 10
3. Introduction 10
3.1. Review Issue List 11
3.1.1. Key Review Issues Relevant to Evaluation of Benefit 11
3.1.1.1. The Adequacy of Study CGP-MD-01 to Support an Efficacy Claim 11
3.1.1.2. Should Atogepant 10 mg Daily Dose Be Recommended for the General Population? 11
3.1.1.3. Are the AIM-D and MSQ v2.1 RFR Appropriate for Inclusion in Labeling? 11
3.1.2. Key Review Issues Relevant to Evaluation of Risk 11
3.1.2.1. Elevation of LFTs and CPK With Atogepant 11
3.1.2.2. Increased Ischemic Vascular Risk 11
3.1.2.3. Decreased Body Weight 11
3.2. Approach to the Review 12
4. Patient Experience Data 15
5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology 16
5.1. Nonclinical Assessment of Potential Effectiveness 19
6. Assessment of Effectiveness 19
6.1. Dose and Dose Responsiveness 19
6.2. Clinical Trials Intended to Demonstrate Efficacy 20
6.2.1. Study CGP-MD-01 20
6.2.1.1. Design 20
6.2.1.2. Eligibility Criteria 20

Reference ID: 4864103

6.2.1.3. Statistical Analysis Plan 21
6.2.1.4. Results of Analyses 23
6.2.2. Study 3101-301-002.....27
6.2.2.1. Design.....27
6.2.2.2. Eligibility Criteria.....28
6.2.2.3. Statistical Analysis Plan 28
6.2.2.4. Results of Analyses 30
6.3. Key Review Issues Relevant to Evaluation of Benefit.....35
6.3.1. The Adequacy of Study CGP-MD-01 to Support an Efficacy Claim.....35
6.3.2. Should the Atogepant 10 mg Daily Dose Be Recommended for the General Population?.....37
6.3.3. Are the AIM-D and MSQ v2.1 RFR Appropriate for Inclusion in Labeling?.....38
7. Risk and Risk Management.....51
7.1. Potential Risks or Safety Concerns Based on Nonclinical Data.....51
7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors 52
7.3. Potential Safety Concerns Identified Through Postmarket Experience 53
7.4. FDA Approach to the Safety Review 53
7.5. Adequacy of Clinical Safety Database 54
7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database.....56
7.6.1. Overall Disposition 56
7.6.2. Deaths.....57
7.6.3. Serious Adverse Events.....57
7.6.4. Dropouts and/or Discontinuations Due to Adverse Events.....60
7.6.5. Treatment-Emergent Adverse Events 61
7.6.6. Laboratory Findings, Controlled Clinical Trials.....68
7.6.7. ECG Review 73
7.6.8. QT Interval Evaluation.....76
7.6.9. 120-Day Safety Update.....76
7.6.10. Analysis of Submission-Specific Safety Issues 77
7.6.10.1. Cardiovascular (Including Hypertension), Cerebrovascular, or Peripheral Vascular Disease 77

7.6.10.2. Hepatotoxicity 77
7.6.10.3. Gastrointestinal Disorders 77
7.6.10.4. Suicidality.....77
7.6.10.5. Pregnancy 79
7.7. Key Review Issues Relevant to Evaluation of Risk 80
7.7.1. Elevation of LFTs and CPK With Atogepant 80
7.7.2. Increased Ischemic Vascular Risk 86
7.7.3. Decreased Body Weight.....91
8. Therapeutic Individualization 94
8.1. Intrinsic Factors 94
8.2. Extrinsic Factors 96
8.2.1. Food Effect.....96
8.3. Drug Interactions 96
8.3.1. Effects of Other Drugs on Atogepant.....96
8.4. Effects of Atogepant on Other Drugs 98
8.4.1. Oral Contraceptives.....98
8.5. Plans for Pediatric Drug Development 99
8.6. Pregnancy and Lactation.....99
9. Product Quality 99
9.1. Device or Combination Product Considerations 99
10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure.....100
11. Advisory Committee Summary.....100
III. Appendices.....101
12. Summary of Regulatory History 101
13. Pharmacology Toxicology: Additional Information and Assessment 104
13.1. Summary Review of Studies Submitted Under the Investigational New Drug Application 104
13.1.1. Pharmacology.....104
13.1.2. Safety Pharmacology 104
13.1.3. PK/ADME.....104
13.1.4. General Toxicology.....104
13.1.5. Genetic Toxicology.....105

13.1.6. Carcinogenicity 105
13.1.7. Reproductive and Developmental Toxicology.....105
13.2. Individual Reviews of Studies Submitted to the New Drug Application..106
13.2.1. Pharmacology.....106
13.2.2. General Toxicology.....106
13.2.2.1. Study CGP-TX-02: A 6-Month Repeat Dose Oral Toxicity Study in Wistar Han Rats with a 1-Month Recovery Period.....107
13.2.2.2. Study TT #12-1164: Three-Month Oral Toxicity Study in Rhesus Monkeys.....111
13.2.2.3. Study TT #13-1074: Nine-Month Oral Toxicity Study in Rhesus Monkeys with a Three-Month Interim Necropsy 114
13.2.3. Genetic Toxicology.....119
13.2.3.1. Study TT #11-1169: Three-Month Oral Range-finding Study in Mice.....119
13.2.3.2. Study CGP-TX-05: A 2-Year Carcinogenicity Study by Oral Gavage in the Mouse 124
13.2.3.3. Study CGP-TX-06: A 2-Year Carcinogenicity Study by Oral Gavage in Wistar Han Rat.....127
13.2.4. Reproductive and Developmental Toxicology.....132
13.2.4.1. Fertility and Early Embryonic Development 132
13.2.4.2. Embryonic Fetal Development.....133
13.2.4.3. Prenatal and Postnatal Development 139
13.2.5. Special Toxicology Studies.....143
14. Clinical Pharmacology: Additional Information and Assessment 143
14.1. In Vitro Studies.....143
14.1.1. Plasma Protein Binding.....143
14.1.2. Metabolism of Atogepant.....143
14.1.3. Inhibition and Induction of CYP Isozymes by Atogepant.....144
14.2. In Vivo Studies 146
14.3. Pharmacometrics Review 153
14.3.1. Summary of Findings.....153
14.3.1.1. Key Review Question: Do Any of the Factors, Including Age, Renal Function (Mild and Moderate Renal Impairment), Sex, Race, and Body Weight, Affect the Pharmacokinetics Profile of Atogepant?153
14.3.2. Label Statements 153

14.3.3. Pertinent Regulatory Background 154
14.3.4. Results of Applicant's Analysis 154
14.3.5. Reviewer's Analysis 158
14.3.5.1. Introduction 158
14.3.5.2. Objectives 158
14.3.5.3. Methods 158
14.3.5.4. Results 159
14.3.6. Listing of Analyses Codes and Output Files 170
14.4. Physiologically Based Pharmacokinetic Modeling Review 170
14.4.1. Applicant's PBPK Modeling Effort 171
14.4.2. FDA's Assessment 172
14.4.3. PBPK Model Application 173
14.5. Summary of Bioanalytical Method Validation and Performance 177
15. Trial Design: Additional Information and Assessment 178
16. Efficacy: Additional Information and Assessment 178
16.1. Sensitivity Analyses for Study CGP-MD-01 178
16.2. Sensitivity Analyses for Study 3101-301-002 180
16.3. Subgroup Analyses for Study CGP-MD-01 181
16.4. Subgroup Analyses for Study 3101-301-002 182
17. Clinical Safety: Additional Information and Assessment 184
18. Mechanism of Action/Drug Resistance: Additional Information and Assessment 186
19. Other Drug Development Considerations: Additional Information and Assessment 186
20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections) 186
21. Labeling Summary of Considerations and Key Additional Information 186
22. Postmarketing Requirements and Commitments 192
23. Financial Disclosure 193
24. References 194
25. Review Team 196

Reference ID: 4864103

Table of Tables

Table 1. Administrative Application Information i
Table 2. Benefit-Risk Framework.....5
Table 3. Clinical Trials Submitted in Support of Efficacy and Safety Determinations.....13
Table 4. Patient Experience Data Submitted or Considered.....15
Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics.....16
Table 6. Steady-State Drug Exposure.....16
Table 7. Food Effect on Atogepant.....17
Table 8. Study CGP-MD-01: Baseline Demographic and Clinical Characteristics, Safety Population.....23
Table 9. Study CGP-MD-01: Patient Screening and Randomization.....24
Table 10. Study CGP-MD-01: Patient Disposition, Safety Population.....24
Table 11. Study CGP-MD-01: Change From Baseline in Mean Monthly Migraine Days 25
Table 12. Study CGP-MD-01: Analyses of Secondary Efficacy Endpoints 26
Table 13. Study 3101-301-002: Baseline Demographic and Clinical Characteristics, Safety Population.....30
Table 14. Study 3101-301-002: Patient Screening and Randomization, All Patients 31
Table 15. Study 3101-301-002: Patient Disposition, Safety Population 31
Table 16. Study 3101-301-002: Change From Baseline in Mean Monthly Migraine Days 32
Table 17. Study 3101-301-002: Analyses of Secondary Efficacy Endpoints.....33
Table 18. Study 3101-301-002: Efficacy Results of COA Endpoints.....41
Table 19. Proportion of Participants With at Least a 25-Point Improvement From Baseline in MSQ v2.1 RFR Domain Score at Week 12 48
Table 20. Proportion of Participants With at Least a 9-Point Improvement From Baseline in AIM-D PDA Domain Score Across 12-Week Treatment Period.....49
Table 21. Proportion of Participants With at Least a 6-Point Improvement From Baseline in AIM-D PI Domain Score Across 12-Week Treatment Period 50
Table 22. ISS Group 3: Duration of Exposure, Safety Population (Includes Pivotal and Long-Term Safety Studies With 1st Assigned Dose/2nd Assigned Dose)[1] 54
Table 23. ISS Group 1: Duration of Exposure, Safety Population.....54
Table 24. Treatment Duration Across All Pivotal and Open-Label Studies.....55
Table 25. ISS Group 1: Patient Disposition.....56
Table 26. ISS Group 2: Patient Disposition.....56

Table 27. ISS Group 1: Serious Adverse Events by System Organ Class and Preferred Term, Safety Population 57

Table 28. ISS Group 1: Adverse Events Leading to Discontinuation, Selected Preferred Terms, Safety Population 61

Table 29. ISS Group 1: Common Adverse Events Occurring at ≥1% of Atogepant-Treated Patients and at a Greater Incidence Than Placebo, Safety Population 62

Table 30. ISS Group 1: Adverse Reactions Occurring at Greater Than 2% in Atogepant-Treated Patients and Greater Than Placebo 63

Table 31. ISS Group 1: Adverse Events by System Organ Class, FDA Medical Query (Broad), and Preferred Term, Frequency ≥1% in Any Arm, Safety Population.....64

Table 32. ISS Group 2: Common Adverse Events Occurring at ≥2% Frequency, Safety Population 67

Table 33. ISS Group 3: Select Adverse Events Occurring at ≥1% Frequency, Safety Population 68

Table 34. ISS Group 1: Patients Meeting Laboratory Abnormality Criteria, Cumulative Worsened Grade[1] From Baseline Through Week 12, Safety Population 69

Table 35. ISS Group 1: Patients With One or More Liver Biochemistry Analyte Values Outside Specified Levels, Safety Population.....72

Table 36. ISS Group 1: Patients With One or More Creatine Phosphokinase Values Outside Specified Levels, Safety Population.....73

Table 37. ISS Group 1: Potential Clinically Significant ECG Parameter Values 74

Table 38. ISS Group 2: Potential Clinically Significant ECG Parameter Values 74

Table 39. ISS Group 1: Cardiac Arrythmia, Safety Population.....75

Table 40. ISS Group 2: Adverse Events by System Organ Class (Subset Within Cardiac Disorders), FDA Medical Query (Broad), and Preferred Term, Safety Population 75

Table 41. The Point Estimates and 90% CI (FDA Analysis) 76

Table 42. ISS Group 1: Grouped Queries, Safety Population 85

Table 43. Group 1: Cerebrovascular Grouped Queries, Safety Population.....87

Table 44. ISS Group 1: Cardiovascular Grouped Queries, Safety Population 88

Table 45. ISS Group 1: Incidence of 5% and 7% Weight Loss and Gain at Any Time in the Study, Safety Population.....93

Table 46. Key Labeling Recommendations.....96

Table 47. Carcinogenicity Studies 105

Table 48. Non-Pivotal Oral Administration Studies in Rats.....106

Table 49. CGP-TX-02: Study Information 107

Reference ID: 4864103

Table 50. CGP-TX-02: Study Design 107

Table 51. CGP-TX-02: Summary of Microscopic Findings, Scheduled Euthanasia (Day 183) 109

Table 52. CGP-TX-02: Summary Mean AGN-241689 Toxicokinetic Parameters on Day 1 109

Table 53. CGP-TX-02: Summary Mean AGN-241689 Toxicokinetic Parameters on Day 28 110

Table 54. CGP-TX-02: Summary Mean AGN-241689 Toxicokinetic Parameters on Day 182 110

Table 55. Non-Pivotal Oral Administration Studies in Monkeys 110

Table 56. TT #12-1164: Study Information 111

Table 57. TT #12-1164: Study Design 111

Table 58. TT #12-1164: Test Article-Related Postmortem Findings 113

Table 59. TT #12-1164: Summary Mean Plasma MK-8031[a] Toxicokinetic Parameters in Monkeys, Day 1 113

Table 60. TT #12-1164: Summary Mean Plasma MK-8031[a] Toxicokinetic Parameters in Monkeys, Week 13 114

Table 61. TT #13-1074: Study Information 114

Table 62. TT #13-1074: Study Design 115

Table 63. TT #13-1074: Summary Mean Plasma MK-8031 Toxicokinetic Parameters in Monkeys, Study Day 1 117

Table 64. TT #13-1074: Summary Mean Plasma MK-8031 Toxicokinetic Parameters in Monkeys, Study Week 5 117

Table 65. TT #13-1074: Summary Mean Plasma MK-8031 Toxicokinetic Parameters in Monkeys, Study Week 13 118

Table 66. TT #13-1074: Summary Mean Plasma MK-8031 Toxicokinetic Parameters in Monkeys, Study Week 39 118

Table 67. Non-Pivotal Single Oral Dose Study in Male Mice 119

Table 68. TT #11-1169: Study Information 119

Table 69. TT #11-1169: Study Design 119

Table 70. TT #11-1169: Mean Body Weight Gain, Week -1 to 13 121

Table 71. TT #11-1169: Summary Mean Plasma MK-8031 Toxicokinetic Parameters, Study Week 13 123

Table 72. CGP-TX-05: Study Information 124

Table 73. CGP-TX-05: Study Design 124

Table 74. CGP-TX-05: Biometrics Review of Malignant Rhabdomyosarcoma Tumors in the Subcutis in Males 125

Table 75. CGP-TX-05: Summary of Microscopic Findings, Preterminal Animals 126

Table 76. CGP-TX-05: Toxicokinetic Summary, Day 28 126

Table 77. CGP-TX-06: Study Information 127

Table 78. CGP-TX-06: Study Design 127

Table 79. CGP-TX-06: Terminal Body Weight, Males 128

Table 80. CGP-TX-06: Terminal Body Weight, Females 128

Table 81. CGP-TX-06: Biometrics Review of Benign Polyps in the Cervix and Uterus in Females 130

Table 82. CGP-TX-06: Summary of AGN-241689-related Non-Neoplastic Microscopic Findings – Early Deaths and Terminal Euthanasia Combined 131

Table 83. CGP-TX-06: Toxicokinetic Summary, Day 28 131

Table 84. TT #12-7380: Study Information 132

Table 85. TT #12-7380: Study Design 132

Table 86. Summary Mean Maternal Plasma MK-8031 Toxicokinetic Parameters, Gestation Day 15 134

Table 87. TT#12-7060: Study Information 134

Table 88. TT#12-7060: Study Design 135

Table 89. TT#12-7060: Summary Mean Maternal Plasma MK-8031 Toxicokinetic Parameters, Gestation Day 15 136

Table 90. TT#12-7060: Cesarean Section Findings 136

Table 91. TT #12-7071: Summary Mean Plasma MK-8031 Toxicokinetic Parameters, Gestation Day 15 137

Table 92. TT #12-7070: Study Information 137

Table 93. TT #12-7070: Study Design 138

Table 94. TT #12-7070: Summary Mean Plasma MK-8031 Toxicokinetic Parameters, Gestation Day 15 139

Table 95. CGP-TX-15: Study Information 139

Table 96. CGP-TX-15: Study Design 140

Table 97. CGP-TX-15: Mean AGN-241689 Plasma and Milk Concentrations, Lactation Day 14 for F_0 Females 141

Table 98. CGP-TX-15: Summary of Litter Mean Pup Body Weights 142

Table 99. Studies MK-8031 PK003, 110337: Effect of Atogepant on Cytochrome P450 Marker Enzyme Activities in Human Liver Microsomes 144

Reference ID: 4864103

Table 100. Evaluation of Drug Transporters Involved in the Disposition of Atogepant.144

Table 101. Evaluation of Inhibition of Drug Transporters by Atogepant.....145

Table 102. Statistical Analysis of Food Effect on Atogepant PK.....148

Table 103. Summary of Statistical Analysis of Plasma Atogepant PK Parameters Following a Single Dose Oral Administration of 60 mg Atogepant in Participants With Mild, Moderate, or Severe Hepatic Impairment as Compared With Participants With Normal Hepatic Function.....149

Table 104. Summary of Atogepant Plasma Protein-Binding (Expressed as Percent Bound) Following Single Dose Oral Administration of 60 mg Atogepant 149

Table 105. Summary of Statistical Analysis of Unbound Plasma Atogepant PK Parameters in Participants With Mild, Moderate, or Severe Hepatic Impairment as Compared With Participants With Normal Hepatic Function 150

Table 106. PK Parameters of Atogepant Following Treatment A and Treatment B in Healthy Subjects 151

Table 107. Summary of Statistical Analysis Results of Plasma Atogepant Pharmacokinetic Parameters Following A Single Dose of 600 mg Rifampin in Combination With 60 mg Atogepant (Treatment B1, Test) in Comparison to 60 mg Atogepant Administered Alone (Treatment A, Reference) 152

Table 108. Summary of Statistical Analysis Results of Plasma Atogepant Pharmacokinetic Parameters Following Oral Administration of Multiple Dose 600 mg Rifampin in Combination With 60 mg Atogepant (Treatment B2, Test) in Comparison to 60 mg Atogepant Administered Alone (Treatment A, Reference) ...152

Table 109. Simulated Pharmacokinetics Parameters by Dose After a Single Dose 157

Table 110. Simulated Pharmacokinetics Parameters by Dose at Steady State 157

Table 111. Analysis Data Sets 158

Table 112. PopPK Model Predicted Steady State AUC Versus Age Group 162

Table 113. PopPK Model Predicted Steady State AUC Versus Renal Impairment 164

Table 114. PopPK Model Predicted Steady State AUC Versus Sex 165

Table 115. PopPK Model Predicted Steady State AUC Versus Race 166

Table 116. PopPK Model Predicted Steady State AUC Versus Weight Quantile.....167

Table 117. Listing of Analyses Codes and Output Files 170

Table 118. Comparison of the Simulated Geometric Means for Atogepant Plasma C_{max} and AUC Ratios in the Absence and Presence of Multiple Doses of Rifampin or Itraconazole With Different Scenarios of Induced or Inhibited Pathways Included in the Rifampin or Itraconazole Models 173

Table 119. Observed and Simulated Atogepant PK Parameters Following a Single and Multiple Oral Doses Administration of Atogepant or a Single Oral Dose

Reference ID: 4864103

Administration of Atogepant in the Presence and Absence of Itraconazole or Rifampin, in Healthy Subjects 174

Table 120. Bioanalytical Method Validation for the Determination of Atogepant in Human Plasma and Whole Blood 177

Table 121. Study CGP-MD-01: Sensitivity Analysis of Change From Baseline in Mean Monthly Migraine Days Using Pattern-Mixture Model 178

Table 122. Study CGP-MD-01: Change From Baseline in Mean Monthly Migraine Days Using ANCOVA 179

Table 123. Study CGP-MD-01: Change From Baseline in Mean Monthly Migraine Days Using Updated Evaluable Requirement 180

Table 124. Study 3101-301-002: Change From Baseline in Mean Monthly Migraine Days During the Double-Blind and Follow-Up Periods 180

Table 125. Study CGP-MD-01: Subgroup Analyses of Change From Baseline in Mean Monthly Migraine Days 181

Table 126. Study 3101-301-002: Subgroup Analyses of Change From Baseline in Mean Monthly Migraine Days 182

Table 127. ISS Group 1: Adverse Events Leading to Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population 184

Table 128. ISS Group 2: Adverse Events Leading to Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population 185

Table 129. Summary of Significant Modifications to the Full Prescribing Information 187

Table 130. Consultations With Respect to Labeling 191

Table 131. Study CGP-MD-01: Covered Clinical Study 193

Table 132. Study 3101-301-002: Covered Clinical Study 194

Table 133. Reviewers of Integrated Assessment 196

Table 134. Additional Reviewers of Application 197

Table 135. Signatures of Reviewers 198

Table of Figures

Figure 1. Study CGP-MD-01: Multiple Comparisons Procedure 23

Figure 2. Study CGP-MD-01: Distribution of Change From Baseline in Mean Monthly Migraine Days by Treatment Group 26

Figure 3. Study 3101-301-002: Multiple Comparisons Procedure 30

Figure 4. Study 3101-301-002: Distribution of the Reduction From Baseline in Mean Monthly Migraine Days Across the 12-Week Treatment Period (mITT Population)[1] 32

Reference ID: 4864103

Figure 5. Conceptual Framework of MSQ v2.1 Role Function-Restrictive Domain 39

Figure 6. Conceptual Framework of AIM-D 40

Figure 7. Study 3101-301-002: Empirical Cumulative Distribution Function Curves for MSQ v2.1 RFR With PGI-S as an Anchor From Day 1 to Week 12.....42

Figure 8. Study 3101-301-002: Empirical Cumulative Distribution Function Curves for MSQ v2.1 RFR With PGI-C as an Anchor From Day 1 to Week 12 43

Figure 9. Study 3101-301-002: Empirical Cumulative Distribution Function Curves for AIM-D PDA With PGI-S as an Anchor From Day 1 to Week 12.....44

Figure 10. Study 3101-301-002: Empirical Cumulative Distribution Function Curves for AIM-D PDA With PGI-C as an Anchor From Day 1 to Week 12.....45

Figure 11. Study 3101-301-002: Empirical Cumulative Distribution Function Curves for AIM-D PI With PGI-S as an Anchor From Day 1 to Week 12 46

Figure 12. Study 3101-301-002: Empirical Cumulative Distribution Function Curves for AIM-D PI With PGI-C as an Anchor From Day 1 to Week 12.....47

Figure 13. Cumulative Distribution Function of Change From Baseline for MSQ v2.1 RFR Domain Score at Week 12 by Treatment Arms (Threshold of 25-Point Improvement).....48

Figure 14. Cumulative Distribution Function of Change From Baseline for AIM-D PDA Domain Score Across the 12-Week Treatment Period.....49

Figure 15. Cumulative Distribution Function of Change From Baseline for AIM-D PI Domain Score Across the 12-Week Treatment Period by Treatment Arms.....50

Figure 16. ISS Group 1: Baseline Versus Maximum Systolic Blood Pressure by Treatment Group, Safety Population 90

Figure 17. ISS Group 1: Mean Change in Weight (kg), Safety Population.....92

Figure 18. TT #11-1169: Summary Body Weight, Males 120

Figure 19. TT #11-1169: Summary Body Weight, Females 121

Figure 20. CGP-TX-06: Summary of Body Weights, Males.....129

Figure 21. CGP-TX-06: Summary of Body Weights, Females 129

Figure 22. Distribution of Etas Versus Continuous Covariates.....155

Figure 23. Distribution of Etas Versus Categorical Covariates.....156

Figure 24. Dependent Variables Versus Individual Predictions.....159

Figure 25. Dependent Variables Versus Individual Predictions Stratified by Studies 160

Figure 26. Concentration Over Time for Subjects With Top-Ranked Deviations Between Observation and PopPK Model Prediction.....161

Figure 27. PopPK Model Predicted Steady State AUC Versus Age Group (Top Panel) and Plasma Concentration Versus Time (Bottom Panel) Stratified by Dose 162

Reference ID: 4864103

Figure 28. PopPK Model Predicted Steady State AUC Versus Renal Impairment (Top Panel) and Plasma Concentration Versus Time (Bottom Panel) Stratified by Dose .163

Figure 29. PopPK Model Predicted Steady State AUC Versus Sex (Top Panel) and Plasma Concentration Versus Time (Bottom Panel) Stratified by Dose 165

Figure 30. PopPK Model Predicted Steady State AUC Versus Race (Top Panel) and Plasma Concentration Versus Time (Bottom Panel) Stratified by Dose 166

Figure 31. PopPK Model Predicted Steady State AUC Versus Weight Quantile (Top Panel) and Plasma Concentration Versus Time (Bottom Panel) Stratified by Dose .167

Figure 32. Change From Baseline Monthly Migraine Days by Dose, Study, and Average Atogepant Concentration.....168

Figure 33. Visual Predictive Checks of Monthly Migraine Days Model by Dose 169

Figure 34. Observed (Dots or Circles) and Simulated (Lines) Atogepant Plasma Concentration-Time Profiles Following a Single (60 mg) (A and B) or Multiple Oral (60 mg, BID) (C and D) Administration of Atogepant in Healthy Subjects[1] 175

Figure 35. Study CGP-MD-01: Change From Baseline in Number of Migraine Days During the Treatment Period 179

Figure 36. Study 3101-301-002: Change From Baseline in Number of Migraine Days During the Treatment Period 181

Reference ID: 4864103

Glossary

AE	adverse event
AIM-D	Activity Impairment in Migraine Diary
ALT	alanine aminotransferase
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUCR	AUC ratio
AUC_x	area under the plasma concentration-time curve to time x
BCRP	breast cancer resistance protein
BID	twice daily
CGRP	calcitonin gene-related peptide
CLcr	creatinine clearance
CM	chronic migraine
C_{max}	maximum concentration
COA	clinical outcome assessment
CPK	creatine phosphokinase
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
eCDF	empirical cumulative distribution function
ECG	electrocardiogram
EM	episodic migraine
ESRD	end-stage renal disease
GAS	Group A streptococcal
GD	gestation day
HD	high dose
Hg	mercury
HI	hepatic impairment
ISS	Integrated Summary of Safety
Ki	inhibitory constant
LD	low dose
LFT	liver function test
MD	mid dose
MMRM	mixed-effects model for repeated measures
MRHD	maximum recommended human dose
MRI	magnetic resonance imaging
MSQ v2.1	Migraine-Specific Quality of Life Questionnaire version 2.1
NDA	new drug application
NOAEL	no observed adverse effect level
OATP	organic anion transporting polypeptide
OPQ	Office of Pharmaceutical Quality
PBPK	physiologically based pharmacokinetics

Reference ID: 4864103

PDA	Performance of Daily Activity
PGI-C	patient global impression of change
PGI-S	patient global impression of severity
P-gp	P-glycoprotein
PI	Physical Impairment
PK	pharmacokinetics
PND	postnatal day
PopPK	population pharmacokinetic
QD	once daily
RFR	Role Function-Restrictive
RI	renal impairment
SAE	serious adverse event
SI	suicidal ideation
SoC	standard of care
SPA	Special Protocol Assessment
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

Reference ID: 4864103

I. Executive Summary

1. Summary of Regulatory Action

This new drug application (NDA) for atogepant was submitted by AbbVie, Inc. (the Applicant). Atogepant is an oral small molecule calcitonin gene-related peptide (CGRP) receptor antagonist, developed for the preventive treatment of episodic migraine (EM) in adults.

This NDA received a priority review designation because of the Applicant's use of a Material Threat Countermeasure Priority Review Voucher. The NDA was reviewed by a multidisciplinary review team (Clinical, Clinical Infectious Disease, Clinical Hepatology, Clinical Pharmacology, Clinical Outcomes Assessment Team, Pharmacology/Toxicology, Chemistry Manufacturing and Controls, and Statistics) that did not identify any issues that preclude approval. I, the signatory authority, agree that the benefit-risk assessment supports approval.

Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by various associated symptoms. Chronic migraine (CM) is defined as 15 or more headache days per month, with features of migraine headache on ≥8 days per month. Patients with 14 or fewer migraine headache days per month are defined as having EM.

The Applicant submitted the results of two adequate and well-controlled trials (Study CGP-MD-01 and Study 3101-301-002) to support the efficacy of atogepant for the preventive treatment of EM in adults. Both trials used a well-validated and clinically meaningful primary efficacy endpoint: the change from baseline in the mean number of monthly migraine days. Study CGP-MD-01 evaluated daily doses of 10 mg, 30 mg, and 60 mg, and twice-daily doses of 30 mg and 60 mg. The primary endpoint was met in all dosage groups. Given the relatively flat dose-response relationship observed in this trial, only the daily doses of 10 mg, 30 mg, and 60 mg were evaluated in Study 3101-301-002. In that study, all atogepant dosage groups had significantly greater reductions in the mean number of monthly migraine days than the placebo group (0.7 to 1.7 fewer monthly migraine days). The treatment effect size on that endpoint is similar to that of other products approved for the preventive treatment of migraine (EM and/or CM). In Study 3101-301-002, significant results were also observed for several secondary endpoints, including reduction in monthly medication use, and patient-reported clinical outcome assessment tools. The results of the secondary efficacy endpoints in Study CGP-MD-01 all numerically favored atogepant.

Atogepant has a favorable safety profile. In the controlled trials, there were no deaths and no serious adverse events with a clear association with atogepant. Common adverse events that occurred at an incidence of at least 2% of patients on atogepant and greater than placebo were nausea, constipation, fatigue, and decreased appetite. Safety signals of interest that were evaluated during the review were vascular ischemic abnormalities, hypertension, and serious gastrointestinal events, based on known pharmacodynamic effects of CGRP and subsequent theoretical risks with CGRP antagonism. No serious vascular events or serious gastrointestinal effects related to the use of atogepant were identified. Hepatotoxicity was also considered a safety signal of interest as the development programs for two older-generation oral CGRP antagonists were discontinued because of cases of serious liver injury. The rate of transaminase

elevations over 3 times the upper limit of normal was similar between atogepant and placebo (1% for atogepant vs. 1.8% for placebo). However, there were a few cases with elevations over three times the upper limit of normal assessed as having a probable or possible relationship with atogepant treatment. All cases resolved after discontinuation of atogepant. Routine monitoring of liver enzymes is not recommended. The risks of atogepant can be mitigated through labeling and pharmacovigilance.

This application triggers the Pediatric Research Equity Act; therefore, pediatric postmarketing requirements to study safety and efficacy of this product for the preventive treatment of EM in patients age 6 to less than 18 years of age will be issued. In addition, postmarketing requirements for a pregnancy registry study, a pregnancy outcomes study, a nonclinical dose-range finding study, and a 2-year nonclinical carcinogenicity study will be issued.

Based on the review of all available efficacy and safety data for atogepant, the benefits outweigh the risks for the preventive treatment of EM in adults. This product provides for a second oral CGRP receptor antagonist for this indication.

For detailed information supporting the basis for the benefit-risk assessment, please refer to the details in this integrated assessment document.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by associated symptoms of nausea, vomiting, and light and/or sound sensitivity. The typical headache of migraine is throbbing, unilateral, and aggravated by motion, but bilateral and nonthrobbing headaches are also commonly reported. Migraine attacks typically last 4 to 72 hours when untreated. About one third of people with migraine experience transient neurological symptoms before and/or during an attack, referred to as migraine aura. Migraine is more prevalent in females than males and peaks in the fourth decade of life. • Migraine patients can be categorized as having either episodic or chronic migraine. Episodic migraine refers to patients with a diagnosis of migraine with or without aura as per the International Classification of Headache Disorders (ICHD)-3 criteria and who have 14 or fewer headache days per month. The ICHD-3 defines chronic migraine as patients with migraine that for at least 3 consecutive months experience 15 or greater headache days a month, in which at least 8 of those monthly headaches have the features of migraine.	Episodic migraine is a common and debilitating disease that can significantly impact the quality of life.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	• There are currently many approved therapies for the preventive treatment of migraine, as well as many others that are used off-label. • Recently, several therapies that act on the calcitonin gene-related peptide (CGRP) pathway were approved for the preventive treatment of migraine (indicated for both patients with episodic migraine and chronic migraine). These include the injectable CGRP antagonist monoclonal antibodies, including erenumab, fremanezumab, galcanezumab, and eptinezumab. Erenumab and galcanezumab are administered as subcutaneous injections monthly; fremanezumab can be administered either monthly or quarterly; eptinezumab is administered intravenously quarterly. Rimegepant, a small molecule CGRP receptor antagonist, was also approved recently for the preventive treatment of episodic migraine (this medication is also indicated for the acute treatment of migraine). • Other treatments approved for the preventive treatment of migraine include onobotulinumtoxinA (approved only for the preventive treatment of chronic migraine), and several oral drugs: propranolol, timolol, divalproex/sodium valproate, and topiramate. Therapies for the preventive treatment of migraine that were approved prior to 2010 have an indication that does not distinguish between episodic or chronic migraine, as the classification into episodic or chronic migraine only appeared a few years before. Most of the drugs currently marketed for the preventive treatment of migraine demonstrate a reduction of monthly migraine days of 0.7 to 2.0 days.	Other drugs within the CGRP antagonist class have been approved for the preventive treatment of migraine. Most are injectable (erenumab, fremanezumab, galcanezumab and eptinezumab). Another oral product,rimegepant, was initially approved for the acute treatment of migraine, and recently approved for the preventive treatment of episodic migraine. Atogepant will be the second oral CGRP receptor antagonist marketed for the preventive treatment of episodic migraine. Rimegepant is dosed every other day based on how the drug was studied in clinical trials and has a postmarketing commitment to study daily dosing, as such a regimen would be consistent with the drugs' pharmacokinetic properities.
Benefit	• The efficacy of atogepant for the preventive treatment of episodic migraine was demonstrated in two adequate and well-controlled trials, Study CGP-MD-01 and Study 3101-301-002. Both studies used a well-validated and clinically meaningful endpoint to establish efficacy, a reduction in the number of monthly migraine days (MMD). Study CGP-MD-01 assessed five dosing regimens, daily doses of 10 mg, 30 mg, and 60 mg and twice daily doses of 30 mg and 60 mg, as compared to placebo. All doses had statistically significantly greater reductions from baseline in MMD compared to placebo: 1.2, 1.0, 0.7, 1.4, and 1.3 for atogepant groups of 10 mg daily (QD), 30 mg QD, 60 mg QD, 30 mg twice daily (BID), and 60 mg BID groups, respecitvely Numerically, the twice-daily dosing regimens performed slightly better than the daily dosing; however, only daily doses were carried forward into the subsequent trial based on overall considerations, including the practicability of twice-daily dosing in the setting of limited additional benefit. Study 3101-301-002 studied three dosing regimens, daily doses of 10 mg, 30 mg, and 60 mg, as compared to placebo. All doses demonstrated efficacy on the primary endpoint with a placebo corrected reduction from baseline in MMD of 1.2, 1.4, and 1.7 for the	Atogepant at daily doses of 10 mg, 30 mg and 60 mg demonstrated efficacy for the preventive treatment of episodic migraine in adults. Other marketed drugs for this indication also have generally modest effect sizes, typically reducing the number of monthly migraine/headache days by 1 to 2 days; like the other marketed products, atogepant is not likely to render patients migraine-free.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	10mg QD, 30 mg QD, and 60 mg QD atogepant groups. There was a slight numerical dose-response relationship. • The Applicant [redacted] (b) (4) • In Studies CGP-MD-01 and 3101-201-0002, efficacy was supported by the demonstration of treatment-related reductions in mean monthly headache days. In Study 3101-301-002, efficacy was also supported by the demonstration of treatment-related benefits in the reduction in mean monthly acute medication use, increase in the 50% responder rate, and effects on patient-reported outcome measures evaluating the impact of migraine on daily functioning: the Migraine-Specific Quality of Life Questionnaire (MSQ) Role Restrictive Function and the the Activity Impairment in Migraine Diary (AIM-D) Physical Function domain score and AIM-D Physical Impairment domain score.	
Risk and risk management	• No serious safety signals were identified in this review. • There were no deaths in the controlled clinical trials. • There were two deaths in the long-term safety study, related to a group A streptococcus infection and homicide, respectively. Neither was assessed as being causally related to atogepant. • There were no serious adverse events that were clearly associated with the use of atogepant. The most common adverse reactions in the controlled clinical efficacy trials in atogepant treated patients, occcuring at greater than 2%, were constipation (6%), nausea (5 to 9%), fatigue/somnolence (4 to 6%), and decreased appetite (1 to 2%). • Hepatic risk was assessed as a safety signal of special interest due to previous experience for earlier oral CGRP receptor antagonists. Overall, the rate of transaminase elevations over 3X ULN were similar between atogepant treatment arms and placebo (1.0% versus 1.8%). There were cases of serum transaminase elevations (alanine aminotransferase 7 to 10X upper limit of normal [ULN] and aspartate aminotransferase 3 to 7X ULN) that were associated with atogepant use in the controlled clinical trials; however, all cases were asymptomatic and resolved after discontinuation of atogepant. Routine monitoring of liver enzymes is not recommended. • Atogepant-treated patients experienced weight loss at a greater frequency than patients treated with placebo. The proportion of patients with a weight decrease greater than or equal to 7% at any point was 2.8% for placebo, 3.8% for atogepant 10 mg, 3.2% for atogepant 30 mg, and 4.9% for atogepant 60 mg QD. • As CGRP is thought to enhance compensatory vasodilatation in the setting of ischemia; there is a theoretical risk that CGRP inhibition may lead to increased	There were no significant safety findings that would preclude the approval of atogepant. Adequate labeling and enhanced pharmacovigilance are sufficient to address the identified safety issues. No serious cases of hepatic injury are associatied with atogepant; however, a possible association of atopant treatment with a liver enzyme elevation will be described in labeling. The data submitted with this application do not support the need to include CV restrictions in labeling; however, these data are also insufficient to definitively establish the CV safety of atogepant. Because the risk of adverse outcomes in pregnancy has not been characterized, and because atogepant will be used in women of childbearing potential, a pregnancy registry and a pregnancy outcome study will

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	ischemic events. No increased risk for vascular ischemic events was noted in the atogepant database. Other uncertainties • The risk of adverse outcomes in pregnancy has not been characterized. • Safety and efficacy in pediatric migraine patients has not been established. • The carcinogenicity of this product in nonclinical studies was not fully characterized.	be issued as postmarkeing requirements (PMRs). Since safety and efficacy of atogepant in pediatric migraine patients has not been established, studies to evaluate atogepant for the preventive treatment of episodic migraine in patients 6 to less than 18 years of age will be required under the Pediatric Research Equity Act. Since the carcinogenicity of this product in nonclinical studies was not fully characterized, a dose-range finding nonclinical study and a 2-year nonclinical carcinogenicity study will be issued as PMRs. Enhanced pharmacovigilance with periodic evaluation of hepatotoxicity, cardiovascular events, hypertensive events, cerebrovascular events, and serious gastrointestinal events will be requested.

Abbreviations: AIM-D, Activity Impairment in Migraine Diary; CGRP, calcitonin gene-related peptide; CV, cardiovascular; ICHD, International Classification of Headache Disorders; MMD, monthly migraine days; MSQ, Migraine-Specific Quality of Life Questionnaire; PMR, postmarketing requirement; QD, once daily; ULN, upper limit of normal;

2.2. Conclusions Regarding Benefit-Risk

Migraine is a condition that may result in significant morbidity and greatly impacts daily function. Although there are a number of drugs approved for the preventive treatment of episodic migraine in adults, additional treatment options remain important. Atogepant is only the second oral CGRP antagonist to seek an indication for the preventive treatment of episodic migraine in adults.

The Applicant has clearly demonstrated the efficacy of atogepant for the proposed indication in two 12-week placebo-controlled, double-blind, parallel-arm clinical trials that enrolled adult migraine patients with 14 or fewer headache days per month. Daily atogepant doses of 10 mg, 30 mg, and 60 mg, resulted in statistically significant reductions in the number of mean monthly migraine days from baseline, relative to placebo (range 0.7 to 1.7 days). The treatment effect size is similar to that of other drugs approved for

the preventive treatment of migraine. Efficacy is further supported by significant treatment-related reductions, compared to placebo, in the number of mean monthly headache days from baseline, reductions in acute medication use, increases in the number of patients having 50% or greater reductions in their baseline migraine frequency, and by the results of patient-reported outcome measures assessing the impact of migraine on daily functioning.

The safety database for atogepant was adequate for the proposed dosing regimens and the intended patient population. Overall, atogepant has a favorable safety profile, and the safety findings can be adequately addressed in labeling and by routine and enhanced pharmacovigilance. Common adverse reactions associated with treatment include constipation, nausea, fatigue, and decreased appetite. Enhanced pharmacovigilance will be requested for serious gastrointestinal toxicity, based on a signal for such events in the CGRP antagonist class, along with a theoretical risk based on the presence of CGRP receptors in the gastrointestinal system. There was no evidence to suggest the presence of an ischemic risk with atogepant, also a theoretical concern with CGRP antagonists; however, enhanced pharmacovigilance for such events will be requested, consistent with the approach taken to all approved drugs of this class. Although there was no signal of serious hepatotoxicity, increases in liver function tests associated with atogepant treatment have been observed and will be described in labeling. Enhanced pharmacovigilance will also be requested for liver injury events.

Based upon review of all available efficacy and safety data, the benefits of atogepant clearly outweigh the risks for the preventive treatment of episodic migraine in adults.

II. Interdisciplinary Assessment

3. Introduction

Atogepant is an orally-administered calcitonin gene-related peptide (CGRP) receptor antagonist. CGRP is widely distributed in the central and peripheral nervous systems. Evidence suggests that CGRP plays an important role in migraine attacks, as CGRP levels have been demonstrated to increase during an acute migraine attack, and infusions of CGRP have been demonstrated to induce migraine-like headaches in patients with a diagnosis of migraine (Goadsby and Edvinsson 1993; Lassen et al. 2002).

Several agents that inhibit the CGRP pathway have been approved for the treatment of migraine in adults. Four monoclonal antibodies (erenumab, galcanezumab, fremanezumab, and eptinezumab) that target CGRP (the peptide), or its receptor, have been approved for the preventive treatment of migraine in adults (comprising both chronic migraine [CM] and episodic migraine [EM]). These drugs are administered either subcutaneously or intravenously. Two small molecules that are orally administered have also been approved for the acute treatment of migraine in adults (ubrogepant and rimegepant) and, most recently, rimegepant was also approved for the preventive treatment of EM in adults.

The approach to the evaluation of efficacy in development programs for the preventive treatment of migraine is well established and includes a comparison between treatment and placebo in the reduction in the mean monthly migraine days and mean monthly headache days in a double-blind treatment period from baseline. Several additional efficacy endpoints are also generally evaluated (e.g., the number of patients with at least a 50% reduction in mean monthly migraine days and the use of monthly acute migraine treatments). Development programs for the preventive treatment of migraine have also sought to evaluate the impact of migraine on patients' daily functioning through the use of existing and novel patient-reported outcome measures.

CGRP has been described in the literature as a microvascular vasodilator that has a role in compensatory vasodilatation in the setting of ischemia. (b) (5)

Development programs for several small molecule CGRP receptor antagonists were previously discontinued because of an association with hepatotoxicity; however, the two recently approved such products, ubrogepant and rimegepant, did not have any indication of hepatotoxicity in their respective development programs. Despite the apparent safety of these more contemporary

agents in this regard, hepatotoxicity remains a safety signal of interest in the small molecule CGRP receptor antagonist development programs.

The review team identified six key review issues listed below; three that have a significant impact on the overall determination of benefit of atogepant and three that contribute to the understanding of safety to inform the benefit-risk profile and labeling.

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. The Adequacy of Study CGP-MD-01 to Support an Efficacy Claim

Assess if Study CGP-MD-01, a Phase 2/3 dose-finding trial, can serve as one of the two adequate and well-controlled efficacy studies needed to support approval.

3.1.1.2. Should Atogepant 10 mg Daily Dose Be Recommended for the General Population?

Assess if the 10 mg daily dose, in addition to the 30 mg and 60 mg daily doses, should be recommended for the general population (and not just specific populations as the Applicant proposes).

3.1.1.3. Are the AIM-D and MSQ v2.1 RFR Appropriate for Inclusion in Labeling?

Evaluate if the Activity Impairment in Migraine Diary (AIM-D) Performance of Daily Activities (PDA) domain score, the AIM-D Physical Impairment (PI) domain score, and the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) Role Function-Restrictive (RFR) domain score results should be described in labeling.

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Elevation of LFTs and CPK With Atogepant

Evaluate cases of elevated liver function tests (LFTs) and creatine phosphokinase (CPK), specifically in the setting of a serious adverse event (SAE) in which elevated LFTs and CPK were associated with a fatality.

3.1.2.2. Increased Ischemic Vascular Risk

Evaluate if there is an increased risk of vascular ischemia, specifically ischemic cardiovascular events, hypertensive events, ischemic cerebrovascular events, or thrombotic events with the use of atogepant.

3.1.2.3. Decreased Body Weight

Evaluate if decreased body weight is appropriate for inclusion in labeling.

3.2. Approach to the Review

Table 3 provides an overview of the clinical trials that were conducted to support an assessment of the benefit-risk profile of atogepant for the preventive treatment of EM in adults. The results from the Phase 2/3 study, the Phase 3 study, and two long-term safety studies provide the primary basis of evaluation of efficacy and safety of atogepant. Efficacy data supporting this application will be discussed first, followed by an evaluation of the three Key Benefit Review Issues (Section 6.3). The safety data supporting this application will then be discussed, followed by an evaluation of the three Key Risk Review Issues (Section 7.7).

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

Trial Identifier	Trial Population	Trial Design	Regimen, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Patients Planned; Actual Enrolled	Number of Centers and Countries
CGP-MD-01	Adults with a history of migraine with or without aura for ≥1 year and who had 4 to 14 migraine days during the 28-day baseline period	Randomized, Double-Blind, Parallel Group, Placebo-Controlled Trial	Atogepant Dose: 10 mg QD to 60 mg BID (specific doses listed below) Number treated: 825 Placebo (186) Total atogepant (639) 10 mg QD (93) 30 mg QD (183) 60 mg QD (186) 30 mg BID (86) 60 mg BID (91) Duration (quantity and units): 12 weeks	Primary: Change from baseline in mean monthly migraine days across the 12-week treatment period	Planned: 810 Actual: 834 randomized, 825 treated	Centers: 78 Countries: 1 (United States)
3101-301-002	Adults with a history of migraine with or without aura for ≥1 year and who had 4 to 14 migraine days during the 28-day baseline period	Randomized, Double-blind, Parallel Group, Placebo-Controlled Trial	Atogepant Dose: 10 mg QD to 60 mg QD (specific doses listed below) Number treated: 902 Placebo (222) Total atogepant (680) 10 mg QD (221) 30 mg QD (228) 60 mg QD (231) Duration (quantity and units): 12 weeks	Primary: Change from baseline in mean monthly migraine days across the 12-week treatment period	Planned: 872 Actual: 910 randomized, 902 treated	Centers: 128 Countries: 1 (United States)

Trial Identifier	Trial Population	Trial Design	Regimen, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Patients Planned; Actual Enrolled	Number of Centers and Countries
3101-302-002	Adults with a history of migraine with or without aura for ≥1 year and who had 4 to 14 migraine days during the 28-day baseline period. Including de novo participants and CGP-MD-01 completers.	Open-label, Long-term Safety Study with Standard of Care arm	Atogepant Dose: 60 mg QD Number treated: 739 Active control (196) Atogepant (543) Duration (quantity and units): 52 weeks	Endpoints not classified as primary or other. Eleven endpoints related to migraine days, headache days, medication use, and patient-reported outcomes.	Planned: 700 Actual: 744	Centers: 111 Countries: 1 (United States)
3101-309-002	Adults with a history of migraine with or without aura for ≥1 year and who had 4 to 14 migraine days during the 28-day baseline period. Including rollover participants who complete Study 3101-301-002.	Open-Label, Single-arm, Long-term Safety Study	Atogepant Dose: 60 mg QD Number treated: 655 Duration (quantity and units): 40 weeks	No endpoints specified in protocol. Objective was to evaluate the safety and tolerability of treatment with atogepant 60 mg once daily over 40 weeks. Endpoint of lead-in study was change from baseline in mean monthly migraine days.	Planned: 750 Actual: 655	Centers: 110 (planned) Countries: 1 (United States)

Source: Clinical Study Report and adsl.xpt
Abbreviations: BID, twice daily; QD, once daily

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	Section 6.3
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☒	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	Section 6.3
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

The clinical pharmacologic properties of atogepant were comprehensively evaluated as summarized in Table 5.

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class	Atogepant is a small molecule, CGRP receptor antagonist.
Mechanism of action	Atogepant is a calcitonin gene-related peptide (CGRP) receptor antagonist.
Active moieties	Atogepant
QT interval prolongation	No significant QTc prolongation effect of atogepant was detected in the QT interval assessment. At five times the highest recommended dose (300 mg), the mean (upper 90% confidence interval) QTcF increase was 1.2 milliseconds.
	General Information
Bioanalysis	Validated HPLC-MS/MS methods were used to determine the concentrations of atogepant and co-administered drugs in human plasma, whole blood (as measured using dry blood spot assay), and urine (as applicable in individual studies).
Healthy subjects versus patients	No clinically relevant differences in PK were noted between healthy subjects and patients.
Drug exposure at steady state following the therapeutic dosing regimen	**Table 6. Steady-State Drug Exposure** **Parameter Mean (SD)** / **Atogepant***: **10 mg QD**: AUC_{24} (ng.h/mL): 525 (340); C_{max} (ng/mL): 81.7 (42); C_{min} (ng/mL): 3.24 (3.1) **30 mg QD**: AUC_{24} (ng.h/mL): 1,830 (1,300); C_{max} (ng/mL): 271 (150); C_{min} (ng/mL): 12.0 (16) **60 mg QD**: AUC_{24} (ng.h/mL): 3,740 (2,300); C_{max} (ng/mL): 561 (270); C_{min} (ng/mL): 23.8 (30) Source:Study CGP-MS-03 report, Table 16 * Based on population pharmacokinetic analyses in patients with episodic migraines dosed with or without food. Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; C_{min}, minimum concentration; SD, standard deviation; QD, once daily
Range of effective dosage(s) or exposure	Based on the efficacy results from the Phase 2/3 and Phase 3 studies (Studies CGP MD-01 and 3101-301-002), there was no clear dose- or exposure- efficacy relationship in the dose range of 10 mg once daily to 60 mg twice daily.
Maximally tolerated dosage or exposure	The highest evaluated dose in humans was a single dose of 300 mg (in a TQT trial).

Characteristic	Drug Information
Dosage proportionality	Atogepant exposures, C_{max}, and AUC_{inf}, increased in an approximately dose-proportional manner when administered as a single dose in the range of 1 mg to 200 mg (Studies MK-8301 P001 and MK-8301 P002) and as multiple doses in the range of 50 mg to 170 mg (Study MK-8301 P002).
Accumulation	0.94 following QD dosing
Time to achieve steady-state	Atogepant exposures are expected to reach steady-state by Day 3 following QD dosing.
Bridge between to-be-marketed and clinical trial formulations	The final to-be-marketed formulation was used in the Phase 3 clinical study 3101-301-002; therefore, no clinical pharmacokinetics (PK)-based bridging study is required.
	Absorption
Bioavailability	Absolute bioavailability of atogepant was not determined.
T_{max}	Approximately 2 hours
Food effect (fed/fasted) Geometric least square mean and 90% CI	**Table 7. Food Effect on Atogepant** **Meal Type** / **AUC_{inf} GMR (90% CI)** / **C_{max} GMR (90% CI)** / **T_{max}** High-fat meal versus fasted / 0.83 (0.72-0.95) / 0.78 (0.64-0.95) / No change Source: Study 3101-105-002 report, Table 11-2 Abbreviations: AUC, area under the plasma concentration-time curve; CI, confidence interval; C_{max}, maximum concentration; GMR, geometric mean ratio; T_{max}, time to maximum concentration A high-fat meal consists of approximately 800 to 1,000 calories, derived approximately of 150 calories from protein, 250 calories from carbohydrates, and 500 to 600 calories from fat.
	Distribution
Volume of distribution	Based on the population PK analyses, the mean estimate of apparent volume of distribution (Vz/F) was 292 L.
Plasma protein binding	Based on in vitro study results, protein binding of atogepant in human plasma was 95%, independent of atogepant concentration of 0.1 to 10µM (60 to 6,030 ng/mL).
Drug as substrate of transporters	Atogepant is a substrate of P-glycoprotein (P-gp), BCRP, OATP1B1, OATP1B3, and OAT1.

Characteristic	Drug Information
	Elimination
Mass balance results	Following administration of 50 mg ^{14}C-atogepant, 89% of the administered dose was recovered in the excreta; 81% of the dose was recovered in feces (42% as unchanged) and 8% was recovered in urine (5% as unchanged). The major circulating forms in plasma were atogepant (75%) and the major metabolite M23 (dioxygenated methylated glucuronide of atogepant, 15% of total exposure in plasma).
Clearance	Based on the population PK analyses, the mean estimate of apparent clearance (CL/F) was 19 L/h.
Half-life	Mean terminal half-life was approximately 11 hours.
Metabolic pathway(s)	Atogepant is metabolized primarily via CYP3A4.
	Intrinsic Factors and Specific Populations
Body weight	Population PK analyses indicated that body weight has no clinically relevant impact on atogepant exposures. Dose adjustment is not needed based on body weight.
Age	Population PK analyses indicated that age has no clinically relevant impact on atogepant exposures. Dose adjustment is not needed based on age.
Renal impairment	No dose adjustment is needed in patients with mild or moderate renal impairment. Dose adjustment is needed in patient with severe renal impairment and ESRD patients (Section 8.1).
Hepatic impairment	No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). In patients with severe hepatic impairment (Child-Pugh Class C), use of atogepant should be avoided (Section 8.1).
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	Based on in vitro studies, atogepant is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4, MAO-A, or UGT1A1. Atogepant does not induce CYP1A2, CYP2B6, or CYP3A4 at clinically relevant concentrations.
Inhibition/induction of transporter systems	Atogepant does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, BSEP, MRP3, NTCP, MRP4, OCT1, MATE1, or MATE2-K at clinically relevant concentrations.
	Drug Interaction Liability (Drug as Victim)
Inhibition/induction of metabolism	Atogepant is a substrate of CYP3A4. Dose adjustment is needed when co-administered with strong CYP3A4 inhibitors, and strong and moderate CYP3A4 inducers. No dose adjustment is needed when co-administered with moderate and weak CYP3A4 inhibitors, and weak CYP3A4 inducers (Section 8.2).
Inhibition/induction of transporter systems	Atogepant is a substrate of P-gp, BCRP, OATP1B1, OATP1B3 and OAT1. Dose adjustment is needed when co-administered with OATP inhibitors (Section 8.2).

Source: Reviewer analysis
Abbreviations: AUC, area under the plasma concentration-time curve; BCRP, breast cancer resistance protein; CGRP, calcitonin gene-related peptide; CI, confidence interval; CYP, cytochrome P450; ESRD, end-stage renal disease; HPLC-MS/MS, high performance liquid chromatography with tandem mass spectrometry; OATP, organic anion transporting polypeptide; P-gp, P-glycoprotein; PK, pharmacokinetics; QD, once daily; QTc, corrected QT interval; T_{max}, time to maximum concentration; TQT, thorough QT interval

5.1. Nonclinical Assessment of Potential Effectiveness

CGRP is thought to be involved in migraine based on studies reporting that administration of CGRP can induce migraine-like headaches, that CGRP levels increase in the cranial circulation during a migraine attack, and that CGRP can induce vasodilation (a proposed mechanism for the underlying cause of migraine). In addition, CGRP antagonists have been shown to alleviate migraine symptoms. Atogepant is a CGRP receptor antagonist.

In in vitro binding and functional assays, atogepant demonstrated low picomolar affinity and antagonist activity against human and monkey CGRP receptors, and low nanomolar antagonist activity against mouse, rat, rabbit, and dog CGRP receptors. In off-target binding assays (>120 receptors, enzymes, and ion channels), atogepant showed no affinity at up to micromolar concentrations.

In isolated human coronary, meningeal, and cerebral artery preparations, atogepant (up to 1µM), antagonized CGRP-induced relaxation. However, atogepant alone (up to 100 µM) did not exhibit any vasoactivity. Atogepant inhibited capsaicin-induced dermal vasodilation at low nanomolar concentrations in monkeys and low micromolar concentrations in rats and rabbits. In monkeys, atogepant antagonized CGRP-induced increases in blood pressure and heart rate at low nanomolar plasma concentrations.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

The Applicant conducted one Phase 2/3 12-week dose-finding study, Study CGP-MD-01, to determine the range of doses to move forward into a Phase 3 confirmatory efficacy study of atogepant for the preventive treatment of migraine. Study CGP-MD-01 was designed to assess both once daily (QD) (10 mg, 30 mg, and 60 mg) and twice daily (BID) dosing (30 mg and 60 mg [total daily doses of 60 mg and 120 mg, respectively]). The results of this study (discussed in detail in Section 6.2.1.4) demonstrated preliminary efficacy of all doses with no clear evidence of a dose-response relationship.

During the November 19, 2018, End of Phase 2 meeting, the Division stated that on face, Study CGP-MD-01 had the characteristics of an adequate and well-controlled efficacy trial, but that a final determination would be made during the review of the application. The doses to be studied in the confirmatory efficacy trial (Study 3101-301-002) were discussed during a Type C meeting in June 2017. At that time, the Division acknowledged that QD dosing may be more feasible for patients than BID dosing, although BID dosing performed slightly better numerically with respect to efficacy in Study CGP-MD-01. The Division recommended that the Applicant also study the 10 mg QD dose in Study 3101-301-002, since efficacy of the 10 mg dose appeared similar to that of the 30 mg and 60 mg QD dose.

A detailed discussion of the evaluation of any dose-response relationship based on the data from these two efficacy studies is provided in Sections 6.3.1 and 6.3.2 of this review.

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Study CGP-MD-01

6.2.1.1. Design

Study CGP-MD-01 was a Phase 2/3 multicenter, randomized, double-blind, placebo-controlled, parallel-group study that enrolled adult patients with a history of EM (4 to 14 migraine days per month) from 78 sites in the United States. Patients were randomized to one of six different arms in a 2:1:2:1:2:1 randomization sequence of placebo, atogepant 10 mg QD, atogepant 30 mg QD, atogepant 30 mg BID, atogepant 60 mg QD, or atogepant 60 mg BID, respectively. The study included a 4-week screening and baseline period, a 12-week double-blind treatment period, and a 4-week follow-up visit. The primary efficacy endpoint was the change from baseline in mean monthly migraine days during the 12-week double-blind treatment period.

6.2.1.2. Eligibility Criteria

Key inclusion criteria:

- Male and female patients, ages 18 to 75, inclusive
- 1-year history of migraine with or without aura, consistent with the International Classification of Headache Disorders
- Age at onset of migraine prior to 50 years
- History of 4 to 14 migraine/probable migraine days per month in prior 3 months and baseline period

Key exclusion criteria:

- History of chronic migraine, new persistent daily headache, trigeminal autonomic cephalgia
- ≥15 headache days per month in prior 3 months or during baseline period
- History of inadequate response to 3 or more medications used for preventive treatment of migraine
- Use of prohibited medications, use of opioids or barbiturates >2 days/month, triptans or ergots ≥10 days/month or simple analgesics (aspirin, nonsteroidal anti-inflammatory drugs, acetaminophen) ≥15 days/month
- Abnormal baseline laboratory or electrocardiogram (ECG) results
- History of acute hepatitis or abnormal results on hepatitis screen, history of clinically significant cardiovascular or cerebrovascular disease, baseline hypertension (>160 mm mercury (Hg) for systolic blood pressure or diastolic blood pressure >100 mm Hg)
- History of prior or current use of CGRP pathway drugs in the last 3 months
- History of significant risk of self-harm based on responses on the Columbia-Suicide Severity Rating Scale (C-SSRS)

- Baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5X the upper limit normal (ULN), total bilirubin greater than >1X ULN, or serum albumin <2.8 gram/dL
- Use of strong or moderate cytochrome P450 (CYP)3A4 inhibitors and inducers and medications with demonstrated efficacy for the prevention of migraine (e.g., topiramate and propranolol) in the 30 days prior to Visit 1 and throughout the study; botulinum toxin injections were prohibited within the 6 months prior to Visit 1

6.2.1.3. Statistical Analysis Plan

Efficacy Endpoints

The primary efficacy endpoint was the change from baseline in mean monthly migraine days across the 12-week treatment period. Migraine days were defined as the combination of migraine headache days and probable migraine headache days.

Secondary efficacy endpoints included (in hierarchical testing order):

- Change from baseline in mean monthly headache days across the 12-week treatment period.
- Proportion of patients with at least a 50% reduction in mean monthly migraine days across the 12-week treatment period.
- Change from baseline in mean monthly acute medication use days across the 12-week treatment period.

Efficacy Analysis Population

The efficacy analyses were based on the modified intent-to-treat population, which consisted of all randomized participants who received at least one dose of study treatment, had an evaluable baseline period of diary data, and had at least one evaluable postbaseline 4-week period (weeks 1 to 4, 5 to 8, and 9 to 12) of diary data. For baseline, evaluable is defined as having at least 20 days of diary data during the 4-week baseline period. For each postbaseline 4-week treatment period, evaluable is defined as having at least 12 days of diary data for that particular period.

Analysis Methods

The primary endpoint was analyzed using mixed-effects model for repeated measures (MMRM). The response variable was the change from baseline to each postbaseline month in monthly migraine days. The model included baseline monthly migraine days as a covariate, treatment group and visit (month) as fixed factors, and treatment group-by-visit and baseline-by-visit as interaction terms. The restricted maximum likelihood method was used. The within-patient correlation was modeled using the unstructured covariance matrix (compound symmetry covariance matrix if convergence failed). The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Contrasts were constructed to obtain the average treatment effects across the 12-week (Months 1 to 3) treatment period to compare each atogepant treatment group versus the placebo group.

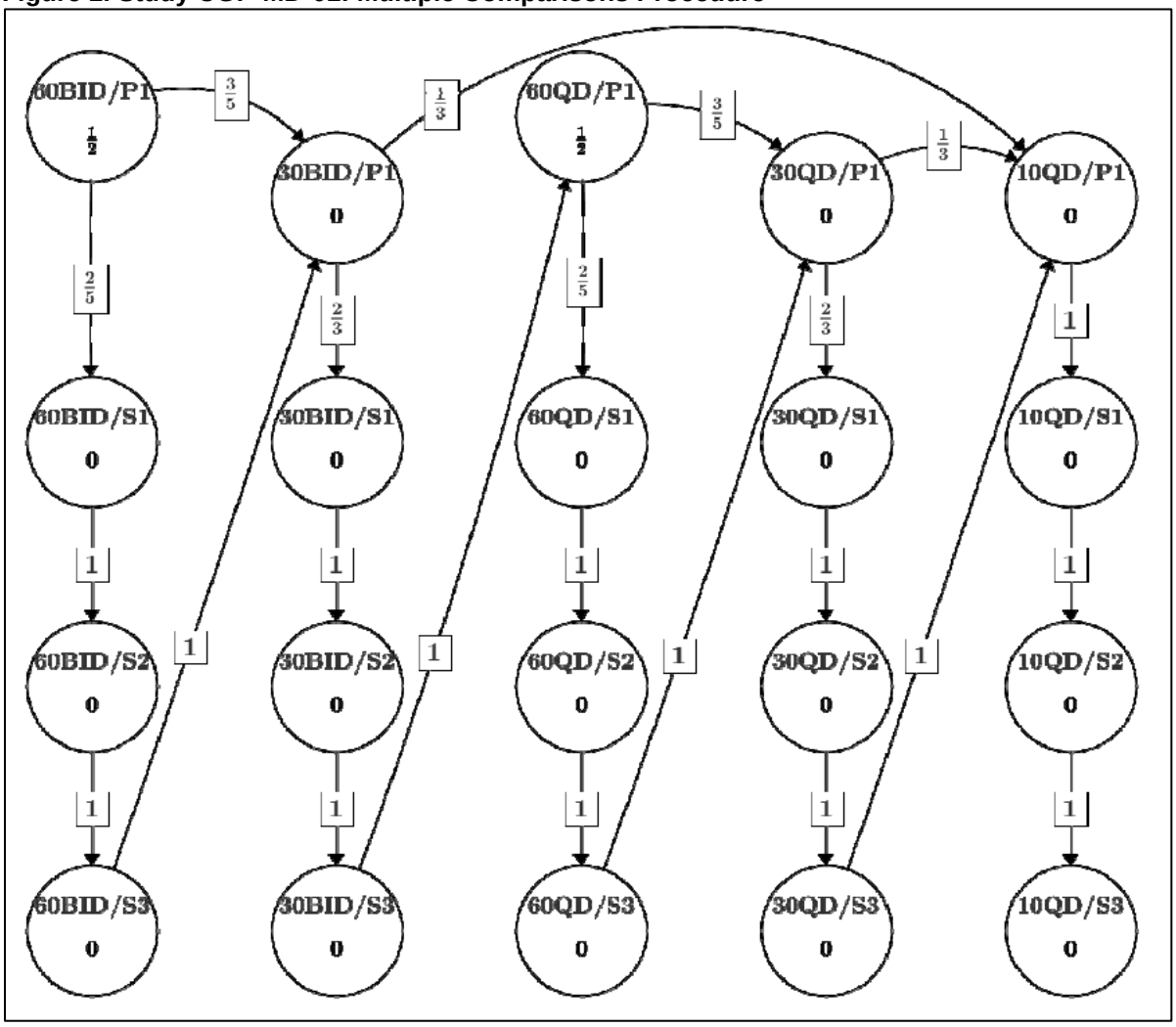
Two sensitivity analyses were planned on the primary analysis. The first used a pattern-mixture model approach based on the reference-based copy reference method for missing value imputation. This analysis used a missing-not-at-random mechanism for missing data to assess the impact of potential deviation from a missing at random assumption in the primary analysis. The second sensitivity analysis used multiple imputations in conjunction with robust regression to assess the robustness of the primary MMRM analysis with respect to the possibility of a violation of the normality assumption. The normality assumption of MMRM analysis is usually not a concern for trials of this size; therefore, the statistical review mainly focused on the sensitivity analysis for missing data.

For secondary endpoints, pairwise comparisons were analyzed using MMRM for continuous variables, and generalized linear mixed model for repeated measures of the binary response of at least 50% reduction.

Multiplicity Adjustment

The overall type I error rate was controlled at α=0.05 for the set of primary and secondary endpoint comparisons between each dose level of atogepant versus placebo using a graphical approach with weighted-Bonferroni test procedure (Figure 1). The weighting strategy of the multiple comparisons was designed to allocate initial alpha equally to the QD and BID dose regimens. Within each dosing regimen, individual atogepant doses were tested in a hierarchical order from high to low dose. In addition, for a given dose comparison versus placebo, the primary endpoint and secondary endpoints were tested in a prespecified order. If the null hypotheses for both the primary and secondary endpoints are rejected for one of the doses, the associated alpha is passed to the other doses to increase the chances of success for the other doses. For example, if the null hypotheses were rejected for all endpoints for the BID doses, the 60 mg QD dose would have 1/2x2/3=1/3 of the alpha from the testing of BID doses in addition to the original half of the alpha. Hence the primary endpoint for 60 mg QD could be tested at a significance level of 0.05*(1/2+1/3)=0.0417, and the adjusted p-value would be nominal p-value*0.05/0.0417.

Figure 1. Study CGP-MD-01: Multiple Comparisons Procedure



Source: Figure 5-1 of the statistical analysis plan for Study CGP-MD-01
Abbreviations: BID, twice daily; QD, once daily

6.2.1.4. Results of Analyses

The following tables present the baseline demographic and clinical characteristics (Table 8), screening and randomization results (Table 9), and disposition (Table 10) of the safety population in Study CGP-MD-01.

Table 8. Study CGP-MD-01: Baseline Demographic and Clinical Characteristics, Safety Population

Characteristic	ATG 10 mg QD N=93	ATG 30 mg QD N=183	ATG 60 mg QD N=186	ATG 30 mg BID N=86	ATG 60 mg BID N=91	Placebo N=186
Sex, n (%)						
Female	82 (88.2)	166 (90.7)	156 (83.9)	73 (84.9)	83 (91.2)	154 (82.8)
Male	11 (11.8)	17 (9.3)	30 (16.1)	13 (15.1)	8 (8.8)	32 (17.2)
Age, years						
Mean (SD)	39.4 (12.4)	41 (13.6)	40.4 (11.7)	38.5 (11.2)	39.7 (11.9)	40.5 (11.7)
Median (min, max)	38 (19, 71)	40 (18, 74)	40 (18, 67)	35 (18, 66)	39 (18, 69)	40.5 (18, 73)

Characteristic	ATG 10 mg QD N=93	ATG 30 mg QD N=183	ATG 60 mg QD N=186	ATG 30 mg BID N=86	ATG 60 mg BID N=91	Placebo N=186
Age group, years, n (%)						
<20	1 (1.1)	3 (1.6)	2 (1.1)	1 (1.2)	2 (2.2)	4 (2.2)
20 to 29	20 (21.5)	46 (25.1)	38 (20.4)	16 (18.6)	19 (20.9)	30 (16.1)
30 to 39	33 (35.5)	42 (23.0)	48 (25.8)	32 (37.2)	26 (28.6)	55 (29.6)
40 to 49	21 (22.6)	41 (22.4)	54 (29.0)	23 (26.7)	25 (27.5)	57 (30.6)
50 to 59	13 (14.0)	31 (16.9)	32 (17.2)	11 (12.8)	13 (14.3)	27 (14.5)
60 to 69	1 (1.1)	17 (9.3)	12 (6.5)	3 (3.5)	6 (6.6)	12 (6.5)
≥70	4 (4.3)	3 (1.6)	0 (0)	0 (0)	0 (0)	1 (0.5)
Ethnicity, n (%)						
Hispanic or Latino	15 (16.1)	32 (17.5)	25 (13.4)	13 (15.1)	13 (14.3)	29 (15.6)
Not Hispanic or Latino	78 (83.9)	151 (82.5)	161 (86.6)	73 (84.9)	78 (85.7)	157 (84.4)
Race, n (%)						
American Indian or Alaska Native	0 (0)	1 (0.5)	2 (1.1)	0 (0)	0 (0)	3 (1.6)
Asian	1 (1.1)	2 (1.1)	3 (1.6)	1 (1.2)	0 (0)	1 (0.5)
Black or African American	20 (21.5)	29 (15.8)	44 (23.7)	11 (12.8)	19 (20.9)	45 (24.2)
Multiple	3 (3.2)	4 (2.2)	4 (2.2)	1 (1.2)	1 (1.1)	0 (0)
Native Hawaiian or Other Pacific Islander	0 (0)	2 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)
White	69 (74.2)	145 (79.2)	133 (71.5)	73 (84.9)	71 (78.0)	137 (73.7)
Country of participation, n (%)						
United States	93 (100)	183 (100)	186 (100)	86 (100)	91 (100)	186 (100)

Source: ISS Group 1 adsl.xpt; Software: R
Abbreviations: ATG, atogepant; BID, twice daily; QD, once daily; max, maximum; min, minimum; N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation

Table 9. Study CGP-MD-01: Patient Screening and Randomization

Disposition	Study CGP-MD-01
No. patients screened	1,772
No. patients not randomized	938
No. patients randomized	834

Source: adsl.xpt and Clinical Study Report; Software: R
The number of patients randomized includes patients who were randomized, but not treated.

Table 10. Study CGP-MD-01: Patient Disposition, Safety Population

Disposition Outcome n (%)	ATG 10 mg QD N=93	ATG 30 mg QD N=183	ATG 60 mg QD N=186	ATG 30 mg BID N=86	ATG 60 mg BID N=91	Placebo N=186
Patients randomized	93 (100)	183 (100)	186 (100)	86 (100)	91 (100)	186 (100)
Discontinued study	14 (15.1)	37 (20.2)	22 (11.8)	17 (19.8)	23 (25.3)	42 (22.6)
Adverse event	4 (4.3)	11 (6)	6 (3.2)	5 (5.8)	7 (7.7)	5 (2.7)
Withdrawal by subject	7 (7.5)	10 (5.5)	6 (3.2)	9 (10.5)	7 (7.7)	20 (10.8)
Lost to follow-up	1 (1.1)	13 (7.1)	6 (3.2)	2 (2.3)	6 (6.6)	9 (4.8)
Noncompliance with study drug	0 (0)	0 (0)	1 (0.5)	0 (0)	0 (0)	4 (2.2)
Protocol deviation	2 (2.2)	2 (1.1)	2 (1.1)	1 (1.2)	3 (3.3)	4 (2.2)
Pregnancy	0 (0)	1 (0.5)	1 (0.5)	0 (0)	0 (0)	0 (0)

Source: ISS Group 1 adsl.xpt; Software: R
Abbreviations: ATG, atogepant; BID, twice daily; QD, once daily; N, number of patients in treatment arm; n, number of patients in specified population or group

As indicated in the preceding tables, most enrolled patients were female, white, and had a mean age of 39 to 42 years. Demographic data were generally balanced across groups. Disposition and reasons for discontinuation did not indicate any clear trends, though the percentage of patients who discontinued due to an adverse event (AE) was highest in the atogepant 60 mg BID study arm by a small margin.

Primary Efficacy Endpoint

As indicated in Table 11, all 5 atogepant doses demonstrated statistically significant treatment differences compared with placebo in the reduction of mean monthly migraine days during the treatment period compared to baseline after multiplicity adjustment. The results of sensitivity analyses (Section 16) were consistent with the results of the primary efficacy analysis.

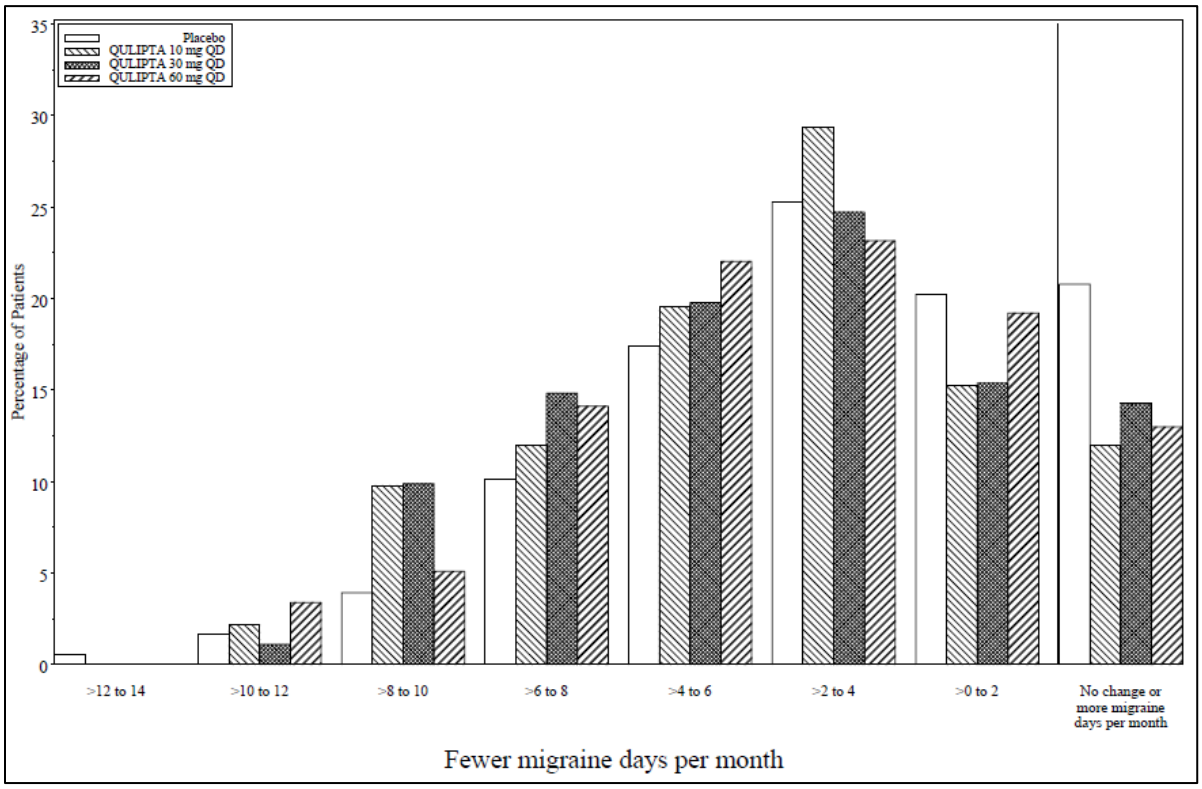
Table 11. Study CGP-MD-01: Change From Baseline in Mean Monthly Migraine Days

Parameter	Statistic	Placebo N=178	ATG 10 mg QD N=92	ATG 30 mg QD N=182	ATG 60 mg QD N=177	ATG 30 mg BID N=79	ATG 60 mg BID N=87
Baseline	Mean (SD)	7.81 (2.51)	7.63 (2.51)	7.64 (2.37)	7.74 (2.59)	7.38 (2.43)	7.62 (2.56)
Change from baseline	LS mean (SE)	-2.85 (0.23)	-4.00 (0.32)	-3.76 (0.23)	-3.55 (0.23)	-4.23 (0.35)	-4.14 (0.33)
Atogepant versus placebo							
	LSMD		-1.15	-0.91	-0.70	-1.39	-1.29
	95% CI		-1.93, -0.37	-1.55, -0.27	-1.35, -0.06	-2.21, -0.56	-2.09, -0.49
	Nominal p-value		0.0039	0.0056	0.0325	0.0010	0.0016
	Adjusted p-value		0.0236	0.0390	0.0390	0.0034	0.0031

Source: Study CGP-MD-01 CSR tables 11-1, 11-2, confirmed by reviewer
Abbreviations: ATG, atogepant; BID, twice daily; CI, confidence interval; LSMD, least squares mean difference; N, number of patients in treatment arm; QD, once daily; SD, standard deviation; SE, standard error

Figure 2 demonstrates the distribution of change from baseline in mean monthly migraine days across the 12-week treatment period in bins of 2 days by treatment group. A treatment benefit over placebo for all 3 doses is seen across a range of changes from baseline in monthly migraine days.

Figure 2. Study CGP-MD-01: Distribution of Change From Baseline in Mean Monthly Migraine Days by Treatment Group



Source: modified from Summary of Clinical Efficacy Figure 3-1, confirmed by reviewer
Abbreviation: QD, once daily

Secondary Endpoints

As indicated in Table 12, there was a statistically significant benefit on the first secondary endpoint (mean monthly headache days) across all dose groups. Analyses of the remaining secondary endpoints only demonstrated statistically significant results in the BID dosing groups; however, results in all treatment groups numerically favored atogepant for all endpoints tested.

Table 12. Study CGP-MD-01: Analyses of Secondary Efficacy Endpoints

Parameter	Placebo N=178	Atogepant 10 mg QD N=92	Atogepant 30 mg QD N=182	Atogepant 60 mg QD N=177	Atogepant 30 mg BID N=79	Atogepant 60 mg BID N=87
Change From Baseline in Mean Monthly Headache Days						
Baseline, mean	9.07	8.89	8.74	8.86	8.71	8.80
Change from baseline, LS mean	-2.93	-4.31	-4.17	-3.86	-4.23	-4.32
Atogepant versus placebo						
LSMD		-1.38	-1.24	-0.94	-1.30	-1.39
95% CI		-2.23, -0.54	-1.94, -0.55	-1.64, -0.24	-2.20, -0.41	-2.26, -0.53
Nominal p-value		0.0014	0.0005	0.0087	0.0044	0.0017
Adjusted p-value		0.0236	0.0390	0.0390	0.0131	0.0083

Parameter	Placebo N=178	Atogepant 10 mg QD N=92	Atogepant 30 mg QD N=182	Atogepant 60 mg QD N=177	Atogepant 30 mg BID N=79	Atogepant 60 mg BID N=87
Proportion of Participants With ≥50% Reduction in Mean Monthly Migraine Days						
Responders, n (%)	72 (40.4)	53 (57.6)	97 (53.3)	92 (52.0)	46 (58.2)	54 (62.1)
Atogepant versus placebo						
Odds ratio		1.50	1.46	1.42	1.83	2.03
95% CI		0.98, 2.31	1.02, 2.08	1.00, 2.03	1.15, 2.91	1.30, 3.18
Nominal p-value		0.0617	0.0369	0.0512	0.0113	0.0019
Adjusted p-value		0.1107	0.1107	0.1537	0.0339	0.0097
Change From Baseline in Mean Monthly Acute Medication Use Days						
Baseline mean	6.57	6.16	6.62	6.79	6.20	6.37
Change from baseline, LS mean	-2.42	-3.71	-3.86	-3.53	-3.77	-3.64
Atogepant versus placebo						
LSMD		-1.30	-1.44	-1.11	-1.35	-1.22
95% CI		-1.99, -0.60	-2.01, -0.87	-1.68, -0.54	-2.08, -0.62	-1.93, -0.52
Nominal p-value		0.0002	<0.0001	0.0001	0.0003	0.0007
Adjusted p-value		0.1107	0.1107	0.1537	0.0339	0.0097

Source: Study CGP-MD-01 CSR tables 11-1, 11-4, 11-5, 11-6, confirmed by reviewer
Abbreviations: BID, twice daily; CI, confidence interval; LS, least squares; LSMD, least squares mean difference; N, number of patients in treatment group; n, number of patients with given characteristic; QD, once daily

Medical Officer's Assessment: *All doses demonstrated statistically significant reductions on the primary endpoint and first secondary endpoint. The reduction in mean monthly migraine days of 0.7 to 1.15 days (difference from placebo) for the daily dosing regimens is in line with other recently approved therapies that act on the CGRP pathway (range 0.7 to 2.0 reduction in mean monthly migraine days). This degree of change was deemed to represent a clinically meaningful change for the other approved therapies for the preventive treatment of migraine and this reviewer concludes that the degree of change detected in this study also represents a clinically meaningful change. No clear dose-response relationship was observed in this study. Refer to details of this issue later in this review (Section 6.3.1).*

6.2.2. Study 3101-301-002

6.2.2.1. Design

Study 3101-301-002 was a Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group study which enrolled adult patients with a history of EM (4 to 14 migraine days per month) from 128 sites in the United States. The primary efficacy endpoint was the change from baseline in mean monthly migraine days during the 12-week double-blind treatment period. Patients were randomized to one of four different arms in a 1:1:1:1 randomization sequence of placebo, atogepant 10 mg QD, atogepant 30 mg QD, or atogepant 60 mg QD. Approximately 70% of randomized participants had to have taken at least one prior medication for the preventive treatment of migraine, and randomization was stratified based on this prior exposure (yes/no). The study included a 4-week screening and baseline period, a 12-week double-blind treatment period, and a 4-week follow-up visit.

Medical Officer's Assessment*: A notable difference between this trial and Study CGP-MD-01 was the requirement that 70% of patients had to have taken at least one prior medication for the preventive treatment of migraine. A discussion of the potential impact of this difference is discussed in Section 6.3.1.*

6.2.2.2. Eligibility Criteria

Key inclusion criteria were the same as Study CGP-MD-01.

Key exclusion criteria were the same as Study CGP-MD-01 (Section 6.2.1.2 above), with the following exceptions:

- Patients with baseline ALT or AST >1X ULN, total bilirubin >1X ULN, serum albumin <2.8 gram/dL, or estimated glomerular filtration rate <30 mL/min/1.73 m^2 were also excluded.
- Patients on prior injectable monoclonal antibodies blocking the CGRP pathway within the last 6 months and/or patients with a history of using more than three doses of ubrogepant or rimegepant were excluded.

Medical Officer's Assessment: *The criteria for abnormal LFTs at baseline in this study are stricter than the criteria listed for Study CGP-MD-01. Additionally, prior use of drugs or biologics that act on the CGRP pathway required a longer time or more specific criteria since last use compared to that of Study CGP-MD-01. Although these are relatively minor differences, they may affect conclusions regarding hepatic safety or the general safety of atogepant when used either as a single CGRP antagonist, or in combination with another product that acts on the CGRP pathway.*

6.2.2.3. Statistical Analysis Plan

Efficacy Endpoints

The primary efficacy endpoint was the change from baseline in mean monthly migraine days across the 12-week treatment period.

Secondary efficacy endpoints included (in hierarchical testing order):

- Change from baseline in mean monthly headache days across the 12-week treatment period
- Change from baseline in mean monthly acute medication use days across the 12-week treatment period
- At least a 50% reduction in 3-month average of monthly migraine days
- Change from baseline in MSQ v2.1 RFR domain score at week 12
- Change from baseline in mean monthly PDA domain score of the AIM-D across the 12-week treatment period
- Change from baseline in mean monthly PI domain score of the AIM-D across the 12-week treatment period

Efficacy Analysis Population

The efficacy analyses were conducted on the modified intent-to-treat population, which consisted of all randomized participants who received at least one dose of study intervention, had an evaluable baseline period of eDiary data, and at least one evaluable postbaseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data during the double-blind treatment period. For baseline, evaluable is defined as having at least 20 days of diary data during the 4-week baseline

period. For each postbaseline 4-week treatment period, evaluable is defined as having at least 14 days of diary data for that particular period.

Analysis Methods

The primary endpoint was analyzed using MMRM. The statistical model included treatment group, visit, prior exposure (yes/no) to a migraine preventive medication, and treatment group-by-visit interaction as categorical fixed effects. It also included the baseline score and baseline-by-visit interaction as covariates. An unstructured covariance matrix was used to model the covariance of within-participant repeated measurements. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom.

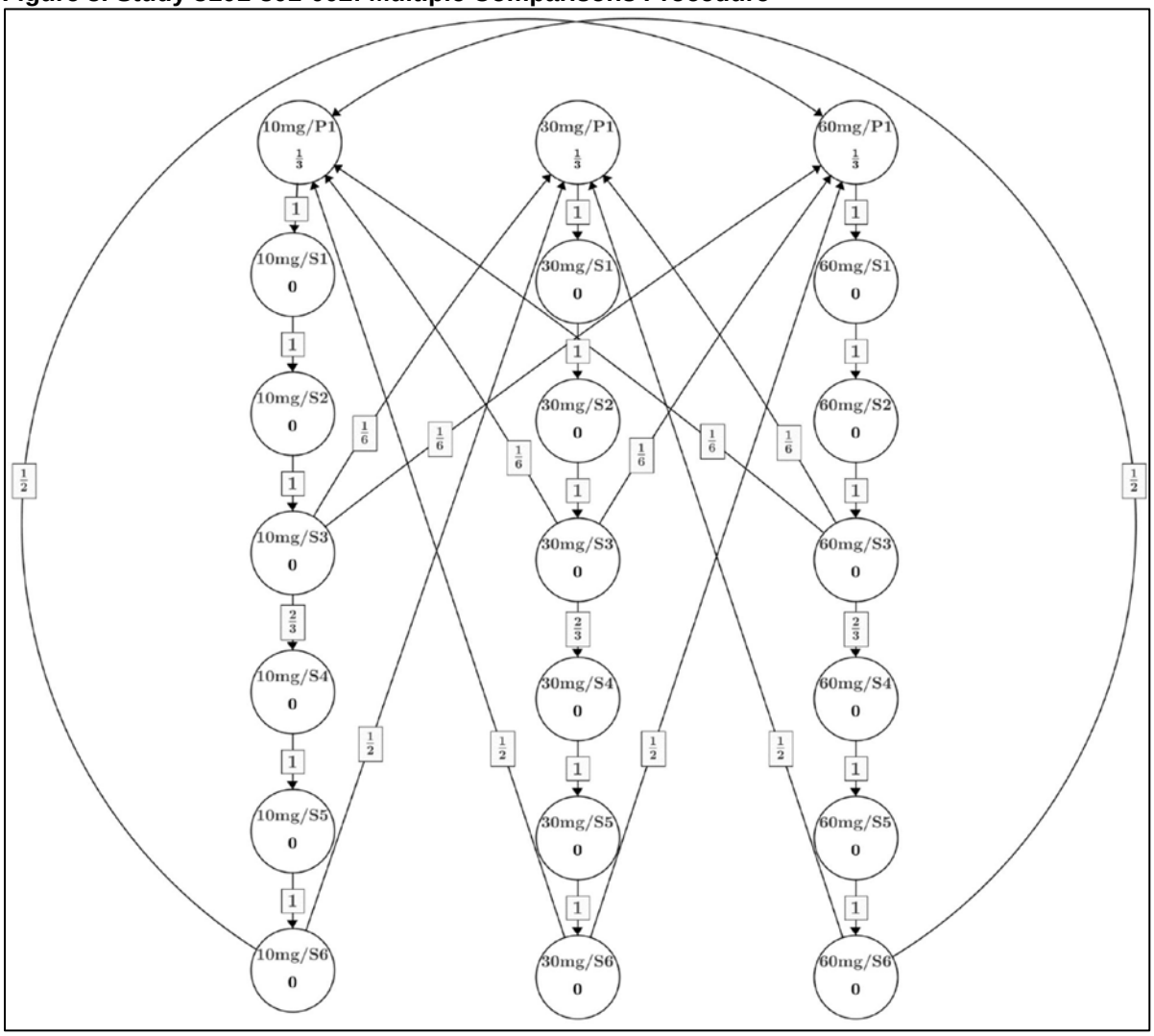
Sensitivity analyses for missing data handling were planned, including: (1) analysis of covariance model based on 3-month average of the monthly migraine days, (2) MMRM based on primary measures collected during the double-blind and follow-up periods, (3) analysis of covariance with multiple imputations within group, and (4) a pattern-mixture model approach based on the reference-based copy reference method. Sensitivity analysis using multiple imputations in conjunction with robust regression were conducted to assess the robustness of the primary MMRM analysis to the possible violation of the normality assumption.

The 50% or greater responder endpoint, where responders were defined as a participant with at least 50% reduction in 3-month average of monthly migraine days, was analyzed using a logistic regression model. The other secondary efficacy endpoints were analyzed in the same manner as that was used to analyze the primary endpoint.

Multiplicity Adjustment

The overall type I error rate was controlled at $\alpha=0.05$ for the set of primary and secondary endpoint comparisons between each dose level of atogepant versus placebo using a graphical approach with weighted-Bonferroni test procedure (Figure 3). The initial allocation of the overall significance level to three primary hypotheses was 1/3 of the overall significance level for each dose. Within each individual dose, testing started from the primary endpoint, and then the secondary endpoints in a prespecified order. If the null hypotheses for both the primary and the first three secondary endpoints were rejected for one of the doses, 1/3 of the associated alpha was passed to the other doses (1/6 fraction for each dose) to increase the chances of success for the other doses in testing endpoints in the primary positions of the hierarchy, and the remaining 2/3 of the associated alpha was reserved for testing null hypothesis endpoints within the same dose. If hypotheses for three null hypothesis endpoints were rejected within a dose based on the remaining alpha, the alpha for this dose was to be propagated to the other two doses to make full use of the alpha.

Figure 3. Study 3101-301-002: Multiple Comparisons Procedure



Source: Figure 10-1 of the statistical analysis plan for Study 3101-301-002

6.2.2.4. Results of Analyses

The following tables present the baseline demographics and clinical characteristics (Table 13), screening and randomization results (Table 14), and disposition (Table 15) of the safety population in Study 3101-301-002.

Table 13. Study 3101-301-002: Baseline Demographic and Clinical Characteristics, Safety Population

Characteristic	ATG 10 mg QD N=221	ATG 30 mg QD N=228	ATG 60 mg QD N=231	Placebo N=222
Sex, n (%)				
Female	200 (90.5)	204 (89.5)	199 (86.1)	198 (89.2)
Male	21 (9.5)	24 (10.5)	32 (13.9)	24 (10.8)
Age, years				
Mean (SD)	41.4 (12)	42.1 (11.7)	42.5 (12.4)	40.3 (12.8)
Median (minimum, maximum)	41 (18, 73)	42 (19, 70)	42 (18, 72)	38.5 (18, 69)

Characteristic	ATG 10 mg QD N=221	ATG 30 mg QD N=228	ATG 60 mg QD N=231	Placebo N=222
Age group, years, n (%)				
<20	3 (1.4)	1 (0.4)	4 (1.7)	6 (2.7)
20 to 29	37 (16.7)	36 (15.8)	38 (16.5)	46 (20.7)
30 to 39	62 (28.1)	62 (27.2)	61 (26.4)	63 (28.4)
40 to 49	61 (27.6)	70 (30.7)	60 (26.0)	48 (21.6)
50 to 59	40 (18.1)	42 (18.4)	43 (18.6)	41 (18.5)
60 to 69	16 (7.2)	16 (7.0)	23 (10.0)	18 (8.1)
≥70	2 (0.9)	1 (0.4)	2 (0.9)	0 (0)
Ethnicity, n (%)				
Hispanic or Latino	21 (9.5)	19 (8.3)	14 (6.1)	23 (10.4)
Not Hispanic or Latino	200 (90.5)	209 (91.7)	217 (93.9)	199 (89.6)
Race, n (%)				
American Indian or Alaska Native	1 (0.5)	1 (0.4)	1 (0.4)	0 (0)
Asian	2 (0.9)	1 (0.4)	7 (3.0)	2 (0.9)
Black or African American	34 (15.4)	38 (16.7)	28 (12.1)	24 (10.8)
Multiple	3 (1.4)	3 (1.3)	2 (0.9)	2 (0.9)
White	181 (81.9)	185 (81.1)	192 (83.1)	194 (87.4)
Missing	0 (0)	0 (0)	1 (0.4)	0 (0)
Country of participation, n (%)				
United States	221 (100)	228 (100)	231 (100)	222 (100)

Source: ISS Group 1 adsl.xpt; Software: R
Abbreviations: ATG, atogepant; N, number of patients in treatment group; n, number of patients with given characteristic; QD, once daily; SD, standard deviation

Table 14. Study 3101-301-002: Patient Screening and Randomization, All Patients

Disposition	3101-301-002
Number of patients screened	2,270
Number of patients not randomized	1,360
Number of patients randomized	910

Source: adsl.xpt and Clinical Study Report; Software: R
The number of patients randomized includes patients who were randomized, but not treated.

Table 15. Study 3101-301-002: Patient Disposition, Safety Population

Disposition Outcome	ATG 10 mg QD N=221	ATG 30 mg QD N=228	ATG 60 mg QD N=231	Placebo N=222
Patients randomized, n (%)	221 (100)	228 (100)	231 (100)	222 (100)
Discontinued study, n (%)	33 (14.9)	27 (11.8)	36 (15.6)	26 (11.7)
Adverse event	9 (4.1)	4 (1.8)	6 (2.6)	6 (2.7)
Withdrawal by subject	12 (5.4)	12 (5.3)	15 (6.5)	13 (5.9)
Lost to follow-up	4 (1.8)	4 (1.8)	7 (3)	3 (1.4)
Noncompliance with study drug	0 (0)	0 (0)	0 (0)	0 (0)
Protocol deviation	5 (2.3)	6 (2.6)	5 (2.2)	3 (1.4)
Pregnancy	1 (0.5)	0 (0)	0 (0)	0 (0)
Lack of efficacy	0 (0)	0 (0)	1 (0.4)	1 (0.5)
Other	2 (0.9)	1 (0.4)	2 (0.9)	0 (0)

Source: Integrated Summary of Safety Group 1 adsl.xpt; Software: R
Risk difference column shows difference (with 95% confidence interval) between 60 mg QD group and placebo.
Abbreviations: ATG, atogepant; QD, once daily; N, number of patients in treatment arm; n, number of patients in specified population or group

As indicated in Table 13, most enrolled patients were female, white, and had a mean age of 40 to 42 years. A recent literature review noted that of 36 recent (since 2011) clinical trials studying migraine, 84.2% of participants were women and 82.9% were white (Robbins and Bernat 2017). The percentage of females (~90%) is slightly higher than is typically seen in migraine clinical

trials yet sensitivity analyses (Section 16) did not suggest differences based on gender, race, or age. Reasons for discontinuation were generally balanced across groups.

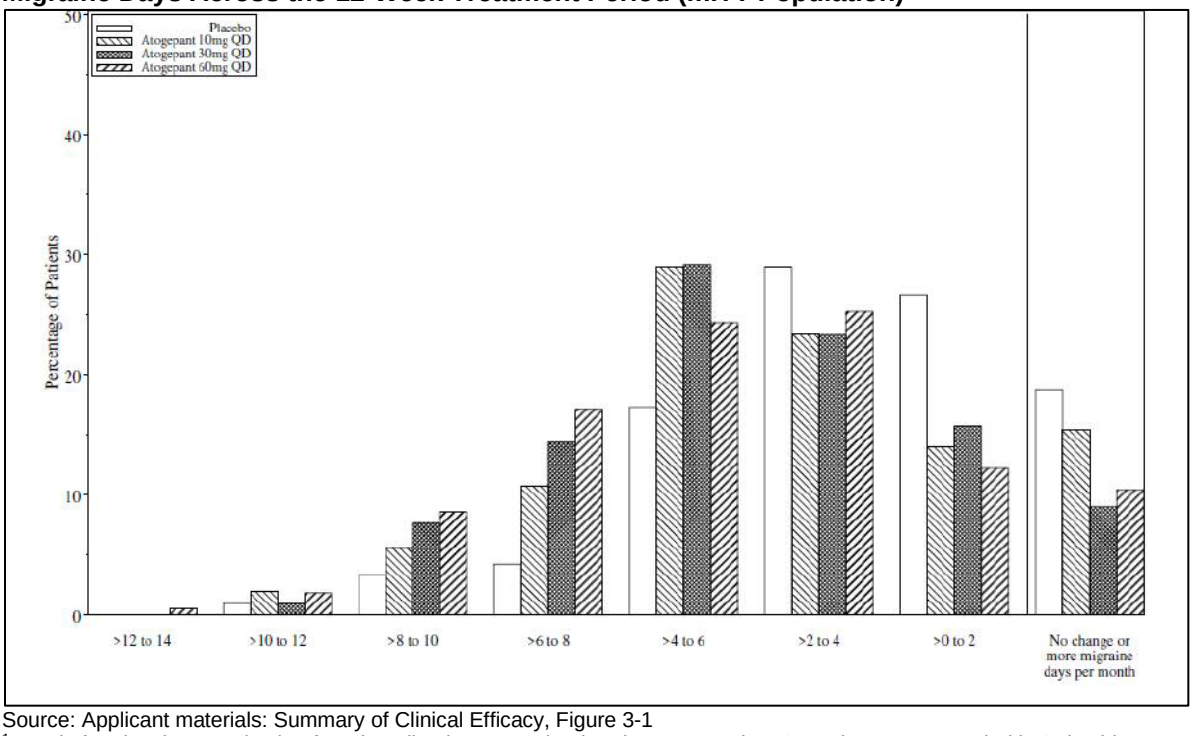
As indicated in Table 16, each of the three atogepant doses demonstrated statistically significant treatment differences compared with placebo in the reduction of mean monthly migraine days across the 12-week treatment period compared to baseline after multiplicity adjustment (adjusted p<0.0001 for all comparisons). The results of sensitivity analyses (Section 16) are consistent with the primary analysis.

Table 16. Study 3101-301-002: Change From Baseline in Mean Monthly Migraine Days

Parameter	Placebo N=214	ATG 10 mg QD N=214	ATG 30 mg QD N=223	ATG 60 mg QD N=222
Baseline				
Mean (SD)	7.51 (2.39)	7.45 (2.46)	7.86 (2.32)	7.75 (2.31)
Change from baseline				
LS mean (SE)	-2.48 (0.21)	-3.69 (0.21)	-3.86 (0.21)	-4.20 (0.21)
Atogepant versus placebo				
LSMD		-1.21	-1.38	-1.72
95% CI		-1.78, -0.64	-1.94, -0.82	-2.28, -1.15
Nominal p-value		<0.0001	<0.0001	<0.0001
Adjusted p-value		<0.0001	<0.0001	<0.0001

Source: Study 3101-301-002 CSR tables 11-1, 11-2, confirmed by reviewer
Abbreviations: ATG, atogepant; CI, confidence interval; LSMD, least squares mean difference; N, number of patients in treatment arm; QD, once daily; SD, standard deviation; SE, standard error

Figure 4. Study 3101-301-002: Distribution of the Reduction From Baseline in Mean Monthly Migraine Days Across the 12-Week Treatment Period (mITT Population)[1]



Source: Applicant materials: Summary of Clinical Efficacy, Figure 3-1
[1] X-axis for plot shows reduction from baseline in mean migraine days across the 12-week treatment period in 2-day bins.
Abbreviations: mITT, modified intent-to-treat; QD, once daily

Figure 4 demonstrates the distribution of change from baseline in mean monthly migraine days across the 12-week treatment period in bins of two days by treatment group. A treatment benefit over placebo for all three doses was seen across a range of changes from baseline in monthly migraine days.

Secondary Efficacy Endpoints

As indicated in Table 17, all three atogepant doses demonstrated statistically significant treatment effects compared to placebo on all secondary endpoints, except for the 10 mg dose of atogepant on both of the clinical outcome assessment measures for the AIM-D, although this result also numerically favored atogepant.

Table 17. Study 3101-301-002: Analyses of Secondary Efficacy Endpoints

	Placebo (N=214)	Atogepant 10 mg QD (N=214)	Atogepant 30 mg QD (N=223)	Atogepant 60 mg QD (N=222)
Change From Baseline in Mean Monthly Headache Days				
Baseline, Mean	8.43	8.41	8.78	9.00
Change from baseline, LS Mean	-2.52	-3.94	-4.04	-4.23
Atogepant versus placebo				
LSMD		-1.42	-1.53	-1.71
95% CI		-2.03, -0.81	-2.13, -0.92	-2.32, -1.10
Nominal p-value		<0.0001	<0.0001	<0.0001
Adjusted p-value		<0.0001	<0.0001	<0.0001
Change From Baseline in Mean Monthly Acute Medication Use Days				
Baseline, Mean	6.48	6.57	6.69	6.89
Change from baseline, LS Mean	-2.35	-3.66	-3.68	-3.85
Atogepant versus placebo				
LSMD		-1.31	-1.33	-1.50
95% CI		-1.81, -0.82	-1.82, -0.83	-2.00, -1.01
Nominal p-value		<0.0001	<0.0001	<0.0001
Adjusted p-value		<0.0001	<0.0001	<0.0001
≥50% Reduction in 3-Month Average of Monthly Migraine Days				
Responders, n (%)	62 (29.0)	119 (55.6)	131 (58.7)	135 (60.8)
Atogepant versus placebo				
Odds ratio		3.06	3.53	3.82
95% CI		2.05, 4.56	2.37, 5.26	2.56, 5.71
Nominal p-value		<0.0001	<0.0001	<0.0001
Adjusted p-value		<0.0001	<0.0001	<0.0001
Change From Baseline in MSQ v2.1 Role Function Restrictive Domain Score at Week 12				
Baseline, Mean	46.8	44.9	44.0	46.8
Change from baseline, LS Mean	20.45	30.35	30.53	31.25
Atogepant versus placebo				
LSMD		9.90	10.08	10.80
95% CI		5.45, 14.36	5.71, 14.46	6.42, 15.18
Nominal p-value		<0.0001	<0.0001	<0.0001
Adjusted p-value		<0.0001	<0.0001	<0.0001

	Placebo (N=214)	Atogepant 10 mg QD (N=214)	Atogepant 30 mg QD (N=223)	Atogepant 60 mg QD (N=222)
Change From Baseline in Mean Monthly Performance of Daily Activities Domain Score of the AIM-D				
Baseline, Mean	15.2	15.5	16.9	15.9
Change from baseline, LS Mean	-6.09	-7.28	-8.63	-9.41
Atogepant versus placebo				
LSMD		-1.19	-2.54	-3.32
95% CI		-2.56, 0.17	-3.91, -1.18	-4.68, -1.96
Nominal p-value		0.0856*	0.0003	<0.0001
Adjusted p-value		0.0856*	0.0005	<0.0001
Change From Baseline in Mean Monthly Physical Impairment Domain Score of the AIM-D				
Baseline, Mean	11.2	11.7	13.0	11.6
Change from baseline, LS Mean	-4.03	-5.11	-6.02	-6.49
Atogepant versus placebo				
LSMD		-1.08	-1.99	-2.46
95% CI		-2.27, 0.11	-3.18, -0.80	-3.65, -1.28
Nominal p-value		0.0743*	0.0011	<0.0001
Adjusted p-value		0.0856*	0.0021	0.0002

Source: Study 3101-301-002 CSR tables 11-1, 11-7, 11-8, 11-9, 11-10, 11-11, 11-12, confirmed by reviewer
* Not statistically or nominally significant
Abbreviations: AIM-D, Activity Impairment in Migraine Diary; CI, confidence interval; LS, least squares; LSMD, least squares mean difference; MSQ v2.1, Migraine-Specific Quality of Life Questionnaire version 2.1; N, number of patients in treatment arm; n, number of patients in specified population or group; QD, once daily

Medical Officer's Assessment: *Study 3101-301-002 demonstrated statistically significant treatment effects favoring atogepant on all primary and secondary endpoints for all doses, with the exception of the 10 mg dose of atogepant on the clinical outcome assessments, the AIM-D PDA domain score and the AIM-D PI domain score (although there was a nonsignificant numerical benefit at this dose). The effect sizes for the primary efficacy endpoint of the change from baseline in mean monthly migraine days were generally consistent with those observed in Study CGP-MD-01; the clinical meaningfulness of which has been discussed previously in this review.*

Unlike Study CGP-MD-01, there was a slight numerical dose-response relationship for all efficacy endpoints, with higher doses demonstrating greater benefit. The 1:1:1:1 allocation of patients to treatments in Study 3101-301-002 may have allowed for an increased ability to identify the apparent dose-response trend. Another factor that may have led to the more predictable estimates for the treatment effect, and thus to seeing a numerical dose response for the doses tested, was the requirement for this study that 70% of patients had to have taken a prior preventive medication, which may have led to a slight reduction in the placebo response rate in this study (-2.48) compared to Study CGP-MD-01 (-2.85). It is important to note that this study was not enriched for prior treatment failures in a manner that could support any related labeling claims. As per the recommendations for study designs described in the Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products,[1] a trial which uses an enrichment strategy of including patients who were treatment failures, nonresponders to a different drug should be randomized to the new drug or to the drug they did not respond to. This Applicant did not employ this strategy. Historical account

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

of taking a prior drug for preventive treatment of migraine does not necessarily mean nonresponse or response to that drug.

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. The Adequacy of Study CGP-MD-01 to Support an Efficacy Claim

Issue

Assess if Study CGP-MD-01, a Phase 2/3 dose-finding trial, can serve as one of the two adequate and well-controlled efficacy studies needed to support approval.

Background

A number of drugs have been approved for the preventive treatment of migraine in adults in recent years, including five drugs that act on the CGRP pathway. Following review of Study CGP-MD-01, the Applicant concluded that, although initially designed as a Phase 2/3 dose-finding study, this trial could be considered an adequate and well-controlled study that could be submitted in the current application as one of the two pivotal efficacy studies required to support the approval of atogepant for the preventive treatment of EM. This was discussed with the Division at the November 19, 2018 End of Phase 2 meeting, and the Division concurred that on face, this study appeared to have the characteristics of such a study, but that the final determination would be a matter of review.

During the new drug application (NDA) review, the Division evaluated the following specific issues with respect to the design and strength of the findings from Study CGP-MD-01:

- The trial was originally designed as a Phase 2/3 dose-finding study and not as a study intended to support marketing approval, so the clinical review team evaluated whether the trial had the characteristics needed to consider this an adequate and well-controlled trial.
- Though the trial demonstrated a statistically significant effect on the prespecified primary endpoint, the treatment effect size (placebo corrected reduction of 0.7 to 1.1 monthly migraine days) was on the lower end of what was seen with other products marketed for this indication (placebo corrected reduction of 0.7 to 2.0 monthly migraine days).
- There was an inverse numerical dose-response relationship, with the highest numerical treatment effect in the QD dose arms occurring in the lowest dose of 10 mg QD and progressively lower numerical effects in the 30 mg and 60 mg QD dose arms. The BID dosing arms had a greater numerical benefit than the QD dosing arms, but, again, the 60 mg QD arm had a smaller numerical effect size as compared to the 30 mg BID arm.
- Although all numerically favoring atogepant, the secondary endpoints (beyond the first secondary endpoint of change from baseline in mean monthly headache days) did not reach statistical significance in any arm of patients treated with daily atogepant compared to placebo. (Section 6.2.1.4)

Assessment

In order to determine whether Study CGP-MD-01 could serve as one of the two adequate and well-controlled efficacy trials to support the current application, this reviewer conducted an assessment to evaluate why the findings in this study appeared to be less robust to those of Study 3101-301-002. This assessment is described below.

The study design and many characteristics of Study CGP-MD-01 were identical to that of Study 3101-301-002, except that in Study 3101-301-002, at least 70% of patients were required to have taken at least one prior preventive treatment for migraine. Study 3101-301-002 was stratified for this factor and Study CGP-MD-01 was not. In Study CGP-MD-01, only 30% percent of patients had tried a prior preventive treatment for migraine. As stated previously, it is possible that the enrollment of a greater percentage of patients who were naïve to preventive treatments for migraine in Study CGP-MD-01 accounts for the somewhat higher placebo response in this study, thereby decreasing the ability to demonstrate statistical significance on the analyses of several secondary efficacy measures.

The Applicant conducted a post hoc analysis of Study CGP-MD-01 comparing the reduction from baseline in the number of monthly migraines over the 12-week treatment period in the subgroup of patients who had taken prior preventive treatment to those who had not (treatment-naïve). This analysis demonstrated that in patients who had previously tried a prior therapy for the preventive treatment of migraine, the effect size was greater (-1.38, -1.51, -2.17 for 10 mg, 30 mg, and 60 mg atogepant, respectively) between atogepant and placebo arms compared to treatment-naïve patients (-0.81, -1.05, -0.66 for 10 mg, 30 mg, and 60 mg atogepant, respectively). The Applicant concluded that the slightly higher placebo response rate seen in Study CGP-MD-01 (-2.85 days) as compared to that of Study 3101-301-002 (-2.48 days) may have contributed to this difference. Please see Section 16 (sensitivity analyses) for results of these analyses. In addition, Study CGP-MD-01 utilized a 2:1:2:1:2:1 randomization ratio unlike the 1:1:1:1 randomization ratio used in Study 3101-301-002, and this unequal allocation may have biased patients leading to a heightened expectation of therapeutic benefit in Study CGP-MD-01 (Hey and Kimmelman 2014).

Conclusion

The review team, including the medical officer, clinical pharmacology, and statistical reviewers, has assessed the design, results, and analysis of Study CGP-MD-01 to evaluate whether this study can be considered an adequate and well-conducted trial to support approval of this application. The team determined that although there are some limitations identified in the trial results, the data provided still support efficacy of atogepant for the preventive treatment of EM in adults. Overall, despite the presence of an inverse numerical dose response, the primary endpoint was positive for all doses, and the secondary endpoints that did not reach statistical significance demonstrated a trend in the correct direction. There was a numerically higher treatment effect in the BID dosing groups as compared to the QD dosing groups, again suggesting the presence of a higher treatment effect and biological activity at these higher exposures. In addition, the unequal allocation of treatment arms in this study and the higher percentage of treatment naive patients, may have increased the placebo response rate, making it more difficult to detect a treatment effect. Ultimately, the data were consistent with atogepant's efficacy. Therefore, the team concludes that this study can serve as an adequate and well-controlled trial in support of the efficacy of atogepant.

6.3.2. Should the Atogepant 10 mg Daily Dose Be Recommended for the General Population?

Issue

Assess if the 10 mg daily dose, in addition to the 30 mg and 60 mg daily doses, should be recommended for the general population (and not just specific populations as the Applicant proposes).

Background

The Applicant studied several doses of atogepant, including daily doses of 10 mg, 30 mg, 60 mg and twice daily doses of 30 mg and 60 mg, in Study CGP-MD-01. The Applicant only studied the three daily doses in Study 3101-301-002. The Applicant initially proposed the 10 mg QD dose be marketed only for specific populations, namely patients with kidney disease (see Pharmacology discussion, Section 8.1 for their final recommendation) and patients taking concomitant CYP3A4 inhibitors; however, it may be advantageous to include the option of a lower effective dose to the general population.

Assessment

Atogepant was effective at all doses studied in Studies CGP-MD-01 and 3101-301-002 (Section 6.2, Table 11, Table 12, Table 16, and Table 17) The primary efficacy endpoint, the change from baseline in mean monthly migraine days over the double-blind treatment period, demonstrated positive results in both trials. In Study CGP-MD-01, the 10 mg daily dose had the numerically largest treatment effect compared to other groups, with an inverse numerical dose-response relationship observed when considering all daily doses studied, although the twice daily dosing regimens did perform numerically better than the daily dosing regimens. In Study 3101-301-002, there was a slight numerical dose- response relationship for the three daily doses studied (10 mg, 30 mg, and 60 mg).

Studies CGP-MD-01 and 3101-301-002 demonstrated statistically significant results for all doses on the key secondary endpoint, change from baseline in mean monthly headache days. Study 3101-301-002 also demonstrated statistically significant results for all doses on secondary endpoints of change from baseline in acute medication use, ≥50% reduction in mean monthly migraine days, and change from baseline in the MSQ v2.1 RFR domain score. The 30 mg and 60 mg dose arm also demonstrated statistically significant results on the analysis of the change from baseline for the AIM-D PDA domain score and the AIM-D PI domain score, while the 10 mg arm did not (see Section 6.3.1).

Given the consistency of results at the 10 mg daily dose with that of the 30 mg and 60 mg daily doses, and the generally flat-dose response relationship across the range of doses investigated, there is support for approving the 10 mg dose in addition to the other doses proposed by the Applicant (30 mg and 60 mg). As discussed in Section 7.6 of this review, the safety profile for atogepant demonstrates a dose-related increase for some of the adverse reactions, such as nausea, decreased appetite, somnolence, and decreased weight.

Conclusion

The 10 mg daily dose demonstrated consistent efficacy across a range of clinically meaningful endpoints in Studies CGP-MD-01 and 3101-301-002. The lack of a statistically significant treatment effect of this dose on the AIM-D scales in Study 3101-301-002, especially in the setting of a numerical benefit, should not preclude the approval of this dose for the general population.

In considering whether to approve this lower dose, the safety profile of atogepant should also be considered. As discussed in detail in the safety sections below, there did appear to be a dose-related increase in several commonly reported adverse reactions, including nausea, decreased appetite, fatigue, and decreased weight. This supports the approval of the lowest effective dose.

The recommended doses of atogepant are 10 mg, 30 mg, and 60 mg QD for the general population.

6.3.3. Are the AIM-D and MSQ v2.1 RFR Appropriate for Inclusion in Labeling?

Issue

Evaluate if the results of the analyses of the AIM-D PDA domain score, AIM-D PI domain score, and MSQ v2.1 RFR domain score should be described in labeling.

Background

The Applicant proposes including in labeling the results of the analyses of three clinical outcome assessment (COA) measures that were included as hierarchically-controlled secondary endpoints in Study 3101-301-002. To support these claims, the Applicant submitted a COA evidence dossier for the MSQ v2.1 RFR domain and the AIM-D.

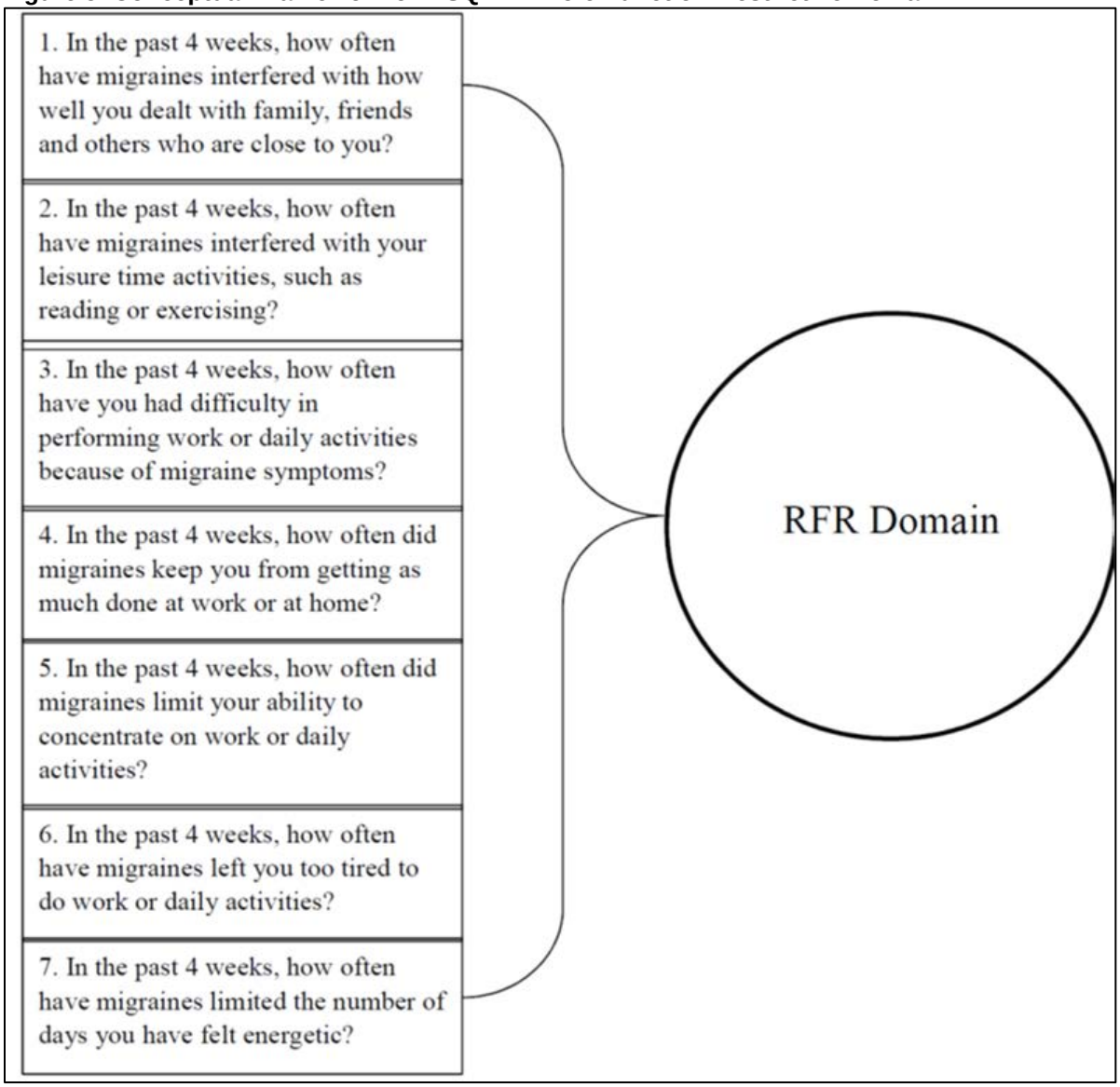
Assessment

The following COAs were prespecified as hierarchically-controlled secondary endpoints in the Study 3101-301-002.

- MSQ v2.1 RFR domain:
  - Evaluates the frequency of the impact of migraine on daily social and work activities
  - Has a 0 to 100 scale, with higher scores indicating better daily functioning (i.e., lesser impact of migraine)
- The AIM-D PDA domain
  - Assesses the difficulty in performance of daily activities due to migraine
  - Has a 0 to 100 scale, with higher scores indicating worse performance of daily activities
- AIM-D PI domain:
  - Assesses physical impairment due to migraine

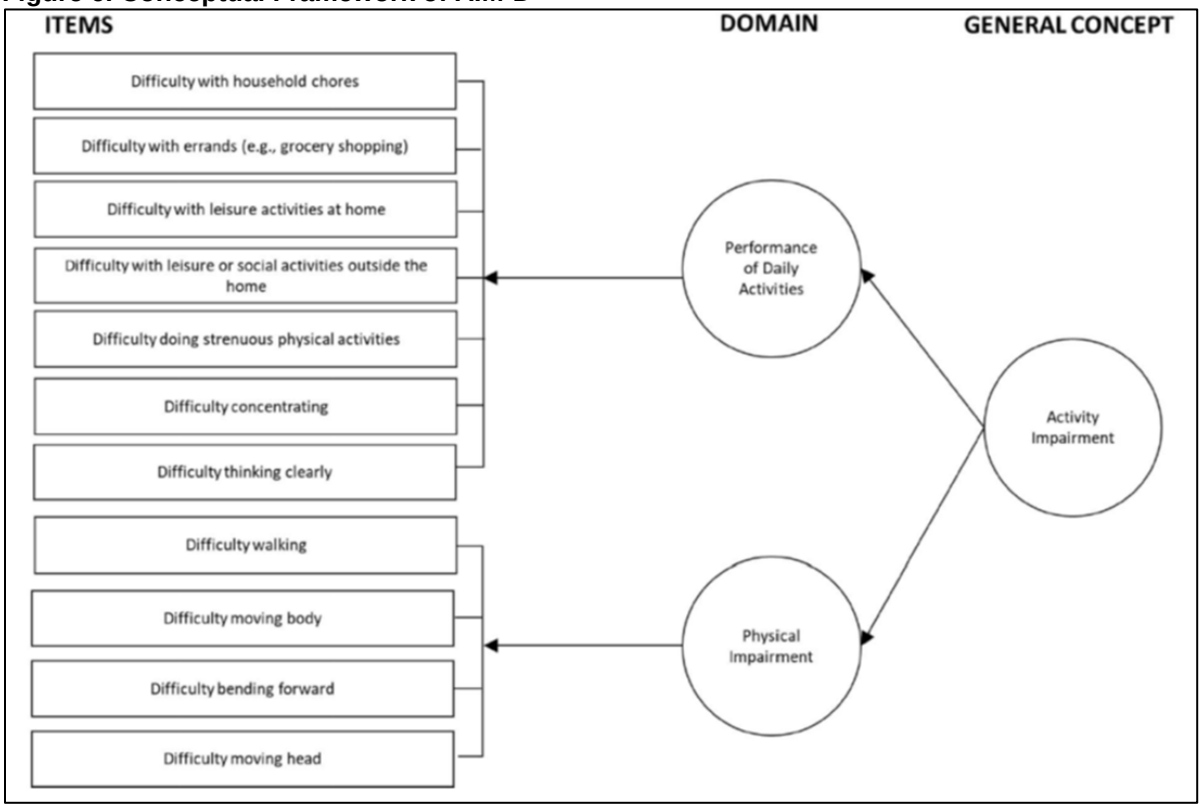
Has a 0 to 100 scale, with higher scores indicating worse physical impairment. The conceptual frameworks of these COAs are presented in the figures below (Figure 5 and Figure 6).

Figure 5. Conceptual Framework of MSQ v2.1 Role Function-Restrictive Domain



Source: PRO Evidence Dossier for MSQ v2.1, Figure 4.1
Abbreviations: MSQ v2.1, Migraine-Specific Quality of Life Questionnaire version 2.1; RFR, Role Function-Restrictive

Figure 6. Conceptual Framework of AIM-D



Source: PRO Evidence Dossier for AIM-D, Figure 5.1

Abbreviation: AIM-D, Activity Impairment in Migraine Diary

Key results for COA-related endpoints from Study 3101-301-002 are summarized below:

- MSQ v2.1 RFR domain score (4th secondary endpoint)
  - A greater improvement from baseline at Week 12 was observed for all atogepant treatment groups compared with the placebo treatment group after multiplicity adjustment ($p<0.0001$), although the endpoint was insensitive to the apparent dose response reflected in the primary and other key secondary endpoints.
- Mean monthly PDA domain score of the AIM-D (5th secondary endpoint)
  - A greater improvement from baseline across the 12-week treatment period was observed for the 30 mg and 60 mg atogepant treatment groups compared with the placebo treatment group after multiplicity adjustment ($p\leq0.0005$).
  - The numerical improvements observed with the 10 mg dose were not statistically significant compared with placebo.
- Mean monthly PI domain score of the AIM-D (6th secondary endpoint)
  - A greater improvement from baseline across the 12-week treatment period was observed for the 30 mg and 60 mg atogepant treatment groups compared with the placebo treatment group after multiplicity adjustment ($p\leq0.0021$).
  - The numerical improvements observed with the 10 mg dose were not statistically significant compared with placebo.

Table 18. Study 3101-301-002: Efficacy Results of COA Endpoints

Parameter	Placebo (N=214)	Atogepant 10 mg QD (N=214)	Atogepant 30 mg QD (N=223)	Atogepant 60 mg QD (N=222)
Secondary Endpoint 4: Change From Baseline in MSQ v2.1 Role Function Restrictive Domain Score at Week 12				
Baseline, Mean	46.8	44.9	44.0	46.8
Change from baseline, LS Mean	20.45	30.35	30.53	31.25
Atogepant versus placebo				
LSMD		9.90	10.08	10.80
95% CI		5.45, 14.36	5.71, 14.46	6.42, 15.18
Secondary Endpoint 5: Change From Baseline in Mean Monthly Performance of Daily Activities Domain Score of the AIM-D				
Baseline, Mean	15.2	15.5	16.9	15.9
Change from baseline, LS Mean	-6.09	-7.28	-8.63	-9.41
Atogepant versus placebo				
LSMD		-1.19	-2.54	-3.32
95% CI		-2.56, 0.17	-3.91, -1.18	-4.68, -1.96
Secondary Endpoint 6: Change From Baseline in Mean Monthly Physical Impairment Domain Score of the AIM-D				
Baseline, Mean	11.2	11.7	13.0	11.6
Change from baseline, LS Mean	-4.03	-5.11	-6.02	-6.49
Atogepant versus placebo				
LSMD		-1.08	-1.99	-2.46
95% CI		-2.27, 0.11	-3.18, -0.80	-3.65, -1.28

Source: Table 1. Study 3101-301-002: Analyses of Secondary Efficacy Endpoints
Abbreviations: AIM-D, Activity Impairment in Migraine Diary; CI, confidence interval; COA, clinical outcome assessment; LS, least squares; LSMD, least squares mean difference; MSQ v2.1, Migraine-Specific Quality of Life Questionnaire version 2.1; N, number of patients in treatment arm; QD, once daily

Anchor-based analyses were conducted using data from Study 3101-301-002 to derive thresholds of clinically meaningful within-patient change in COA scores. The anchor-based methods, analyses, and anchors, patient global impression of severity (PGI-S) scale and patient global impression of change (PGI-C) scale, are considered appropriate. Estimated clinically meaningful change thresholds listed below were based on one-point improvement in PGI-S scale, which have clear separations from “no change” category in PGI-S scale. Additionally, the one-point improvement thresholds are consistent with the thresholds presented in the literature, which relied on receiver operating characteristic methods to incorporate various anchors into the psychometric analysis (Speck et al. 2019). However, a one-point improvement as specified a priori by the Applicant is not always sufficient, and the interpretation of within patient change employing a two-point improvement was also considered in our interpretation of clinically meaningful improvement on the clinical efficacy endpoints.

Derived thresholds using one-point improvement in PGI-S scale:

- Improvement from baseline of at least 25.7 points in the MSQ v2.1 RFR domain
- Improvement from baseline of at least 9.0 points in the AIM-D PDA domain
- Improvement from baseline of at least 6 points in the AIM-D PI domain

Derived thresholds using two-point improvement in PGI-S scale:

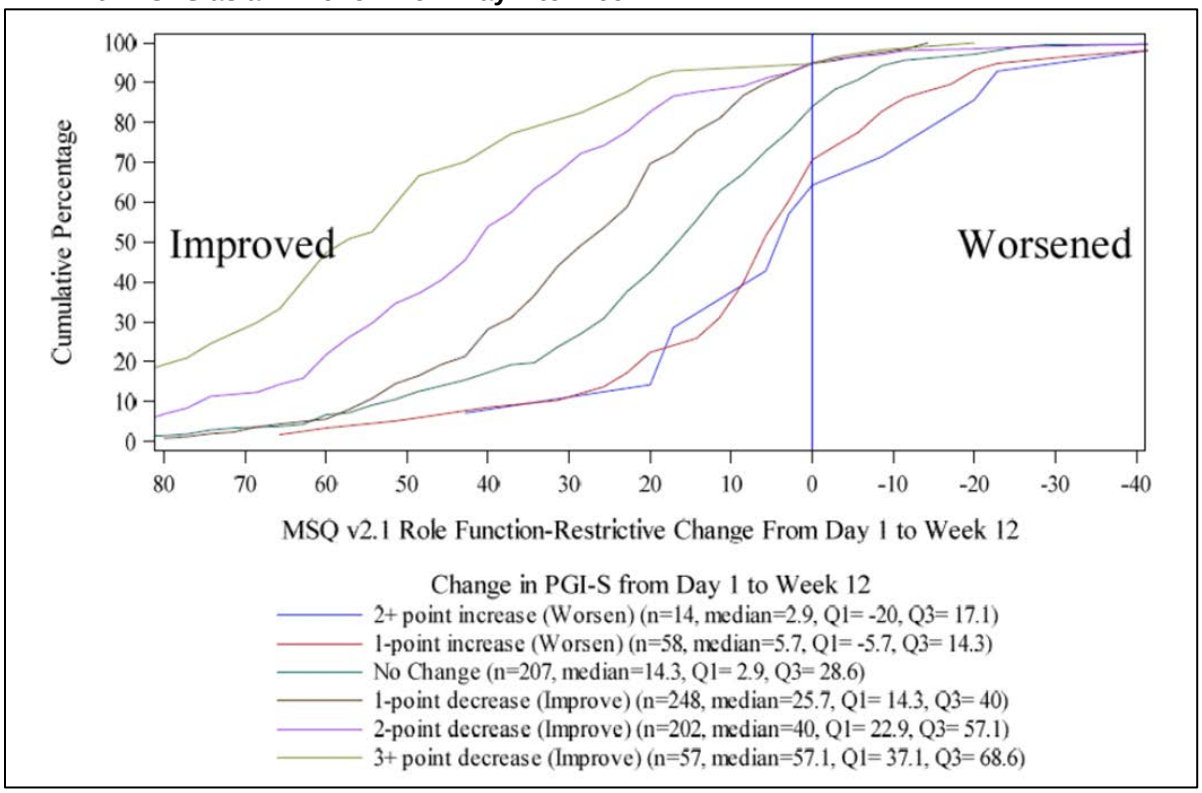
- Improvement from baseline of at least 40.0 points in the MSQ v2.1 RFR domain
- Improvement from baseline of at least 9.5 points in the AIM-D PDA domain
- Improvement from baseline of at least 6.2 points in the AIM-D PI domain

Derived thresholds using "much better" response category in PGI-C scale:

- Improvement from baseline of at least 22.9 points in the MSQ v2.1 RFR domain
- Improvement from baseline of at least 8.4 points in the AIM-D PDA domain
- Improvement from baseline of at least 5.5 points in the AIM-D PI domain

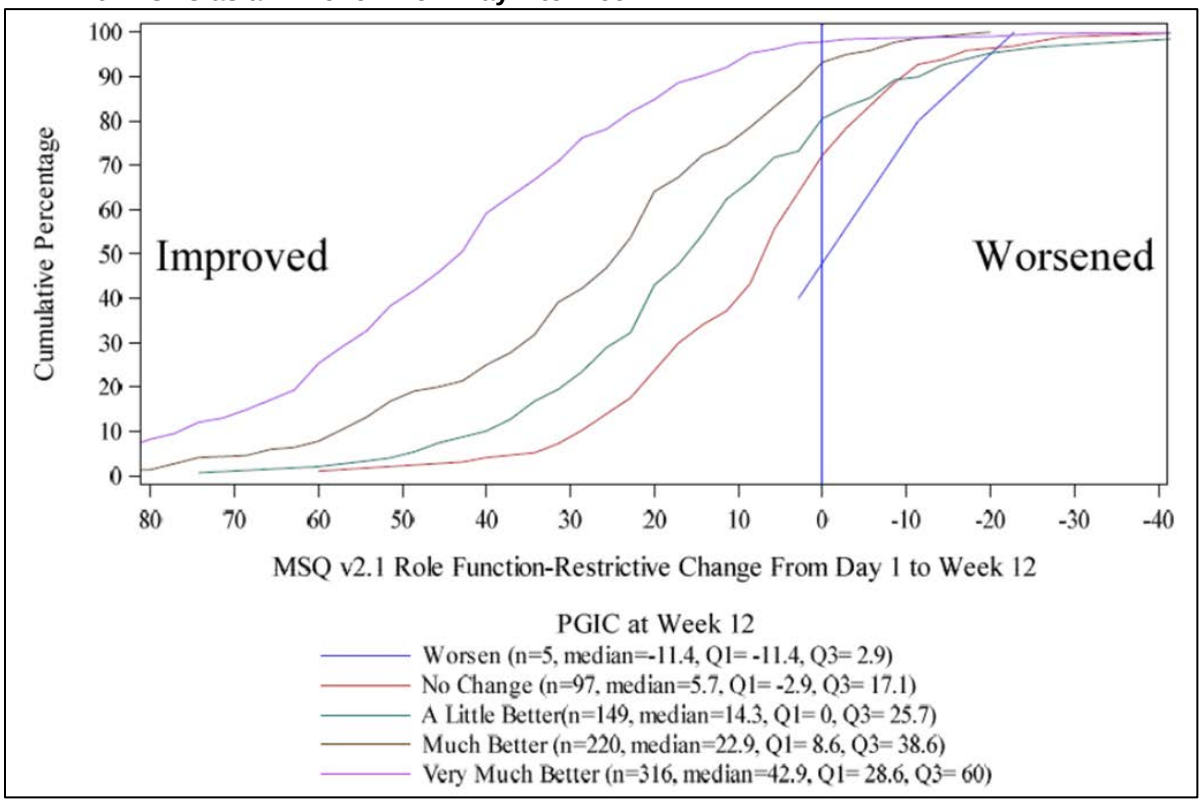
Figure 7 through Figure 12 show the empirical cumulative distribution function (eCDF) curves that the Applicant provided based on patient global scales (PGI-S and PGI-C) to derive these thresholds of clinically meaningful within-patient changes.

Figure 7. Study 3101-301-002: Empirical Cumulative Distribution Function Curves for MSQ v2.1 RFR With PGI-S as an Anchor From Day 1 to Week 12



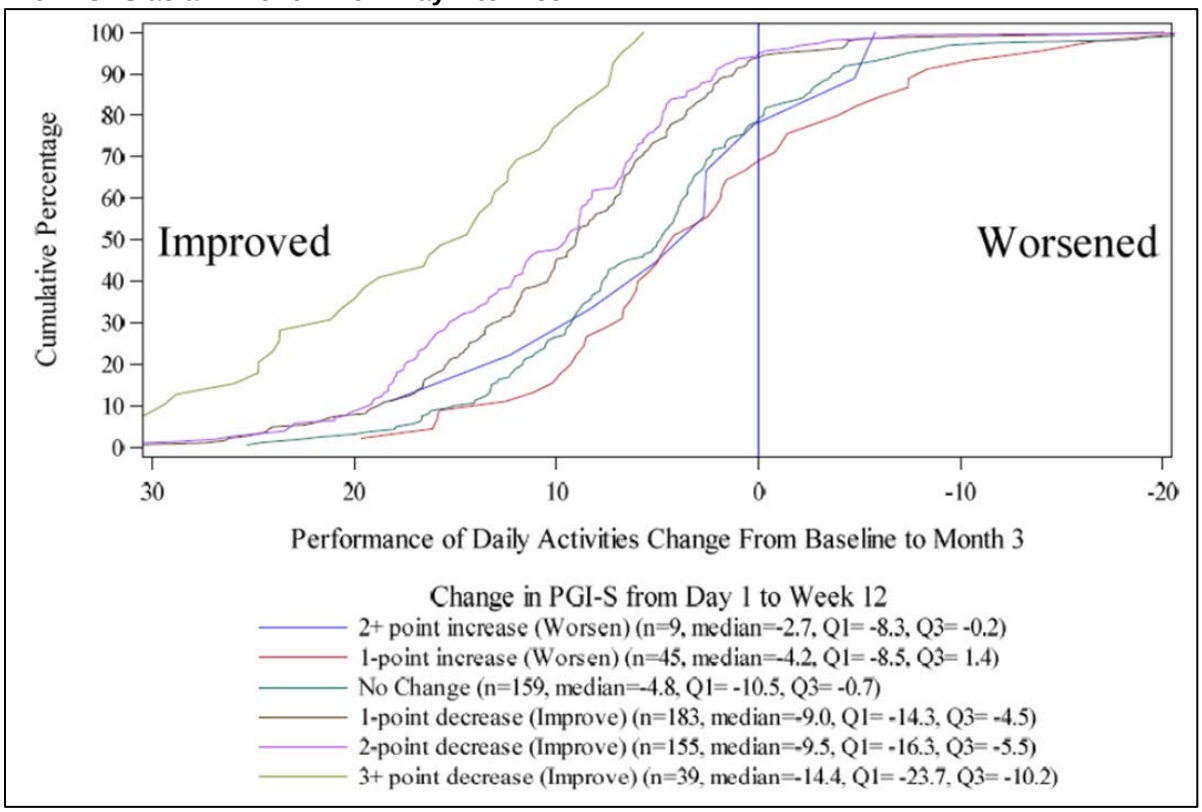
Source: PRO Evidence Dossier for MSQ v2.1, Figure 7.3, Abbreviations: PGI-S, patient global impression of severity; MSQ v2.1, Migraine-Specific Quality of Life Questionnaire version 2.1; n, number of patients in specified population or group; Q1, first quartile; Q3, third quartile; RFR, Role Function-Restrictive

Figure 8. Study 3101-301-002: Empirical Cumulative Distribution Function Curves for MSQ v2.1 RFR With PGI-C as an Anchor From Day 1 to Week 12



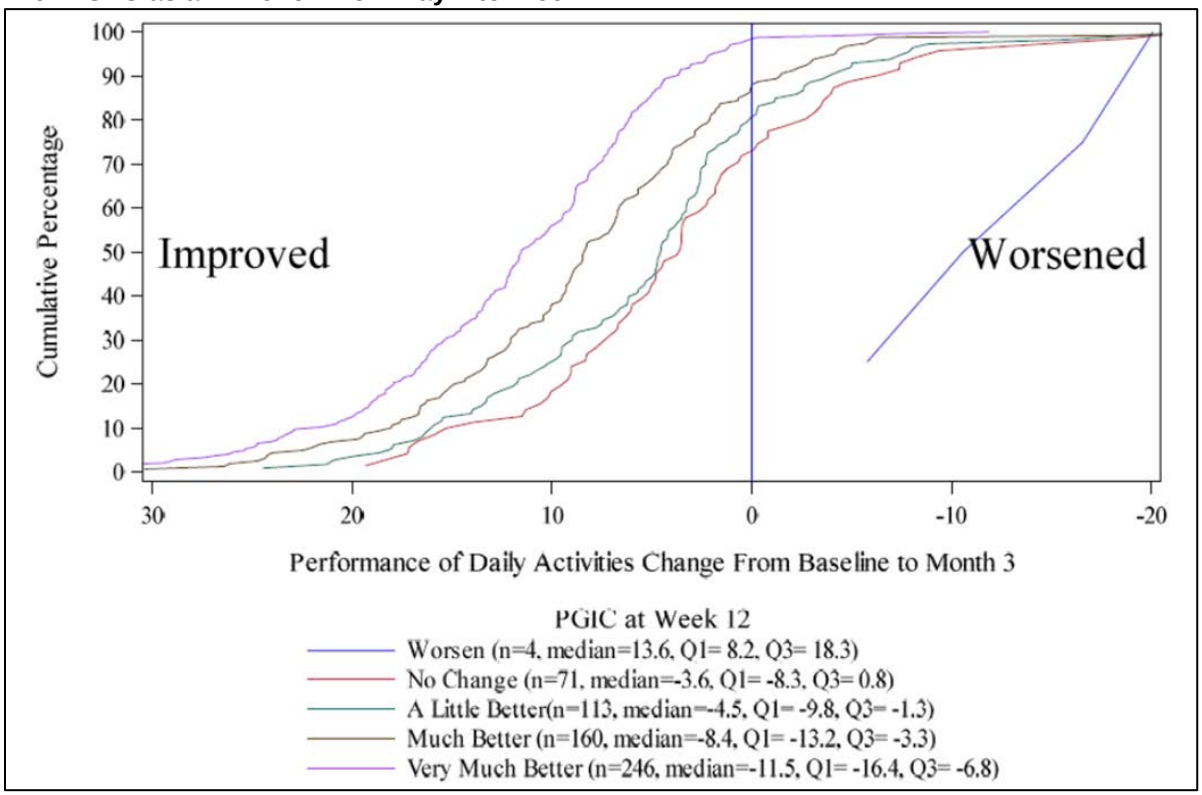
Source: PRO Evidence Dossier for MSQ v2.1,
Abbreviations: PGI-C, patient global impression of change; MSQ v2.1, Migraine-Specific Quality of Life Questionnaire version 2.1; n, number of patients in specified population or group; Q1, first quartile; Q3, third quartile; RFR, Role Function-Restrictive

Figure 9. Study 3101-301-002: Empirical Cumulative Distribution Function Curves for AIM-D PDA With PGI-S as an Anchor From Day 1 to Week 12



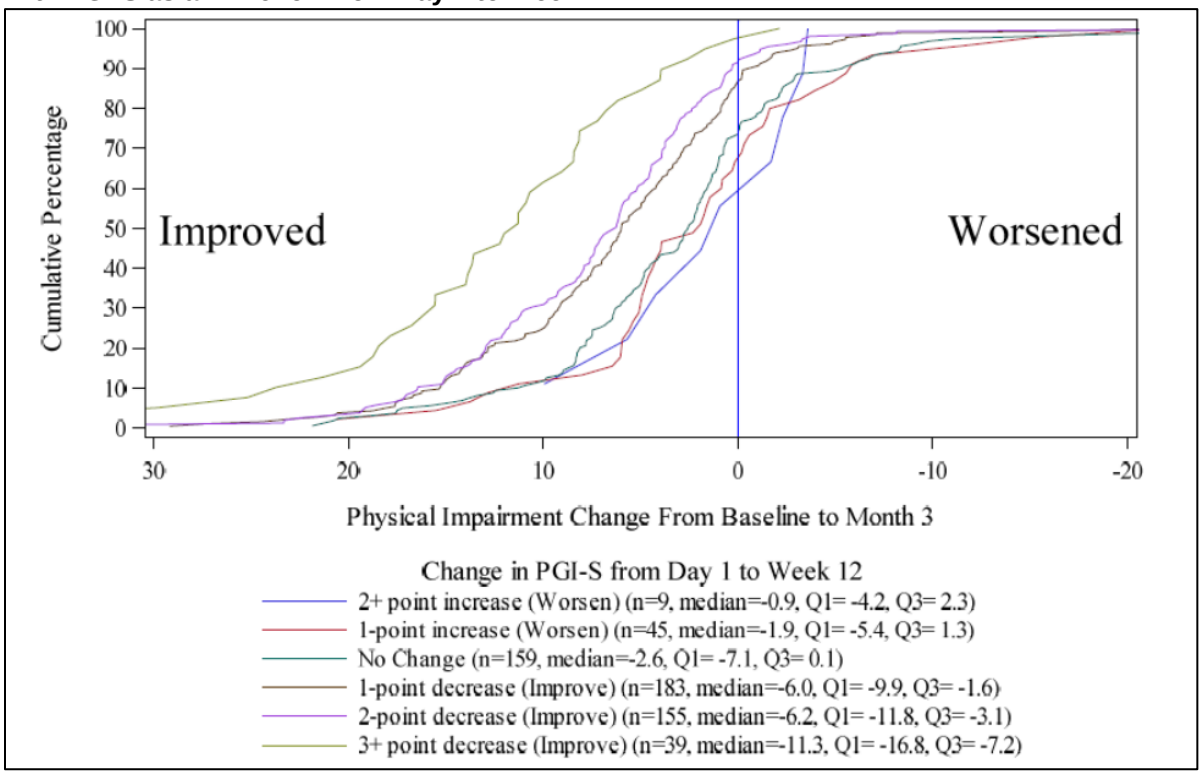
Source: PRO Evidence Dossier for AIM-D, Figure 8.2,
Abbreviations: AIM-D, Activity Impairment in Migraine Diary; n, number of patients in specified population or group; PDA, Performance of Daily Activity; PGI-S, patient global impression of severity; Q1, first quartile; Q3, third quartile

Figure 10. Study 3101-301-002: Empirical Cumulative Distribution Function Curves for AIM-D PDA With PGI-C as an Anchor From Day 1 to Week 12



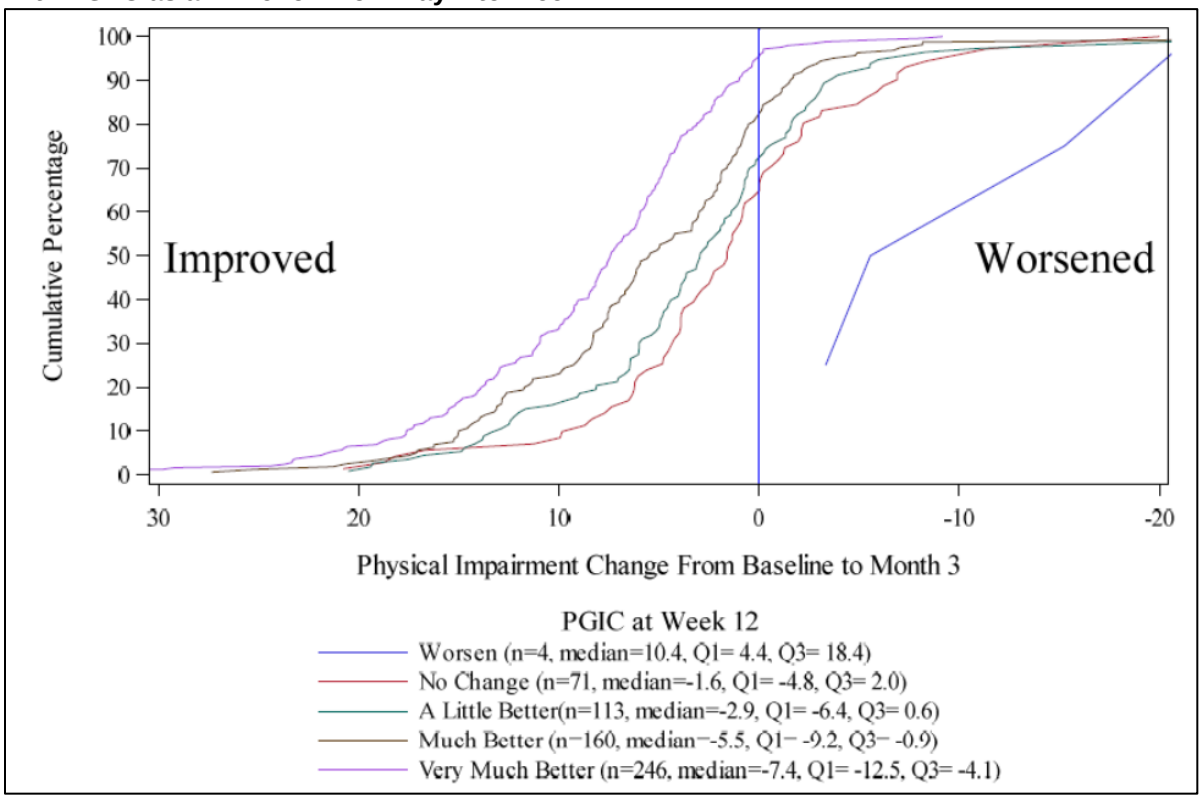
Source: PRO Evidence Dossier for AIM-D, Figure 8.10,
Abbreviations: AIM-D, Activity Impairment in Migraine Diary; n, number of patients in specified population or group; PDA, Performance of Daily Activity; PGI-C, patient global impression of change; Q1, first quartile; Q3, third quartile

Figure 11. Study 3101-301-002: Empirical Cumulative Distribution Function Curves for AIM-D PI With PGI-S as an Anchor From Day 1 to Week 12



Source: PRO Evidence Dossier for AIM-D, Figure 8.4,
Abbreviations: AIM-D, Activity Impairment in Migraine Diary; n, number of patients in specified population or group; PGI-S, patient global impression of severity; PI, Physical Impairment; Q1, first quartile; Q3, third quartile

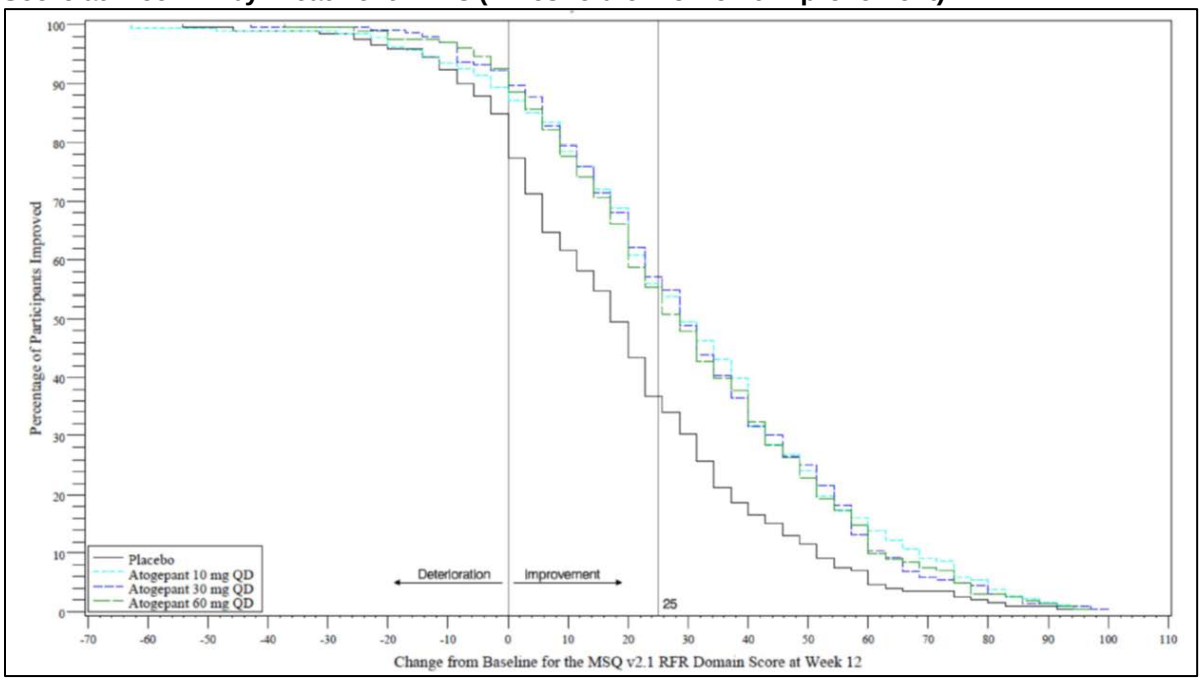
Figure 12. Study 3101-301-002: Empirical Cumulative Distribution Function Curves for AIM-D PI With PGI-C as an Anchor From Day 1 to Week 12



Source: PRO Evidence Dossier for AIM-D, Figure 8.12,
Abbreviations: AIM-D, Activity Impairment in Migraine Diary; n, number of patients in specified population or group; PGI-C, patient global impression of change; PI, Physical Impairment; Q1, first quartile; Q3, third quartile

To evaluate whether the results of COA endpoints are clinically meaningful, the eCDF curves by treatment arms in Study 3101-301-002 were examined. The eCDF curves by treatment arms below showed a clear separation between all three treatment arms and placebo arm in MSQ v2.1 RFR domain across the range of clinically meaningful thresholds derived from the anchor-based analyses. There was however a considerable overlap among the treatment arms indicating that the MSQ v2.1was insensitive to the apparent dose response reflected in the primary and other key secondary endpoints (Figure 13). Table 19 shows the proportion of participants with at least a 25-point improvement from baseline in MSQ v2.1 RFR domain score at Week 12.

Figure 13. Cumulative Distribution Function of Change From Baseline for MSQ v2.1 RFR Domain Score at Week 12 by Treatment Arms (Threshold of 25-Point Improvement)



Source: Responder Analyses for MSQ v2.1 RFR, and AIM-D PDA and PI Domains, Figure 1.
Abbreviations: MSQ v2.1, Migraine-Specific Quality of Life Questionnaire version 2.1; QD, once daily; RFR, Role Function-Restrictive

Table 19. Proportion of Participants With at Least a 25-Point Improvement From Baseline in MSQ v2.1 RFR Domain Score at Week 12

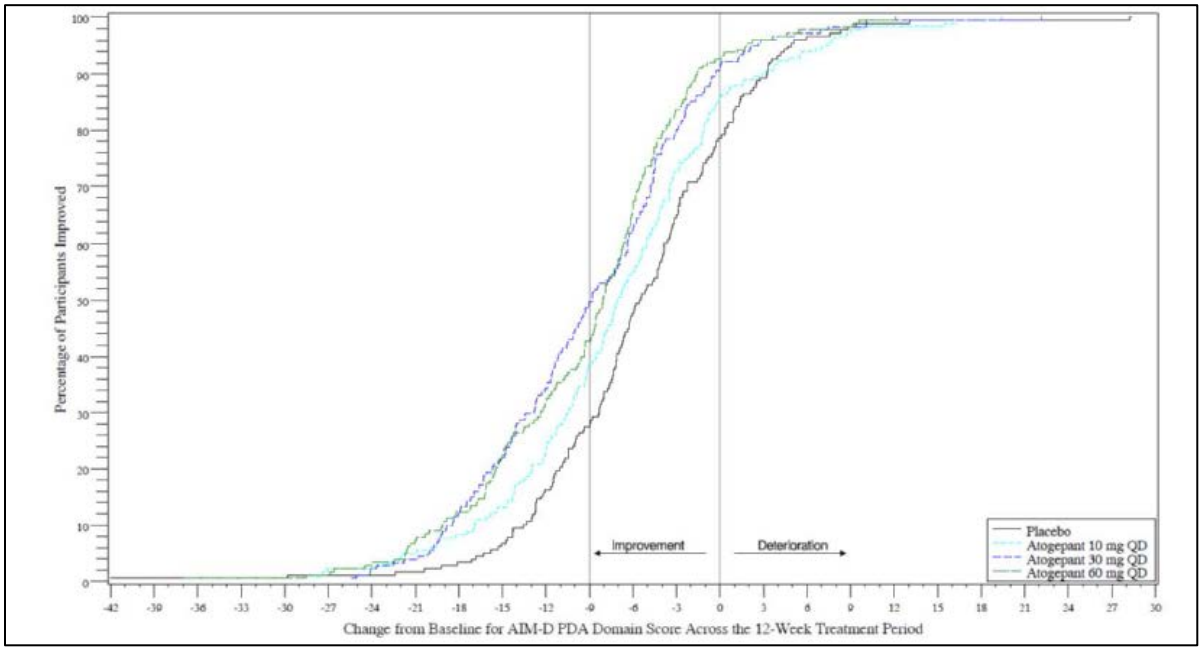
Statistics	Placebo (N = 214)	Atogepant 10 mg QD (N = 214)	Atogepant 30 mg QD (N = 223)	Atogepant 60 mg QD (N = 222)
Responders, n/N1(%)	73/198 (36.9)	104/186 (55.9)	116/203 (57.1)	111/201 (55.2)
Non-responders, n/N1(%)	125/198 (63.1)	82/186 (44.1)	87/203 (42.9)	90/201 (44.8)
Odds Ratio vs. Placebo [1]		2.11	2.23	2.22
95% CI		(1.38, 3.24)	(1.47, 3.39)	(1.46, 3.38)
p-value		0.0006	0.0002	0.0002

Source:: Responder Analyses for MSQ v2.1 RFR Domain, and AIM-D PDA and PI Domains, Table 1.
[1] Analyses are based on generalized linear mixed model for repeated measures. The model includes baseline as a covariate, prior exposure to migraine prevention medications (yes/no), treatment group, and visit as fixed factors, and treatment group-by-visit and baseline-by-visit as interaction terms. Participants are included as random effects with unstructured covariance matrix in the model. P-values are from the test between the atogepant dose group and placebo.
Abbreviations: CI, confidence interval; MSQ v2.1, Migraine-Specific Quality of Life Questionnaire version 2.1; QD, once daily; n, number of participants in a specific category; N, number of participants in study arm; N1, number of participants available for analysis at a specific time point in the completers population; RFR, Role Function-Restrictive; QD, once daily

The eCDF curves by treatment arm below show that there is a modest separation between the 30 mg and 60 mg treatment arms and placebo arm and a small separation between the 10 mg treatment arm and placebo arm in both AIM-D domains across the range of clinically meaningful thresholds derived from the anchor-based analyses (Figure 14 and Figure 15). Table 20 shows the proportion of participants with at least a 9-point improvement from baseline in AIM-D PDA

domain score across the 12-week treatment period. Table 21 shows proportion of participants with a least a 6-point improvement from baseline in AIM-D PI domain score across the 12-week treatment period.

Figure 14. Cumulative Distribution Function of Change From Baseline for AIM-D PDA Domain Score Across the 12-Week Treatment Period



Source:: Responder Analyses for MSQ v2.1 RFR Domain, and AIM-D PDA and PI Domains, Figure 2.

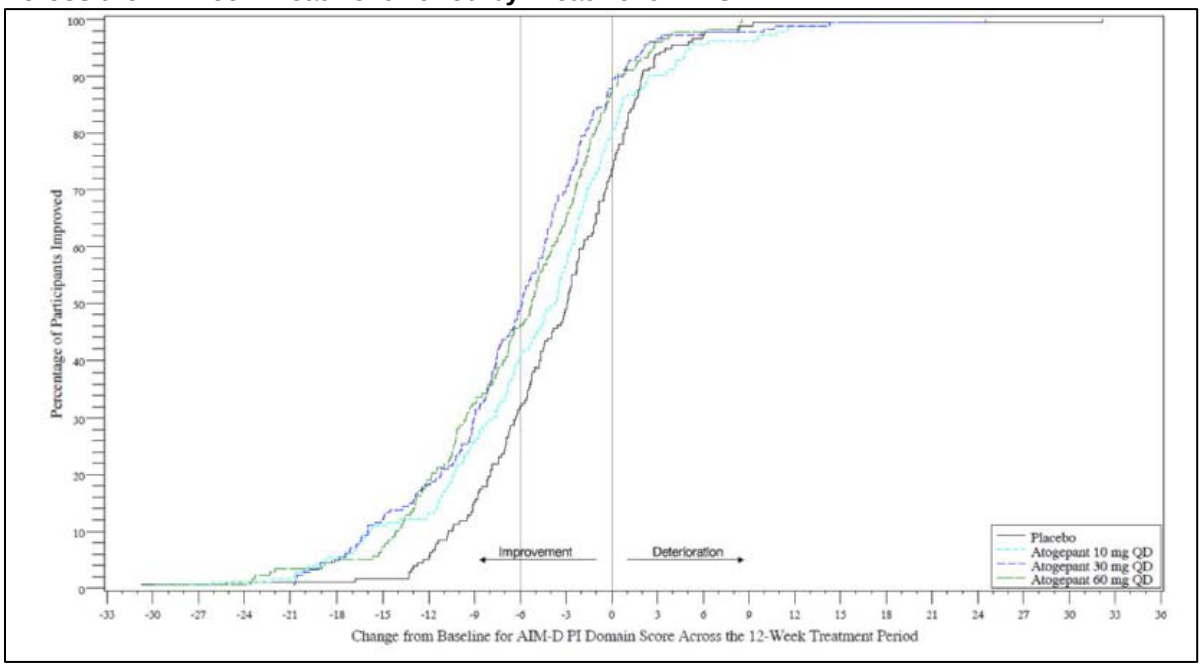
Abbreviations: AIM-D, Activity Impairment in Migraine Diary; PDA, Performance of Daily Activities; QD, once daily

Table 20. Proportion of Participants With at Least a 9-Point Improvement From Baseline in AIM-D PDA Domain Score Across 12-Week Treatment Period

Statistics	Placebo (N = 214)	Atogepant 10 mg QD (N = 214)	Atogepant 30 mg QD (N = 223)	Atogepant 60 mg QD (N = 222)
Responders, n/N1(%)	49/178 (27.5)	70/182 (38.5)	90/181 (49.7)	76/178 (42.7)
Non-responders, n/N1(%)	129/178 (72.5)	112/182 (61.5)	91/181 (50.3)	102/178 (57.3)
Odds Ratio vs. Placebo [1]		1.71	2.45	2.05
95% CI		(1.02, 2.85)	(1.48, 4.06)	(1.23, 3.42)
p-value		0.0421	0.0005	0.0062

Source: Responder Analyses for MSQ v2.1 RFR Domain, and AIM-D PDA and PI Domains, Table 2.
[1] Odds ratio (95% CI) and p-value are based on logistic regression with treatment group, baseline value, and prior exposure (yes/no) to migraine prevention medication with proven efficacy as explanatory variables.
Abbreviations: AIM-D, Activity Impairment in Migraine Diary; CI, confidence interval; n, number of participants in a specific category; N, number of participants in study arm; N1, number of participants available for analysis at a specific time point in the modified intent-to-treat population; PDA, Performance of Daily Activities; QD, once daily

Figure 15. Cumulative Distribution Function of Change From Baseline for AIM-D PI Domain Score Across the 12-Week Treatment Period by Treatment Arms



Source: Responder Analyses for MSQ v2.1 RFR Domain, and AIM-D PDA and PI Domains, Figure 3.
Abbreviations: AIM-D, Activity Impairment in Migraine Diary; PI, Physical Impairment; QD, once daily

Table 21. Proportion of Participants With at Least a 6-Point Improvement From Baseline in AIM-D PI Domain Score Across 12-Week Treatment Period

Statistics	Placebo (N = 214)	Atogepant 10 mg QD (N = 214)	Atogepant 30 mg QD (N = 223)	Atogepant 60 mg QD (N = 222)
Responders, n/N1(%)	57/178 (32.0)	74/182 (40.7)	89/181 (49.2)	82/178 (46.1)
Non-responders, n/N1(%)	121/178 (68.0)	108/182 (59.3)	92/181 (50.8)	96/178 (53.9)
Odds Ratio vs. Placebo [1]		1.39	1.81	1.90
95% CI		(0.85, 2.30)	(1.11, 2.95)	(1.16, 3.11)
p-value		0.1909	0.0176	0.0110

Source:Responder Analyses for MSQ v2.1 RFR Domain, and AIM-D PDA and PI Domains, Table 3.
[1] Odds ratio (95% CI) and p-value are based on logistic regression with treatment group, baseline value, and prior exposure (yes/no) to migraine prevention medication with proven efficacy as explanatory variables.
Abbreviations: AIM-D, Activity Impairment in Migraine Diary; CI, confidence interval; n, number of participants in a specific category; N, number of participants in study arm; N1, number of participants available for analysis at a specific time point in the modified intent-to-treat population; PI, Physical Impairment; QD, once daily

Conclusion

The MSQ v2.1 RFR domain, AIM-D PDA domain, and AIM-D PI domain measures appear fit-for-purpose in this context of use, and the corresponding clinical efficacy endpoints are defined appropriately and positioned as alpha-controlled endpoints in the endpoint model. Therefore, these measures can be described in labeling. For future drug development, we recommend that Applicants focus on measuring the most relevant and important concepts to patients rather than a broad, disease-specific, health-related quality of life measurement. With

that respect, the AIM-D domains are more consistent, interpretable, and sensitive to the apparent dose-response relationship reflected in the primary and other key secondary endpoints (see Table 17).

The results of the COA measures based on the above three clinical efficacy endpoints have been confirmed by the FDA Statistical Reviewer. The anchor-based analysis results of the COA endpoints showed the following:

- There is a clear separation between all three treatment arms and placebo arm in MSQ v2.1 RFR domain across the range of clinically meaningful thresholds, suggesting that all three treatment arms had clinically meaningful within-patient improvements in the impact of migraine on daily social and work activities, as assessed by the MSQ v2.1 RFR domain score.
- There is a more complex pattern of results in the anchor-based analysis of the AIM-D endpoints.
  - There is a modest separation between the 30 mg and 60 mg treatment arms and the placebo arm in both AIM-D PDA and PI domains across the range of clinically meaningful thresholds, suggesting that both 30 mg and 60 mg treatment arms had clinically meaningful within-patient improvement in performance of daily activities due to migraine and reduction in physical impairment due to migraine.
  - There is a small separation between the 10 mg treatment arm and the placebo arm in both AIM-D PAD and PI domains within the range of clinically meaningful thresholds, suggesting that the 10 mg treatment arm improves performance of daily activities due to migraine, as assessed by the AIM-D PDA, and reduces physical impairment due to migraine, as assessed by the PI domain scores, but minimally.
  - Overall, there is a clear dose-response relationship observable in the change from baseline results for the AIM-D domains, which is consistent with other clinical efficacy endpoints (e.g., headache days and acute medication use).
- Given the conceptual overlap between the MSQ v2.1 and the AIM-D, consideration should be given in the label to avoid overweighting the apparent treatment benefit. For example, listing overlapping items twice in the label to document the two COA measures or presenting multiple p-values that document a common inference may be misleading.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

A complete nonclinical package was submitted to the NDA, which included general toxicology studies of up to 6 and 9 months' duration in rat and monkey, respectively; a standard battery of genetic toxicology assays (Ames, in vitro clastogenicity in CHO cells, and in vivo rat micronucleus); 2-year carcinogenicity studies in mouse and rat; and reproductive and development studies (fertility and early embryonic, embryofetal development, and pre- and postnatal development studies in rat; embryofetal development study in rabbit).

Dosing in the pivotal general toxicology studies was based on decreases in body weight gain in rats and emesis in monkeys in the nonpivotal studies. No target organ toxicity was identified in the general toxicology studies.

Atogepant was negative in Organisation for Economic Cooperation and Development-compliant Ames, *in vitro* chromosomal aberration, and rat bone marrow micronucleus assays. Atogepant was not carcinogenic in 2-year mouse and rat studies.

The following safety concerns were identified:

(1) In the 2-year carcinogenicity study conducted in male and female mice, females were not adequately evaluated because none of the criteria for an adequate high dose (HD) was met.

(2) In animal studies, oral administration of atogepant during organogenesis resulted in embryolethality, adverse effects on embryofetal development (decreased fetal body weight in rats, increased incidences of fetal variations in rats and rabbits) at maternal exposures greater those used clinically.

The nonclinical data support approval of atogepant. However, to address the concerns regarding the assessment of carcinogenic potential, the sponsor will need to conduct a dose range-finding study to determine if the HD in the 2-year carcinogenicity study in female mice was adequate (e.g., a maximum tolerated dose or maximum feasible dose). If the HD is determined not to be adequate, the carcinogenicity study will need to be repeated in female mice with an adequate HD. These may be conducted as postmarketing requirements.

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

The following potential risks based on drug class or other drug-specific factors have been identified for evaluation in this review:

- Several oral CGRP receptor antagonists that are no longer in development caused serious cases of drug-induced liver injury (DILI). Modifications were made to drugs developed in this class, resulting in the development of products, such as atogepant, that are not expected to be associated with this safety finding (such findings have not been associated with either ubrogepant or rimegepant, to date). However, given the history of DILI in previously developed oral CGRP antagonists, liver injury was analyzed as a safety signal of interest in this review (see Section 7.7.1).
- Since CGRP is thought to play a role in compensatory vasodilatation in the setting of ischemia, there is a theoretical concern that CGRP inhibition may increase the risk of cardiovascular and cerebrovascular events. Although an increased risk of such events has not been identified as a safety signal in the other marketed products in this class, this risk is evaluated as a safety signal of interest in this review (see Section 7.7.2).
- Due to the diffuse presence of CGRP receptors in the gastrointestinal system, and the labeled Warning for constipation with erenumab, the effects on this system, including the risk of constipation, were assessed as a safety area of interest in this review (see Section 7.7.3).

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Not applicable.

7.4. FDA Approach to the Safety Review

The safety review focuses on the safety of atogepant for the preventive treatment of EM in adults. The data sources include the results from Studies CGP-MD-01, 3101-301-002, 3101-302-002, and 3101-309-002 (refer to Table 3). The safety population is defined as any patient who received one or more doses of atogepant in any of these studies. The cut-off date for the original submission was May 25, 2020. The Applicant provides safety data in the Integrated Summary of Safety (ISS) based on the following groups:

- Group 1: Controlled clinical efficacy studies (CGP-MD-01 and 3101-301-002) involving several doses of atogepant (10 mg, 30 mg, 60 mg, 30 mg BID, and 60 mg BID) or placebo (Section 6.2)
- Group 2: Open-label long-term safety studies (3101-302-002 and 3101-309-002) with atogepant 60 mg or standard of care (SoC) (Section 7.6)
- Group 3: Group 1 and Group 2 pooled

In this review, summaries of the Applicant's findings with confirmatory analyses conducted by the Clinical Data Scientist, Dr. Anne Bunner, will be presented. AE tables in this review refer to treatment-emergent adverse events (TEAEs) by "actual dose" treatment group (the dose the patient received). Tables are either reproduced from the Applicant's submission (where noted) or created by Dr. Bunner.

All placebo-controlled data will be included in tables and figures, and data from the long-term safety studies will be included, only when indicated. All doses (including the 30 mg BID and 60 mg BID doses) will be examined to provide the most complete information regarding evidence of dose-related AEs. When discussing ISS Group 2, only the 60 mg dose was evaluated, since this is the highest dose proposed for marketing and the only dose studied in the long-term safety studies.

A 120-Day Safety Update Report was submitted on May 19, 2021 (which included a cut-off date of November 13, 2020). The report includes an additional 30 patients who were exposed to atogepant 60 mg daily and additional long-term exposure data for patients enrolled in extension Study 3101-309-002.

The 120-Day Safety Update also included safety information from four additional ongoing studies regarding patients with elevated LFTs (per the Division's request for an analysis of postbaseline aminotransferase elevations in ongoing studies at the September 22, 2020 preNDA meeting). The ongoing studies include Study 3101-303-002 (a double-blind, randomized, placebo-controlled trial of atogepant for the preventive treatment of CM), Study 3101-306-002 (the long-term extension study for 3101-303-002), and two clinical pharmacology studies. These studies are not reviewed here; however, the pertinent hepatic safety data from these studies is presented as part of Section 7.7.1.

7.5. Adequacy of Clinical Safety Database

Data sources to support the proposed indication are summarized in Table 3. Of note, the doses in Table 22 below, which summarizes the duration of exposure in all patients (ISS Group 3), represent the first assigned dose (during the placebo-controlled trial) and the second assigned dose (during the open-label study, for those patients who rolled over from the pivotal trials). Patients with only the 60 mg QD dose listed were de novo patients enrolled in the long-term safety study (i.e., had not previously received atogepant). Importantly, there could be a gap of 6 months up to 2 years from the time of the completion of the placebo-controlled study to enrollment in the long-term safety study (Study 3101-302-002), due to a delay in its initiation.

Table 22. ISS Group 3: Duration of Exposure, Safety Population (Includes Pivotal and Long-Term Safety Studies With 1st Assigned Dose/2nd Assigned Dose)[1]

Variable	PBO/ATG 60 mg QD N=161	ATG 10/60 mg QD N=221	ATG 30/60 mg QD N=228	ATG 60 mg QD N=695	PBO/SoC N=229
Duration of exposure, weeks					
Mean (SD)	22 (13.8)	18.5 (13.6)	19.9 (13)	34.2 (19.4)	33.5 (22.2)
Median	20	12.7	16	40.3	37.7
(Q1, Q3)	(9, 36)	(7.9, 31.9)	(9, 31.9)	(12.4, 52)	(12.1, 55.9)
Minimum, maximum	0.3, 41.4	0.1, 41	0.1, 42.1	0.1, 54.9	0.1, 58
Total exposure (person years)	68	77	83	451	142
Patients treated, by duration, n (%)					
<12 weeks	45 (28.0)	80 (36.2)	62 (27.2)	140 (20.1)	51 (22.3)
≥12 to <24 weeks	42 (26.1)	64 (29.0)	79 (34.6)	96 (13.8)	43 (18.8)
≥24 to <48 weeks	74 (46.0)	73 (33.0)	76 (33.3)	134 (19.3)	20 (8.7)
≥48 weeks	0	0	0	319 (45.9)	107 (46.7)

Source: adex.xpt; Software: R
[1] This data are as off the cut-off date of the initial NDA submission.
Abbreviations: ATG, atogepant; ISS, Integrated Summary of Safety; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; PBO, placebo; Q1, first quartile; Q3, third quartile; QD, once daily; SD, standard deviation; SoC, standard of care

Exposure information from the two pivotal placebo-controlled trials (ISS Group 1) are shown below.

Table 23. ISS Group 1: Duration of Exposure, Safety Population

Variable	ATG 10 mg QD N=314	ATG 30 mg QD N=411	ATG 60 mg QD N=417	ATG 30 mg BID N=86	ATG 60 mg BID N=91	Total ATG N=1,319	Placebo N=408
Duration of exposure, weeks							
Mean (SD)	11.2 (2.9)	11.2 (2.7)	11.2 (2.9)	10.3 (4.1)	10.7 (3.4)	11.1 (3)	11.1 (3)
Median	12.1	12.1	12.1	12.1	12.1	12.1	12.1
(Q1, Q3)	(12, 12.3)	(12, 12.3)	(12, 12.3)	(11.9, 12.1)	(11.9, 12.1)	(12, 12.3)	(12, 12.3)
Minimum, maximum	0.1, 15	0.1, 15.1	0.1, 15.7	0.1, 13.7	0.1, 13.1	0.1, 15.7	0.1, 15.9
Total exposure (person years)	67	88	90	17	19	281	87

Variable	ATG 10 mg QD N=314	ATG 30 mg QD N=411	ATG 60 mg QD N=417	ATG 30 mg BID N=86	ATG 60 mg BID N=91	Total ATG N=1,319	Placebo N=408
Patients treated, by duration, n (%)							
<6 weeks	28 (8.9)	29 (7.1)	34 (8.2)	15 (17.4)	11 (12.1)	117 (8.9)	33 (8.1)
≥6 to <12 weeks	40 (12.7)	61 (14.8)	52 (12.5)	8 (9.3)	14 (15.4)	175 (13.3)	45 (11.0)
≥12 to <13 weeks	229 (72.9)	307 (74.7)	321 (77.0)	62 (72.1)	64 (70.3)	983 (74.5)	317 (77.7)
≥13 weeks	17 (5.4)	14 (3.4)	10 (2.4)	1 (1.2)	2 (2.2)	44 (3.3)	13 (3.2)

Source: adsl.xpt; Software: R
Abbreviations: BID, twice daily; ISS, Integrated Summary of Safety; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation; Q1, first quartile; Q3, third quartile; QD, once daily

At the time of the cutoff date for the original application, Studies CGP-MD-01, 3101-301-002 and 3101-302-002 were complete. Only Study 3101-309-002 was still ongoing, and the Applicant submitted a 120-Day Safety Update on May 19, 2021, to provide updated safety analyses. Per this safety update, as of November 13, 2020, 2,479 unique participants were exposed to at least one dose of atogepant during the clinical development program; 997 of these participants received atogepant for ≥6 months (715 at the 60 mg once-daily dose) and 670 received atogepant for ≥12 months (469 at the 60 mg once-daily dose). The updated overall mean treatment duration in the long-term safety studies was 278.9 days in the standard of care group and 253.9 days in the atogepant 60 mg once daily group.

Including the 120-Day Safety Update Report, the following table (provided by the Applicant and confirmed by the reviewer) summarizes the total number of patients exposed to atogepant.

Table 24. Treatment Duration Across All Pivotal and Open-Label Studies

	Unique Participants[1]		Exposure to Atogepant CGP-MD-01 Completers Counted Independently[2]	
Treatment Duration	**Atogepant 60 mg QD**	**Atogepant Overall**	**Atogepant 60 mg QD**	**Atogepant Overall**
≥1 dose of atogepant in any clinical study, n	1,417	2,479	1,438	2,544
Treatment for ≥6 months, n	715	997	715	997
Treatment for ≥12 months, n	469	670	469	670

Source: Applicant materials submitted May 19, 2021: Module 5.3.5.3, 120-Day update Table 2-1.2.1 and Table 2-1.2.1.A
Atogepant clinical database: CGP-MD-01, 3101-301-002, 3101-302-002, 3101-309-002, CGP-PK-01, CGP-PK-02, CGP-PK-03, CGP-PK-04, CGP-PK-06, CGP-PK-12, CGP-PK-13, 3101-101-002, 3101-102-002, 3101-103-002, MK-8031-001, MK-8031-002, MK-8031-003, MK-8031-004, MK-8031-005, MK-8031-008, and 3101-105-002.
[1] Study CGP-MD-01 Completers enrolled into Study 3101-302-002 were counted once based on the maximum duration of exposure to atogepant in either of the 2 studies (CGP-MD-01 and 3101-302-002).
[2] Study CGP-MD-01 Completers enrolled into Study 3101-302-002 were counted as independent participants (due to the large gap between the 2 studies (~6 months to 2 years).
Abbreviations: n, number of subjects with given treatment duration; QD, once daily

The safety database is adequate to allow for a comprehensive safety assessment of atogepant for the proposed indication, patient population, dosage regimen, and duration of therapy. The overall exposure to atogepant exceeds the minimum number of patients recommended by the International Council for Harmonisation E1 Guideline for chronically administered medication.

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

7.6.1. Overall Disposition

The disposition and reasons for discontinuation of patients in the placebo-controlled trials (ISS Group 1) are shown below, followed by the disposition and reasons for discontinuation of patients in the long-term safety studies (ISS Group 2).

Table 25. ISS Group 1: Patient Disposition

Disposition Outcome, n (%)	ATG 10 mg QD N=314	ATG 30 mg QD N=411	ATG 60 mg QD N=417	ATG 30 mg BID N=86	ATG 60 mg BID N=91	Total ATG N=1,319	Placebo N=408
Safety population	314 (100.0)	411 (100.0)	417 (100.0)	86 (100.0)	91 (100.0)	1,319 (100.0)	408 (100.0)
Discontinued study	47 (15.0)	64 (15.6)	58 (13.9)	17 (19.8)	23 (25.3)	209 (15.8)	68 (16.7)
Adverse event	13 (4.1)	15 (3.6)	12 (2.9)	5 (5.8)	7 (7.7)	52 (3.9)	11 (2.7)
Withdrawal by subject	19 (6.1)	22 (5.4)	21 (5.0)	9 (10.5)	7 (7.7)	78 (5.9)	33 (8.1)
Lost to follow-up	5 (1.6)	17 (4.1)	13 (3.1)	2 (2.3)	6 (6.6)	43 (3.3)	12 (2.9)
Noncompliance with study drug	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	4 (1.0)
Protocol deviation	7 (2.2)	8 (1.9)	7 (1.7)	1 (1.2)	3 (3.3)	26 (2.0)	7 (1.7)
Pregnancy	1 (0.3)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)
Lack of efficacy	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)
Other	2 (0.6)	1 (0.2)	2 (0.5)	0 (0.0)	0 (0.0)	5 (0.4)	0 (0.0)

Source: adsl.xpt; Software: R
Abbreviations: ATG, atogepant; BID, twice daily; ISS, Integrated Summary of Safety; N, number of patients in treatment arm; n, number of patients in specified population or group; QD, once daily.

Table 25 shows that patients on BID dosing discontinued at a slightly higher rate than those on QD dosing. In addition, patients on atogepant discontinued due to AEs at a slightly higher rate than placebo, but this did not occur in a dose dependent fashion.

Table 26. ISS Group 2: Patient Disposition

Disposition Outcome, n (%)	Atogepant 60 mg QD N=1,198	Standard of Care N=196
Patients randomized	1,198 (100.0)	196 (100.0)
Safety population	1,198 (100.0)	196 (100.0)
Discontinued study drug	328 (27.4)	68 (34.7)
Adverse event	48 (4.0)	5 (2.6)
Lost to follow-up	35 (2.9)	20 (10.2)
Noncompliance with study drug	6 (0.5)	1 (0.5)
Protocol deviation	44 (3.7)	5 (2.6)
Protocol-specified withdrawal criterion met	41 (3.4)	0
Site terminated by Applicant	3 (0.3)	0
Withdrawal by subject	123 (10.3)	33 (16.8)
Pregnancy	6 (0.5)	2 (1.0)
Lack of efficacy	6 (0.5)	2 (1.0)
Other	16 (1.3)	0

Source: adsl.xpt; Software: R
Abbreviations: ISS, Integrated Summary of Safety; N, number of patients in treatment arm; n, number of patients in specified population or group; QD, once daily

Table 26 shows that more patients discontinued drug in the SoC arm than the atogepant arm in the long-term safety study.

7.6.2. Deaths

There were no deaths in the placebo-controlled studies, and two deaths in the open-label long-term safety studies. One death in Study 3101-302-002 was in a 50-year-old female who was the victim of homicide, and this case is not summarized in this review as it was assessed as not related to atogepant by FDA reviewers. The second death (due to beta hemolytic streptococcal infection) is reviewed in detail in Section 7.7.1 and was also assessed as not related to atogepant use by FDA reviewers.

7.6.3. Serious Adverse Events

There were eight SAEs in the placebo-controlled safety population in the atogepant arms and five SAEs in the placebo arms. These are reviewed below.

There were no trends in SAEs by organ class or by preferred terms.

Group 1 – SAEs

Table 27. ISS Group 1: Serious Adverse Events by System Organ Class and Preferred Term, Safety Population

System Organ Class Preferred Term	ATG 10 mg QD N=314 n (%)	ATG 30 mg QD N=411 n (%)	ATG 60 mg QD N=417 n (%)	ATG 30 mg BID N=86 n (%)	ATG 60 mg BID N=91 n (%)	Total ATG N=1,319 n (%)	Placebo N=408 n (%)
Gastrointestinal disorders	0	0	0	0	0	0	1 (0.2)
Gastric ulcer hemorrhage	0	0	0	0	0	0	1 (0.2)
Hepatobiliary disorders	1 (0.3)	0	0	0	0	1 (0.08)	0
Cholecystitis	1 (0.3)	0	0	0	0	1 (0.08)	0
Infections and infestations	0	1 (0.2)	0	0	0	1 (0.08)	0
Ureteritis	0	1 (0.2)	0	0	0	1 (0.08)	0
Injury, poisoning and procedural complications	0	0	1 (0.2)	0	0	1 (0.08)	0
Overdose	0	0	1 (0.2)	0	0	1 (0.08)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	0	0	1 (0.2)
Hodgkin's disease	0	0	0	0	0	0	1 (0.2)
Nervous system disorders	1 (0.3)	1 (0.2)	0	0	0	2 (0.2)	1 (0.2)
Migraine	0	1 (0.2)	0	0	0	1 (0.08)	0
Optic neuritis	1 (0.3)	0	0	0	0	1 (0.08)	0
Brain injury	0	0	0	0	0	0	1 (0.2)
Psychiatric disorders	0	0	1 (0.2)	0	0	1 (0.08)	0
Major depression	0	0	1 (0.2)	0	0	1 (0.08)	0

System Organ Class Preferred Term	ATG 10 mg QD N=314 n (%)	ATG 30 mg QD N=411 n (%)	ATG 60 mg QD N=417 n (%)	ATG 30 mg BID N=86 n (%)	ATG 60 mg BID N=91 n (%)	Total ATG N=1,319 n (%)	Placebo N=408 n (%)
Renal and urinary disorders	0	0	0	0	0	0	1 (0.2)
Ureterolithiasis	0	0	0	0	0	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	0	0	0	0	1 (0.08)	1 (0.2)
Asthma	1 (0.3)	0	0	0	0	1 (0.08)	0
Negative pressure pulmonary oedema	0	0	0	0	0	0	1 (0.2)
Surgical and medical procedures	0	0	1 (0.2)	0	0	1 (0.08)	0
Abortion induced	0	0	1 (0.2)	0	0	1 (0.08)	0

Source: adae.xpt; Software: R
Abbreviations: BID, twice daily; ISS, Integrated Summary of Safety; N, number of patients in treatment arm; n, number of patients with adverse event; QD, once daily

The narratives of the SAEs in the safety population in the placebo-controlled studies were reviewed, and a brief summary of select SAEs, related to safety signals of interest, follows by study:

Study CGP-MD-01:

(1) Patient [redacted] (b) (6) was a 41-year-old white female with a history of migraine who was randomized to atogepant 30 mg QD on [redacted] (b) (6), and developed right-sided weakness, right hand tingling, nausea, eye twitching, and right eye blurry vision on [redacted] (b) (6). She went on to develop her typical migraine and took paracetamol and study drug with no change. She developed right jaw pain, slurred speech, and her blood pressure was 138/82 with a normal pulse and ECG. Magnetic resonance imaging (MRI) of the brain was conducted in the emergency room and was negative, but computerized tomography showed sinusitis. She was treated with analgesics and fluids and discharged on [redacted] (b) (6) Atogepant was discontinued on [redacted] (b) (6) due to the SAE. There are multiple confounders, including possible sinusitis, the history of migraine and the possibility that this may have represented a complicated migraine; however, given the theoretical association of CGRP antagonists and increased risk of cerebrovascular disease, and given that transient ischemic attack is a diagnostic consideration in this case, a relationship of this event and atogepant cannot definitively be ruled out.

(2) Patient [redacted] (b) (6) was a 26-year-old white female with a history of migraine, nephrolithiasis, status-post-lithotripsy [redacted] (b) (6) who was randomized to atogepant 30 mg QD [redacted] (b) (6) The patient stopped study treatment on the last planned day of dosing (Day 84). On Day 96, the patient developed an SAE of ureteritis. She presented with right kidney pain and fever and was admitted with an infected right ureteral calculus. The patient underwent stent placement in the hospital and had an outpatient lithotripsy. These events were not considered to be related to study treatment given the patient's medical history of a previous similar event prior to her participation in this trial. This case is described because it represents an infection. Due to the death reported in this application from sepsis, additional attention was given to cases of severe infection in this application.

(3) Patient (b) (6) was a 55-year-old white male with a history of migraine, gastrointestinal reflux disease, seasonal allergy, and chronic urticaria who was randomized to atogepant 10 mg QD who experienced acute right upper quadrant abdominal pain and cholelithiasis of severe intensity on Day 34 that resolved the same day. On Day 38, the patient presented to the emergency room with recurrent symptoms of right upper quadrant abdominal pain. Work-up revealed a distended gallbladder, with cholelithiasis, potential acute cholecystitis, and no gross stone in the common bile duct. The patient was treated in the emergency room with resolution of the pain. The next morning (Day 39) the patient had recurrent pain and was admitted with a diagnosis of cholecystitis (SAE). The patient underwent a cholecystectomy successfully and was discharged on Day 40. The patient completed study treatment with no further events; therefore, a relationship of this event to atogepant use is unlikely.

(4) Patient (b) (6) was a 28-year-old white female with a history of migraine who presented with an overdose attempt. This case is described in further detail in Section 7.6.10.4 Suicidality.

Medical Officer's Assessment*: Although an association with treatment cannot be definitively ruled out in the case of the 41-year-old female (Patient (b) (6) described above, the first three SAEs listed do not appear to be related to study drug. The overdose SAE is discussed separately in Section 7.6.10.4 Suicidality.*

Study 3101-301-002

There were four total treatment-emergent SAEs (two in the 10 mg arm [described below] and two in the placebo arm).

- Patient (b) (6) was a 23-year-old female randomized to atogepant 10 mg who experienced an event of optic neuritis on Day 23 of the study. Her ophthalmological exam was inconsistent and variable, MRI brain and orbits, and visual-evoked potentials were reported as normal. She was treated with steroids and improved on Day 108. Atogepant was discontinued after diagnosis. The patient has a positive family history of optic neuritis and multiple sclerosis. The Applicant assessed the event as not likely to represent optic neuritis and not related to study intervention.

Medical Officer's Assessment: *This reviewer disagrees with the Applicant and believes this event could represent optic neuritis. Additionally, a role of atogepant in this event cannot be entirely ruled out since the event did occur close to initiation of this drug; however, a relationship to atogepant remains unlikely given the patient's age, family history, and the increased risk of clinically isolated events in her demographic group. The patient's risk factors confound assessing the relationship between atogepant initiation and the optic neuritis event. In addition, there were no other similar cases observed in the development program, even though patients in this database are in the demographic group that would have a high risk for developing multiple sclerosis or optic neuritis.*

- Patient (b) (6) was a 56-year-old black female with an extensive past medical history (including asthma, tobacco use, obesity, hypertension, drug abuse, and sleep apnea) who experienced an SAE of an asthma attack on Day 1 of receiving study medication (atogepant 10 mg daily). The day of treatment (Day 1), she started feeling an "itchy/scratchy" throat with shortness of breath and wheezing. Atogepant was

temporarily interrupted on Day 2. On Day 4, she went to the emergency room and was treated for an asthma attack. She was started on steroids and nebulizer treatments. She also experienced myalgia of moderate severity and musculoskeletal pain with coughing. On Day 6, she reported nausea and was discharged from the hospital. Atogepant was resumed on Day 9. On Day 11, she experienced pelvic pain and hematuria. These events were not considered related to treatment. She was withdrawn from the study due to the pelvic pain and hematuria and did not complete the safety follow-up visit.

Medical Officer's Assessment: *The Applicant assessed these events as not related to treatment. It is difficult to assess causality due to multiple confounders; however, it is possible that atogepant use led to the initial asthma attack, although the mechanism for such an association is unclear. The patient was on concomitant medications for asthma and was an active smoker. The events of myalgia and musculoskeletal pain may be associated with atogepant (this is reviewed separately as part of Section 7.7.1), but these events are also confounded in this patient due to multiple factors.*

Group 2 SAEs

In the long-term safety study, Study 3101-302-002, there were 24 SAEs in the atogepant 60 mg once daily arm and 7 SAEs in the SoC arm. There were no trends in SAEs by organ class or by preferred terms, and individual SAEs pertaining to specific organ systems are evaluated separately (e.g., suicidality, beta hemolytic streptococcal infection).

The following is a notable case of a generalized seizure that occurred in the long-term safety study.

- Patient (b) (6) was a 31-year-old female receiving atogepant 60 mg in the long-term safety study who discontinued due to a seizure on Day 33 of treatment with atogepant. This patient did not report that she had a history of epilepsy, for which she was taking topiramate, at screening. The patient had a history of complex partial seizures, was status-post-amygdalohippocampectomy in (b) (6), and experienced an SAE of generalized seizure (after a 10-year history of not having generalized seizures and only having continued complex partial seizures). She was discontinued from the study. It is unlikely the seizure was related to atogepant, given the patient's epilepsy diagnosis and the much greater likelihood of the occurrence representing a breakthrough seizure.

7.6.4. Dropouts and/or Discontinuations Due to Adverse Events

In Study CGP-MD-01, three patients discontinued due to an SAE (two patients in an atogepant arm and one patient in the placebo arm). Five patients discontinued due to elevated LFTs: three patients discontinued due to elevated ALT or AST, one in the atogepant 10 mg QD arm and two in the 60 mg atogepant QD arm. These patients are further described in Section 7.7.1.

In Study 3101-301-002, three patients discontinued due to an SAE (two in the atogepant 10 mg arm and one in the placebo arm). There were no discontinuations due to cardiovascular or LFT abnormalities. One patient in the placebo arm discontinued because of suicidal ideation.

Table 28. ISS Group 1: Adverse Events Leading to Discontinuation, Selected Preferred Terms, Safety Population

Preferred Term, n (%)	ATG 10 mg QD N=314	ATG 30 mg QD N=411	ATG 60 mg QD N=417	ATG 30 mg BID N=86	ATG 60 mg BID N=91	Total ATG N=1,319	Placebo N=408	Risk Difference (95% CI)
Any AE leading to discontinuation	13 (4.1)	14 (3.4)	12 (2.9)	5 (5.8)	6 (6.6)	50 (3.8)	11 (2.7)	1.1 (-0.8, 3.0)
Constipation	**1 (0.3)**	**3 (0.7)**	**2 (0.5)**	**0**	**1 (1.1)**	**7 (0.5)**	**0**	**0.5 (0.1, 0.9)**
Nausea	**1 (0.3)**	**3 (0.7)**	**1 (0.2)**	**0**	**1 (1.1)**	**6 (0.5)**	**0**	**0.5 (0.1, 0.8)**
Fatigue	**1 (0.3)**	**0**	**1 (0.2)**	**0**	**3 (3.3)**	**5 (0.4)**	**0**	**0.4 (0.0, 0.7)**
Dizziness	0	2 (0.5)	0	0	2 (2.2)	4 (0.3)	0	0.3 (0.0, 0.6)
ALT increased	0	1 (0.2)	1 (0.2)	0	0	2 (0.2)	0	0.2 (-0.1, 0.4)
Decreased appetite	0	0	1 (0.2)	0	1 (1.1)	2 (0.2)	0	0.2 (-0.1, 0.4)
Insomnia	0	0	1 (0.2)	0	1 (1.1)	2 (0.2)	0	0.2 (-0.1, 0.4)
Product use complaint	0	0	1 (0.2)	0	1 (1.1)	2 (0.2)	0	0.2 (-0.1, 0.4)
Rash	0	0	2 (0.5)	0	0	2 (0.2)	0	0.2 (-0.1, 0.4)
Migraine	0	1 (0.2)	1 (0.2)	0	0	2 (0.2)	2 (0.5)	-0.3 (-1.0, 0.4)

Source: adae.xpt; Software: R
Risk difference column shows comparison of total atogepant and placebo groups.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ATG, atogepant; BID, twice daily; CI, confidence interval; ISS, Integrated Summary of Safety; N, number of patients in treatment arm; n, number of patients meeting criteria; QD, once daily

In the placebo-controlled trials (ISS Group 1), 50 (3.9%) patients in the atogepant arms and 11 (2.7%) patients in the placebo arms discontinued due to a TEAE. Common AEs leading to discontinuation in the atogepant arms included constipation (7 patients), nausea (6 patients), fatigue (5 patients, with 3 patients in 60 mg BID arm), and dizziness (4 patients).

Though constipation and nausea were the most common reasons for discontinuation in the placebo-controlled trials, the absolute number of patients who discontinued due to these TEAEs was small. There were no dose-related trends for discontinuation. TEAEs that led to discontinuation in less than 2 atogepant-treated patients are not included to simplify the table above, and because these are less likely to be related to atogepant in the absence of any trends. The full table is included in Section 17 (Table 127).

In the long-term safety studies (ISS Group 2), the most common reasons for discontinuation in the atogepant-treated arms were nausea or vomiting in seven patients (0.6%), fatigue or somnolence in five patients (0.4%), and abdominal pain in four patients (0.3%). Please see Table 128 in Section 17 for the full table in ISS Group 2.

7.6.5. Treatment-Emergent Adverse Events

Analyses of common TEAEs based on the pooled groupings for the safety analyses of this application are presented below.

Group 1 – Controlled Clinical Trials

Table 29 below includes TEAEs that occurred in at least 1% of atogepant-treated patients and at a greater incidence than placebo in the placebo-controlled trials (ISS Group 1).

Table 29. ISS Group 1: Common Adverse Events Occurring at ≥1% of Atogepant-Treated Patients and at a Greater Incidence Than Placebo, Safety Population

Preferred Term	ATG 10 mg QD N=314 n (%)	ATG 30 mg QD N=411 n (%)	ATG 60 mg QD N=417 n (%)	ATG 30 mg BID N=86 n (%)	ATG 60 mg BID N=91 n (%)	Total ATG N=1,319 n (%)	Placebo N=408 n (%)	Risk Difference (95% CI)
Any AE	178 (56.7)	234 (56.9)	231 (55.4)	52 (60.5)	53 (58.2)	748 (56.7)	218 (53.4)	3.3 (-2.3, 8.8)
Constipation	19 (6.1)	26 (6.3)	25 (6.0)	3 (3.5)	6 (6.6)	79 (6.0)	5 (1.2)	4.8 (3.1, 6.4)
Nausea	16 (5.1)	23 (5.6)	36 (8.6)	8 (9.3)	9 (9.9)	92 (7.0)	13 (3.2)	3.8 (1.6, 6)
Decreased appetite	5 (1.6)	4 (1.0)	10 (2.4)	0	4 (4.4)	23 (1.7)	1 (0.2)	1.5 (0.6, 2.4)
Blood creatine phosphokinase increased	9 (2.9)	5 (1.2)	9 (2.2)	6 (7.0)	2 (2.2)	31 (2.4)	5 (1.2)	1.2 (-0.2, 2.5)
Dizziness	5 (1.6)	8 (1.9)	6 (1.4)	1 (1.2)	3 (3.3)	23 (1.7)	2 (0.5)	1.2 (0.3, 2.2)
Somnolence	9 (2.9)	8 (1.9)	10 (2.4)	1 (1.2)	0	28 (2.1)	4 (1.0)	1.1 (-0.1, 2.4)
Nasopharyngitis	7 (2.2)	19 (4.6)	22 (5.3)	1 (1.2)	3 (3.3)	52 (3.9)	12 (2.9)	1 (-0.9, 2.9)
Abdominal pain or discomfort	4 (1.2)	9 (2.2)	4 (1.0)	2 (2.4)	2 (2.2)	21 (1.6)	3 (0.7)	0.9 (-0.2, 1.9)
Gastroenteritis	3 (1.0)	10 (2.4)	9 (2.2)	3 (3.5)	0	25 (1.9)	5 (1.2)	0.7 (-0.6, 2)
Muscle strain	5 (1.6)	5 (1.2)	2 (0.5)	0	2 (2.2)	14 (1.1)	2 (0.5)	0.6 (-0.3, 1.4)
Abnormal dreams	2 (0.6)	1 (0.2)	3 (0.7)	1 (1.2)	0	7 (0.5)	0	0.5 (0.1, 0.9)
Dyspepsia	4 (1.3)	3 (0.7)	6 (1.4)	0	0	13 (1.0)	2 (0.5)	0.5 (-0.4, 1.4)
Fatigue	4 (1.3)	10 (2.4)	14 (3.4)	2 (2.3)	9 (9.9)	39 (3.0)	10 (2.5)	0.5 (-1.3, 2.3)
Hypertension	1 (0.3)	4 (1.0)	0	1 (1.2)	1 (1.1)	7 (0.5)	0	0.5 (0.1, 0.9)

Source: adae.xpt; Software: R
Duration is 12 weeks (median 85 days, range 1 to 111 days).
Coded as Medical Dictionary for Regulatory Activities preferred terms.
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: BID, twice daily; CI, confidence interval; ISS, Integrated Summary of Safety; N, number of patients in treatment arm; n, number of patients with adverse event; QD, once daily

Common AE Table for Labeling

Table 30 summarizes the common adverse reactions seen in at least 2% of atogepant-treated patients and at a greater incidence than placebo (rounded to the nearest whole number), including nausea, constipation, fatigue, and decreased appetite. Table 30 is recommended for inclusion in labeling.

Table 30. ISS Group 1: Adverse Reactions Occurring at Greater Than 2% in Atogepant-Treated Patients and Greater Than Placebo

Preferred Term (%)	Placebo (N=408)	Atogepant 10 mg (N=314)	Atogepant 30 mg (N=411)	Atogepant 60 mg (N=417)
Nausea	3	5	6	9
Constipation	1	6	6	6
Fatigue/somnolence	3	4	4	6
Decreased Appetite	<1	2	1	2

Source: Reviewer analysis
Abbreviations: ISS, Integrated Summary of Safety; N, number of patients in treatment arm

A more comprehensive analysis of TEAEs in the controlled clinical trials by system organ class using groupings by FDA medical query is included below in Table 31.

Table 31. ISS Group 1: Adverse Events by System Organ Class, FDA Medical Query (Broad), and Preferred Term, Frequency ≥1% in Any Arm, Safety Population

System Organ Class FMQ (Narrow)	Atogepant 10 mg QD N=314 n (%)	Atogepant 30 mg QD N=411 n (%)	Atogepant 60 mg QD N=417 n (%)	Atogepant 30 mg BID N=86 n (%)	Atogepant 60 mg BID N=91 n (%)	Total Atogepant N=1,319 n (%)	Placebo N=408 n (%)	Risk Difference (95% CI)
Blood and lymphatic system disorders								
Anemia	4 (1.3)	0	4 (1.0)	0	0	8 (0.6)	1 (0.2)	0.4 (-0.3, 1)
Thrombocytopenia	0	0	0	0	0	0	1 (0.2)	-0.2 (-0.7, 0.2)
Cardiac disorders								
Systemic hypertension	2 (0.6)	4 (1.0)	1 (0.2)	1 (1.2)	1 (1.1)	9 (0.7)	0	0.7 (0.2, 1.1)
Arrhythmia	2 (0.6)	4 (1.0)	1 (0.2)	0	0	7 (0.5)	1 (0.2)	0.3 (-0.3, 0.9)
Palpitations	1 (0.3)	3 (0.7)	1 (0.2)	1 (1.2)	0	6 (0.5)	1 (0.2)	0.3 (-0.4, 0.8)
Tachycardia	2 (0.6)	3 (0.7)	0	0	1 (1.1)	6 (0.5)	4 (1.0)	-0.5 (-1.5, 0.5)
Ear and labyrinth disorders								
Vertigo	3 (1.0)	3 (0.7)	0	2 (2.3)	2 (2.2)	10 (0.8)	1 (0.2)	0.6 (-0.2, 1.2)
Gastrointestinal disorders								
Constipation	19 (6.1)	26 (6.3)	25 (6.0)	3 (3.5)	6 (6.6)	79 (6.0)	5 (1.2)	4.8 (3.1, 6.4)
Nausea	16 (5.1)	23 (5.6)	36 (8.6)	8 (9.3)	9 (9.9)	92 (7.0)	14 (3.4)	3.6 (1.3, 5.8)
Abdominal pain	7 (2.2)	10 (2.4)	4 (1.0)	1 (1.2)	2 (2.2)	24 (1.8)	3 (0.7)	1.1 (0, 2.2)
Dyspepsia	6 (1.9)	7 (1.7)	8 (1.9)	1 (1.2)	0	22 (1.7)	3 (0.7)	1 (-0.1, 2)
Diarrhea	3 (1.0)	6 (1.5)	9 (2.2)	2 (2.3)	3 (3.3)	23 (1.7)	6 (1.5)	0.2 (-1.1, 1.6)
Vomiting	4 (1.3)	1 (0.2)	8 (1.9)	4 (4.7)	3 (3.3)	20 (1.5)	8 (2.0)	-0.5 (-1.9, 1.1)
Dry mouth	1 (0.3)	2 (0.5)	3 (0.7)	0	0	6 (0.5)	5 (1.2)	-0.7 (-1.9, 0.4)
General disorders and administration site conditions								
Decreased appetite	5 (1.6)	4 (1.0)	11 (2.6)	0	4 (4.4)	24 (1.8)	1 (0.2)	1.6 (0.7, 2.4)
Fatigue	5 (1.6)	10 (2.4)	16 (3.8)	2 (2.3)	9 (9.9)	42 (3.2)	10 (2.5)	0.7 (-1, 2.5)
Pyrexia	2 (0.6)	2 (0.5)	0	1 (1.2)	1 (1.1)	6 (0.5)	1 (0.2)	0.3 (-0.4, 0.8)
Peripheral edema	0	2 (0.5)	0	0	1 (1.1)	3 (0.2)	1 (0.2)	0 (-0.6, 0.5)
Hepatobiliary disorders								
Cholecystitis	2 (0.6)	0	0	0	0	2 (0.2)	0	0.2 (-0.1, 0.4)
Hepatic injury	6 (1.9)	5 (1.2)	7 (1.7)	1 (1.2)	1 (1.1)	20 (1.5)	10 (2.5)	-1 (-2.6, 0.7)
Infections and infestations								
Nasopharyngitis	9 (2.9)	25 (6.1)	29 (7.0)	1 (1.2)	3 (3.3)	67 (5.1)	14 (3.4)	1.7 (-0.5, 3.8)
Pneumonia	1 (0.3)	3 (0.7)	0	1 (1.2)	0	5 (0.4)	2 (0.5)	-0.1 (-0.9, 0.6)

System Organ Class FMQ (Narrow)	Atogepant 10 mg QD N=314 n (%)	Atogepant 30 mg QD N=411 n (%)	Atogepant 60 mg QD N=417 n (%)	Atogepant 30 mg BID N=86 n (%)	Atogepant 60 mg BID N=91 n (%)	Total Atogepant N=1,319 n (%)	Placebo N=408 n (%)	Risk Difference (95% CI)
Musculoskeletal and connective tissue disorders								
Arthritis	1 (0.3)	0	2 (0.5)	1 (1.2)	0	4 (0.3)	0	0.3 (0, 0.6)
Back pain	6 (1.9)	5 (1.2)	6 (1.4)	0	3 (3.3)	20 (1.5)	7 (1.7)	-0.2 (-1.6, 1.2)
Myalgia	1 (0.3)	3 (0.7)	3 (0.7)	0	0	7 (0.5)	4 (1.0)	-0.5 (-1.5, 0.6)
Nervous system disorders								
Dizziness	7 (2.2)	12 (2.9)	6 (1.4)	3 (3.5)	5 (5.5)	33 (2.5)	5 (1.2)	1.3 (-0.1, 2.6)
Somnolence	11 (3.5)	9 (2.2)	12 (2.9)	2 (2.3)	1 (1.1)	35 (2.7)	6 (1.5)	1.2 (-0.3, 2.6)
Paresthesia	3 (1.0)	3 (0.7)	3 (0.7)	1 (1.2)	1 (1.1)	11 (0.8)	2 (0.5)	0.3 (-0.5, 1.2)
Dysgeusia	0	0	0	1 (1.2)	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Syncope	0	1 (0.2)	0	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Tremor	0	0	1 (0.2)	0	0	1 (0.08)	1 (0.2)	-0.1 (-0.7, 0.3)
Headache	3 (1.0)	9 (2.2)	9 (2.2)	3 (3.5)	0	24 (1.8)	13 (3.2)	-1.4 (-3.2, 0.5)
Psychiatric disorders								
Irritability	0	5 (1.2)	4 (1.0)	0	0	9 (0.7)	0	0.7 (0.2, 1.1)
Anxiety	4 (1.3)	3 (0.7)	5 (1.2)	1 (1.2)	1 (1.1)	14 (1.1)	4 (1.0)	0.1 (-1, 1.2)
Depression	5 (1.6)	6 (1.5)	4 (1.0)	2 (2.3)	0	17 (1.3)	5 (1.2)	0.1 (-1.2, 1.3)
Parasomnia	2 (0.6)	1 (0.2)	4 (1.0)	1 (1.2)	0	8 (0.6)	2 (0.5)	0.1 (-0.7, 0.9)
Insomnia	7 (2.2)	3 (0.7)	7 (1.7)	0	4 (4.4)	21 (1.6)	7 (1.7)	-0.1 (-1.6, 1.3)
Mania	0	1 (0.2)	0	0	0	1 (0.08)	1 (0.2)	-0.1 (-0.7, 0.3)
Renal and urinary disorders								
Acute kidney injury	0	0	1 (0.2)	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Reproductive system and breast disorders								
Abnormal uterine bleeding	4 (1.3)	3 (0.7)	5 (1.2)	0	1 (1.1)	13 (1.0)	1 (0.2)	0.8 (0, 1.5)
Excessive menstrual bleeding	1 (0.3)	0	2 (0.5)	0	1 (1.1)	4 (0.3)	0	0.3 (0, 0.6)
Decreased menstrual bleeding	1 (0.3)	1 (0.2)	0	0	1 (1.1)	3 (0.2)	0	0.2 (0, 0.5)
Amenorrhea	0	0	0	0	1 (1.1)	1 (0.08)	0	0.1 (-0.1, 0.2)
Gynecomastia	1 (0.3)	0	0	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Bacterial vaginosis	1 (0.3)	1 (0.2)	1 (0.2)	0	2 (2.2)	5 (0.4)	2 (0.5)	-0.1 (-0.9, 0.6)

System Organ Class FMQ (Narrow)	Atogepant 10 mg QD N=314 n (%)	Atogepant 30 mg QD N=411 n (%)	Atogepant 60 mg QD N=417 n (%)	Atogepant 30 mg BID N=86 n (%)	Atogepant 60 mg BID N=91 n (%)	Total Atogepant N=1,319 n (%)	Placebo N=408 n (%)	Risk Difference (95% CI)
Respiratory, thoracic and mediastinal disorders								
Bronchospasm	1 (0.3)	2 (0.5)	1 (0.2)	0	1 (1.1)	5 (0.4)	0	0.4 (0, 0.7)
Dyspnea	2 (0.6)	0	1 (0.2)	0	0	3 (0.2)	1 (0.2)	0 (-0.6, 0.5)
Cough	5 (1.6)	1 (0.2)	2 (0.5)	0	0	8 (0.6)	3 (0.7)	-0.1 (-1.1, 0.8)
Skin and subcutaneous tissue disorders								
Pruritus	3 (1.0)	2 (0.5)	4 (1.0)	0	1 (1.1)	10 (0.8)	2 (0.5)	0.3 (-0.6, 1.1)
Erythema	1 (0.3)	0	0	0	0	1 (0.08)	1 (0.2)	-0.1 (-0.7, 0.3)
Urticaria	0	0	0	0	0	0	1 (0.2)	-0.2 (-0.7, 0.2)
Rash	5 (1.6)	0	5 (1.2)	0	1 (1.1)	11 (0.8)	7 (1.7)	-0.9 (-2.2, 0.5)
Vascular disorders								
Hypotension	0	0	2 (0.5)	0	0	2 (0.2)	0	0.2 (-0.1, 0.4)
Hemorrhage	6 (1.9)	8 (1.9)	6 (1.4)	3 (3.5)	2 (2.2)	25 (1.9)	9 (2.2)	-0.3 (-1.9, 1.3)

Source: adae.xpt; Software: R
Duration is 12 weeks (median 85 days, range 1-111 days).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
For specific preferred terms under each FMQ, see the table “Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…”

Abbreviations: BID, twice daily; CI, confidence interval; FMQ, FDA medical query; ISS, Integrated Summary of Safety; N, number of patients in treatment arm; n, number of patients with adverse event; QD, once daily

The groupings in Table 31 demonstrate the highest risk difference for the system organ class of gastrointestinal disorders, which was mostly driven by the preferred terms of constipation, nausea, and abdominal pain.

Group 2 –Long-Term Safety Studies

Table 32 presents the TEAEs that occurred at a frequency of at least 2% in the open-label long-term safety studies (ISS Group 2). Gastrointestinal events, constipation, and weight decreased occurred more commonly in the atogepant-treated patients than in the SoC arm.

Table 32. ISS Group 2: Common Adverse Events Occurring at ≥2% Frequency, Safety Population

Preferred Term, n (%)	Atogepant 60 mg QD N=1,198	Standard of Care N=196	Risk Difference % (95% CI)
Any adverse event	689 (57.5)	154 (78.6)	-21.1 (-27.4, -14.7)
Gastroenteritis	24 (2.0)	0	2 (1.2, 2.8)
Constipation	58 (4.8)	6 (3.1)	1.7 (-0.9, 4.5)
Weight decreased	25 (2.1)	3 (1.5)	0.6 (-1.3, 2.5)
Influenza	35 (2.9)	5 (2.6)	0.3 (-2, 2.8)
Sinusitis	35 (2.9)	6 (3.1)	-0.2 (-2.7, 2.5)
Nasopharyngitis	56 (4.7)	10 (5.1)	-0.4 (-3.7, 2.9)
Urinary tract infection	47 (3.9)	9 (4.6)	-0.7 (-3.8, 2.5)
Anxiety	26 (2.2)	11 (5.6)	-3.4 (-6.8, -0.1)
Fatigue	20 (1.7)	12 (6.1)	-4.4 (-7.9, -1)
Upper respiratory tract infection	91 (7.6)	24 (12.2)	-4.6 (-9.5, 0.2)
Nausea	22 (1.8)	9 (4.6)	-2.8 (-5.8, 0.3)
Dizziness	27 (2.3)	22 (11.2)	-8.9 (-13.5, -4.5)

Source: adae.xpt; Software: R
Duration is mean 32.5 weeks (standard deviation, 18.7; median, 36.1; minimum, 0.1; maximum, 58).
Treatment-emergent adverse events defined as any AE that began or worsened (increased in severity or became serious) on or after the date of the first dose of double-blind study treatment and with an onset date before 30 days after the last dose of double-blind study treatment or Visit 8, whichever comes later.
Coded as MedDRA preferred terms.
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; ISS, Integrated Summary of Safety; N, number of patients in treatment arm; n, number of patients with adverse event; QD, once daily

Group 3 – Pooled Controlled and Long-Term Safety Studies

TEAEs occurring in Group 3 are displayed in Table 33. Group 3 includes patients with the longest exposure to atogepant (up to 15 months of treatment in some patients). Constipation had the highest risk difference in atogepant-treated patients as compared to the SoC arm. Nausea and decreased appetite occurred slightly more frequently in the atogepant treated patients than those in the SoC arm.

Table 33. ISS Group 3: Select Adverse Events Occurring at ≥1% Frequency, Safety Population

Preferred Term, n (%)	PBO/ATG 60 mg QD N=161	ATG 10/60 mg QD N=221	ATG 30/60 mg QD N=228	ATG 60 mg QD N=695	PBO/SoC N=229	Risk Difference (95% CI)
Any adverse event	84 (52.2)	150 (67.9)	155 (68.0)	453 (65.2)	168 (73.4)	-8.2 (-14.9, -1.5)
Constipation	10 (6.2)	22 (10.0)	18 (7.9)	45 (6.5)	6 (2.6)	3.9 (1.1, 6.6)
Nausea	5 (3.1)	14 (6.3)	13 (5.7)	42 (6.0)	12 (5.2)	0.8 (-2.6, 4.2)
Fatigue	1 (0.6)	4 (1.8)	8 (3.5)	24 (3.5)	10 (4.4)	-0.9 (-3.9, 2.1)
Somnolence	2 (1.2)	9 (4.1)	5 (2.2)	9 (1.3)	6 (2.6)	-1.3 (-3.6, 0.9)
Decreased appetite	1 (0.6)	3 (1.4)	1 (0.4)	9 (1.3)	1 (0.4)	0.9 (-0.3, 2.1)

Source: adae.xpt; Software: R
Abbreviations: ATG, atogepant; ISS, Integrated Summary of Safety; PBO, placebo; QD, once daily; SoC, standard of care

7.6.6. Laboratory Findings, Controlled Clinical Trials

Table 34 summarizes the results of the outlier analyses for the blood chemistry safety testing from the placebo-controlled trials (ISS Group 1).

Table 34. ISS Group 1: Patients Meeting Laboratory Abnormality Criteria, Cumulative Worsened Grade[1] From Baseline Through Week 12, Safety Population

Laboratory Parameter, n (%)	Atogepant 10 mg QD N=314	Atogepant 30 mg QD N=411	Atogepant 60 mg QD N=417	Atogepant 30 mg BID N=86	Atogepant 60 mg BID N=91	Total Atogepant N=1,319	Placebo N=408	Risk Difference (95% CI)
Sodium, low (mEq/L)								
Level 1 (<134)	4/312 (1.3)	8/404 (2.0)	7/409 (1.7)	2/84 (2.4)	2/88 (2.3)	23/1,297 (1.8)	1/399 (0.3)	1.52 (0.65, 2.39)
Level 2 (<132)	0/312 (0)	4/404 (1.0)	2/409 (0.5)	1/84 (1.2)	0/88 (0)	7/1,297 (0.5)	0/399 (0)	0.54 (0.14, 0.94)
Level 3 (<125)	0/312 (0)	0/404 (0)	0/409 (0)	0/84 (0)	0/88 (0)	0/1,297 (0)	0/399 (0)	0 (0, 0)
Sodium, high (mEq/L)								
Level 1 (>144)	33/312 (10.6)	45/404 (11.1)	38/409 (9.3)	12/84 (14.3)	12/88 (13.6)	140/1,297 (10.8)	31/399 (7.8)	3.02 (-0.10, 6.15)
Level 2 (>150)	0/312 (0)	2/404 (0.5)	1/409 (0.2)	0/84 (0)	0/88 (0)	3/1,297 (0.2)	0/399 (0)	0.23 (-0.03, 0.49)
Level 3 (>155)	0/312 (0)	0/404 (0)	0/409 (0)	0/84 (0)	0/88 (0)	0/1,297 (0)	0/399 (0)	0 (0, 0)
Potassium, low (mEq/L)								
Level 1 (<3.6)	18/312 (5.8)	23/404 (5.7)	24/409 (5.9)	8/84 (9.5)	11/88 (12.5)	84/1,297 (6.5)	24/399 (6.0)	0.46 (-2.23, 3.15)
Level 2 (<3.4)	6/312 (1.9)	4/404 (1.0)	4/409 (1.0)	1/84 (1.2)	4/88 (4.5)	19/1,297 (1.5)	6/399 (1.5)	-0.04 (-1.40, 1.32)
Level 3 (<3)	0/312 (0)	0/404 (0)	0/409 (0)	0/84 (0)	0/88 (0)	0/1,297 (0)	1/399 (0.3)	-0.25 (-0.74, 0.24)
Potassium, high (mEq/L)								
Level 1 (>5.5)	16/312 (5.1)	20/404 (5.0)	24/409 (5.9)	4/84 (4.8)	6/88 (6.8)	70/1,297 (5.4)	15/399 (3.8)	1.64 (-0.60, 3.87)
Level 2 (>6)	4/312 (1.3)	3/404 (0.7)	2/409 (0.5)	1/84 (1.2)	1/88 (1.1)	11/1,297 (0.8)	2/399 (0.5)	0.35 (-0.51, 1.20)
Level 3 (>6.5)	1/312 (0.3)	1/404 (0.2)	0/409 (0)	0/84 (0)	0/88 (0)	2/1,297 (0.2)	0/399 (0)	0.15 (-0.06, 0.37)
Chloride, low (mEq/L)								
Level 1 (<95)	3/312 (1.0)	7/404 (1.7)	7/409 (1.7)	2/84 (2.4)	4/88 (4.5)	23/1,297 (1.8)	4/399 (1.0)	0.77 (-0.44, 1.98)
Level 2 (<88)	0/312 (0)	0/404 (0)	0/409 (0)	0/84 (0)	0/88 (0)	0/1,297 (0)	0/399 (0)	0 (0, 0)
Level 3 (<80)	0/312 (0)	0/404 (0)	0/409 (0)	0/84 (0)	0/88 (0)	0/1,297 (0)	0/399 (0)	0 (0, 0)
Chloride, high (mEq/L)								
Level 1 (>108)	4/312 (1.3)	6/404 (1.5)	6/409 (1.5)	0/84 (0)	0/88 (0)	16/1,297 (1.2)	8/399 (2.0)	-0.77 (-2.27, 0.73)
Level 2 (>112)	0/312 (0)	0/404 (0)	0/409 (0)	0/84 (0)	0/88 (0)	0/1,297 (0)	0/399 (0)	0 (0, 0)
Level 3 (>115)	0/312 (0)	0/404 (0)	0/409 (0)	0/84 (0)	0/88 (0)	0/1,297 (0)	0/399 (0)	0 (0, 0)
Bicarbonate, low (mEq/L)								
Level 1 (<20)	69/312 (22.1)	78/404 (19.3)	69/409 (16.9)	5/84 (6.0)	6/88 (6.8)	227/1,297 (17.5)	63/399 (15.8)	1.71 (-2.42, 5.84)
Level 2 (<18)	14/312 (4.5)	10/404 (2.5)	19/409 (4.6)	2/84 (2.4)	1/88 (1.1)	46/1,297 (3.5)	11/399 (2.8)	0.79 (-1.11, 2.69)
Level 3 (<15)	0/312 (0)	0/404 (0)	1/409 (0.2)	0/84 (0)	0/88 (0)	1/1,297 (0.08)	1/399 (0.3)	-0.17 (-0.69, 0.34)

Laboratory Parameter, n (%)	Atogepant 10 mg QD N=314	Atogepant 30 mg QD N=411	Atogepant 60 mg QD N=417	Atogepant 30 mg BID N=86	Atogepant 60 mg BID N=91	Total Atogepant N=1,319	Placebo N=408	Risk Difference (95% CI)
Bicarbonate, high (mEq/L)								
Level 1 (NA)	3/312 (1.0)	6/404 (1.5)	4/409 (1.0)	1/84 (1.2)	4/88 (4.5)	18/1,297 (1.4)	5/399 (1.3)	0.13 (-1.13, 1.40)
Level 2 (NA)	3/312 (1.0)	6/404 (1.5)	4/409 (1.0)	1/84 (1.2)	4/88 (4.5)	18/1,297 (1.4)	5/399 (1.3)	0.13 (-1.13, 1.40)
Level 3 (>30)	3/312 (1.0)	6/404 (1.5)	4/409 (1.0)	1/84 (1.2)	4/88 (4.5)	18/1,297 (1.4)	5/399 (1.3)	0.13 (-1.13, 1.40)
Glucose, low (mg/dL)								
Level 1 (<70)	1/312 (0.3)	1/404 (0.2)	1/409 (0.2)	0/84 (0)	1/88 (1.1)	4/1,297 (0.3)	3/399 (0.8)	-0.44 (-1.34, 0.46)
Level 2 (<54)	1/312 (0.3)	1/404 (0.2)	1/409 (0.2)	0/84 (0)	1/88 (1.1)	4/1,297 (0.3)	3/399 (0.8)	-0.44 (-1.34, 0.46)
Level 3 (<40)	0/312 (0)	0/404 (0)	0/409 (0)	0/84 (0)	0/88 (0)	0/1,297 (0)	0/399 (0)	0 (0, 0)
Glucose, high (mg/dL)								
Level 1 (>200)	1/312 (0.3)	5/404 (1.2)	7/409 (1.7)	0/84 (0)	2/88 (2.3)	15/1,297 (1.2)	3/399 (0.8)	0.40 (-0.62, 1.43)
Level 2 (>250)	0/312 (0)	5/404 (1.2)	6/409 (1.5)	0/84 (0)	1/88 (1.1)	12/1,297 (0.9)	1/399 (0.3)	0.67 (-0.04, 1.39)
Level 3 (>500)	0/312 (0)	3/404 (0.7)	5/409 (1.2)	0/84 (0)	0/88 (0)	8/1,297 (0.6)	1/399 (0.3)	0.37 (-0.28, 1.02)
Calcium, low (mg/dL)								
Level 1 (<8.4)	9/312 (2.9)	8/404 (2.0)	9/409 (2.2)	1/84 (1.2)	1/88 (1.1)	28/1,297 (2.2)	9/399 (2.3)	-0.10 (-1.75, 1.56)
Level 2 (<8)	1/312 (0.3)	0/404 (0)	2/409 (0.5)	0/84 (0)	0/88 (0)	3/1,297 (0.2)	1/399 (0.3)	-0.02 (-0.58, 0.54)
Level 3 (<7.5)	1/312 (0.3)	0/404 (0)	1/409 (0.2)	0/84 (0)	0/88 (0)	2/1,297 (0.2)	0/399 (0)	0.15 (-0.06, 0.37)
Calcium, high (mg/dL)								
Level 1 (>10.5)	14/312 (4.5)	15/404 (3.7)	29/409 (7.1)	2/84 (2.4)	3/88 (3.4)	63/1,297 (4.9)	16/399 (4.0)	0.85 (-1.41, 3.10)
Level 2 (>11)	1/312 (0.3)	2/404 (0.5)	5/409 (1.2)	0/84 (0)	0/88 (0)	8/1,297 (0.6)	3/399 (0.8)	-0.14 (-1.08, 0.81)
Level 3 (>12)	0/312 (0)	0/404 (0)	0/409 (0)	0/84 (0)	0/88 (0)	0/1,297 (0)	0/399 (0)	0 (0, 0)
Protein, total, low (g/dL)								
Level 1 (<6)	7/312 (2.2)	16/404 (4.0)	7/409 (1.7)	1/84 (1.2)	1/88 (1.1)	32/1,297 (2.5)	10/399 (2.5)	-0.04 (-1.79, 1.71)
Level 2 (<5.4)	1/312 (0.3)	0/404 (0)	2/409 (0.5)	0/84 (0)	0/88 (0)	3/1,297 (0.2)	4/399 (1.0)	-0.77 (-1.78, 0.24)
Level 3 (<5)	0/312 (0)	0/404 (0)	1/409 (0.2)	0/84 (0)	0/88 (0)	1/1,297 (0.08)	0/399 (0)	0.08 (-0.07, 0.23)
CPK, high (U/L)								
Level 1 (>3X ULN)	14/312 (4.5)	13/404 (3.2)	13/409 (3.2)	4/84 (4.8)	3/88 (3.4)	47/1,297 (3.6)	16/399 (4.0)	-0.39 (-2.56, 1.79)
Level 2 (>5X ULN)	9/312 (2.9)	7/404 (1.7)	7/409 (1.7)	2/84 (2.4)	1/88 (1.1)	26/1,297 (2.0)	7/399 (1.8)	0.25 (-1.25, 1.75)
Level 3 (>10X ULN)	3/312 (1.0)	5/404 (1.2)	5/409 (1.2)	1/84 (1.2)	0/88 (0)	14/1,297 (1.1)	4/399 (1.0)	0.08 (-1.05, 1.20)

Source: adlb.xpt; Software: R
Duration is 12 weeks (median 85 days, range 1-111 days).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: BID, twice daily; CI, confidence interval; CPK, creatine phosphokinase; ISS, Integrated Summary of Safety; N, number of patients in treatment arm; n, number of patients meeting criteria; QD, once daily; ULN, upper limit of normal

An increase in sodium to 145 to 149 mEq/L was observed in 10.8% of atogepant-treated patients compared to 7.8% of placebo-treated patients at any time in the study. Sodium levels did not trend higher than 155 for any patient, and only three patients (0.23%) in the atogepant arms had a level 2 sodium increase (>150). There were no reported AEs associated with these laboratory abnormalities. These findings likely reflect natural variations over time as there is no clear mechanism for this finding based on what is currently known about the pharmacodynamics of atogepant.

An increase in potassium of 5.6 to 5.9 mEq/L at any time was observed in 70 (5.4%) patients in the atogepant arms compared to 15 (3.8%) patients in the placebo arm, with a risk difference of 1.64 (-0.6 to 3.87). There were no reported AE terms associated with these findings. These findings likely reflect natural variation over time as there is no clear mechanism for this finding either, based on what is currently known about pharmacodynamics of atogepant.

Lastly, the bicarbonate levels in 227 (17.5%) of atogepant-treated patients were lower than 20 mEq/L at some point during the study compared to 63 (15.8%) of patients in the placebo arm. The risk difference is 1.71 (-2.42 to 5.84). This may be due to some degree of hyperventilation or metabolic acidosis, but the mechanism of this is unclear, and the changes are similar in the placebo arm (with a smaller population of patients) with a less than 2% risk difference.

Kidney function

Laboratory values related to kidney function were evaluated over the course of the placebo-controlled trials (ISS Group 1). There were no patients in either atogepant or placebo groups with elevated creatinine of at least 1.5X baseline values during the study.

Liver biochemistry

Table 35 summarizes the results of the outlier analyses for the liver biochemistry testing from the placebo-controlled trials (ISS Group 1).

Table 35. ISS Group 1: Patients With One or More Liver Biochemistry Analyte Values Outside Specified Levels, Safety Population

Laboratory Parameter n (%)	Atogepant 10 mg QD N=314	Atogepant 30 mg QD N=411	Atogepant 60 mg QD N=417	Atogepant 30 mg BID N=86	Atogepant 60 mg BID N=91	Total Atogepant N=1,319	Placebo N=408	Risk Difference (95% CI)
Alkaline phosphatase, high (U/L)								
Level 1 (>1.5X ULN)	5/312 (1.6)	2/404 (0.5)	1/409 (0.2)	0/84 (0)	0/88 (0)	8/1,297 (0.6)	4/399 (1.0)	-0.39 (-1.45, 0.68)
Level 2 (>2X ULN)	2/312 (0.6)	0/404 (0)	0/409 (0)	0/84 (0)	0/88 (0)	2/1,297 (0.2)	0/399 (0)	0.15 (-0.06, 0.37)
Level 3 (>3X ULN)	0/312 (0)	0/404 (0)	0/409 (0)	0/84 (0)	0/88 (0)	0/1,297 (0)	0/399 (0)	0 (0, 0)
Alanine aminotransferase, high (U/L)								
Level 1 (>3X ULN)	4/312 (1.3)	2/405 (0.5)	3/409 (0.7)	0/84 (0)	1/88 (1.1)	10/1,298 (0.8)	5/399 (1.3)	-0.48 (-1.67, 0.71)
Level 2 (>5X ULN)	1/312 (0.3)	1/405 (0.2)	1/409 (0.2)	0/84 (0)	0/88 (0)	3/1,298 (0.2)	2/399 (0.5)	-0.27 (-1.01, 0.47)
Level 3 (>10X ULN)	1/312 (0.3)	0/405 (0)	0/409 (0)	0/84 (0)	0/88 (0)	1/1,298 (0.08)	0/399 (0)	0.08 (-0.07, 0.23)
Aspartate aminotransferase, high (U/L)								
Level 1 (>3X ULN)	1/312 (0.3)	3/405 (0.7)	3/409 (0.7)	1/84 (1.2)	0/88 (0)	8/1,298 (0.6)	4/399 (1.0)	-0.39 (-1.45, 0.68)
Level 2 (>5X ULN)	1/312 (0.3)	0/405 (0)	2/409 (0.5)	0/84 (0)	0/88 (0)	3/1,298 (0.2)	3/399 (0.8)	-0.52 (-1.41, 0.37)
Level 3 (>10X ULN)	1/312 (0.3)	0/405 (0)	0/409 (0)	0/84 (0)	0/88 (0)	1/1,298 (0.08)	0/399 (0)	0.08 (-0.07, 0.23)

Source: adlb.xpt; Software: R
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: BID, twice daily; CI, confidence interval; ISS, Integrated Summary of Safety; N, number of patients in treatment arm; n, number of patients meeting criteria; QD, once daily; ULN, upper limit of normal

There were no clear imbalances or significant risk differences in LFTs (alkaline phosphatase [AP], ALT, or AST) between atogepant-treated and placebo-treated groups over the course of these studies. Further consideration of hepatotoxicity as a safety signal (Section 7.7.1) is discussed in detail below.

Creatine phosphokinase levels

Table 36 summarizes the results of an outlier analysis of the blood CPK results from the placebo-controlled trials (ISS Group 1).

Table 36. ISS Group 1: Patients With One or More Creatine Phosphokinase Values Outside Specified Levels, Safety Population

Laboratory Parameter n (%)	ATG 10 mg QD N=314	ATG 30 mg QD N=411	ATG 60 mg QD N=417	ATG 30 mg BID N=86	ATG 60 mg BID N=91	Total ATG N=1,319	Placebo N=408	Risk Difference (95% CI)
CPK, high (U/L)								
Level 1	14/312	13/404	13/409	4/84	3/88	47/1,297	16/399	-0.39
(>3X ULN)	(4.5)	(3.2)	(3.2)	(4.8)	(3.4)	(3.6)	(4.0)	(-2.56, 1.79)
Level 2	9/312	7/404	7/409	2/84	1/88	26/1,297	7/399	0.25
(>5X ULN)	(2.9)	(1.7)	(1.7)	(2.4)	(1.1)	(2.0)	(1.8)	(-1.25, 1.75)
Level 3	3/312	5/404	5/409	1/84	0/88	14/1,297	4/399	0.08
(>10X ULN)	(1.0)	(1.2)	(1.2)	(1.2)	(0)	(1.1)	(1.0)	(-1.05, 1.20)

Source: adlb.xpt; Software: R
Duration is 12 weeks (median 85 days, range 1-111 days).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: ATG, atogepant; BID, twice daily; CI, confidence interval; CPK, creatine phosphokinase; ISS, Integrated Summary of Safety; N, number of patients in treatment arm; n, number of patients meeting criteria; QD, once daily; ULN, upper limit of normal

There were similar fluctuations in CPK values across all treatment arms, including placebo, with approximately 4% of patients in both the atogepant- and placebo-treated arms experiencing an increase in CPK of greater than 3X ULN, and 1% with a CPK greater than 10X ULN. There were no dose-related increases in CPK elevations.

7.6.7. ECG Review

ECG findings related to ischemic events are discussed in Section 7.7.2. Other ECG findings and arrythmia events are reviewed below.

Evaluations were conducted based on predefined criteria for potentially clinically significant ECG changes. There were few ECG changes that met these criteria.

Table 37 displays these changes from the placebo-controlled trials (ISS Group 1), and Table 38 displays these ECG changes from the long-term safety studies (ISS Group 2).

Table 37. ISS Group 1: Potential Clinically Significant ECG Parameter Values

ECG Parameter (Unit)	PCS Criterion	Placebo (N=408)		Atogepant 10 mg QD (N=314)		Atogepant 30 mg QD (N=411)		Atogepant 60 mg QD (N=417)		Atogepant 30 mg BID (N=86)		Atogepant 60 mg BID (N=91)	
		n/N1	%	n/N1	%	n/N1	%	n/N1	%	n/N1	%	n/N1	%
QRS duration (msec)	≥ 150	0/383	0	1/303	(0.3)	1/385	(0.3)	2/400	(0.5)	0/80	0	0/83	0
PR interval (msec)	≥ 250	0/383	0	1/303	(0.3)	0/385	0	0/400	0	0/79	0	1/84	(1.2)
QTcB interval (msec)	> 500	0/383	0	0/303	0	0/385	0	1/400	(0.3)	0/80	0	0/84	0
	Increase > 60	1/383	(0.3)	3/303	(1.0)	0/385	0	3/400	(0.8)	0/80	0	0/84	0
QTcF interval (msec)	> 500	0/383	0	0/303	0	0/385	0	0/400	0	0/80	0	0/84	0
	Increase > 60	1/383	(0.3)	1/303	(0.3)	0/385	0	1/400	(0.3)	0/80	0	0/84	0

Source: Module 5.3.5.3 ISS Table 10-1.1.1
Based on Group 1 Studies (CGP-MD-01 and 3101-301-002).
Percentages are calculated as 100 × (n/N1).
Abbreviations: BID, twice daily; ECG, electrocardiogram; ISS, Integrated Summary of Safety; N, number of participants in the safety population of the treatment group; n, number of participants who met the specified criteria; N1, number of participants with available non-PCS baseline values and at least one postbaseline assessment; PCS, potentially clinically significant; QD, once daily

As indicated in Table 37, these changes occurred in both the placebo and atogepant-treatment arms, with no clear relationship to dose or notable trends in specific parameters.

Table 38. ISS Group 2: Potential Clinically Significant ECG Parameter Values

ECG Parameter (Unit)	PCS Criterion	Standard of Care (N=196)		Atogepant 60 mg QD (N=1198)	
		n/N1	%	n/N1	%
QRS duration (msec)	≥ 150	0/180	0	2/1028	(0.2)
PR interval (msec)	≥ 250	0/179	0	3/1028	(0.3)
QTcB interval (msec)	> 500	0/180	0	1/1029	(0.1)
	Increase > 60	1/180	(0.6)	3/1029	(0.3)
QTcF interval (msec)	> 500	0/180	0	0/1029	0
	Increase > 60	1/180	(0.6)	1/1029	(0.1)

Source: Module 5.3.5.3 ISS Table 10-2.1.1
Based on Group 2 Studies (3101-302-002 and 3101-309-002 with the interim data cut as of May 25, 2020).
Percentages are calculated as 100 × (n/N1).
Abbreviations: ECG, electrocardiogram; ISS, Integrated Summary of Safety; N, number of participants in the safety population of the treatment group; n, number of participants who met the specified criteria; N1, number of participants with available non-PCS baseline values and at least one postbaseline assessment; PCS, potentially clinically significant; QD, once daily

As indicated in Table 38, there were few potentially clinically significant ECG changes that occurred in patients in the long-term safety trial and these also occurred in both the atogepant- and SoC-treatment arms.

In the placebo-controlled trials (ISS Group 1), there were some rare cases of cardiac arrhythmia, with no clear dose-response and no clear increase in atogepant-treated patients over placebo. Four patients on atogepant (one on 10 mg QD, one on 30 mg QD, and two on 60 mg QD) and one patient on placebo developed cardiac arrhythmias (Table 39). All events were mild and resolved without treatment.

Table 39. ISS Group 1: Cardiac Arrythmia, Safety Population

Group Query[1] Preferred Term	ATG 10 mg QD N=314 n (%)	ATG 30 mg QD N=411 n (%)	ATG 60 mg QD N=417 n (%)	ATG 30 mg BID N=86 n (%)	ATG 60 mg BID N=91 n (%)	Total ATG N=1,319 n (%)	Placebo N=408 n (%)	Risk Difference (95% CI)
Cardiac arrhythmias	1 (0.3)	1 (0.2)	2 (0.5)	0	0	4 (0.3)	1 (0.2)	0.1 (-0.5, 0.6)
Atrioventricular block second degree	1 (0.3)	0	0	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Bundle branch block left	0	0	1 (0.2)	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Supraventricular extrasystoles	0	1 (0.2)	0	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Ventricular extrasystoles	0	0	1 (0.2)	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Atrioventricular block first degree	0	0	0	0	0	0	1 (0.2)	-0.2 (-0.7, 0.2)

Source: modified from adae.xpt; Software: R
[1] Grouped queries were based on terms found in Applicant clinical study report ISS Table 7-1.1.1, ISS Table 7-1.2.1, ISS Table 7-1.3.1, ISS Table 7-1.4.1, and ISS Table 7-1.5.1 and the MedDRA version 22.0 narrow SMQ for ischemic heart disease (includes 62 preferred terms).
Risk difference column shows comparison of total atogepant and placebo groups.
Abbreviations: ATG, atogepant; BID, twice daily; CI, confidence interval; ISS, Integrated Summary of Safety; N, number of patients in treatment arm; n, number of patients meeting criteria; QD, once daily; SMQ, standard medical query

In the long-term safety studies (ISS Group 2), the most commonly identified events in the cardiovascular FDA medical query were for arrhythmia, and most of these events occurred under the preferred term of dizziness. Yet, the frequency of dizziness was much lower in the atogepant arm than in the SoC arm. In addition, as stated above, dizziness was not reported in a higher frequency than placebo in the placebo-controlled studies (refer to Table 40). Five patients in the atogepant 60 mg arm experienced a cardiac arrhythmia, one patient each with atrioventricular block (first degree), left bundle branch block, prolonged QT interval on electrocardiogram, sinus bradycardia, and sinus node dysfunction. The patient with sinus node dysfunction had numerous confounders including overdose attempt, initiation of new antidepressants, and a hypotensive episode.

Table 40. ISS Group 2: Adverse Events by System Organ Class (Subset Within Cardiac Disorders), FDA Medical Query (Broad), and Preferred Term, Safety Population

System Organ Class FMQ (Broad) Preferred Term	Atogepant 60 mg QD N=1,198 n (%)	Standard of Care N=196 n (%)	Risk Difference (%) (95% CI)
Palpitations	3 (0.3)	1 (0.5)	-0.2 (-1.3, 0.8)
Palpitations	3 (0.3)	1 (0.5)	-0.2 (-1.3, 0.8)
Acute coronary syndrome	10 (0.8)	3 (1.5)	-0.7 (-2.5, 1.1)
Blood creatine phosphokinase increased	10 (0.8)	3 (1.5)	-0.7 (-2.5, 1.1)
Tachycardia	2 (0.2)	3 (1.5)	-1.3 (-3.1, 0.4)
Tachycardia	2 (0.2)	3 (1.5)	-1.3 (-3.1, 0.4)

System Organ Class FMQ (Broad) Preferred Term	Atogepant 60 mg QD N=1,198 n (%)	Standard of Care N=196 n (%)	Risk Difference (%) (95% CI)
Arrhythmia	38 (3.2)	26 (13.3)	-10.1 (-14.9, -5.2)
Syncope	3 (0.3)	0	0.3 (0, 0.5)
Loss of consciousness	1 (0.08)	0	0.1 (-0.1, 0.2)
Presyncope	1 (0.08)	0	0.1 (-0.1, 0.2)
Sinus bradycardia	1 (0.08)	0	0.1 (-0.1, 0.2)
Sinus node dysfunction	1 (0.08)	0	0.1 (-0.1, 0.2)
Palpitations	3 (0.3)	1 (0.5)	-0.2 (-1.3, 0.8)
Bradycardia	0	1 (0.5)	-0.5 (-1.5, 0.5)
Tachycardia	2 (0.2)	3 (1.5)	-1.3 (-3.1, 0.4)
Dizziness	27 (2.3)	22 (11.2)	-8.9 (-13.5, -4.5)

Source: modified from adae.xpt; Software: R
Duration is mean 32.5 weeks (standard deviation, 18.7; median, 36.1; minimum, 0.1; maximum, 58).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; ISS, Integrated Summary of Safety; N, number of patients in treatment arm; n, number of patients with adverse event; QD, once daily

7.6.8. QT Interval Evaluation

This application was reviewed by the Interdisciplinary Review Team for cardiac safety studies. The Interdisciplinary Review Team concludes that there was no significant corrected QT interval prolongtation effect of atogepant detected.

The Applicant conducted a thorough study (CGP-PK-04) and evaluated the highest dose of 300 mg atogepant. The results of an analysis of the data from this study did not suggest that atogepant is associated with a significant corrected QT interval prolonging effect (Table 41). Nonclinical data support this finding.

Table 41. The Point Estimates and 90% CI (FDA Analysis)

ECG Parameter	Treatment	Time (Hours)	ΔΔQTcF	90% CI (msec)
QTc	Atogepant 30 mg	24	1.2	(-1.0, 3.2)
QTc	Moxifloxacin 400 mg	3	10.8	(8.7, 12.9)

Source: Table 1 Interdisciplinary Review Team review
Abbreviations: CI, confidence interval; ECG, electrocardiogram; QTc, corrected QT interval; QTcF, Fredericia-corrected QT interval

The Interdisciplinary Review Team recommends including in section 12.2 of labeling the following:

Pharmacodynamics

Cardiac Electrophysiology

At a dose 5 times the maximum approved recommended dose, TRADENAME does not prolong the QT interval to any clinically relevant extent.

7.6.9. 120-Day Safety Update

As of November 13, 2020, 2,479 unique participants were exposed to at least one dose of atogepant during the clinical development program for episodic migraine; 997 of these participants received atogepant for ≥6 months (715 at 60 mg QD) and 670 received atogepant for ≥12 months (469 at 60 mg QD).

There were no deaths since the May 25, 2020 cut-off date for the initial NDA.

There were six additional treatment-emergent SAEs (gastritis, *Clostridium difficile* colitis, road traffic accident and concussion, basal cell carcinoma, prostate cancer, and ureterolithiasis), all of which are considered unrelated to study drug.

There were no reports of suicidal ideation with intent to act or of suicidal behavior in Study 3101-309-002.

One additional participant in Study 3101-309-002 (atogepant 60 mg once daily) had a treatment-emergent AST value ≥3X ULN since the safety reporting cut-off for the initial NDA; the Clinical Adjudication Committee adjudicated the elevation as unlikely related to atogepant.

As of January 31, 2021, a total of five participants had ALT and/or AST value ≥3X ULN reported during participation in ongoing studies (one study in CM and one pharmacokinetics [PK] study). Please see review in Section 7.7.1 by Dr. Paul Hayashi for details of these cases and assessment.

7.6.10. Analysis of Submission-Specific Safety Issues

7.6.10.1. Cardiovascular (Including Hypertension), Cerebrovascular, or Peripheral Vascular Disease

Please refer to Section 7.7.2 for a detailed description of this safety issue and an analysis of findings in this application.

7.6.10.2. Hepatotoxicity

Please refer to Section 7.7.1 for a detailed description of this safety issue and an analysis of findings in this application.

7.6.10.3. Gastrointestinal Disorders

Gastrointestinal disorders have been associated with CGRP antagonism, and the erenumab label has a Warning for constipation, including the potential for serious cases. A review of gastrointestinal AEs was conducted to assess if there is an increased risk of these events associated with atogepant use.

Evaluation of TEAEs demonstrated that constipation and nausea were among the most commonly reported in atogepant-treatment patients at 6% (compared to 1% in placebo) and 7% (compared to 3% in placebo), respectively. In addition, constipation and nausea were the most common reasons for discontinuation in the placebo-controlled trials, although the absolute number of patients who discontinued due to these events was small. In the long-term safety studies, constipation was cited as a reason for discontinuation in one patient (0.08%), though other terms in the gastrointestinal disorders category (including nausea, abdominal pain, vomiting, constipation, and dyspepsia) were cited as AEs leading to discontinuation in a total of 13 patients (1.1%).

There is no apparent association with atogepant treatment and serious gastrointestinal events; however, the risk of such events should continue to be evaluated in the postmarketing setting through enhanced pharmacovigilance.

7.6.10.4. Suicidality

Suicidal ideation (SI) and suicidal behavior evaluations were conducted across all clinical trials of atogepant (based on the recommendations to evaluate such risk in the development programs

for all drugs with central nervous system activity as described in the Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials[2]). The clinical trials excluded patients who had significant risk of self-harm based on clinical interview or responses on the C-SSRS (type 4 or 5 on the C-SSRS) in the past 6 months or suicidal behavior in the past 6 months. The C-SSRS has categories with binary responses (yes/no) with Category 1 ("wish to be dead") to Category 5 ("active suicidal ideation with specific plan and intent") and further categorizations with aborted, interrupted, actual and completed suicide (Category 10).

Group 1 - Placebo-Controlled Studies

In Study CGP-MD-01, there was one patient with SI in the 30 mg BID arm ("wish to be dead" with no specific plan or intent). No patients reported suicidal behavior.

In Study 3101-301-002, one patient in atogepant 10 mg arm and two patients in placebo arm reported SI during the double-blind treatment period. No patients reported SI with intent to act. One patient in the placebo arm discontinued the study due to SI with aborted attempt and this patient is not reviewed here.

In total 2 out of 1,142 (0.2%) patients in atogepant-treated arms reported SI compared to 3 out of 408 (0.7%) in the placebo arms.

Group 2 - Long-Term Safety Studies

In the long-term safety study, nine patients (0.8%) in the atogepant 60 mg arm reported SI on the C-SSRS assessment (three with "wish to be dead," three with nonspecific suicidal thoughts, one with active suicidal ideation with some intent to act without a specific plan, and one with a plan and intent), and five patients (2.6%) in the SoC arm reported SI. In the safety follow-up period, an additional three patients (0.3%) reported suicidal ideation in the atogepant 60 mg QD arm.

Suicidal behavior was reported on the C-SSRS assessment by two (0.2%) of atogepant-treated patients during the open-label treatment (both were discontinued from the study) due to actual attempts and one patient (0.5%) reported suicidal behavior in the follow-up period. Two of these cases are described below:

Review of Cases With Suicidal Behavior

(1) Patient (b) (6) was a 28-year-old white female with a history of migraine, obesity, anxiety, major depression, and post-traumatic stress disorder who was enrolled in Study CGP-MD-01 (60 mg QD) and then rolled over to the long-term safety study. On Day 34 of treatment, she took 28 tablets of acetaminophen for abdominal pain and migraine, but she denied suicidal ideation (though a friend thought it was an attempt to self-harm). She was admitted for accidental overdose with acetaminophen. Study treatment was temporarily discontinued, and she was treated for the acetaminophen overdose. On Day 37 that patient self-admitted for post traumatic reaction. The patient then entered the long-term safety study and was placed on atogepant 60 mg daily. On Day 60 of the long-term safety study, she was started on escitalopram 5 mg daily for worsening depression. She was reported to have sinus node dysfunction (tachy-brady syndrome) on Day 71 with

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

low blood pressure and was started on fludrocortisone. On Day 155, the patient had an overdose of escitalopram (exact dose unclear), denied being suicidal and was not admitted. On Day 158, she had suicidal ideation (type 4 C-SSRS) of moderate severity.Study treatment was discontinued on Day 167. This reviewer concludes that an association between her behaviors and atogepant cannot be excluded; however, these events are confounded by her significant psychiatric history.

(2) Patient (b) (6) reported nonsuicidal self-injurious behavior, "active suicidal ideation with specific plan and intent" and an actual attempt (SAE) and was discontinued from the study. This patient was a 36-year-old black woman with a history of migraine, two prior suicide attempts, depression, prior hospitalization for ecstasy use, epilepsy, and a family history of schizophrenia and bipolar disorder per the SAE report. The patient had a history of being abused, had five children, and reported that she was unemployed. On Day 63 of treatment in the long-term safety study with atogepant 60 mg QD, she experienced an SAE of suicide attempt (chronic major depressive disorder with suicidal attempt and psychosis), contusion, and nausea. She reported taking 5 to 10 pills, but the investigator noted that 16 pills were unaccounted for. She was admitted and atogepant was discontinued. She was discharged from the hospital on Day 71. This is a highly confounded case due to prior suicide attempts and psychiatric history, therefore, a relationship of this event to atogepant use is unlikely.

Assessment of SI/Suicidal Behavior

In the placebo-controlled pivotal studies, there were infrequent reports of SI. There were several reports of both SI and suicidal behavior in the long-term safety studies, including one active SI with specific plan and intent, and three overdose attempts that reportedly did not have associated SI, but were clearly overdose situations. All SI in atogepant-treated patients were in patients with a medical history of psychiatric illness except for one patient who reported a nonserious TEAE of SI that resolved. In the placebo-controlled trials, the rate of SI was higher in the placebo arm than in the atogepant treatment arm, and all cases described are confounded, making it unlikely that atogepant contributed to these events. Comorbid depression is common in migraineurs and the risk of suicide or SI in patients with depression is higher than in the general population. This reviewer recommends routine pharmacovigilance in the postmarketing setting to evaluate for suicidality.

7.6.10.5. Pregnancy

Three patients in the safety population in Study CGP-MD-01 became pregnant during the study. Two of the three patients delivered babies that were reportedly healthy (one patient received 27 days of treatment with atogepant 30 mg QD during the first trimester and a second patient ended treatment with atogepant at Day 87 and became pregnant approximately 13 days after discontinuing atogepant 30 mg QD), and the third patient elected to terminate the pregnancy. The patient who terminated the pregnancy was a 19-year-old woman who received atogepant 60 mg daily for 82 days with first trimester exposure. She elected to terminate the pregnancy on Day 96 with an SAE of abortion.

Two patients in Study 3101-301-002 became pregnant during the study. Both patients were randomized to 10 mg daily, treated for 8 and 21 days, respectively, and reportedly gave birth to

full-term healthy infants. One patient who was a 29-year-old white female on atogepant 10 mg daily experienced a ruptured ectopic pregnancy.

Medical Officer's Assessment: *No conclusions can be drawn from the limited information in this application about atogepant and pregnancy outcomes. This reviewer recommends the standard pregnancy registry and postmarketing pregnancy outcomes study to further assess the effect of atogepant on pregnancy and the unborn fetus.*

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Elevation of LFTs and CPK With Atogepant

Issue

Evaluate cases of elevated LFTs and CPK, specifically in the setting of an SAE in which elevated LFTs and CPK were associated with a fatality.

Background

Two oral CGRP receptor antagonists discontinued development (i.e., telcagepant and MK-3207) due to an association with DILI. In the Phase 3 studies with telcagepant, liver injury signals occurred with a relatively short latency of seven days (Holland and Goadsby 2018). The mechanism of liver injury for these agents was postulated to be predominantly the result of a combination of bile acid accumulation (transport inhibition) and oxidative stress (reactive metabolite formation), and less so from mitochondrial toxicity (Smith et al. 2020). In vitro and in silico testing have led to the development of newer CGRP receptor antagonists with the expectation that these agents would not be associated with hepatotoxicity.

At the time of this review, neither of the two recently approved small molecule drugs that act on the CGRP pathway, ubrogepant and rimegepant, have included warnings of DILI based on either the premarketing or postmarketing data.

Of specific interest related to these concerns was one fatal SAE in the development program for atogepant in which a 26-year-old woman experienced elevated LFTs and CPK and an influenza-like illness within 4 weeks of starting atogepant de novo in Study 3101-302-002 (long-term safety).

The DILI team of the Division of Hepatology and Nutrition was asked to review this fatal SAE, as well as the entirety of the application, to evaluate whether there may be a signal for hepatotoxicity with atogepant use (Dr. Paul Hayashi was the reviewer). The Division of Anti-Infectives was also consulted.

Lastly, given the association of elevated CPK with the elevated LFTs, an analysis of any effect of atogepant on CPK, and an evaluation of AE terms related to muscle injury, were also conducted.

Assessment

SAE of Specific Interest

A 26-year-old black female (Patient [redacted] (b) (6) died 43 days after initiating treatment with atogepant 60 mg daily de novo in the long-term safety study. On Day 2, she was started on sertraline 50 mg daily. On Day 4, she reported a "mild influenza like illness" that left her bedridden for several days with fever and myalgias that she treated with over-the-counter drugs, including acetaminophen. She did not seek medical attention for this illness. This event reportedly resolved on Day 8. On Day 29, she experienced elevated LFTs (up to 20X ULN for AST) and CPK (200X ULN) without a reported increase in total bilirubin or changes in coagulation tests. She had no associated signs or symptoms (specifically, no fever, myalgias, abdominal pain, weakness, rash, or fatigue, and a normal physical and neurological exam). Atogepant was discontinued, however her LFTs continued to trend upward (with ALT 205, AST 677, and CPK 38,607). She had been working with a personal trainer and was told to stop exercising. On Day 42, the patient reported "feeling fine" per a MedWatch report. Her ALT and AST had fallen by 50% and her CPK was in the 400s. On Day 43, the patient experienced chest pain and became unresponsive. Emergency services was called by her family. She required cardiopulmonary resuscitation on the way to the hospital, and was successfully resuscitated, but subsequently went into cardiac arrest again and died that day. Autopsy report findings determined that she died from Group A beta hemolytic streptococcal infection (toxic shock syndrome) with the same organism growing from her spleen, lung, and blood. She was noted to have elevated creatinine and CPK at death. The Applicant's assessment was that this event was not related to study treatment.

The DILI team considers it unlikely that this case of elevated transaminases is associated with atogepant use and considers the presence of myositis or myopathy to be better explanations for the elevated AST and ALT, given the extremely high CPK levels. They suggest that the myopathy may have been related to sertraline or excess exercise. The patient's CPK and liver enzymes had fallen by greater than 50% before the onset of shock; therefore, the Division of Anti-Infectives consultant considers it unlikely that the elevated LFTs had a direct relationship to the development of this patient's overwhelming group A streptococcal (GAS) infection and death. Therefore, no clear relationship of atogepant to the elevated transaminases or the infection was identified by these consultants.

The Division of Anti-Infectives Clinical Reviewer's Assessment of this fatal case is extracted from her review, as described below:

Despite this being an atypical case, this patient's clinical history does appear to be consistent with streptococcal toxic shock syndrome related to invasive group A streptococcal infection.

Per the autopsy report, postmortem cultures grew GAS from spleen, lung, and blood. There was no mention of an overt skin or soft tissue infection or other potential nidus. Therefore, the fact that lung cultures were positive supports GAS pneumonia as the most likely source. Although GAS is an uncommon causative pathogen, most cases of GAS pneumonia are community-acquired and occur in immune competent hosts. GAS pneumonia also tends to be aggressive, with approximately 80% of cases leading to bacteremia and a case fatality rate of 38% (Muller et al. 2003).

Of significance, this patient developed a flu-like illness on study Day 4 and was reportedly "bedridden for several days with fever and myalgias." However, she did not seek medical care and presumably was not tested for influenza or other respiratory viruses. Patients with a recent history of respiratory viral infection are at increased risk for bacterial superinfections, including GAS (Muller et al. 2003). Although the five-week delay from the inciting viral illness in this case may have been somewhat prolonged, she may still have been at increased risk for a secondary bacterial pneumonia.

Approximately one third of invasive GAS infections lead to development of streptococcal toxic shock syndrome (Svensson et al. 2000; Ekelund et al. 2005). Toxic shock syndrome is defined by rapid onset (within hours) of shock/hypotension and multiorgan failure. The mortality rate for toxic shock syndrome ranges from 30 to 70% despite aggressive treatment (Nelson et al. 2016). This patient reportedly "felt fine" a day prior to onset of symptoms, but subsequently developed chest pain and shortness of breath the next morning, with rapid clinical deterioration and cardiac arrest within hours of symptom onset. Although this is an example of a severe case, it could certainly be consistent with the typical clinical course of invasive GAS infection/toxic shock syndrome.

Based on the patient's clinical course, including improvement in liver tests prior to onset of infection, lack of evidence of synthetic dysfunction, and potential pulmonary risk factors, it is unlikely that the suspected drug-induced liver injury significantly contributed to her overwhelming GAS infection and subsequent death.

Evaluation of LFTs

A review of LFTs (transaminases) in the atogepant safety database was conducted to evaluate whether there may be a signal for hepatotoxicity with atogepant use.

Overall, there were no clear imbalances in elevation of ALT or AST between the placebo (1.8%) and atogepant treatment arms (1.0%) in the placebo-controlled trials. There were also no cases meeting Hy's Law criteria. In addition, no clear differences in LFTs were observed in the long-term safety studies between the atogepant and SoC arms.

Despite the lack of imbalances in the elevations of LFTs between treatment arms in the controlled trials, there were a total of 10 cases of liver injury identified by Dr. Hayashi in the atogepant database (including the original submission and the 120-Day Safety Update) that were designated as having evidence of a probable or possible relationship to atogepant use. Of the six cases of at least possible DILI that were identified in the original application, he considered four cases as possible, and two cases as probable. The two cases of probable DILI and one representative case of possible DILI due to atogepant are summarized below.

In addition, the 120-Day Safety Update Report included five new cases of transaminase elevations that Dr. Hayashi assessed as follows: one unlikely, one possible, and three probable DILI due to atogepant. Of the four at least possible cases, one case occurred in a healthy volunteer PK study (CGP-PK-14), two cases in a preventive treatment of CM open-label safety study (Study 3101-306-002), and one case in Study 3101-302-002 (a long-term extension study of a preventive treatment of EM study). These were reviewed in detail by Dr. Hayashi in the addendum to his review. No cases met Hy's Law criteria.

Review of the 120-Day Safety Update Report also introduced a concern that the risk of developing transaminase elevations was higher for patients of Asian descent, since Study

3101-306-002, which was an open-label study of 113 Japanese patients, demonstrated a higher rate of transaminase elevation than the overall rate observed in this application. Ultimately, the DILI team concluded that the data do not warrant labeling of a difference in liver injury risk for Asians. Although the ongoing open-label safety study of 113 Japanese patients (Study 3101-306-002) indicated a higher rate of transaminase elevation than the overall rate in the NDA's ISS, no such increase was seen for Asians in the ISS nor the randomized controlled trial from which patient's entered Study 3101-306-002. Therefore, the number of Asians in the ISS is too low to draw conclusions. In addition, the randomized controlled trial had 248 Asians randomized across three arms (placebo, atogepant 30 mg, and atogepant 60 mg), and in that study only 1 out of 248 Asians had elevations in transaminases, which is unlikely to be attributable to study drug. Given that the open-label safety study had no comparator, the DILI team concludes that they cannot definitively assign an increased risk of DILI among Asians based on the current data.

A summary of representative cases of DILI are as follows:

Probable DILI due to atogepant:

- Patient (b) (6) in Study 3101-301-002 was a 39-year-old white female who had elevated LFTs without jaundice 3 weeks after starting atogepant 30 mg QD. At baseline, the patient was on acetaminophen but had normal liver function and CPK tests. She developed elevated LFTs on a routine follow-up visit at 3 weeks but was asymptomatic. Her ALT was 248, AST 107, AP 169, and bilirubin 0.2. Atogepant was held and her LFTs normalized within 9 days. She was restarted on atogepant and her ALT and AST rose to 96 and 55, respectively. She remained asymptomatic. Atogepant was stopped again and follow-up labs 15 days later were normal. She was lost to follow-up thereafter. Given that this patient had a positive rechallenge, a relationship of this event to study drug seems probable.

Probable DILI due to atogepant:

- Patient (b) (6) in Study CGP-MD-01 was a 39-year-old white female who developed elevated transaminases without jaundice 12 days after starting atogepant 60 mg QD. The patient had no history of pre-existing liver disease and drank one alcoholic beverage per week. The patient had normal LFTs at baseline, with a slight increase at screening (only slightly higher than 1X ULN). On Day 13, she had elevated ALT (10X ULN) and AST was 7X ULN (with normal bilirubin and AP). The study drug was stopped 5 days after onset of elevated LFTs. Viral hepatitis serology was negative, autoimmune hepatitis markers were negative, and ultrasound was unrevealing. The patient was taking Excedrin Migraine frequently (every other day) but precise dosing was not provided, and this drug was continued through the washout after stopping study drug.
  - Per Dr. Hayashi, this case is a weak probable DILI due to atogepant. The acetaminophen is a confounder, but its use continued throughout the washout period. The Applicant suggested this case represented nonalcoholic fatty liver disease, but that disease is not typically associated with such an acute rise and fall of ALT. The Applicant also noted that on the day of DILI onset (ALT reported as >300), the patient took a double dose of atogepant. While a relationship of this event is probable, one fact suggesting that this elevation may have been due to another underlying etiology is the high/normal LFTs reported in this patient at baseline; however,

considering the rapid drop in the transaminase levels when the drug was stopped (dechallenge) a relationship of this event to study drug is probable.

Possible DILI due to atogepant:

- Patient [redacted] (b) (6) in Study 3101-302-002 was a 56-year-old white female who developed elevated transaminases without jaundice 24 weeks after initiating treatment with atogepant 60 mg QD. She was taking acetaminophen at baseline and AP was mildly elevated (slightly greater than 1X ULN) at baseline, but her LFTs and CPK were normal. She developed asymptomatic elevation in transaminase levels at 24 weeks, which peaked to ALT 177 and AST 83 one week later. She did have a positive cytomegalovirus immunoglobin M and a flu-like illness that came on after the transaminitis was noted. She continued study drug and her liver enzymes decline by 50% from the peak level, but her LFTs stayed elevated over baseline for weeks 22 to 27 on study drug. The LFTs returned to normal 9 weeks after stopping atogepant.
  - Per Dr. Hayashi, this may be a case of chronic DILI while on atogepant with partial or slow adaptation; however, the 24-week onset (compared to the other probable DILI case) is a long latency. Autoimmune hepatitis may have played a role but the fact that the injury did resolve without treatment and after the drug was discontinued makes it less consistent with a diagnosis of autoimmune hepatitis.

Evaluation of CPK

Given that there were several cases of elevated CPK in association with elevated LFTs, an analysis of CPK-related findings (as a TEAE and as a laboratory abnormality) was conducted.

There have been no definite associations of elevated CPK values with the approved drugs/biologics that act on the CGRP pathway to date.

As noted previously during the review of laboratory findings (Section 7.6.6), CPK results fluctuated across all treatment arms, including placebo, with approximately 4% of both the atogepant- and placebo-treated patients experiencing an increase in CPK of >3X ULN and 1% with a CPK >10X ULN. There was no dose-related increase in CPK elevations.

Discontinuations due to elevated CPK or muscle symptoms were also assessed. In Study CGP-MD-01, one patient (Patient [redacted] (b) (6)) discontinued due to elevated CPK on Day 43, and two patients discontinued due to myalgia, one reported on study Day 2 (Patient [redacted] (b) (6)) and one on study Day 21 (Patient [redacted] (b) (6)). Patient [redacted] (b) (6), a 21-year-old black female who was randomized to atogepant 10 mg daily, was found to have a mild severity elevation in CPK on Day 43 and was discontinued from the study. Patient [redacted] (b) (6) was assigned to placebo and reported myalgia on Day 2 and was discontinued from the study. Patient [redacted] (b) (6) a 62-year-old white female, reported myalgia and palpitations on Day 21 (and heartburn on Day 28). In Study 3101-301-002, one patient (Patient [redacted] (b) (6)) discontinued due to leg cramps that began within a month of starting treatment.

TEAEs related to elevated CPK were also analyzed. As noted previously, the preferred term “blood creatine phosphokinase increased” was assessed. This AE term was reported in 2.4% of patients across all atogepant-treated groups compared to 1.2% of patients in the placebo arms for a risk difference of 1.2 (CI: -0.2, 2.5); however, there did not appear to be any dose-related increase in this finding (Table 42).

Additionally, the following grouped queries from the placebo-controlled trials were conducted to assess muscle injury and musculoskeletal pain.

Table 42. ISS Group 1: Grouped Queries, Safety Population

Grouped Query	ATG 10 mg QD N=314 n (%)	ATG 30 mg QD N=411 n (%)	ATG 60 mg QD N=417 n (%)	ATG 30 mg BID N=86 n (%)	ATG 60 mg BID N=91 n (%)	Total ATG N=1,319 n (%)	Placebo N=408 n (%)	Risk Difference (95% CI)
Muscle injury	17 (5.4)	19 (4.6)	18 (4.3)	6 (7.0)	4 (4.4)	64 (4.9)	16 (3.9)	1 (-1.3, 3.1)
Musculoskeletal symptoms	10 (3.2)	14 (3.4)	16 (3.8)	0	3 (3.3)	43 (3.3)	15 (3.7)	-0.4 (-2.5, 1.6)

Source: adae.xpt; Software: R
Group query muscle injury contains: blood creatine phosphokinase increased, musculoskeletal stiffness, musculoskeletal pain, muscle strain, muscle tightness, musculoskeletal chest pain, myalgia, blood creatinine increased, muscle spasms, muscle twitching, muscular weakness. Group query musculoskeletal symptoms contains: back pain, neck pain, musculoskeletal stiffness, musculoskeletal pain, muscle tightness, musculoskeletal chest pain, myalgia, neuropathic muscular atrophy, muscle spasms, flank pain, muscle twitching, fibromyalgia, muscular weakness.
Duration is 12 weeks (median 85 days, range 1-111 days).
Abbreviations: BID, twice daily; CI, confidence interval; ISS, Integrated Summary of Safety; N, number of subjects in treatment arm; n, number of subjects with adverse event; QD, once daily

This analysis did not indicate an increase in muscle injury or musculoskeletal AEs in the atogepant-treated groups compared to placebo. The analysis of individual TEAE terms (related to muscle injury or CPK elevations) and laboratory analyses of CPK elevations also did not indicate an increase in these events in the atogepant-treated groups compared to placebo.

Conclusion

The analysis for liver injury demonstrates that there were several cases of transaminase elevations in patients taking atogepant in clinical trials where the relationship to atogepant was considered either probable or possible. No Hy's law cases were identified, and there was no imbalance of LFT abnormalities overall between atogepant and placebo-treated patients.

The Division of Hepatology and Nutrition DILI team concludes that there was no significant liver toxicity that would threaten approval of atogepant. The fatal case did not involve DILI. The team also notes that there were 10 DILI cases described in the atogepant safety database that were assessed as having either a probable or possible relationship to atogepant use. All cases were asymptomatic and resolved with discontinuation of atogepant. The DILI team recommends language for lableing and also concluded the following:

(1) Routine blood tests for liver enzyme monitoring is not necessary.

(2) The use of atogepant should be avopided in patients with severe hepatic impairment.

Following labeling negiotiations, the following language for Section 6 of the Prescribing Information was agreed-upon related to this issue:

> In Study 1 and Study 2, the rate of transaminase elevations over 3 times the upper limit of normal was similar between patients treated with QULIPTA (1.0%) and those treated with placebo (1.8%). However, there were cases with transaminase elevations over 3 times the upper limit of normal that were temporally associated with QULIPTA treatment; these were asymptomatic, and resolved within 8 weeks of discontinuation. There were no cases of severe liver injury or jaundice.

Regarding the evaluation of whether there is a signal in the current database for muscle injury, the analyses conducted of CPK values, AE terms related to muscle injury, and the review of specific cases, did not demonstrate a clear increased risk for muscle injury in patients taking atogepant.

7.7.2. Increased Ischemic Vascular Risk

Issue

Evaluate if there is an increased risk of vascular ischemia, specifically ischemic cardiovascular events, hypertensive events, ischemic cerebrovascular events, or thrombotic events with the use of atogepant.

Background

Theoretical safety concerns associated with CGRP inhibition include cardiovascular, cerebrovascular, and peripheral vascular events. Specifically, CGRP is thought to play a role in compensatory vasodilatation in the setting of tissue ischemia; therefore, there is a concern that CGRP antagonism may increase the risk of ischemic events (Aradi et al. 2019; Mulder et al. 2020).

The prescribing information for erenumab (Aimovig), another drug that acts on the CGRP pathway, was amended after initial approval to include hypertension in the Warnings and Precautions section after postmarketing surveillance revealed an association between elevated blood pressure and erenumab (Saely et al. 2021).

Assessment

Ischemic vascular events discussed in this section focus on ischemic cardiovascular disease, hypertension, ischemic cerebrovascular disease, and thrombotic events. The general approach provides an analysis of SAEs, AEs, discontinuations, and relevant narratives by safety signal, followed by an overall assessment of the safety signal as it relates to atogepant use.

Ischemic Cardiovascular Disease

An analysis of AEs, SAEs, ECG changes related to ischemia, and discontinuations related to cardiovascular risk was conducted to assess if there is an increased risk of cardiovascular ischemic events with atogepant use compared to placebo in the pivotal trials (ISS Group 1) and long-term safety studies (ISS Group 2).

Patients with cardiovascular risk factors at baseline were enrolled in the placebo-controlled trials. A baseline history of hypertension was reported by approximately 10 to 11% of patients in each arm across the placebo-controlled studies.

A search of the preferred term “ischemic heart disease” yielded no cases in any group for the placebo-controlled trials (ISS Group 1) and long-term safety studies (ISS Group 2). There were no discontinuations related to ischemic events.

No ECG changes seen in this application appeared to be related to cardiovascular ischemic events. ECG changes not related to ischemic changes are discussed in Section 7.6.7of this review.

Medical Officer's Assessment: *Few cardiovascular events were reported across groups (presented previously) and no dose-dependent relationship in the risk of these events was evident. There were no ischemic heart disease events in the atogepant arms of the placebo-controlled or long-term safety studies. The data do not indicate an increased risk of ischemic cardiovascular events with use of atogepant; however, enhanced pharmacovigilance in the postmarketing setting is recommended. This approach is consistent with that taken for all of approved drugs of this class, to date.*

Cerebrovascular Ischemic Events

Cerebrovascular ischemic events were evaluated. There were few cerebrovascular events reported across the placebo-controlled trials (ISS Group 1) (Table 43).

Table 43. Group 1: Cerebrovascular Grouped Queries, Safety Population

Group Query1 Preferred Term	ATG 10 mg QD N=314 n (%)	ATG 30 mg QD N=411 n (%)	ATG 60 mg QD N=417 n (%)	ATG 30 mg BID N=86 n (%)	ATG 60 mg BID N=91 n (%)	Total ATG N=1,319 n (%)	Placebo N=408 n (%)	Risk Difference (95% CI)
Central nervous system vascular disorders	0	1 (0.2)	1 (0.2)	0	0	2 (0.2)	0	0.2 (-0.1, 0.4)
Hemiparesthesia	0	0	1 (0.2)	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Intracranial aneurysm	0	1 (0.2)	0	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)

Source: adae.xpt; Software: R
[1] Grouped queries were based on terms found in Applicant clinical study report ISS Table 7-1.1.1, ISS Table 7-1.2.1, ISS Table 7-1.3.1, ISS Table 7-1.4.1, and ISS Table 7-1.5.1
Abbreviations: ATG, atogepant; BID, twice daily; CI, confidence interval; ISS, Integrated Summary of Safety; N, number of subjects in treatment arm; n, number of subjects with adverse event; QD, once daily

The following are narratives of patients who experienced possible cerebrovascular events in a placebo-controlled trial (first patient) and long-term safety study (second patient).

(1) Patient (b) (6) in Study 3101-301-002 was a 44-year-old white female randomized to atogepant 60 mg QD who experienced hemiparesthesia on Day 19 of the study that resolved on Day 36. The patient continued on atogepant treatment She also had reported anxiety on Day 26. Treatment was discontinued on Day 39 due to lack of efficacy. Although this patient discontinued treatment early, the rationale provided was that it was related to lack of efficacy, not this event.

(2) Patient (b) (6) was a 41-year-old white female with a history of migraine, hyperlipidemia, obesity, and was on oral contraceptives (estrogen containing) who experienced transient blindness (of left eye reported as moderate severity) on Day 22 of treatment with atogepant 60 mg QD. This event resolved on the same day and was not considered related to treatment. On Day 32, she reported intractable headache (status migrainosus) and study drug was discontinued. On Day 36, she had an MRI of the brain performed that showed no evidence of acute infarct and normal circle of Willis, but did demonstrate tiny nonspecific foci of T2/flair hyperintensity in cerebral white matter. She was admitted and treated for status migrainosus and discharged on Day 44 after resolution.

***Medical Officer's Assessment**: The first patient's event of hemiparesthesia may have been related to a transient ischemic attack, but this may have also been related to anxiety or a complicated migraine. Another patient in this database, discussed previously, experienced an SAE that may also have represented a transient ischemic attack. Both of these cases were confounded by other concomitant diagnoses, but a relationship between atogepant use and these possible cerebrovascular symptoms cannot definitively be ruled out.*

The second patient's transient vision loss may have been the result of ischemia, but it may also have resulted from an aura occurring with the migraine. Given that a workup followed to evaluate this patient for ischemia, it seems that transient ischemic attack was in the differential. Since an MRI (~14 days later) did not show evidence of acute/subacute infarct, no conclusive diagnosis can be made.

Overall, a relationship of these events to atogepant cannot be ruled out. Given the continued uncertainty of the relationship of atogepant to possible cerebrovascular ischemic events, this reviewer recommends enhanced pharmacovigilance in the postmarketing setting to evaluate for this possible safety signal. This approach is consistent with that taken for all of approved drugs of this class, to date.

Hypertensive Events

Events related to hypertension were evaluated. As mentioned above, a history of hypertension was reported by 10 to 11% of patients across all treatment groups in the placebo-controlled studies. Hypertension events were reported in 0.2% of the placebo group, compared to 0.6%, 1.0%, and 0.2% in the atogepant 10 mg, 30 mg, and 60 mg arms, respectively. The narratives are reviewed below. New antihypertensive medication use was examined by the Applicant and occurred in 0.5%, 0.6%, 1.0% and 0% of patients in the placebo, 10 mg, 30 mg, and 60 mg arms, respectively.

Table 44. ISS Group 1: Cardiovascular Grouped Queries, Safety Population

Group Query[1] Preferred Term	ATG 10 mg QD N=314 n (%)	ATG 30 mg QD N=411 n (%)	ATG 60 mg QD N=417 n (%)	ATG 30 mg BID N=86 n (%)	ATG 60 mg BID N=91 n (%)	Total ATG N=1,319 n (%)	Placebo N=408 n (%)	Risk Difference (95% CI)
Hypertension	2 (0.6)	4 (1.0)	1 (0.2)	1 (1.2)	1 (1.1)	9 (0.7)	1 (0.2)	0.4 (-0.2, 1.1)
Hypertension	1 (0.3)	4 (1.0)	0	1 (1.2)	1 (1.1)	7 (0.5)	0	0.5 (0.1, 0.9)
Blood pressure diastolic increased	1 (0.3)	0	1 (0.2)	0	0	2 (0.2)	0	0.2 (-0.1, 0.4)
Blood pressure increased	0	1 (0.2)	0	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Blood pressure fluctuation	0	0	0	0	0	0	1 (0.2)	-0.2 (-0.7, 0.2)

Source:: adae.xpt; Software: R
[1] Grouped queries were based on terms found in Applicant clinical study report ISS Table 7-1.1.1, ISS Table 7-1.2.1, ISS Table 7-1.3.1, ISS Table 7-1.4.1, and ISS Table 7-1.5.1 and the MedDRA version 22.0 narrow SMQ for ischemic heart disease (includes 62 preferred terms).
Abbreviations: ATG, atogepant; BID, twice daily; CI, confidence interval; ISS, Integrated Summary of Safety; N, number of subjects in treatment arm; n, number of subjects with adverse event; QD, once daily

Cases of new-onset or worsening hypertension were also reviewed. In the placebo-controlled trials (ISS Group 1), hypertension events occurred in 0.7% (9) of patients in the atogepant groups

compared to 0.2% (1) in the placebo group. All narratives were reviewed; however, selected narratives are summarized below.

- Patient (b) (6) was a 33-year-old black female, randomized to atogepant 30 mg BID, who had worsening hypertension and was discontinued from treatment on Day 54. The hypertension was mild in severity. Her predose sitting blood pressure was 136/96 mm Hg. On Day 54, her sitting blood pressure was 150/108 mm Hg. Atogepant was discontinued due to worsening hypertension and noted as not related to study treatment by the Applicant.
- Patient (b) (6) was a 48-year-old white female with a history of hypertension on medications, who received atogepant 30 mg QD with predose blood pressure of 142/91 mm Hg. The patient had worsening hypertension (no reading recorded) and urinary tract infection on Day 63. She had valsartan increased to 80 mg twice daily. Her blood pressure medications were changed during the study with repeat measurements as high as 148/92 mm Hg. She completed the study as this was not considered related to study treatment by the Applicant.

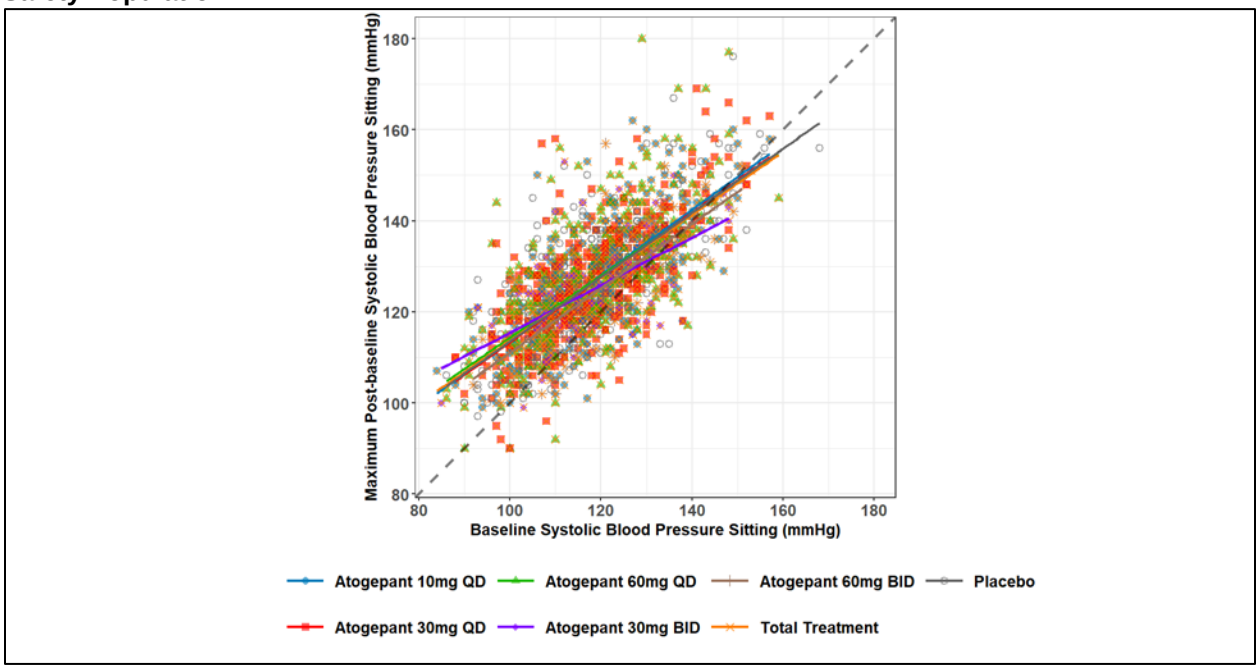
The risk of hypertensive events was examined in the long-term safety studies. Interpretation of these data are limited by the open-label nature of these studies.

A baseline history of hypertension was reported by 9.2% of patients in the SoC group and 12.7% of patients in the atogepant 60 mg QD group. Changes to existing medications to treat hypertension occurred in 3.0% of the atogepant 60 mg daily group. Analysis of blood pressure changes over the course of the long-term safety studies did not reveal any changes or safety concerns. Evaluation of patients based on predefined criteria for potentially clinically significant elevations demonstrated similar changes across groups for both the SoC and atogepant-treated arms in the long-term safety studies.

In ISS Group 2, Patient (b) (6) discontinued study drug due to worsening of hypertension. This event was assessed as mild in severity.

An analysis of systolic blood pressure data in the placebo-controlled trials (Figure 16) did not reveal any imbalances, dose-dependent changes, or clear safety concerns linking elevated blood pressure with atogepant use as compared to placebo.

Figure 16. ISS Group 1: Baseline Versus Maximum Systolic Blood Pressure by Treatment Group, Safety Population



Source: advs.xpt; Software: R
Gray line represents no increase.
Abbreviations: BID, twice daily; ISS, Integrated Summary of Safety; QD, once daily

Medical Officer's Assessment: *It is difficult to assess a causal association with study drug in any of the cases with hypertensive events, since all the patients had a baseline or predose (i.e., prior to the first dose of atogepant) elevated blood pressure reading. Several patients had been on antihypertensive agents or were started on treatment for high blood pressure during the trial. Some patients had blood pressure readings normalize during continued treatment with atogepant and others had continued slight elevations in blood pressure readings. There was no clear dose-related increase in high blood pressure as slight elevations occurred with most doses (ranging from 10 mg QD to 30 mg BID to 60 mg QD, but none in the 60 mg BID arm).*

Only one patient had study drug discontinued and she was not rechallenged. Given that all patients had an elevated blood pressure reading at follow-up in the cases reviewed, and that the vital sign outlier analyses of both systolic and diastolic blood pressure did not demonstrate an imbalance in the atogepant-treated arms as compared to placebo arms, it is unclear at this time if atogepant causes worsening hypertension in patients with baseline high blood pressure.

Therefore, the review of all the hypertensive events associated with atogepant use does not indicate a clear safety signal; however, this reviewer recommends enhanced pharmacovigilance in the postmarketing setting based on mechanistic plausibility and the occurrence of similar events noted with at least one other drug that acts on the CGRP pathway. This approach is consistent with that taken for other approved drugs of this class.

Thrombotic events

There were two patients in the placebo-controlled trials (ISS Group 1) who experienced thrombotic events. The narratives are provided below:

- Patient (b) (6) was a 35-year-old white female with a BMI of 45.4 kg/m^2 in Study CGP-MD-01 who experienced a deep vein thrombosis on Day 6 of the study that was assessed by the Applicant as not related to atogepant 60 mg BID. The drug was continued, and the event resolved on Day 109.
- Patient (b) (6) was a 50-year-old white female with a BMI 39.1 kg/m^{2}in Study 3101-301-002 who, experienced a postoperative thrombosis on Day 17 of the study (following an unspecified preplanned procedure) and study drug (atogepant 60 mg QD) was continued.

There was one patient who experienced a thrombotic event in the long-term safety study (ISS Group 2). The narrative is provided below:

- Patient (b) (6) was a 57-year-old white female with a history of migraine, peripheral artery occlusion and peripheral artery stent who completed the pivotal study on atogepant 10 mg QD and rolled over into the long-term safety study on 60 mg QD. She experienced an event of worsening peripheral arterial occlusive disease (unclear start date but was started on cilostazol 100 mg daily to treat this on Day 41). Atogepant was discontinued on Day 56.

Medical Officer's Assessment: *The cases described in the placebo- controlled trials patients have an unclear association with atogepant although the postoperative case was most likely procedure related. The event that occurred in the open-label safety study of worsening peripheral vascular disease is confounded since the patient had underlying disease with a history of a stent. It is unclear if atogepant contributed to this event since the patient had been on a 10 mg dose for 3 months without a similar event and then transitioned to a higher dose when the event occurred.*

Overall, the data do not indicate an increase in the risk of thrombotic events in the atogepant safety database.

Conclusion

Vascular risk related to atogepant was assessed by analyzing cardiovascular (ischemic) events, hypertensive events, cerebrovascular ischemic events, and thrombotic events. The analysis of SAEs, TEAEs, selected patient narratives, vital signs, and ECG data did not reveal an increase in cardiovascular or cerebrovascular ischemic events related to atogepant use in this application. There were several patients with baseline/predose high blood pressure readings who had continued elevated blood pressure readings after treatment with atogepant. The safety data provided in this application related to vascular risk do not support inclusion of language regarding vascular risk in the label of atogepant. Enhanced pharmacovigilance in the postmarketing setting for cardiovascular events, cerebrovascular events, and hypertension is recommended by this reviewer.

7.7.3. Decreased Body Weight

Issue

Evaluate if decreased body weight is appropriate for inclusion in labeling.

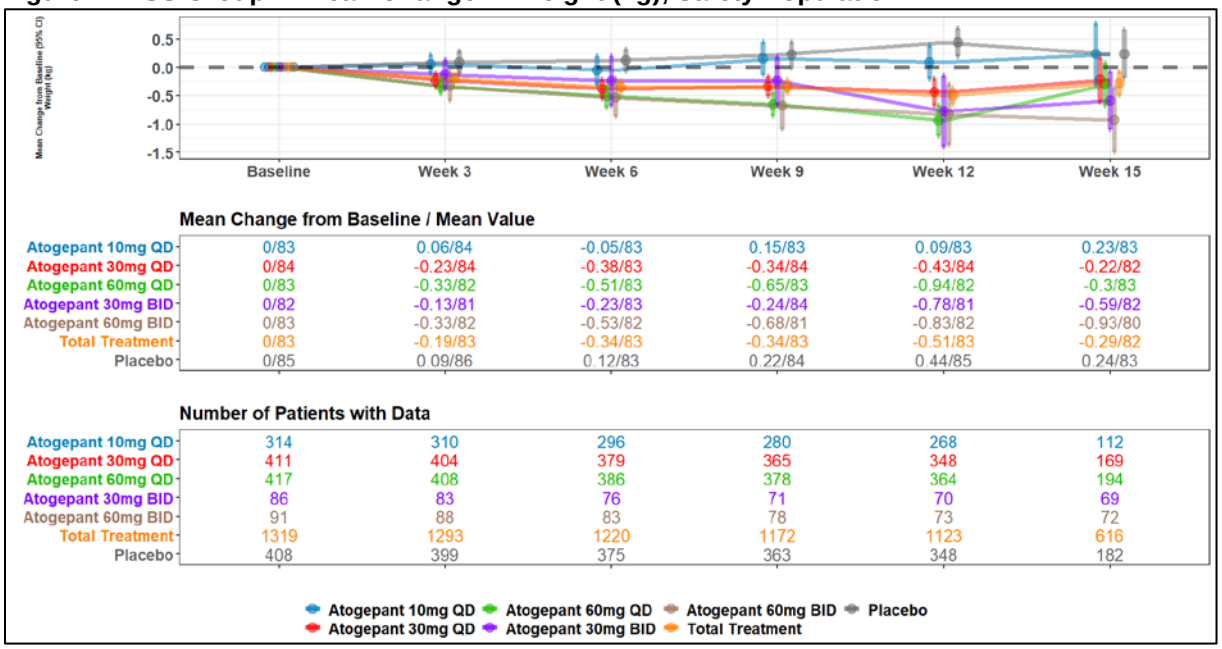
Background

The Applicant asserts that data from the atogepant development program demonstrate an increased risk of weight loss with treatment that should be described in labeling; however, the potential also exists that such a statement could also be viewed as promotional. Therefore, an assessment of this risk was conducted along with a consideration of any appropriate related description in labeling.

Assessment

As displayed in Figure 17, Dr. Bunner analyzed the mean change and percent change from baseline for weight (kg) and BMI (kg/m^2).

Figure 17. ISS Group 1: Mean Change in Weight (kg), Safety Population



Mean Change from Baseline / Mean Value

	Baseline	Week 3	Week 6	Week 9	Week 12	Week 15
Atogepant 10mg QD	0/83	0.06/84	-0.05/83	0.15/83	0.09/83	0.23/83
Atogepant 30mg QD	0/84	-0.23/84	-0.38/83	-0.34/84	-0.43/84	-0.22/82
Atogepant 60mg QD	0/83	-0.33/82	-0.51/83	-0.65/83	-0.94/82	-0.3/83
Atogepant 30mg BID	0/82	-0.13/81	-0.23/83	-0.24/84	-0.78/81	-0.59/82
Atogepant 60mg BID	0/83	-0.33/82	-0.53/82	-0.68/81	-0.83/82	-0.93/80
Total Treatment	0/83	-0.19/83	-0.34/83	-0.34/83	-0.51/83	-0.29/82
Placebo	0/85	0.09/86	0.12/83	0.22/84	0.44/85	0.24/83

Number of Patients with Data

	Baseline	Week 3	Week 6	Week 9	Week 12	Week 15
Atogepant 10mg QD	314	310	296	280	268	112
Atogepant 30mg QD	411	404	379	365	348	169
Atogepant 60mg QD	417	408	386	378	364	194
Atogepant 30mg BID	86	83	76	71	70	69
Atogepant 60mg BID	91	88	83	78	73	72
Total Treatment	1319	1293	1220	1172	1123	616
Placebo	408	399	375	363	348	182

Source: advs.xpt; Software: R
Abbreviations: BID, twice daily; CI, confidence interval; ISS, Integrated Summary of Safety; QD, once daily

The mean change in weight across arms appeared to be greatest at the end of treatment visit (Week 12) and demonstrated a dose-response, with doses up to 60 mg BID having the greatest decrease in weight. With respect to the three daily doses, the 10 mg dose appeared to be associated with an increase in weight of 0.09 kg compared to a decrease in the 30 mg QD (weight loss of 0.22 kg) and 60 mg daily arms (weight loss of 0.94 kg) at the end of treatment (12 weeks of placebo-controlled treatment).

To evaluate for a change that may be considered clinically meaningful, Dr. Bunner also conducted an analysis to evaluate how many patients had experienced a ≥5% weight loss and ≥7% weight loss at any time during the study (Table 45). The ≥5% cutoff was chosen based on the clinically meaningful threshold used in Prescribing Information (PI) for orlistat (Zenical) (Cheplapharm) and phentermine (Qsymia) (Vivus), two drug products indicated for weight loss. Furthermore, the ≥7% cutoff was chosen based on the PI for sertraline (Zoloft) (Pfizer) where weight loss is described as a safety finding.

Table 45. ISS Group 1: Incidence of 5% and 7% Weight Loss and Gain at Any Time in the Study, Safety Population

Weight Category	ATG 10 mg QD N=314 n (%)	ATG 30 mg QD N=411 n (%)	ATG 60 mg QD N=417 n (%)	ATG 30 mg BID N=86 n (%)	ATG 60 mg BID N=91 n (%)	Total ATG N=1,319 n (%)	Placebo N=408 n (%)	Risk Difference (95% CI)
≥5% loss	24 (7.6)	29 (7.1)	56 (13.4)	10 (11.6)	10 (11)	129 (9.8)	28 (6.9)	2.92 (-0.01, 5.85)
≥7% loss	12 (3.8)	13 (3.2)	20 (4.8)	4 (4.7)	6 (6.6)	55 (4.2)	11 (2.7)	1.47 (-0.43, 3.38)
≥5% gain	24 (7.6)	21 (5.1)	18 (4.3)	2 (2.3)	3 (3.3)	68 (5.2)	28 (6.9)	-1.71 (-4.44, 1.02)
≥7% gain	7 (2.2)	6 (1.5)	4 (1)	1 (1.2)	0	18 (1.4)	12 (2.9)	-1.58 (-3.33, 0.18)

Source: ISS Group 1 advs, adsl. Software: R
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: ATG, atogepant; BID, twice daily; CI, confidence interval; ISS, Integrated Summary of Safety; N, number of patients in treatment arm; n, number of patients meeting criteria; QD, once daily

Weight Changes

Table 45 demonstrates that ≥5% and ≥7% weight loss occurred at any time during the study at similar frequencies in the atogepant 10 mg and 30 mg arms and placebo arms; however, the 60 mg QD arm had a 13.4% incidence of ≥5% weight loss and a 4.7% incidence of ≥7% weight loss, which is a 6.5% and 2% risk difference, respectively, from placebo. Across all arms, the treatment difference for ≥5% weight loss was ~3% between all atogepant-treated and placebo arms. Approximately 2/3 of patients who experienced ≥5% or ≥7% weight loss at any time, had this weight loss demonstrated at the end of treatment (Week 12) visit. Treatments were discontinued at this visit, so the end of study visit would represent 4 weeks off treatment. Almost half of patients had the weight loss ≥5% sustained at the end of study visit.

Of the 157 experiencing ≥5% weight loss:

- 47 patients were normal weight (BMI ≤25)
- 54 patients were overweight (BMI 25 to ≤30)
- 56 patients were obese (BMI ≥30 [range 30 to 53.8])

An outlier analysis of weight gain was also conducted. The data (not shown) suggest that more patients in the placebo arms gained weight compared to those on higher doses (≥30 mg daily) of atogepant.

In the long-term safety study, weight loss ≥5% had an incidence of 30.9% in the atogepant 60 mg QD arm and 24.5% in the SoC arm. Of note, ~36% of patients in the SoC arm were taking topiramate, which has an established relationship with weight loss. The maximum weight loss of -1.7 kg (3.7 pounds) occurred at Months 6 to 9. The weight loss appeared sustained out to 12 months in the long-term safety study, though there was a two-thirds attrition of patients by the end of the long-term safety study, limiting interpretability of these results.

There are no clear patterns to weight change, in terms of which patients were disproportionately affected (higher or lower weight, gender, race, or age).

Associated symptoms and weight changes:

Given that nausea and decreased appetite were examined in association with weight changes and that there was a relatively low frequency of any these preferred terms (e.g., nausea, decreased

appetite and reported weight loss), no associations could be drawn from these subgroup analyses (not shown).

Conclusion

A mild degree of weight loss (mean weight loss of 0.43 kg [0.95 pounds] to 0.94 kg [2.1 pounds]) appears to be associated with use of atogepant 30 mg and 60 mg daily, respectively. Across all arms of the placebo-controlled studies, 9.8% of atogepant-treated patients, compared to 6.9% of placebo-treated patients experienced ≥5% weight loss. In addition, the proportion of patients with a weight decrease ≥7% at any point was 2.8% for placebo, 3.8% for atogepant 10 mg, 3.2% for atogepant 30 mg, and 4.9% for atogepant 60 mg. Weight gain does not appear to be associated with atogepant use.

Based on the review of weight changes in the placebo-controlled trials, this reviewer recommends including the following statement in labeling:

> The proportion of patients with a weight decrease (b) (4) 7% at any point was 2.8% for placebo, 3.8% for atogepant 10 mg, 3.2% for atog pant 30 mg, and 4.9% for (b) (4) 60 mg.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Hepatic Impairment

In a dedicated hepatic impairment (HI) clinical study (CGP-PK-01) in subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) HI, the total atogepant area under the plasma concentration-time curve (AUC) increased by 24%, 15%, and 38%, respectively relative to healthy controls. Based on the magnitude of impact of HI on the total atogepant exposures, the Applicant proposed (b) (4)

The protein binding data collected at predose and 2 hours postdose from the HI study indicated that the subjects with normal hepatic function, mild, moderate, or severe HI showed varied free fraction (% unbound) of atogepant at 1.8%, 2.6%, 2.9%, and 4.7%, in human plasma, respectively. Based on protein binding data collected from all the subjects, the unbound atogepant AUC increased to 1.84, 1.91, and 3.66-fold in subjects with mild, moderate, or severe HI relative to healthy controls, respectively. Based on the absorption, distribution, metabolism, and excretion properties, atogepant is likely to be considered as a low hepatic extraction drug and the clinical significance of changes in unbound concentrations of atogepant is not clear. In addition, the analysis on unbound atogepant PK has few limitations, e.g., plasma protein binding data were collected at limited time-points to derive unbound exposures, and thus the characterization of unbound atogepant PK should be interpreted as an exploratory assessment (refer to Section 14.2, Study CGP-PK-01 for additional details).

Based on the magnitude of impact of mild and moderate HI on total and unbound atogepant exposures (i.e., less than 2-fold increase in AUC based on unbound concentrations noted above as a worst-case scenario), the review team agrees with the Applicant's proposal to not adjust

doses in subjects with mild or moderate HI. This is because a clear dose-/exposure-efficacy relationships in the dose range of 10 mg QD to 60 mg BID was not observed in the Phase 2 and Phase 3 studies. In addition, there is adequate benefit/risk for the 10 mg to 60 mg QD dose (refer to Section 7.6). Although the 60 mg BID is not proposed for general dosing, the review team believes that the clinical experience with this dosing regimen provides appropriate safety coverage if potential increases in unbound atogepant concentrations in hepatic impairment have any clinical relevance. In patients with severe HI, dose adjustment to 10 mg QD may be a reasonable approach from a PK perspective, based on less than 4-fold increase in AUC on unbound concentrations noted above as a worst-case scenario, and lack of a clear dose-exposure-efficacy relationship in more than 6-fold range in dosing regimen noted above. However, a DILI assessment of atogepant suggests a potential for liver toxicities with atogepant (refer to Section 7.7.1). Therefore, the review team agrees with the recommendation from DILI team to avoid the use of atogepant in patients with severe HI.

In conclusion, the review team recommends that no dose adjustment is needed in patients with mild or moderate HI and avoid use in patients with severe HI.

Renal Impairment

Renal elimination is a minor excretion pathway for atogepant (5% excreted in urine as unchanged) and the Applicant did not conduct a dedicated renal impairment (RI) study. The population PK analysis using pooled PK data from clinical studies CGP MD-01 and 3101-301-002 did not reveal a significant difference in the PK of atogepant in patients with mild (creatinine clearance [CLcr] 60 to 89 mL/min, N=161) or moderate (CLcr 30 to 59 mL/min, N=13) RI, relative to those with normal renal function (CLcr >90 mL/min, N=1,182). Therefore, the Applicant proposed that no dose adjustment is needed in subjects with mild or moderate RI. Based on a lack of a clinically relevant impact of mild and moderate RI on atogepant exposures, the review team agrees with the Applicant's labeling proposal to not adjust doses in subjects with mild or moderate RI.

There were no subjects with CLcr less than 30 mL/min in the population PK analysis dataset. The Applicant used a physiologically based pharmacokinetics (PBPK) model to predict atogepant exposure in subjects with severe RI and proposed atogepant (b) (4) However, owing to concerns related to the reliability of the predictive performance of PBPK modeling in the RI population, the review team does not agree with relying PBPK predictions to guide dose adjustment in patients with severe RI and ESRD at this time. The review team recommends dose adjustment in patient with severe RI (CLcr 15 to 29 mL/mL) and ESRD (CLcr <15 mL/min) as 10 mg QD. The key considerations to support this recommendation include: (1) renal excretion is a minor route for atogepant elimination, as noted above; (2) RI of any degree is not expected to significantly affect exposures and the population PK analysis confirmed the minimal impact on atogepant exposure in patients with mild or moderate RI; (3) Even if there is some increase in exposures in subjects with CLcr less than 30 mL/min, there is over 6-fold margin (as noted above) with the lowest dose recommended (i.e., 10 mg); (4) there is no clear dose-/exposure-response relationship for efficacy in the atogepant dose range of 10 mg QD to 60 mg BID; and (5) if RI affects hepatic function, the observed increase in total and unbound AUC in severe HI is 1.38 and 3.66-fold, respectively. Even under such a worst-case scenario using unbound exposures, the 10 mg dose can be adequately justified. For ESRD patients with

intermittent dialysis, we recommend dose adjustment to 10 mg QD. Because atogepant is a highly protein bound drug (>95% protein binding), dialysis may not have a significant impact on atogepant exposures. As a cautionary measure, the review team suggests taking atogepant after dialysis session in such patients.

In conclusion, the review team agrees with the Applicant's labeling proposal to have no dose adjustment for patients with mild and moderate RI, and recommends a lower dose of 10 mg QD in patients with CLcr less than 30 mL/min. For patients with ESRD undergoing intermittent dialysis, the review team recommends taking atogepant 10 mg QD after dialysis.

Other Intrinsic Factors

The population PK analysis indicated that sex, race, age, and body weight do not have a clinically relevant effect on atogepant PK. Therefore, no dose adjustments are warranted based on these factors (Section 14.3).

8.2. Extrinsic Factors

8.2.1. Food Effect

Study 3101-105-002 evaluated the impact of a high-fat meal (total calories of approximately 800 to 1,000, derived approximately 150 calories from protein, 250 calories from carbohydrates, and 500 to 600 calories from fat) on atogepant PK. The geometric mean values of AUC and C_{max} were reduced by 18% and 22%, respectively, while the median time to maximum concentration was unaffected. Atogepant was administered without regard to food in Phase 2 and 3 studies (CGP MD-01 and 3101-301-002). Since administration of atogepant with a high-fat meal did not reveal clinically relevant effects on atogepant PK, the review team agrees with the Applicant's proposed labeling that atogepant can be taken without regard to food-intake (see Section 14.2).

8.3. Drug Interactions

Key labeling recommendations based on drug interactions are summarized below.

Table 46. Key Labeling Recommendations

Concomitant Drugs	Recommended Dose(s)
Strong CYP3A4 inhibitors	10 mg
Weak/moderate CYP3A4 inhibitors	No dose adjustments necessary. Follow general dosing scheme.
Strong CYP3A4 inducers	30 mg or 60 mg
Moderate CYP3A4 inducers	30 mg or 60 mg
Weak CYP3A4 inducers	No dose adjustments necessary. Follow general dosing scheme.
OATP inhibitors	10 mg or 30 mg

Source: Reviewer analysis
Abbreviations: OATP, organic anion transporting polypeptide

8.3.1. Effects of Other Drugs on Atogepant

Atogepant is predominately metabolized by CYP3A4 through oxidation. Atogepant is a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1, OATP1B3, and OAT1 transporters.

The Applicant investigated the effects of a strong CYP3A4 inhibitor, a strong CYP3A4 inducer, an OATP inhibitor, and a P-gp inhibitor on atogepant PK in clinical drug-drug interaction (DDI) studies. The Applicant also evaluated the effects of a moderate or weak CYP3A4 inhibitor, and a BCRP inhibitor on atogepant PK via PBPK modeling and simulation.

CYP3A4 Inhibitors

In a clinical DDI study (CGP-PK-02), coadministration of atogepant with itraconazole, a strong CYP3A4 inhibitor, resulted in a 5.5-fold increase in atogepant $AUC_{0\text{-}inf}$ and a 2.2-fold increase in C_{max}. Atogepant dose should be reduced to 10 mg when administered concomitantly with strong CYP3A4 inhibitors (see Section 14.2).

The Applicant used a PBPK model to predict the effects of moderate and weak CYP3A4 inhibitors on atogepant PK. The PBPK model predicted that concomitant administration of 60 mg atogepant with fluconazole, a moderate CYP3A4 inhibitor, would result in increased AUC and C_{max} by 68% and 21%, respectively. Concomitant administration with cimetidine, a weak CYP3A4 inhibitor, is predicted to increase AUC and C_{max} by 8% and 5%, respectively. The review team agrees with the Applicant's PBPK prediction for effects of concomitant administration of fluconazole and cimetidine on atogepant PK and these changes are not considered to be clinically relevant. Therefore, no dose adjustment is needed with concomitant use of moderate or weak CYP3A4 inhibitors (see Section 14.4).

CYP3A4 Inducers

In a clinical DDI study (CGP-PK-12), coadministration of atogepant after multiple doses of rifampin resulted in a 60% reduction in atogepant $AUC_{0\text{-}inf}$ and a 30% reduction in C_{max}. Rifampin, in addition to its effects in inducing CYP3A4, also affects other transporter pathways such as OATPs, P-gp etc. As noted above, atogepant is a substrate of CYP3A4, OATP1B1/1B3 and P-gp. Therefore, the impact of concomitant administration of atogepant after multiple doses of rifampin is likely a composite interaction mediated by induction of CYP3A4, inhibition of OATP1B1/1B3, induction of OATPs, and induction of P-gp. Although the induction potential of rifampin on OATP1B1/1B3 cannot be ruled out, there is uncertainty on the magnitude of the impact of OATP1B1/1B3 induction on atogepant exposures. The review team conducted PBPK simulations for multiple scenarios to evaluate the impact of different combinations of DDI mechanisms on atogepant PK after multiple doses of rifampin. These simulations indicated that the net effect of rifampin (at steady state) on OATP1B1/1B3 is not expected to be significant. PBPK simulations on rifampin's impact on CYP3A4 induction alone indicated that atogepant AUC ratio (relative to controls) was 0.63 (refer to Section 14.4). Given the lack of clear dose-exposure-response relationship for efficacy in the dose range of 10 mg QD to 60 mg BID, the review team recommends adjusting atogepant doses to 30 mg or 60 mg with concomitant use of strong CYP3A4 inducers. (see Section 14.4).

Coadministration of atogepant with moderate CYP3A4 inducers was not evaluated. The magnitude of interaction with concomitant administration of moderate CYP3A4 inducers on atogepant is expected be lower than that noted with strong CYP3A4 inducers. Therefore, the review team recommends the same dose adjustment strategy when administering atogepant with moderate CYP3A4 inducers as with strong CYP3A4 inducers.

Coadministration of atogepant with weak CYP3A4 inducers was not evaluated. According to the FDA Guidance for Clinical Drug Interaction Studies,[3] a weak inducer is expected to decrease the AUC of a sensitive index CYP substrate by ≥20% to <50%. These changes are not considered to have a clinically relevant impact because of a lack of a clear dose-/exposure-response relationship for efficacy in the range of 10 mg QD to 60 mg BID. Therefore, no dose adjustment is needed when coadministering weak CYP3A4 inducers.

OATP, P-gp, and BCRP inhibitors

In a clinical DDI study (CGP-PK-12), coadministration of atogepant with a single dose of rifampin resulted in a 2.9-fold increase in atogepant $AUC_{0\text{-}inf}$ and a 2.2-fold increase in C_{max}. When rifampin was administered at single dose, rifampin's effect on atogepant PK is likely to be predominately mediated by inhibition on OATP (refer to Section 14.4). Therefore, the review team recommends adjusting atogepant doses to 10 mg or 30 mg with concomitant use of OATP inhibitors (see Section 14.2).

In a clinical DDI study (3101-103-002), coadministration of atogepant with quinidine, a P-gp inhibitor, resulted in a 1.3-fold increase in atogepant $AUC_{0\text{-}inf}$ and a 1.04-fold increase in C_{max}. Results of PBPK simulations showed that coadministration of atogepant with a BCRP inhibitor would result in a 1.2-fold increase of atogepant $AUC_{0\text{-}inf}$ and a 1.3-fold increase in C_{max}. Therefore, no dose adjustment is needed when coadministering with P-gp and BCRP inhibitors.

Other Drugs for Migraine Treatment

In clinical DDI studies conducted with commonly coadministered drugs for migraine treatment, e.g., sumatriptan (Study CGP-PK-13), naproxen (Study CGP-PK-06), and acetaminophen (Study CGP-PK-06), no clinically relevant interactions were observed. Therefore, no dose adjustment is needed when coadministering with sumatriptan, naproxen, and acetaminophen.

Drugs that Increase Gastric pH

In clinical DDI studies with esomeprazole (Study 3101-102-002), a proton pump inhibitor, and famotidine (Study MK-8031 P008), a H_2 receptor blocker, no clinically relevant interactions were observed. Therefore, no dose adjustment is needed when coadministering with pH-altering agents.

8.4. Effects of Atogepant on Other Drugs

8.4.1. Oral Contraceptives

In a clinical DDI study (Study MK-8031-P005), coadministration of multiple doses of atogepant with a combined oral contraceptive containing ethinyl estradiol (EE) and levonorgestrel (LNG) did not result in clinically relevant changes in EE or LNG exposures (C_{max} and AUC). Therefore, no dose adjustments in combined oral contraceptives are needed when coadministered with atogepant.

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

8.5. Plans for Pediatric Drug Development

The initial approval of atogepant for the preventive treatment of episodic migraine with be limited to adults. This development program triggers the Pediatric Research and Equity Act, therefore pediatric postmarketing studies to evaluate safety and efficacy of atogepant in pediatric migraine patients will be required. Please refer to Section 22 of this review for details.

8.6. Pregnancy and Lactation

Due to the lack of information on pregnancy and lactation outcomes for atogepant-treated patients, postmarketing studies will be required for a pregnancy registry study and a pregnancy outcomes study. Please see Section 22 of this review for details.

Oral administration of atogepant (0, 5, 20, or 125 mg/kg/day) to male and female rats prior to and during mating and continuing in females to Gestation Day 7 resulted in no adverse effects on fertility or reproductive performance. Plasma exposures (AUC) at the highest dose tested (125 mg/kg/day) were approximately 15 times that in humans at the maximum recommended human dose (MRHD) of 60 mg/day.

Oral administration of atogepant (0, 5, 15, 125, or 750 mg/kg/day) to pregnant rats during the period of organogenesis resulted in decreases in fetal body weight and skeletal ossification at the two highest doses. At the no-effect dose (15 mg/kg/day) for adverse effects on embryofetal development in rats, plasma exposure (AUC) was approximately 4 times that in humans at the MRHD.

Oral administration of atogepant (0, 30, 90, or 130 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in an increase in fetal visceral and skeletal variations at the highest dose tested, which was associated with minimal maternal toxicity. At the no-effect dose (90 mg/kg/day) for adverse effects on embryofetal development in rabbits, plasma exposure (AUC) was approximately 3 times that in humans at the MRHD.

Oral administration of atogepant (0, 15, 45, or 125 mg/kg/day) to rats throughout gestation and lactation resulted in decreased pup body weight at the highest dose, which persisted into adulthood. At the no-effect dose (45 mg/kg/day) for adverse effects on pre- and postnatal development, plasma exposure (AUC) was approximately 5 times that in humans at the MRHD.

9. Product Quality

The Office of Pharmaceutical Quality Review team has assessed NDA 215206 with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such OPQ recommends approval of this NDA from a quality perspective.

9.1. Device or Combination Product Considerations

Not applicable.

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

The results of the clinical site inspections support the conclusion that the studies were conducted adequately, and the data generated support the proposed indication. Review of the financial disclosures did not raise any concerns about the validity or reliability of the data. Please see Section 20 for a summary of inspection findings and Section 23 for financial disclosures.

11. Advisory Committee Summary

This application was not referred to an FDA advisory committee because the clinical trial design was acceptable, the efficacy findings were clear, and the safety profile was acceptable for use in the intended population.

III. Appendices

12. Summary of Regulatory History

On June 5, 2012, Merck Sharp and Dohme Corp., a subsidiary of Merck and Co., Inc., submitted investigational new drug (IND) application 114780 to study MK-8031 (atogepant) for the acute treatment of migraine. Initial Agency reviews described MK-8031 as a selective antagonist of the neuropeptide transmitter, calcitonin gene-related peptide (CGRP).

The Division of Neurology Products concluded that the Sponsor may proceed with its proposed clinical investigation for the treatment of migraine on July 5, 2012. The Division determined that safety and tolerability, as the primary endpoint, should be assessed based on clinical evaluation with monitoring of elevation of hepatic transaminases, mainly serum alanine aminotransferase as increases in alanine aminotransferase have been observed with a number of CGRP receptor antagonists.

In an email dated February 11, 2013, the Sponsor notified the Division of its intent to develop MK-8031 for the treatment of migraine prophylaxis, rather than for the acute treatment of migraine.

On August 24, 2015, the application underwent a change of sponsorship from Merck Sharp and Dohme Corp. to Aptalis Pharma Ltd. On July 21, 2016, the Division was notified of a change in Sponsor from Aptalis to Allergan Pharmaceuticals International Limited, with Allergan Sales, LLC. as the Sponsor's United States Agent contact.

The Sponsor submitted Special Protocol Assessment (SPA) requests for its proposed rat (CGP-TX-06, SPA-2) and mouse (CGP-TX-05, SPA-3) carcinogenicity studies on March 10, 2017. An agreement letter was issued for the SPA-2 and a no agreement letter for SPA-3 on April 14, 2017. The Executive Carcinogenicity Assessment Committee was unable to concur on doses for females because the 3-month study did not identify a maximum tolerated dose or a dose that produced plasma exposures (area under the plasma concentration-time curve, AUC) 25-fold above that at the maximum human dose.

A Type C guidance (teleconference) meeting between the Division and Allergan took place on June 27, 2017, to discuss nonclinical and clinical development plans. The Sponsor's intent for this meeting was to obtain feedback from the Division regarding the adequacy and potential for its planned study, Study CGP-MD-01, titled "A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Safety, and Tolerability of Multiple Dosing Regimens of Oral AGN-241689 in Episodic Migraine Prevention," to be used as a pivotal trial. The Division stated that Study CGP-MD-01 was inadequate to be a pivotal trial. At the time of this meeting, the proposed trial's statistical testing procedure allows for the possibility of statistical significance to occur at a low dose when a high dose may not demonstrate stataistical significance. The Division stated that the results of the study could be uninterpretable if the high dose does not meet statistical significance when the low dose does. Additionally, the Division recommended that the primary endpoint be analyzed based on a comparison of the change from baseline in the number of migraine headache days over the entire double-blind treatment period rather than only the last four weeks of the treatment period, as proposed. The Division advised Allergan to provide justification for excluding patients

with hemiplegic migraine, or to remove the exclusion criteria if no data exist to support increased risk to patients with this diagnosis.

The Division concluded that a drug discrimination study with atogepant was not necessary; however, it requested that the Sponsor conduct a self-administration study in rats.

Following the June 2017 meeting, Allergan submitted a revised protocol to Study CGP-MD-01, and a revised Statistical Analysis Plan in response to the Division's feedback. The subsequent changes made to both the protocol and Statistical Analysis Plan adequately addressed the Division's concerns regarding the proposed analysis of the primary endpoint, the addition of a secondary endpoint to assess the use of rescue medication, the Sponsor's overall study design, and the plan for testing the proposed doses.

In a submission dated June 29, 2018, the Sponsor requested a meeting to discuss the suitability of patient-reported outcome instruments for atogepant clinical studies. In the FDA preliminary meeting comments, the Division expressed concerns regarding the lack of definition for "headache," and the lack of clear instructions for patients in the instructions for the Sponsor's novel patient-reported outcome, the Activity Impairment in Migraine Diary (AIM-D). The Division stated that it was unclear how the Sponsor planned to analyze AIM-D scores during headache and nonheadache days. The Division provided additional recommendations concerning the firm's proposed psychometric study protocol synopsis and statistical plan. The Sponsor canceled the meeting, indicating that the preliminary comments sent by the Division were sufficiently clear and complete. The Division issued Final Written Responses to Allergan on September 11, 2018.

An End of Phase 2 meeting was held on November 19, 2018, to discuss the Sponsor's Phase 3 clinical development plan for the [redacted] (b) (4). In the November 14, 2018, meeting preliminary comments, the Division advised the Sponsor to consider including the 10 mg dose in the Phase 3 study, as this dose may provide a better safety profile compared to the higher doses selected. Additionally, the Division recommended that the primary efficacy analysis be calculated based on the 3-month average of the mean monthly migraine days rather than using the mixed effects model for repeated measures. The Division stated that the rationale for the [redacted] (b) (4) The Division recommended the inclusion of multiple anchor scales to provide several assessments to assist in determining what may be a clinically meaningful within-patient change in the AIM-D scores from the patient perspective. Specifically, the Division recommended the addition of a patient global impression of severity scale in addition to a 5-point patient global impression of change scale.

In addition, the Division acknowledged and accepted the Sponsor's preference to use the 7-point patient global impression of change scale over a 5-point scale, based on patients' preferences, and to keep the patient global impression of change scale consistent with the version used in their Phase 2 trial. The Division acknowledged Allergan's concerns about twice daily (BID) dosing, but suggested that if higher efficacy for a lower dose given BID versus once daily (QD) was demonstrated, the benefit of the improved efficacy may balance out the inconvenience of BID dosing, and that it may be worthwhile to continue to explore BID dosing, specifically 10 mg BID

or 30 mg BID. The Division issued the End of Phase 2 meeting minutes to Allergan on December 18, 2018.

An End of Phase 2 chemistry, manufacturing, and controls meeting was requested on February 19, 2019, granted on March 8, 2019, and preliminary comments issued on April 11, 2019. The Sponsor found these responses to be acceptable and the meeting scheduled for April 15, 2019, was cancelled.

An Initial Agreement letter was issued on August 15, 2019, for the Sponsor's proposed pediatric study plan (b) (4)

On October 23, 2019, the Sponsor requested a meeting to discuss considerations for their planned new drug application (NDA). A Type C meeting was granted on November 13, 2019. Discussion at this meeting focused on questions regarding the appropriateness of the pivotal studies, and the AIM-D, and the Migraine-Specific Quality of Life Questionnaire Version 2.1. FDA Written Responses were issued to the Sponsor on January 6, 2020.

The Sponsor requested a chemistry, manufacturing, and controls-focused meeting on December 19, 2019, to obtain FDA agreement regarding its proposed control and manufacture strategy of the atogepant drug substance and adequacy the drug product's dissolution method in the NDA. A Type C Guidance meeting was granted on January 10, 2020, and written responses issued on February 25, 2020.

A Type B preNDA meeting to discuss the Sponsor's incoming NDA was held on September 22, 2020. During this meeting, the Sponsor was advised to include exposure of atogepant of at least 300 patients at 6 months and 100 patients at 1 year, with a substantial number of patients exposed at the highest planned marketed dose at 1 year. The Division determined that the receptor binding studies, nonclinical data, and abuse-related adverse event profile assessment did not suggest an abuse potential signal associated with atogepant. The Division stated that a human abuse potential study and clinical physical dependence study were not required for the proposed NDA. Allergan agreed to include tables for each Phase 2 and Phase 3 study which specify the number of unique patients for each dose level with duration of exposure, and to include safety analyses to evaluate whether there was hepatotoxicity associated with atogepant.

Allergan and its subsidiaries were acquired by AbbVie Inc. in May 2020. AbbVie sent a Notification of Intent to submit an NDA with a Material Threat Medical Countermeasure Priority Review Voucher on October 30, 2020.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the Investigational New Drug Application

13.1.1. Pharmacology

Atogepant is a calcitonin gene-related peptide (CGRP) receptor antagonist, with activity at human and monkey CGRP receptors at low picomolar concentrations, and mouse, rat, rabbit, and dog CGRP receptors at low nanomolar concentrations. In vivo, atogepant inhibited capsaicin-induced dermal vasodilation up to 90% at nanomolar concentrations in monkeys and approximately 45% at micromolar concentrations in rat and rabbit.

In secondary pharmacology assays, atogepant demonstrated low micromolar binding affinity at CGRP-related receptors (AMY1 and AMY3), but only weak binding affinity at 2 of 116 receptors, enzymes, and ion channel assays (half inhibitory concentration >20µM).

13.1.2. Safety Pharmacology

A complete battery of safety pharmacology (CNS, cardiovascular, and respiratory) endpoints was adequately assessed and showed no safety concerns.

13.1.3. PK/ADME

In rats and monkeys following IV or PO administration, the half-life was between 1 and 4 hours, oral bioavailability was 27%, and plasma protein binding was 92%. ^{14}C-atogepant (total radioactivity) was eliminated in the urine (~9%), bile (~55%), and feces (~18%). Peak tissue concentrations in rat were as follows (highest to lowest concentration): GI tract > liver > bile duct > salivary gland (submaxillary). Oxidative metabolism primarily occurred by CYP3A4. Atogepant was a substrate for membrane-bound efflux transporters P-gp and BCRP, hepatic uptake transporters OATP1B1 and OATP1B3, and the renal uptake transporter, OAT1. There were no major or unique circulating metabolites in humans.

13.1.4. General Toxicology

The toxicologic and toxicokinetic profile of orally administered atogepant was assessed in a series of single and repeat dose studies in rats and monkeys up to 6- and 9-months' duration, respectively. At the high dose (HD) in the 14-day (250 mg/kg) and 3-month (200 mg/kg) toxicology studies in rat, there were body weight decreases of 23 and 16%, respectively, and vacuolation in the small intestine. In the 3-month rat (10/sex/group) study (0, 5, 20, or 200 mg/kg), the no observed adverse effect level (NOAEL) was the mid dose (MD) based on a 16% decrease in body weight gain at the HD. In the pivotal 6-month study in rat (15/sex/group; 0, 10, 30, or 100 mg/kg), there were non-adverse findings consisting of decreases in body weight of up to 10% at the HD, which correlated with a decrease in food consumption. These findings partially resolved during the recovery period. There was also minimum to marked vacuolation in

the villous epithelium of the small intestine in MD and HD animals, which resolved during the recovery period. The HD was justified based on decreases in body weight gain at ≥200 mg/kg in the 14-day and 3-month studies. The safety margin based on plasma AUC at the NOAEL of 100 mg/kg was 27 times relative to that at the maximum recommended human dose (MRHD) of 60 mg. Plasma AUC_{0-t} generally increased dose proportionally.

In the single dose (up to 1000 mg/kg) studies in monkey, vomiting was observed at 150 and 300 mg/kg and liquid feces was observed at 300 mg/kg. In the pivotal 9-month oral toxicology study in monkey (4/sex/group, 0, 15, 40, or 300 mg/kg) there were no drug-related findings. Plasma C_{max} and $AUC_{0-24\,h}$ increased dose proportionally from the low dose (LD) to MD and less than dose proportionally from the MD to HD. The NOAEL was the HD. The study was considered adequate based on the vomiting observed at the 150 and 300 mg/kg doses in the single dose studies. At the HD (300 mg/kg) in the 9-month study, the safety margin was 10-fold compared to that at the MRHD based on plasma AUC at the NOAEL.

13.1.5. Genetic Toxicology

Atogepant was negative in Organisation for Economic Cooperation and Development-compliant Ames, in vitro chromosomal aberration, and in vivo rat bone marrow micronucleus assays.

13.1.6. Carcinogenicity

Based on the FDA statistical analysis of the 2-year mouse and rat carcinogenicity studies, atogepant was not carcinogenic. The study in female mice was not adequate because the HD was not adequately justified; it was not demonstrated to be a maximum tolerated dose or maximum feasible dose and did not achieve plasma exposures at least 25-fold that at in humans at the MRHD.

Table 47. Carcinogenicity Studies

Species and Number	Duration	Dosing (mg/kg)
Mouse (60/sex/group)	2 years	0 (water, M&F), 0 (vehicle, M&F) 5 (M&F), 20 (M), 30 (F), 75 (M) 160 (F)
Rat (60/sex/group)	2 years	M: 0 (water), 0 (vehicle: 100% PEG-400), 10, 20, and 100 F: 0 (water), 0 (vehicle: 100% PEG-400), 25, 65 and 200

Source: Reviewer
Abbreviations: F, female; M, male; PEG, polyethylene glycol

13.1.7. Reproductive and Developmental Toxicology

A fertility study in male and female rats (20/sex/group) administered oral doses of 0, 5, 20, or 125 mg/kg (QD) for 15 days prior to cohabitation, showed no effects on the testes, sperm motility or number, pregnancy status, corpora lutea, uterine implants, live or dead fetuses, or resorptions. The HD was justified based on decreases in body weight gain at ≥200 mg/kg in the 14-day and 3-month studies. No toxicokinetic data were collected. (The exposure data from the rat embryofetal development study was used to calculate margins.) At the high dose, plasma exposure (AUC) was approximately 15 times that in humans at the maximum recommended human dose (MRHD) of 60 mg/day.

In a preliminary oral embryo-fetal development study in rat (12/group), animals were orally administered doses of 0, 5, 20, 250, or 750 mg/kg (QD) on gestation days (GDs) 6 through 20. Findings consisted of decreased fetal body weight (11-14%) at 250 and 750 mg/kg. There were

no effects on fetal viability, weight, sex ratio, and external or visceral morphology. In the pivotal study, doses of 0, 5, 15, 125, or 750 mg/kg (PO) was administered QD (20/group) on GDs 6 through 20. There were no adverse findings in the dam. The fetal NOAEL was 15 mg/kg based on increases in total resorptions and post-implantation loss (125 and 750 mg/kg) and incomplete ossification (125 and 750 mg/kg). Exposure increased greater than dose proportionally between 5 and 125 mg/kg and decreased between 125 and 750 mg/kg. At the no-effect dose (15 mg/kg), plasma exposure (AUC) was approximately 4 times that at the MRHD.

In the preliminary embryofetal development study in rabbits (12/group), animals were orally administered doses of 0, 15, 45, 100, or 325 mg/kg (QD) on GDs 7 through 20. There was a 6% decrease in maternal body weight gain at the high dose. At necropsy (GD 28) corpora lutea, gross morphology, fetal viability and weight, sex, and fetal external and visceral morphology were assessed. At the HD, there were decreases in male and female fetal weight of 10 and 14%, respectively, compared to control. In the pivotal study, oral doses of 0, 30, 90, or 130 mg/kg (23/group) were administered daily on GDs 7 through 20 and the necropsy was conducted on GD 28. Maternal body weight loss (18%) was observed at the HD. The fetal NOAEL was the MD based on an increase in skeletal and visceral variations at the HD. Plasma exposure (AUC) at the NOAEL for adverse development effects was approximately 3 times that in humans at the MRHD.

In the pre and postnatal development study, rats (21/group) were orally administered doses of 0, 15, 45 or 125 mg/kg (QD) from GD 6 through Lactation Day 20. The NOAEL was at the MD based on a decrease (8-13%) in pup body weight that persisted into adulthood. Toxicokinetic data were not collected. (The data from the rat embryofetal development study were used to estimate plasma exposure at 45 mg/kg.) Plasma exposure (AUC) at the NOAEL for adverse effects on pre- and postnatal development was approximately 5 times that in humans at the MRHD.

13.2. Individual Reviews of Studies Submitted to the New Drug Application

13.2.1. Pharmacology

Primary, secondary, and safety pharmacology studies, and pharmacokinetics/ADME studies are summarized above (Section 13.1).

13.2.2. General Toxicology

Table 48. Non-Pivotal Oral Administration Studies in Rats

Duration	Dose
Single dose	5 mg/kg
7-day	150 or 1000 mg/kg, once daily
	300 or 400 mg/kg, once daily
14-day	0, 5, 20, or 250 mg/kg, once daily
3-month	0, 5, 20, or 200 mg/kg, once daily

Source: Reviewer; Summaries of the 14-day and 3-month studies were based on Donald C. Thompson's SRD review, July 12, 2012
Note: There were findings in the 14-day and 3-month studies consisting of body weight decreases of 23 and 16%, respectively, and vacuolation in the small intestine (both studies).

13.2.2.1. Study CGP-TX-02: A 6-Month Repeat Dose Oral Toxicity Study in Wistar Han Rats with a 1-Month Recovery Period

Table 49. CGP-TX-02: Study Information

Parameter	Information
Study number	CGP-TX-02
Study report location	Electronic data record
Date of study initiation	February 5, 2016
GLP compliance	Yes
Quality assurance statement	Yes
Drug, lot number, and % purity	AGN-241689, lot: L-004880174-008A007, purity: 99.5%

Source: Reviewer
Abbreviations: GLP, good laboratory practice

Key Study Findings

The NOAEL was at the HD (C_{max} values were 22.8 and 30.0µmol/L and AUC_{0-t} values were 193 and 192µmol·hr/L for males and females, respectively, on Day 182).

Table 50. CGP-TX-02: Study Design

Parameter	Information
Doses	0, 10, 30, or 100 mg/kg
Frequency of dosing	Once daily
Route of administration	Oral gavage
Dose volume	2 mL/kg
Formulation/Vehicle	100% polyethylene glycol 400
Species/Strain	Rat/Wistar Hannover (b) (4)
Number/Sex/Group	Main: 15/sex/group; recovery: 5/sex/group (C & HD) TK: 3/sex/group (C), 9/sex/group (LD, MD, HD)
Age at initiation of dosing	5 weeks of age
Weight	Male: 80 to 122 g; Female: 80 to 119 g
Satellite groups	None
Unique study design	None
Deviation from study protocol	There were minor deviations which did not affect study validity

Source: Reviewer
Abbreviations: C, control; HD, high dose; LD, low dose; MD, mid dose; TK, toxicokinetics

Observations and Results

Mortality

Assessments were made twice daily.

There were no unscheduled deaths.

Clinical Signs

Detailed observations were made weekly.

Wet fur on the lower jaw was observed in all AGN-241689 groups.

Body Weights

Recordings were made weekly.

Body weight and overall body weight gain were reduced (1 to 9% and 10%, respectively) in HD males. In females, body weight was reduced at the MD and HD (2 to 6% and 1 to 6%, respectively) and body weight gain was reduced (11%) at both doses. During the recovery period, body weight normalized in males but remained lower (8%) in females compared to controls.

Food Consumption

Recordings were made weekly.

Food consumption was reduced (up to 14%) at the MD and HD in males and females. Recovery was observed in males, and partial recovery was observed in females.

Ophthalmoscopy

Examinations (fundoscopy and biomicroscopy) were conducted prior to dosing and during Week 26.

There were no drug-related findings.

Electrocardiogram

Not assessed.

Hematology

A standard battery of parameters was assessed.

There were no drug-related findings.

Coagulation

Activated partial thromboplastin time, fibrinogen, and prothrombin time were assessed.

There were no drug-related findings.

Clinical Chemistry

A standard battery of parameters was assessed.

There were no drug-related findings.

Urinalysis

Osmolality, volume, pH, protein, glucose, bilirubin, ketones, and blood content were assessed.

There were no drug-related findings.

Gross Pathology

There were no drug-related findings.

Organ Weights

There were no drug-related findings.

Histopathology

Signed pathologist report: Yes

Adequate Battery: Yes

Peer Review: Yes

Histological Findings

Minimal to marked vacuolation of villous epithelium was observed in the jejunum of MD males, HD males, and HD females. The vacuoles resolved during the recovery period (Table 51).

Table 51. CGP-TX-02: Summary of Microscopic Findings, Scheduled Euthanasia (Day 183)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (mg/kg/day)	**0**	**10**	**30**	**100**	**0**	**10**	**30**	**100**
No. Animals Examined	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**
Jejunum (No. Examined)	15	15	15	15	15	14	15	15
Vacuolation; epithelial	(0)[a]	(0)	(1)	(10)	(0)	(0)	(0)	(8)
Minimal	0	0	1	4	0	0	0	5
Mild	0	0	0	2	0	0	0	2
Moderate	0	0	0	3	0	0	0	1
Marked	0	0	0	1	0	0	0	0

[a] Numbers in parentheses represent the number of animals with the finding.
Source: Sponsor's table.
Abbreviations: No, number

Toxicokinetics

T_{max} was between 30 minutes and 4 hours, and the elimination halflife was between 2 and 5 hours. Exposure (AUC_{0-t}) generally increased dose proportionally but was similar at the MD and HD in males during Week 26 (Table 52, Table 53, and Table 54).

Table 52. CGP-TX-02: Summary Mean AGN-241689 Toxicokinetic Parameters on Day 1

Dose (mg/kg)	Gender	Tmax (hr)	Cmax ± SE (µmol/L)	Cmax/D (µmol/L)/(mg/kg)	AUC(0-t) ± SE (hr*µmol/L)	AUC(0-t)/D (hr*µmol/L)/(mg/kg)	$T_{1/2}$ (hr)
10	Female	2	1.00 ± 0.470	0.100	3.43 ± 0.713	0.343	NC
10	Male	4	1.02 ± 0.613	0.102	5.06 ± 1.81	0.506	NC
30	Female	1	4.47 ± 1.79	0.149	22.1 ± 2.99	0.735	2.36
30	Male	1	4.72 ± 0.895	0.157	28.4 ± 3.81	0.946	2.52
100	Female	1	13.1 ± 3.89	0.131	119 ± 32.6	1.19	2.93
100	Male	1	18.2 ± 3.20	0.182	190 ± 45.8	1.90	2.15

Source: Sponsor's table.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; D; dose; NC, result not reported because the elimination slope had fewer than three terminal quantifiable concentrations; SE, standard error; T_{max}, time to maximum concentration

Table 53. CGP-TX-02: Summary Mean AGN-241689 Toxicokinetic Parameters on Day 28

Dose (mg/kg)	Gender	Tmax (hr)	Cmax ± SE (µmol/L)	Cmax/D (µmol/L)/ (mg/kg)	AUC(0-t) ± SE (hr*µmol/L)	AUC(0-t)/D (hr*µmol/L)/ (mg/kg)	$T_{1/2}$ (hr)	R_{AUC}	R_{Cmax}
10	Female	2	1.49 ± 0.369	0.149	5.19 ± 0.698	0.519	4.60	1.52	1.49
10	Male	0.5	1.76 ± 0.808	0.176	7.30 ± 1.10	0.730	2.42	1.44	1.72
30	Female	0.5	7.55 ± 1.46	0.252	25.1 ± 3.37	0.836	3.35	1.14	1.69
30	Male	1	7.35 ± 2.86	0.245	38.0 ± 11.0	1.27	2.57	1.34	1.56
100	Female	2	13.0 ± 4.57	0.130	64.1 ± 11.6	0.641	3.58	0.540	0.990
100	Male	2	20.9 ± 5.78	0.209	133 ± 20.9	1.33	2.74	0.700	1.15

Source: Sponsor's table.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; D; dose; R_{AUC}, Day 28 $AUC_{(0-t)}$/Day 1 $AUC_{(0-t)}$; RC_{max}, Day 28 C_{max}/Day 1 C_{max}; SE, standard error; T_{max}, time to maximum concentration

Table 54. CGP-TX-02: Summary Mean AGN-241689 Toxicokinetic Parameters on Day 182

Dose (mg/kg)	Gender	Tmax (hr)	Cmax ± SE (µmol/L)	Cmax/D (µmol/L)/ (mg/kg)	AUC(0-t) ± SE (hr*µmol/L)	AUC(0-t)/D (hr*µmol/L)/ (mg/kg)	$T_{1/2}$ (hr)	R_{AUC}	R_{Cmax}
10	Female	1	1.92 ± 0.862	0.192	7.91 ± 1.80	0.791	5.01	2.31	1.92
10	Male	0.5	3.01 ± 1.70	0.301	16.2 ± 3.95	1.62	2.65	3.21	2.95
30	Female	2	7.42 ± 4.12	0.247	47.8 ± 8.39	1.59	3.53	2.17	1.66
30	Male	4	24.1 ± 13.6*	0.802	116 ± 41.3	3.87	NC	4.09	5.10
100	Female	4	30.0 ± 11.4	0.300	192 ± 49.7	1.92	NC	1.62	2.29
100	Male	4	22.8 ± 6.35	0.228	193 ± 51.8	1.93	NC	1.01	1.25

Source: Sponsor's table
* The mean C_{max} value at 30 mg/kg was high due to a very high plasma concentration value (51.1µM) in one rat at the 4 hour timepoint and no clear cause could be determined following investigation; the remaining values at that timepoint were 12.2µM and 8.81µM.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; D; dose; NC, result not reported because the elimination slope had fewer than three terminal quantifiable concentrations excluding C_{max}; R_{AUC}, Day 182 $AUC_{(0-t)}$/Day 1 $AUC_{(0-t)}$; RC_{max}, Day 182 C_{max}/Day 1 C_{max}; SE, standard error; T_{max}, time to maximum concentration

Dosing Solution Analysis

All formulations were within ±10% of nominal.

Table 55. Non-Pivotal Oral Administration Studies in Monkeys

Duration	Dose
Single dose	2, 20, 200, 750 mg/kg 300 or 500 mg/kg 150 or 1000 mg/kg 300 mg/kg* 150 mg/kg*
6-day	150 mg/kg, once daily
7-day	40 or 75 mg/kg, once daily 0, 300 mg/kg, once daily
14-day	5 mg/kg, once daily
3-month	0, 4, 15, or 150 mg/kg, once daily 0 or 300 mg/kg, QD once daily

Source: Reviewer; Summaries of the 14-day and 3-month studies were based on Donald C. Thompson's SRD review, July 12, 2012.
* Studies with findings: in the single oral dose studies, there was vomiting at 150 and 300 mg/kg and liquid feces at 300 mg/kg.

13.2.2.2. Study TT #12-1164: Three-Month Oral Toxicity Study in Rhesus Monkeys

Table 56. TT #12-1164: Study Information

Parameter	Information
Study number	TT #12-1164
Study report location	Electronic data record
Date of study initiation	December 10, 2012
GLP compliance	Yes
Quality assurance statement	Yes
Drug, lot number, and % purity:	MK-8031, lot: L-004880174-008A019, purity: 98.2%

Source: Reviewer
Abbreviations: GLP, good laboratory practice

Table 57. TT #12-1164: Study Design

Parameter	Information
Doses	0 or 300 mg/kg
Frequency of dosing	Once daily
Route of administration	Oral by nasogastric gavage
Dose volume	2 mL/kg
Formulation/Vehicle	100% Polyethylene glycol 400
Species/Strain	Monkey, rhesus
Number/Sex/Group	3/sex/group
Age	1 to 3 years of age
Weight	Male: 2.7 to 4.4 kg; Female: 2.6 to 3.9 kg
Satellite groups	None
Unique study design	None
Deviation from study protocol	There were minor deviations that did not affect study validity.

Source: Reviewer

Observations and Results

Mortality

Observations were made daily.

There were no schedulable deaths.

Clinical Signs

Observations were made daily.

There were no drug-related findings.

Body Weights

Recordings were made weekly.

There were no drug-related findings.

Food Consumption

Assessments were made daily.

There were no drug-related findings.

Ophthalmoscopy

Slit lamp biomicroscopy and indirect ophthalmoscopy examinations were conducted prior to dosing and during Week 12.

There were no drug-related findings.

Electrocardiogram

Electrocardiogram examinations were conducted prior to dosing and during Week 12.

There were no drug-related findings.

Hematology

A standard battery of parameters was assessed.

There were no drug-related findings.

Coagulation

Activated partial thromboplastin time, prothrombin time, and fibrinogen were assessed.

There were no drug-related findings.

Clinical Chemistry

A standard battery of parameters was assessed.

There were no drug-related findings.

Urinalysis

Volume, pH, specific gravity, protein, bilirubin, glucose, occult blood, and ketones were assessed.

There were no drug-related findings.

Gross Pathology

There were no drug-related findings.

Organ Weights

There were no drug-related findings.

Histopathology

Signed pathologist report: Yes

Adequate Battery: Yes

Peer Review: Yes

Histological Findings

There was very slight inflammation and medial hypertrophy of the artery within the connective tissue surrounding the testis and epididymis in one monkey administered MK-8031 (Table 58).

Table 58. TT #12-1164: Test Article-Related Postmortem Findings

	Females	Males
Dose, mg/kg/day	300	300
Number of Animals	3	3
Histomorphology (Incidence)		
Testis	NA	
Artery, inflammation, focal		1
Artery, medial hypertrophy, focal		1
Epididymis	NA	
Artery, inflammation, focal		1
Artery, medial hypertrophy, focal		1

Source: Sponsor's table
Abbreviations: NA, not applicable

Special Evaluation

Metabolite profile was evaluated in pooled plasma samples collected on Study Day 1 and in Study Week 13 from the 300 mg/kg/day group.

No major metabolites were identified.

Toxicokinetics

Exposure was similar between sexes. C_{max} and $AUC_{0\text{-}24\ h}$ decreased by 39 and 33%, respectively, from Day 1 to Week 13 (Table 59 and Table 60).

Table 59. TT #12-1164: Summary Mean Plasma MK-8031[a] Toxicokinetic Parameters in Monkeys, Day 1

Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
Female	302 ± 86.2	26.1 ± 9.35	4.7 ± 1.8
Male	369 ± 27.3	34.9 ± 3.10	4.0 ± 0.0
All	336 ± 43.1	30.5 ± 4.82	4.3 ± 0.80

Source: Sponsor's table
[a] MK-8031 concentrations in plasma from all control group animals were below the lower limit of quantitation (0.008µM) of the bioanalytical method on Study Day 1.
Values are ± the standard error.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; T_{max}, time to maximum concentration

Table 60. TT #12-1164: Summary Mean Plasma MK-8031[a] Toxicokinetic Parameters in Monkeys, Week 13

Sex	$AUC_{0-24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
Female	78.8 ± 12.9	8.24 ± 1.32	4.0 ± 0.0
Male	142 ± 33.6	15.8 ± 4.99	5.3 ± 1.3
All	110 ± 21.4	12.0 ± 2.86	4.7 ± 0.67

Source: Sponsor's table
[a] MK-8031 concentrations in plasma from control animal #12-0257 was above the lower limit of quantitation (0.008µM) of the bioanalytical method in Study Week 13 at 8 hours following dose administration. This value was approximately 0.12% of the mean C_{max} value of the 300 mg/kg/day dose group. Based on the low level of MK-8031 in this control sample, it is concluded that this finding did not impact the integrity and interpretation of the toxicokinetic results.
Values are ± the standard error.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; T_{max}, time to maximum concentration

Dosing Solution Analysis

Two-thirds of the formulations were within ±15% of nominal.

13.2.2.3. Study TT #13-1074: Nine-Month Oral Toxicity Study in Rhesus Monkeys with a Three-Month Interim Necropsy

Table 61. TT #13-1074: Study Information

Parameter	Information
Study number	TT #13-1074
Study report location	Electronic data record
Date of study initiation	June 11, 2013
GLP compliance	Yes
Quality assurance statement	Yes
Drug, lot number, and % purity	Drug: MK-8031; lots: L-004880174-008A019 and L-004880174-008A018; purity: 98.2%

Key Study Findings

The NOAEL was at the HD (C_{max}: 7.53µM [male] and 7.81µM [female]; $AUC_{0-24\ h}$: 70.2µM*h [male] and 70.7µM*h [female]). The study was considered adequate based on emesis observed in the single dose studies at 150 and 300 mg/kg.

Table 62. TT #13-1074: Study Design

Parameter	Information
Doses	0, 15, 40, or 300 mg/kg
Frequency of dosing	Once daily
Route of administration	Oral (nasogastric gavage)
Dose volume	2 mL/kg
Formulation/Vehicle	100% Polyetheylene glycol 400
Species/Strain	Monkey, rhesus
Number/Sex/Group	Main: 4/sex/group; Interim necropsy: 6 mid dose males
Age	1 to 3 years of age
Weight	Male: 2.5 to 3.5 kg; Female: 2.4 to 3.5
Satellite groups	Interim necropsy mid dose males and control males
Unique study design	Interim necropsy at Week 14 in mid dose males and control males. Objective: to establish a no observed effect level for the inflammation and medial hypertrophy of the artery within the connective tissue surrounding the testis and epididymis observed in the 300 mg/kg group in the 3-month study.
Deviation from study protocol	There were minor deviations that did not affect study validity.

Source: Reviewer

Observations and Results

Mortality

Observations were made daily.

There were no drug-related deaths.

Clinical Signs

Observations were made daily.

There were no drug-related findings.

Body Weights

Recordings were made weekly.

There were no drug-related findings.

Food Consumption

Assessments were made daily.

There were no drug-related findings.

Ophthalmoscopy

Slit lamp biomicroscopy and indirect ophthalmoscopy examinations were conducted during pretest and Weeks 13, 26, and 39.

There were no drug-related findings.

ECG

Examinations were conducted during pretest and Weeks 13 and 37.

There were no drug-related findings.

Hematology

A standard battery of parameters was assessed.

There were no drug-related findings.

Coagulation

Prothrombin time, activated partial thromboplastin time, and fibrinogen were assessed.

There were no drug-related findings.

Clinical Chemistry

A standard battery of parameters was assessed.

There were no drug-related findings.

Urinalysis

Occult blood, bilirubin, glucose, protein, pH, ketones, and specific gravity were assessed.

There were no drug-related findings.

Gross Pathology

There were no drug-related findings.

Organ Weights

A standard battery of parameters was assessed.

Histopathology

Signed pathology report: Yes

Adequate Battery: Yes

Peer Review: Yes

Histological Findings

There were no drug-related findings.

Special Evaluation

None

Toxicokinetics

Exposure (C_{max} and $AUC_{0\text{-}24\ h}$) was similar between sexes. Exposure increased approximately dose proportionally from the LD to MD, and less than dose proportionally from the MD to HD on Day1 and during Weeks 5 and 39. In Week 13, exposure increased less than dose proportionally across all doses (Table 63, Table 64, Table 65, and Table 66).

Table 63. TT #13-1074: Summary Mean Plasma MK-8031 Toxicokinetic Parameters in Monkeys, Study Day 1

Day	Dose[a] (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM*hr)	C_{max} (µM)	T_{max} (hr)
1	15	Female	15.3 ± 4.72	2.71 ± 1.01	3.5 ± 0.50
		Male	17.1 ± 3.67	2.79 ± 0.634	3.5 ± 0.50
		All	16.2 ± 2.79	2.75 ± 0.553	3.5 ± 0.33
	40	Female	27.0 ± 2.57	4.48 ± 0.584	3.5 ± 0.50
		Male	48.6 ± 10.9	6.00 ± 1.36	3.2 ± 0.35
		All	42.9 ± 8.28	5.59 ± 1.01	3.3 ± 0.28
	300	Female	155 ± 108	12.0 ± 5.28	3.8 ± 1.2
		Male	89.3 ± 16.2	9.56 ± 2.12	4.5 ± 1.3
		All	126 ± 58.4	10.9 ± 2.95	4.1 ± 0.82

Source: Sponsor's table
[a] MK-8031 concentrations in plasma from all control group animals on Study Day 1 were below the lower limit of quantitation (0.00828µM) of the bioanalytical method.
Values are ± the standard error.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; T_{max}, time to maximum concentration

Table 64. TT #13-1074: Summary Mean Plasma MK-8031 Toxicokinetic Parameters in Monkeys, Study Week 5

Week	Dose[a] (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM*hr)	C_{max} (µM)	T_{max} (hr)
5	15	Female	15.4 ± 2.76	2.51 ± 0.392	3.5 ± 0.50
		Male	11.3 ± 3.34	1.69 ± 0.526	2.8 ± 0.75
		All	13.4 ± 2.15	2.10 ± 0.340	3.1 ± 0.44
	40	Female	24.3 ± 4.20	3.97 ± 0.753	3.0 ± 0.58
		Male	35.2 ± 7.14	4.96 ± 0.935	3.6 ± 0.27
		All	32.1 ± 5.32	4.68 ± 0.696	3.4 ± 0.25
	300	Female	60.3 ± 40.8	5.29 ± 2.90	3.5 ± 1.5
		Male	56.3 ± 20.5	5.55 ± 1.47	4.0 ± 0.0
		All	58.3 ± 21.1	5.42 ± 1.50	3.8 ± 0.70

Source: Sponsor's table
[a] MK-8031 concentrations in plasma from all control group animals in Study Week 5 were below the lower limit of quantitation (0.00828µM) of the bioanalytical method.
Values are ± the standard error.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; T_{max}, time to maximum concentration

Table 65. TT #13-1074: Summary Mean Plasma MK-8031 Toxicokinetic Parameters in Monkeys, Study Week 13

Week	Dose[a] (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM*hr)	C_{max} (µM)	T_{max} (hr)
13	15	Female	11.4 ± 0.856	2.15 ± 0.263	2.8 ± 0.75
		Male	13.0 ± 3.50	1.93 ± 0.417	2.8 ± 0.75
		All	12.2 ± 1.69	2.04 ± 0.232	2.8 ± 0.49
	40	Female	23.7 ± 6.41	4.00 ± 1.21	3.0 ± 0.58
		Male	17.1 ± 2.04	2.56 ± 0.320	2.9 ± 0.38
		All	19.0 ± 2.34	2.97 ± 0.425	2.9 ± 0.31
	300	Female	28.8 ± 14.7	3.23 ± 1.50	2.5 ± 0.50
		Male	34.6 ± 19.2	3.51 ± 1.51	4.0 ± 0.0
		All	31.7 ± 11.2	3.37 ± 0.986	3.3 ± 0.37

Source: Sponsor's table
[a] MK-8031 concentrations in 8 plasma samples from the control group animals in Study Week 13 were above the lower limit of quantitation (0.00828µM) of the bioanalytical method. The measureable concentrations in these control samples were less than 2% of the mean C_{max} value of the low dose group (15 mg/kg/day) in Study Week 13 and did not impact the quality or integrity of the study.
Values are ± the standard error.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; T_{max}, time to maximum concentration

Table 66. TT #13-1074: Summary Mean Plasma MK-8031 Toxicokinetic Parameters in Monkeys, Study Week 39

Week	Dose[a] (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM*hr)	C_{max} (µM)	T_{max} (hr)
39	15	Female	5.93 ± 1.32	1.21 ± 0.315	2.8 ± 0.75
		Male	12.1 ± 3.10	2.35 ± 0.641	3.0 ± 0.58
		All	9.00 ± 1.94	1.78 ± 0.395	2.9 ± 0.44
	40	Female	16.7 ± 1.69	3.34 ± 0.486	2.5 ± 0.50
		Male	35.7 ± 10.2	5.19 ± 1.21	4.0 ± 0.0
		All	26.2 ± 5.99	4.27 ± 0.698	3.3 ± 0.37
	300	Female	71.1 ± 32.4	8.09 ± 4.22	4.0 ± 0.0
		Male	70.2 ± 31.7	7.53 ± 2.62	4.0 ± 0.0
		All	70.7 ± 21.0	7.81 ± 2.30	4.0 ± 0.0

Source: Sponsor's table
[a] MK-8031 concentrations in plasma from all control group animals in Study Week 39 were below the lower limit of quantitation (0.00828µM) of the bioanalytical method.
Values are ± the standard error.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; T_{max}, time to maximum concentration

Dosing Solution Analysis

Drug formulations were within ±15% of nominal.

13.2.3. Genetic Toxicology

MK-8031 was negative in Ames, in in vitro chromosomal aberration, and in in vivo micronucleus (rat bone marrow) assays. (Summary was based on Donald C. Thompson's SRD review, July 12, 2012)

Carcinogenicity

Table 67. Non-Pivotal Single Oral Dose Study in Male Mice

Dose	Findings
0, 100, 200, or 750 mg/kg	None
1, 100, or 750 mg/kg	None

Source: Reviewer; Summary was based on Donald C Thompson's SRD review, July 12, 2012

13.2.3.1. Study TT #11-1169: Three-Month Oral Range-finding Study in Mice

Table 68. TT #11-1169: Study Information

Parameter	Information
Study number	TT #11-1169
Study report location	Electronic data record
Date of study initiation	December 9, 2011
GLP compliance	Yes
Quality assurance statement	Yes
Drug, lot number, and % purity	Drug: MK-8031, lot #: L-004880174-008A008 and L-004880174-008A012, purity: 99.5%

Source: Reviewer
Abbreviations: GLP, good laboratory practice

Table 69. TT #11-1169: Study Design

Parameter	Information
Doses	0, 0.5, 1, 5, 20, and 100 mg/kg/day
Frequency of dosing	Daily
Route of administration	Oral gavage
Dose volume	10 mL/kg
Formulation/Vehicle	10% polysorbate 80 in deionized water
Species/Strain	Mice/Crl: CD1 (IRC)
Number/Sex/Group	10/sex/group
Age	Approximately 6 weeks at study start.
Weight at study start	Males: 26.1 to 36.9 g; females: 19.8 to 26.7 g
Satellite groups	Toxicokinetic analysis: Controls: 5/sex; test article: 11/sex/group
Unique study design	None
Deviation from study protocol	None

Source: Reviewer

Observations and Results

Mortality and Clinical Signs

Animals were observed once daily.

There were no drug-related deaths or clinical signs observed.

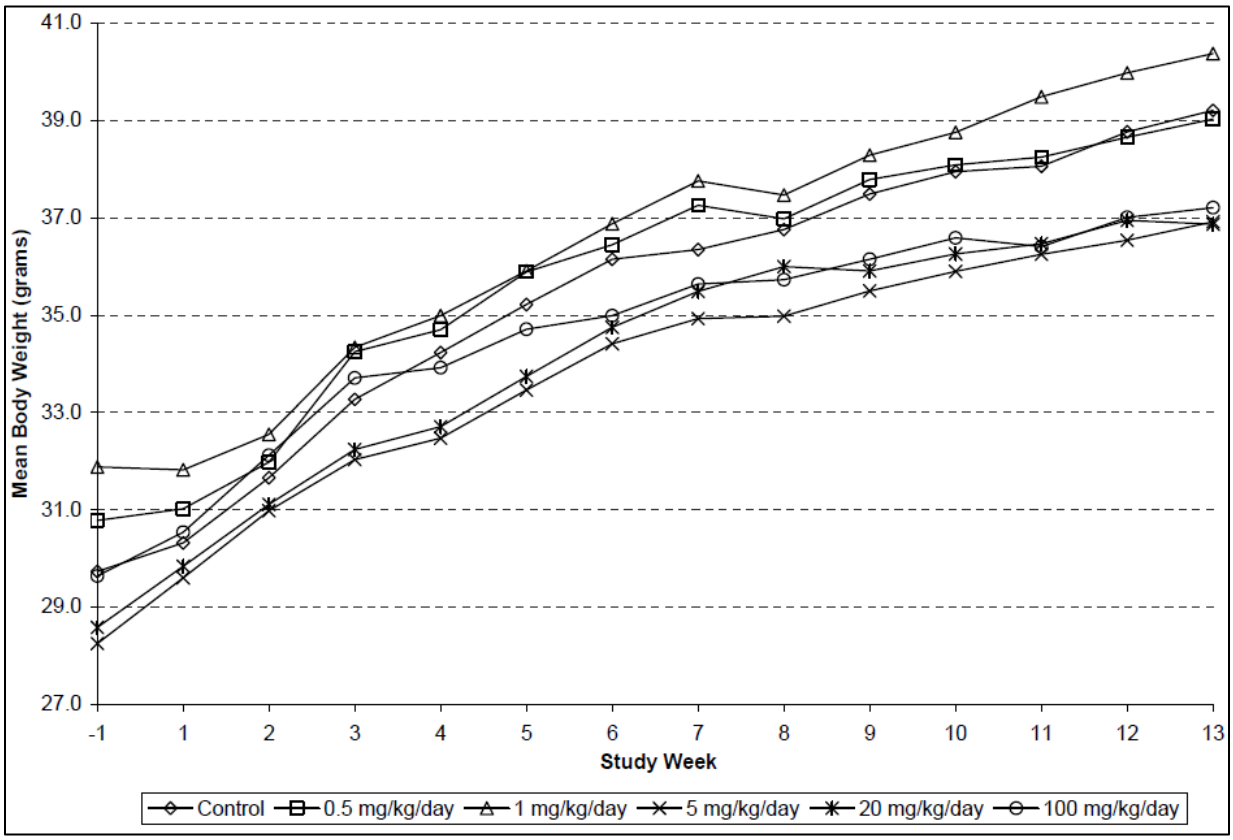
Body Weights

Body weights were measured during pretest and then weekly during the dosing period (Figure 18 and Figure 19).

In males, there was a trend for reduced body weight gain, compared to controls, over the 13-week period in the 20 and 100 mg/kg groups, and from Weeks 4 through 13 in the 5 mg/kg/day group. By Week 13, in males, body weight gain decreases at 20 mg/kg were between 8 and 13% (not dose-related) and the decrease at 100 mg/kg was 21% (Table 70).

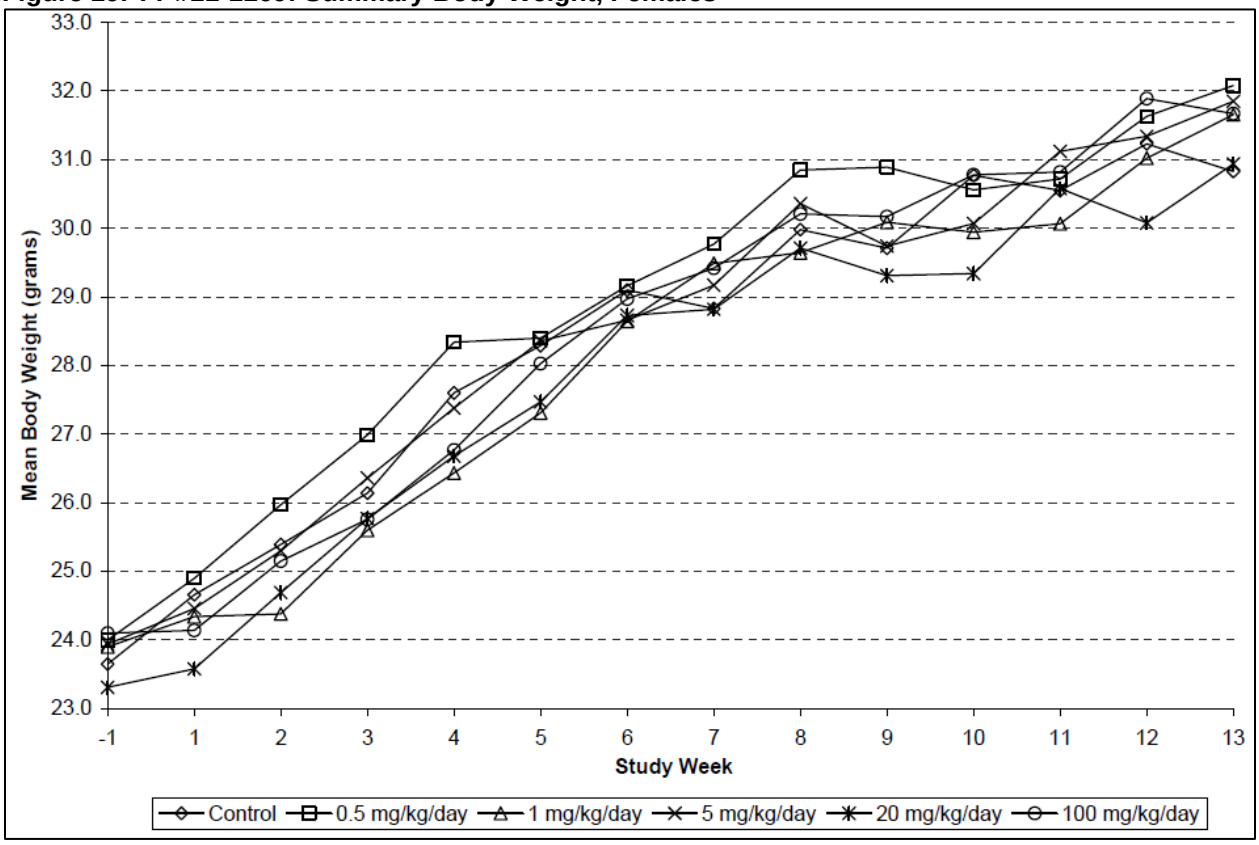
There was no change in body weight gain compared to controls in females.

Figure 18. TT #11-1169: Summary Body Weight, Males



Source: Sponsor's figure

Figure 19. TT #11-1169: Summary Body Weight, Females



Source: Sponsor's figure

Table 70. TT #11-1169: Mean Body Weight Gain, Week -1 to 13

Dose	Male		Female	
(mg/kg/day)	Weight Gain (g)	Versus Control (%)	Weight Gain (g)	Versus Control (%)
0	9.5±3.6	-	7.2±1.6	-
0.5	8.3±3.0	-13	8.1±1.9	+10
1	8.5±2.9	-11	7.6±1.5	+6
5	8.7±2.6	-8	7.9±2.3	+10
20	8.3±1.8	-13	7.6±2.2	+6
100	7.5±2.0	-21	7.6±2.1	+6

Source: Reviewer

Food Consumption

Food consumption was measured once a week.

There were no drug-related findings.

Hematology

Whole blood was collected via the vena cava from overnight-fasted animals during Week 14. The following parameters were measured: red blood cell count, reticulocyte count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, platelet count, mean platelet volume, white blood cell count, and white blood cell differential count.

There were no drug-related findings.

Clinical Chemistry

Whole blood was collected via the vena cava from overnight-fasted animals during Week 14. A standard battery of clinical chemistry parameters was assessed.

There were no drug-related findings.

Gross Pathology

All animals were subject to a complete necropsy.

In one HD female, a medulloblastoma was observed in the cerebellum and extending along the exterior surface of the brain stem.

Organ Weights

The following organ weights were recorded for all mice at scheduled necropsy: brain, heart, kidneys, liver, spleen, thymus, and testes.

There were no drug-related findings.

Histopathology

Signed and dated pathologist report: Yes

Adequate Battery: Yes

Peer Review: Yes

Histological Findings

In females, at 20 and 100 mg/kg/day, there was very slight vacuolation in the small intestine at the tip of the villi (1 of 10 at each dose).

Special Evaluation

None

Toxicokinetics

Plasma exposures were assessed during Week 13.

Plasma C_{max} and $AUC_{0\text{-}24\ h}$ were independent of sex. C_{max} values were less than dose proportional from 0.5 to 100 mg/kg. $AUC_{0\text{-}24\ h}$ values were approximately dose proportional from 0.5 to 5 mg/kg and then less than dose proportional between 5 and 100 mg/kg (Table 71).

Table 71. TT #11-1169: Summary Mean Plasma MK-8031 Toxicokinetic Parameters, Study Week 13

Dose[a] (mg/kg/day)	Sex	$AUC_{0-24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
0.5	Female	0.243 ± 0.0398	0.177 ± 0.0363	0.50 ± NC
	Male	0.475 ± 0.123	0.255 ± 0.114	0.50 ± NC
	All	0.359 ± 0.0655	0.216 ± 0.0563	0.50 ± NC
1	Female	0.479 ± 0.0497	0.330 ± 0.0400	0.50 ± NC
	Male	0.597 ± 0.0806	0.217 ± 0.0636	0.50 ± NC
	All	0.538 ± 0.0514	0.273 ± 0.0420	0.50 ± NC
5	Female	2.66 ± 0.415	1.29 ± 0.0731	0.50 ± NC
	Male	3.12 ± 0.524	0.819 ± 0.139	0.50 ± NC
	All	2.89 ± 0.312	1.05 ± 0.127	0.50 ± NC
20	Female	4.47 ± 0.555	1.53 ± 0.408	0.50 ± NC
	Male	10.1 ± 1.59	1.98 ± 0.462	0.50 ± NC
	All	7.27 ± 1.04	1.76 ± 0.293	0.50 ± NC
100	Female	18.6 ± 3.18	3.45 ± 0.405	0.50 ± NC
	Male	38.7 ± 8.15	4.29 ± 0.394	2.0 ± NC
	All	28.7 ± 4.82	3.34 ± 0.225	0.50 ± NC

Source: Sponsor's table
[a] MK-8031 concentrations in plasma from all control group animals were below the lower limit of quantitation (0.008µM) of the bioanalytical method.
Values are ± the standard error.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; NC, not calculated; T_{max}, time to maximum concentration

Dosing Solution Analysis

Dosing formulations were within ±15% of nominal.

13.2.3.2. Study CGP-TX-05: A 2-Year Carcinogenicity Study by Oral Gavage in the Mouse

Table 72. CGP-TX-05: Study Information

Parameter	Information
Study number	CGP-TX-05
Study report location	Electronic data record
Date of study initiation	May 6, 2020
GLP compliance	Yes
Quality assurance statement	Yes
Drug, lot number, and % purity	Drug: AGN-241689, batch: C11051808-H17601, purity 100%
CAC concurrence on dose selection	Males: yes; females: no

Source: Reviewer
Abbreviations: CAC, Carcinogenicity Assessment Committee; GLP, good laboratory practice

Table 73. CGP-TX-05: Study Design

Parameter	Information
Doses	0 (water), 0 (vehicle), 5, 20, 75 mg/kg for males; 0 (water), 0 (vehicle), 5, 30, 160 mg/kg for females
Frequency of dosing	Once daily
Dose volume	10 mL/kg
Route of administration	Oral
Formulation/Vehicle	Vehicle: 10% polysorbate 80 in water.
Basis of dose selection	Males: the HD was selected based on decreased body weight gain at 100 mg/kg in the 3-month dose-ranging study. The LD and MD were selected to provide a 10-fold range of plasma exposures (AUC). Females: doses were selected by the sponsor based on extrapolation of exposures above 100 mg/kg to determine the dose level anticipated to have a similar exposure as the proposed 75 mg/kg dose in males.
Species/Strain	Mice/CD1(ICR)
Number/Sex/Group	60/sex/group
Age at initiation	6 weeks of age.
Animal housing	Animals were group housed (up to 4 animals of the same sex from the same dosing group).
Paradigm for dietary restriction	*ad libitum*
Dual control employed	Yes
Interim sacrifice	None
Satellite groups	TK: 9/sex/group
Deviation from study protocol	There were minor deviations that did not affect study validity.

Source: Reviewer
Abbreviations: AUC, area under the plasma concentration-time curve; HD, high dose; LD, low dose; MD, mid dose

Observations and Results

Mortality

Observations were made twice daily.

There was no drug-related mortality.

Clinical Signs

Observations were made every two weeks.

There were no drug-related findings.

Palpable Masses

There were no drug-related findings.

Body Weights

Recordings were made weekly for the first 16 weeks and then every 4 weeks thereafter.

There were no drug-related findings.

Food Consumption

Recordings were made weekly for the first 16 weeks and then every 4 weeks thereafter.

There were no drug-related findings.

Gross Pathology

There were no drug-related findings.

Histopathology

Complete battery of tissues: Yes

Peer Review: Yes

Signed and dated pathologist report: Yes

Neoplastic

There was a significant trend for the rare malignant rhabdomyosarcoma tumor in subcutis in male mice, as determined by the CDER, Office of Biostatistices, Division of Biometrics; however, pairwise comparisons to water or vehicle control were not statistically significant (Table 74).

Table 74. CGP-TX-05: Biometrics Review of Malignant Rhabdomyosarcoma Tumors in the Subcutis in Males

	0 mg/kg/day	5 mg/kg/day	20 mg/kg/day	75 mg/kg/day	0 mg/kg/day
Parameter	**Trend**	**WC Versus L**	**WC Versus M**	**WC Versus H**	**WC Verus VC**
X/ZZ (YY)	0/60 (44)	0/60 (50)	0/60 (47)	3/60 (49)	1/60 (44)
p-value	0.0164*	NS	NS	0.1420	0.5000

Source: CDER, Office of Biostatistices, Division of Biometrics table.
X/ZZ (YY): X = number of tumor-bearing animals; YY = mortality weighted total number of animals; ZZ = unweighted total number of animals observed
* statistically significant dose response at 0.005 and 0.025 for a common tumor and a rare tumor, respectively
Abbreviations: L, low; M, mid; NS, not significant; VC, vehicle control; WC, water control

Non-Neoplastic

Minimal to mild epithelial vacuolation was observed in the duodenum and jejunum of the HD animals euthanized prematurely (Table 75).

Table 75. CGP-TX-05: Summary of Microscopic Findings, Preterminal Animals

	Males					Females				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**6**	**7**
Dose (mg/kg/day)	**0[a]**	**0[b]**	**5**	**20**	**75**	**0[a]**	**0[b]**	**5**	**30**	**160**
No. Animals Examined	**32**	**30**	**23**	**28**	**30**	**31**	**30**	**26**	**27**	**25**
Small intestine, duodenum (No. Examined)	31	29	22	27	30	31	30	25	27	25
Vacuolation; epithelial	(0)[c]	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(3)
Minimal	—	—	—	—	2	—	—	—	—	3
Small intestine, jejunum (No. Examined)	30	29	22	28	30	30	30	26	27	25
Vacuolation; epithelial	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(1)
Minimal	—	—	—	—	—	1	—	—	—	—
Mild	—	—	—	—	—	—	—	—	—	1

Source: Sponsor's table
[a] Water control; ultra-pure water
[b] vehicle control; 10% polysorbate 80
[c] Numbers in parentheses represent the number of animals with the finding
Abbreviaitons: No, number

Toxicokinetics

Exposure (C_{max} and AUC_{0-t}) increased less than dose proportionally, except between the MD and HD in males, where exposure increased dose proportionally (Table 76).

Table 76. CGP-TX-05: Toxicokinetic Summary, Day 28

Dose (mg/kg/day)	Sex	C_{max} (µM)	$AUC_{(0-t)}$ (µM hr)
5	Male	2.01	6.22
20	Male	3.44	14.1
75	Male	7.11	53.0
5	Female	2.26	5.69
30	Female	6.99	23.4
160	Female	8.70	51.2
5	Sex Combined	2.13	5.96

Sponsor's table
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration

Dosing Solution Analysis

All study samples were within ±20% of nominal.

13.2.3.3. Study CGP-TX-06: A 2-Year Carcinogenicity Study by Oral Gavage in Wistar Han Rat

Table 77. CGP-TX-06: Study Information

Parameter	Information
Study number	CGP-TX-06
Study report location	Electronic data record
Date of study initiation	February 24, 2015
GLP compliance	Yes
Quality assurance statement	Yes
Drug, lot number, and % purity	Drug: AGN-241689, batch: C11051808-H17601, purity: 100%
CAC concurrence on dose selection	Yes

Source: Reviewer
Abbreviations: CAC, Carcinogenicity Assessment Committee; GLP, good laboratory practice

Table 78. CGP-TX-06: Study Design

Parameter	Information
Doses	0 (water), 0 (100% PEG-400), 10, 20, and 100 mg/kg for males; 0 (water), 0 (vehicle: 100% PEG-400), 25, 65, and 200 mg/kg for females.
Frequency of dosing	Daily
Dose volume	2 mL/kg
Route of administration	Oral gavage.
Formulation/Vehicle	100% PEG-400.
Basis of dose selection	Males: the HD was selected based on a 9% decrease in body weight (relative to control) at 100 mg/kg in the 6-month study and a 16% decrease in body weight gain at 200 mg/kg in the 3-month dose-ranging study. Females: the HD was selected based on the TK data in females from the 3-month study in which plasma exposures (AUC) at 200 mg/kg were approximately 25 times that (8µM*hr) at the maximum anticipated clinical dose.
Species/Strain	Rat/Wistar Hannover, (b) (4)
Number/Sex/Group	60/sex/group
Age at initiation	At initiation: 6 weeks of age.
Animal housing	Animals were group housed (up to 3 animals of the same sex from the same dosing group).
Paradigm for dietary restriction	*ad libitum*
Dual control employed	Yes
Interim sacrifice	None
Satellite groups	TK: 9/sex/group
Deviation from study protocol	There were minor deviations that did not affect study validity.

Source: Reviewer
Abbreviations: AUC, area under the plasma concentration-time curve; HD, high dose; PEG, polyethylene glycol; TK, toxicokinetics

Observations and Results

Mortality

Observations were made twice daily.

There were no drug-related findings.

Clinical Signs

Detailed observations were made every 2 weeks.

Drug-related salivation at ≥10 mg/kg in males and ≥25 mg/kg in females.

Palpable Masses

There were no drug-related findings.

Body Weights

Recordings were made weekly for the first 16 weeks and then every 4 weeks thereafter.

In the MD male and HD male groups, mean body weights were 5 and 10% lower, respectively, then the vehicle control (10% polysorbate 80) group at the end of the study (Table 79 and Figure 20). In the MD female and HD female groups, mean body weights were 6 and 8% lower, respectively, then the vehicle control group at the end of the study (Table 80 and Figure 21).

Table 79. CGP-TX-06: Terminal Body Weight, Males

Parameter	Result				
Vehicle	Water	10% polysorbate 80			
Dose level	0 mg/kg	0 mg/kg	10 mg/kg	20 mg/kg	100 mg/kg
Terminal body weight (g)	647	613	609	584	550
% change relative to water control	-	-5%	-6%	-10%	-15%

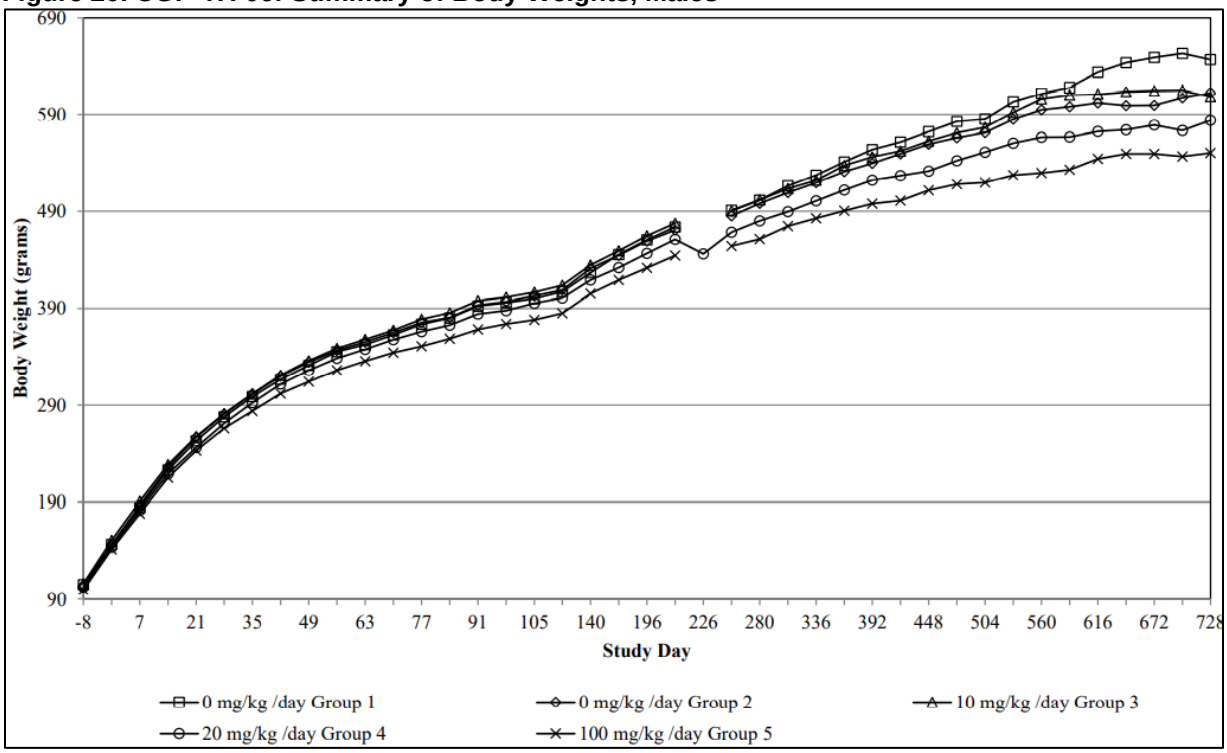
Source: Reviewer

Table 80. CGP-TX-06: Terminal Body Weight, Females

Parameter	Result				
Vehicle	Water	10% polysorbate 80			
Dose level	0 mg/kg	0 mg/kg	10 mg/kg	20 mg/kg	100 mg/kg
Terminal body weight (g)	368	343	365	320	312
% change relative to water control	-	-7%	-1%	-13%	-15%

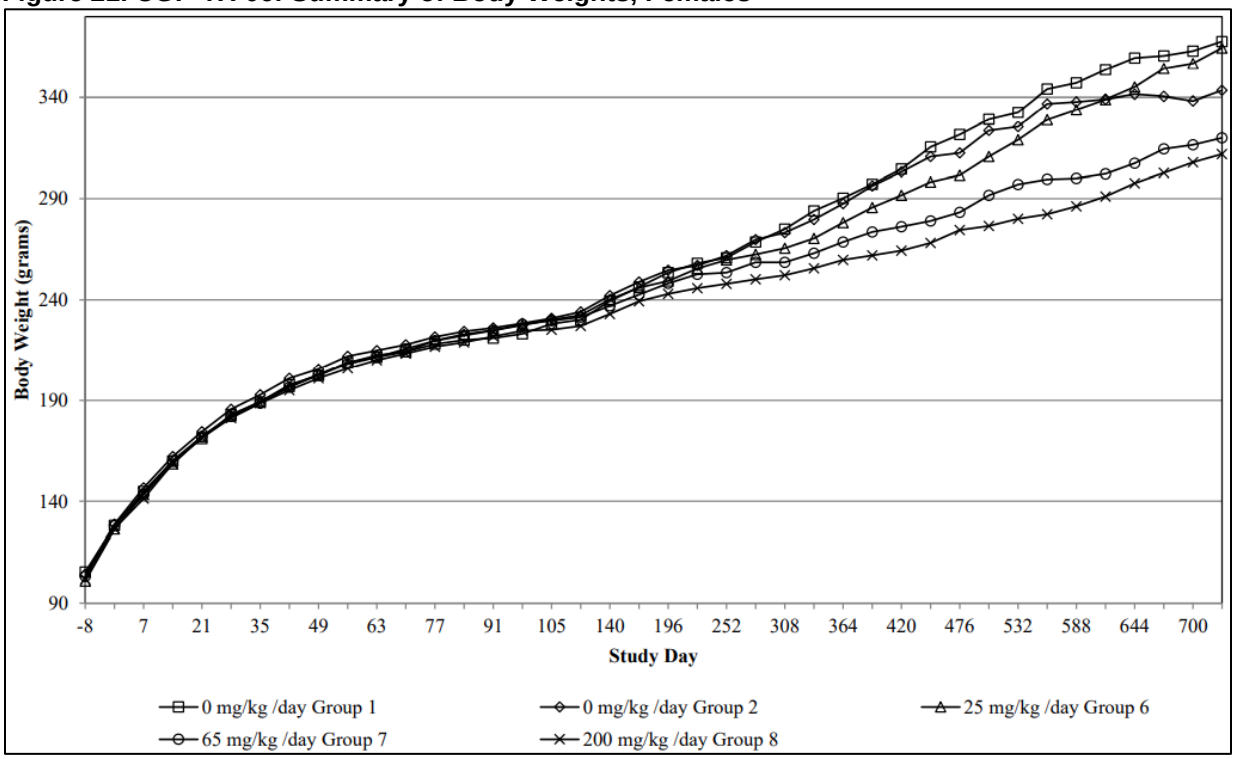
Source: Reviewer

Figure 20. CGP-TX-06: Summary of Body Weights, Males



Source: Sponsor's figure

Figure 21. CGP-TX-06: Summary of Body Weights, Females



Source: Sponsor's figure

Food Consumption

Recordings were made weekly for the first 16 weeks and then every 4 weeks thereafter.

There were no drug-related findings.

Gross Pathology

There was drug-related pale discoloration of the small intestine (see non-neoplastic histopathology findings below).

Histopathology

Complete battery of tissues: Yes

Peer Review: Yes

Signed and dated pathologist report: Yes

Neoplastic

There was a dose-related increase in a rare polyp tumor in the cervix that was determined to be statistically significant by the CDER, Office of Biostatistices, Division of Biometrics; however, pairwise comparisons to the water and vehicle controls were not statistically significant.

The combined incidence of benign polyps in the cervix and uterus was not statistically significant for trend or pairwise comparison (Table 81).

Table 81. CGP-TX-06: Biometrics Review of Benign Polyps in the Cervix and Uterus in Females

	0 mg/kg/day	25 mg/kg/day	65 mg/kg/day	200 mg/kg/day	0 mg/kg/day
Parameter	**Trend**	**VC Versus L**	**VC Versus M**	**VC Versus H**	**VC Verus WC**
Cervix					
X/ZZ (YY)	0/59 (50)	0/59 (52)	0/56 (46)	3/58 (50)	1/59 (46)
p-value	0.0154*	NS	NS	0.1212	0.4792
Cervix and uterus					
X/ZZ (YY)	6/59 (50)	8/59 (52)	9/56 (47)	7/58 (51)	10/59 (49)
p-value	0.4939	0.4182	0.2446	0.5155	0.1943

Source: CDER, Office of Biostatistices, Division of Biometrics table.
X/ZZ (YY): X = number of tumor-bearing animals; YY = mortality weighted total number of animals; ZZ = unweighted total number of animals observed
* statistically significant dose response at 0.005 and 0.025 for a common tumor and a rare tumor, respectively
Abbreviations: L, low; M, mid; NS, not significant; VC, vehicle control; WC, water control

Non-Neoplastic

There was dose-related minimal to marked epithelial vacuolation along the mucosa of the duodenum and jejunum, with no epithelial degeneration or necrosis (Table 82).

Table 82. CGP-TX-06: Summary of AGN-241689-related Non-Neoplastic Microscopic Findings – Early Deaths and Terminal Euthanasia Combined

	Males					Females				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**6**	**7**	**8**
Dose (mg/kg/day)	**0[b]**	**0[c]**	**10**	**20**	**100**	**0[b]**	**0[c]**	**25**	**65**	**200**
No. Animals Examined	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Jejunum (No. Examined)	60	60	59	60	60	60	60	60	59	60
Vacuolation; epithelial	(0)[a]	(0)	(6)	(23)	(39)	(0)	(0)	(14)	(30)	(41)
Minimal	0	0	4	13	7	0	0	10	7	6
Mild	0	0	1	2	13	0	0	3	9	3
Moderate	0	0	1	8	17	0	0	1	11	15
Marked	0	0	0	0	2	0	0	0	3	17
Duodenum (No. Examined)	60	60	60	60	60	60	60	60	59	60
Vacuolation; epithelial	(0)	(0)	(0)	(7)	(7)	(0)	(0)	(4)	(4)	(10)
Minimal	0	0	0	4	4	0	0	2	2	5
Mild	0	0	0	3	3	0	0	2	0	3
Moderate	0	0	0	0	0	0	0	0	2	2

Source: Sponsor's table
[a] Numbers in parentheses represent the number of animals with the finding
[b] Water control
[c] Vehicle control
Abbreviations: No, number

Toxicokinetics

Exposure (C_{max} and AUC_{0-t}) in males increased greater than dose proportional between the LD and MD, and approximately dose proportionally between the MD and HD. In females, exposure between the LD and HD increased greater than dose proportionally, and between the MD and HD, exposure increase less than dose proportionally (Table 83).

Table 83. CGP-TX-06: Toxicokinetic Summary, Day 28

Dose (mg/kg/day)	Sex	C_{max} (µM)	$AUC_{(0-t)}$ (µM*hr)
10	Male	1.56	8.86
20	Male	4.09	23.8
100	Male	20.1	136
25	Female	5.03	24.4
65	Female	16.4	101
200	Female	41.6	214

Source: Sponsor's table
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration

Dosing Solution Analysis

All drug formulations were within ±20% of nominal.

13.2.4. Reproductive and Developmental Toxicology

13.2.4.1. Fertility and Early Embryonic Development

13.2.4.1.1. Study TT #12-7380: Oral Fertility Study in Female and Male Rats

Table 84. TT #12-7380: Study Information

Parameter	Information
Study number	TT #12-7380
Study report location	Electronic data record
Date of study initiation	January 24, 2013
GLP compliance	Yes
Quality assurance statement	Yes
Drug, lot #, and % purity	Drug: MK-8031, lot: L-004880174-008A019, purity: 98.2%

Source: Reviewer
Abbreviations: GLP, good laboratory practice

Key Study Findings

The NOAEL was at the HD. The HD was justified based on decreases in body weight gain (16%) at 200 mg/kg in the 3-month toxicology study in rat.

Table 85. TT #12-7380: Study Design

Parameter	Information
Doses	0, 5, 20, or 125 mg/kg
Frequency of dosing	Once daily
Dose volume	2 mL/kg
Route of administration	Oral gavage
Formulation/Vehicle	100% polyethylene glycol 400
Species/Strain	Rat/ (b) (4) WI(HAN)
Number/Sex/Group	20/se oup
Satellite groups	None
Study design	The fertility of male and female rats was assessed following oral administration of MK-8031 for 15 days prior to cohabitation.
Deviation from study protocol	There were minor deviations that did not affect study validity.

Observations and Results

Mortality

Observations were made daily.

There were no unscheduled deaths.

Clinical Signs

Observations were made daily.

There were no drug-related findings.

Body Weights

Females: recordings were made twice a week prior to mating and every 2 days after mating confirmation.

Males: recordings were made twice a week.

In the HD female group, there was a decrease in body weight from premating day 1 to 4 (-3 grams compared to +3 grams for control); there was a decrease in body weight gain between GD 0 and 8 (11%).

In the MD males and HD males, prior to cohabitation (Weeks 1 to 3) there were decreases in mean body weight gain ranging from 13 to 31%. During cohabitation (Weeks 3 to 7), there was a 23% decrease in mean body weight gain in HD males.

Food Consumption

Recordings were made twice a week.

In HD females, there was a decrease in food consumption on premating days 4 and 11 of 19% and 12%, respectively.

In HD males, there was a 12% decrease in food consumption during Week 2.

Fertility Parameters

Males were examined for testes descent and penile alterations. Females were examined for pregnancy status, corpora lutea, uterine implants, live and dead fetuses, and resorptions.

There were no drug-related findings.

Sperm Motility and Number Analysis

There were no drug-related findings.

13.2.4.2. Embryonic Fetal Development

13.2.4.2.1. Study TT #12-7061: Preliminary Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rats

Rats were orally administered MK-8031 (0, 5, 20, 250, or 750 mg/kg, QD, 12/group) from GDs 6 through 20. The animals were assessed for mortality, physical signs, body weights, food consumption, and toxicokinetics. On GD 21, animals were euthanized and assessed for number of corpora lutea and gross placental morphology. The following developmental parameters were assessed: fetal viability, fetal weight, sex ratio, and external and visceral morphology. Maternal body weight between GDs 6 and 18 was decreased up to 36% compared to control in the 250 and 750 mg/kg groups. Fetal weights were decreased 11 to 14% in the same groups. Exposure ($AUC_{0\text{-}24\,h}$) increased greater than dose proportionally between 5 and 20 mg/kg and less than dose proportionally between 20 and 750 mg/kg (Table 86).

Table 86. Summary Mean Maternal Plasma MK-8031 Toxicokinetic Parameters, Gestation Day 15

Dose[a] (mg/kg/day)	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
5[b]	3.93 ± ID	0.586 ± ID	1.5 ± ID
20[c]	35.9 ± 4.58	3.90 ± 0.376	2.3 ± 0.88
250	66.9 ± 12.8	8.17 ± 1.99	2.8 ± 0.75
750[b]	126 ± ID	12.4 ± ID	3.0 ± ID

Source: Sponsor's table
[a] MK-8031 concentrations in plasma from all control group animals were below the lower limit of quantitation (0.008µM) of the bioanalytical method.
[b] n=2
[c] n=3
Values are ± the standard error.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; ID, insufficient data; T_{max}, time to maximum concentration

13.2.4.2.2. Study TT#12-7060: Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rats

Table 87. TT#12-7060: Study Information

Parameter	Information
Study number	TT#12-7060
Study report location	Electronic data record
Conducting laboratory and location	(b) (4)
Date of study initiation	March 1, 2012
GLP compliance	Yes
Quality assurance statement	Yes
Drug, lot number, and % purity	Drug: MK-8031 (L-004880174), lot #: L-004880174-008A015, purity 99.5%.

Source: Reviewer
Abbreviations: GLP, good laboratory practice

Key Study Findings

The NOAEL for the dams was at the HD (C_{max}: 6µmol/L; $AUC_{0\text{-}t}$: 9µmol·h/L). The NOAEL for the fetuses was 15 mg/kg, based on increases in total resorptions and post-implantation loss, visceral variations, skeletal variations, and incomplete ossification in the 125 and 750 mg/kg groups.

Table 88. TT#12-7060: Study Design

Parameter	Information
Doses	0, 5, 15, 125, or 750 mg/kg
Frequency of dosing	Once daily
Dose volume	2 mL/kg
Route of administration	Oral gavage
Formulation/Vehicle	100% polyethylene glycol 400
Species/Strain	Rat (b) (4) WI(HAN)
Number/Sex/Group	Main: 20/F/5 and 15 mg/kg groups; 21/F/125 and 750 mg/kg groups. TK: 3/F/C group, 6/F/MK-8031 groups.
Satellite groups	None
Study design	Main study animals were dosed on GDs 6 through 20. TK animals were dosed on GDs 6 through 15.
Deviation from study protocol	There were minor deviations that did not affect study validity.

Source: Reviewer
Abbreviations: F, female; GD, gestation day; M, male; TK, toxicokinetic

Observations and Results

Mortality

Observations were made daily.

There were no unscheduled deaths.

Clinical Signs

Observations were made daily.

There were no drug-related findings.

Body Weights

Recordings were made every other day.

There were no drug-related findings.

Food Consumption

Recordings were made over two-day intervals ending on GDs 8, 14, and 20.

There were no drug-related findings.

Toxicokinetics

$AUC_{0\text{-}24\ h}$ increased less than dose proportionally, except between the 125 and 750 mg/kg groups, where it decreased (Table 89).

Table 89. TT#12-7060: Summary Mean Maternal Plasma MK-8031 Toxicokinetic Parameters, Gestation Day 15

Dose[a] (mg/kg/day)	$AUC_{0\text{-}24\ hr}$ (μM•hr)	C_{max} (μM)	T_{max} (hr)
5	8.85 ± 1.93	1.06 ± 0.337	2.0 ± NC
15	25.8 ± 6.83	4.53 ± 1.43	1.0 ± NC
125	96.2 ± 12.3	13.7 ± 1.08	1.0 ± NC
750	62.5 ± 11.3	8.65 ± 2.70	0.50 ± NC

Source: Sponsor's table
[a] MK-8031 plasma concentration was above the lower limit of quantitation in one sample from control animals which was less than 1% of the mean C_{max} value of the 5 mg/kg/day group.
Values are ± the standard error.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; NC, not calculated; T_{max}, time to maximum concentration

Dosing Solution Analysis

Dosing solutions were within ±15% of nominal.

Necropsy

There were no drug-related findings.

Cesarean Section Data (Implantation Sites, Resorptions, Live and Dead Fetuses, and Fetus Weight)

There was a dose-related increase in total resorptions and post-implantation loss at ≥15 mg/kg (Table 90).

Table 90. TT#12-7060: Cesarean Section Findings

	Dose (mg/kg)				
Finding	**0**	**5**	**15**	**125**	**750**
% Resorptions, litter mean	1.4	1	2.9	6.2	7.4
% Post implantation loss, litter mean	1.4	1	2.9	6.2	7.4

Source: Reviewer

Offspring (Live Fetuses, Sex, and Visceral and Skeletal Abnormalities)

Visceral examinations

In the 15, 125, and 750 mg/kg groups, azygos vein variations were observed in 1 of 18 (1 fetus), 2 of 19 (4 fetuses), and 4 of 20 (6 fetuses) litters, respectively. Overall, there were 0 (control), 0 (5 mg/kg), 1 (6%, 15 mg/kg), 2 (11%, 125 mg/kg), and 4 (20%, 750 mg/kg) fetal variations observed per litter.

Skeletal examinations

In the 15, 125, and 750 mg/kg groups, there were skull bone abnormalities in 1 of 18 (1 fetus), 1 of 19 (1 fetus), and 3 of 20 (4 fetuses) litters, respectively. Overall, there were 0 (control), 0 (5 mg/kg), 1 (6%, 15 mg/kg), 1 (6%, 125 mg/kg), and 3 (15%, 750 mg/kg) fetal head skeletal variations observed per litter.

Fetal ossification data

In the 5, 15, 125, and 750 mg/kg groups, there was incomplete ossification of the skull bone in 1 of 18 (1 fetus), 1 of 18 (2 fetus), 4 of 19 (6 fetus), and 4 of 20 (6 fetuses) litters, respectively. Overall, there were 0 (control), 1 (5%, 5 mg/kg), 1 (6%, 15 mg/kg), 4 (21%, 125 mg/kg), and 4 (20%, 750 mg/kg) fetal incomplete head ossifications observed per litter.

13.2.4.2.3. TT #12-7071: Preliminary Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rabbits

Rabbits (12 females per group) were orally administered MK-8031 (0, 15, 45, 100, or 325 mg/kg/day) from GD 7 through 20. Animals were assessed for mortality, physical signs, body weights, food consumption, and toxicokinetics. At the HD, from GD 6 to 21, there was a 6% decrease in mean maternal body weight gain, compared to control. $AUC_{0\text{-}24\ h}$ increased greater than dose proportionally from 15 to 100 mg/kg and decrease from 100 to 325 mg/kg (Table 91).

Table 91. TT #12-7071: Summary Mean Plasma MK-8031 Toxicokinetic Parameters, Gestation Day 15

Dose[a] (mg/kg/day)	$AUC_{0\text{-}24\ hr}$ (μM•hr)	C_{max} (μM)	T_{max} (hr)
15	2.06 ± 0.504	0.561 ± 0.226	2.0 ± 1.0
45	7.42 ± 0.521	1.63 ± 0.193	1.7 ± 0.33
100	28.8 ± 3.92	5.22 ± 1.04	4.0 ± 0.0
325	7.76 ± 1.80	1.31 ± 0.393	2.0 ± 0.0

Source: Sponsor's table
[a] MK-8031 plasma concentration was above the lower limit of quantitation in three samples from control animals. These values were about 0.43 to 5.8% of the mean C_{max} value of the 15 mg/kg/day dose group.
Values are ± the standard error.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; T_{max}, time to maximum concentration

On GD 28, a necropsy was conducted, and uterine contents were examined for corpora lutea, gross morphology, fetal viability and weight, sex ratios, and fetal external and visceral morphology. In the HD group, there was a decrease in male and female fetal mean body weight of 10 and 14%, respectively, compared to control.

13.2.4.2.4. Study TT #12-7070: Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rabbits

Table 92. TT #12-7070: Study Information

Parameter	Information
Study number	TT #12-7070
Study report location	Electronic data record
Date of study initiation	July 20, 2012
GLP compliance	Yes
Quality assurance statement	Yes
Drug, lot number, and % purity	Drug: MK-8031; lot: L-004880174-008A019; purity: 98.6%

Source: Reviewer
Abbreviations: GLP, good laboratory practice

Key Study Findings

The NOAEL for the dams was the LD (C_{max}: 2µmol/L; $AUC_{0\text{-}24\,h}$: 11µmol·h/L), based on body weight loss resulting in euthanasia in the MD and HD groups. The NOAEL for the fetuses was at the MD (C_{max}: 3µmol/L; $AUC_{0\text{-}12\,h}$: 17µmol·h/L), based on skeletal and visceral variations in the HD group.

Table 93. TT #12-7070: Study Design

Parameter	Information
Doses	0, 30, 90, or 130 mg/kg
Frequency of dosing	Once daily
Dose volume	1 mL/kg
Route of administration	Oral gavage
Formulation/Vehicle	100% polyethylene glycol 400
Species/Strain	Rabbit, New Zealand White
Number/Sex/Group	23 females/group
Satellite groups	None
Study design	MK-8031 was orally administered daily on GDs 7 through 20. Animals were euthanized on GD 28
Deviation from study protocol	There were minor deviations that did not affect study validity

Source: Reviewer
Abbreviations: GD, gestation day

Observations and Results

Mortality

Observations were made daily.

One female in the MD group (#12-0475) and one female in the HD group (#12-0495) were euthanized early on GD 21 and 15, respectively, due to maternal body weight loss.

Clinical Signs

Observations were made daily.

There were no drug-related findings.

Body Weight

Recordings were made every other day.

In the HD group, there was a decrease in mean maternal body weight gain (GDs 7 to 28) of 18%, compared to control (adjusted for total fetal weights).

Food Consumption

Recordings were made twice a week.

There were no drug-related findings.

Toxicokinetics

Exposure (C_{max} and $AUC_{0\text{-}24\,h}$) increased less than dose proportionally between 30 and 90 mg/kg and greater than dose proportionally between 90 and 130 mg/kg (Table 94).

Table 94. TT #12-7070: Summary Mean Plasma MK-8031 Toxicokinetic Parameters, Gestation Day 15

Dose (mg/kg/day)[a]	$AUC_{0-24\ hr}$ (μM•hr)	C_{max} (μM)	T_{max} (hr)
30	10.7 ± 4.45	2.18 ± 0.924	1.6 ± 0.38
90[b]	16.6 ± 5.51	3.03 ± 1.01	2.3 ± 0.63
130	44.1 ± 7.79	7.97 ± 1.25	4.0 ± 0.0

Source: Sponsor's table
[a] MK-8031 concentrations in plasma from all four control animals were above the lower limit of quantitation (0.002M) at one, two, or three time oints on Gestation Day 15. These values were less than 1.5% of the mean C_{max} value of the low dose group (30 mg/kg/day) on Gestation Day 15.
[b] Based on the dose formulation assay results, the actual dose administered was about 71% of the nominal dose.
Values are ± the standard error.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; T_{max}, time to maximum concentration

Dosing Solution Analysis

The dose administered to the MD group was 71% of nominal; all other groups were administered dosing formulations within ±15% of nominal.

Necropsy

There were no drug-related findings.

Cesarean Section Data (Implantation Sites, Resorptions, Live and Dead Fetuses, Fetus Weight, and Fetal Abnormalities)

There were no drug-related findings.

Offspring (Sex, and External, Visceral, and Skeletal Abnormalities.)

In the HD group, the litter mean incidence of absent caudate lobe of the lung was 12%, which was above the concurrent and historical control values (4 and 8%, respectively). Total visceral variations were 47%, which was above the concurrent control (33%).

The litter incidence of sternebral variations at the HD (3.5%) was increased compared to concurrent (0) and historical controls (0.85%).

13.2.4.3. Prenatal and Postnatal Development

13.2.4.3.1. Study CGP-TX-15: Pre and Postnatal Developmental Study in Wistar Hannover Rats by Oral Gavage

Table 95. CGP-TX-15: Study Information

Parameter	Information
Study number	CGP-TX-15
Study report location	Electronic data report
Date of study initiation	June 23, 2017
GLP compliance	Yes
Quality assurance statement	Yes
Drug, lot number, and % purity	Drug: AGN-241689, batch: C11051808-H18601, purity: 100%

Source: Reviewer
Abbreviations: GLP, good laboratory practice

Key Study Findings

The NOAEL was at the MD, based on pup body weight decreases at the HD.

Table 96. CGP-TX-15: Study Design

Parameter	Information
Doses	0, 15, 45, or 125 mg/kg
Frequency of dosing	Once daily
Dose volume	2 mL
Route of administration	Oral Gavage
Formulation/Vehicle	100% Polyethylene glycol 400
Species/Strain	Rat/Wistar Hannover (b) (4)
Number/Sex/Group	21 females per group
Satellite groups	None
Study design	AGN-241689 was administered to the F_0 Dams daily from GD 6 through lactation day 20. Animals were euthanized on GD 28.
Deviation from study protocol	There were minor deviations that did not affect study validity.

Source: Reviewer
Abbreviations: GD, gestation day

Observations and Results

F_0 Dams

Survival

Observations were made twice daily.

There were no drug-related findings.

Clinical Signs

Detailed observations were made weekly.

There were no drug-related findings.

Body Weights

Recordings were made 2 to 3 times per week.

Food Consumption

Recordings were made over 3-day intervals.

At the HD, food consumption was 8% lower between GDs 6 and 20 compared to control, and 11 to 17% lower between lactation days 0 and 14.

Uterine Content/Maternal Performance

Gestation period, pregnancy rate, live and dead pups, malformations, and sex ratio were assessed.

There were no drug-related findings.

Necropsy observations

There were no drug-related findings.

Toxicokinetics

Drug distributes to the milk (Table 97).

Table 97. CGP-TX-15: Mean AGN-241689 Plasma and Milk Concentrations, Lactation Day 14 for F_0 Females

Dose (mg/kg/day)	Plasma Concentration ± SD (µM)[d]	Milk Concentration ± SD (µM)[d]	Milk to Plasma Concentration Ratio
15	1.77 ± 0.62	4.36 ± 1.65	2.46
45 [a]	4.54 ± 3.84	11.11 ± 7.70	2.45
125 [b,c]	18.12 ± 11.86	38.18 ± 22.18	2.11

Source: Sponsor's table
Lower limit of quantitation for plasma and mi k: theoretical concentration 0.00804µM
Upper limit of quantitation for milk: theoretical concentration 8.04µM. Three mi k samples (detailed below) were determined to be greater than the upper limit of quantitation even when initially analyzed with dilution; the extrapolated values were reported for information purposes only.
[a] Extrapolated value for information purposes for animal number 358 (45 mg/kg/day). Analyzed with a dilution factor of 5.
[b] Extrapolated values for information purposes for animal number 455 and 456 (125 mg/kg/day). Analyzed with a dilution factor of 5.
[c] Animal number 457 (125 mg/kg/day) was excluded from the mean values as only plasma was collected and no milk was collected for this animal.
[d] Conversion from ng/mL to µM: concentration value in ng/mL divided by the molecular weight of AGN-241689 amjudrate (i.e., 603.529).
Plasma collection was 2 hours post dose, mi k collection was 2 hours ±20 minutes post dose
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; T_{max}, time to maximum concentration

Dosing Solution Analysis

Drug formulations were within ±20% of nominal.

Other

Ovary and uterus were weighed.

There were no drug-related findings

F_1 Generation

Survival

Observations were made twice daily.

There were no drug-related deaths.

Clinical signs

Observations were made daily.

There were no drug-related findings.

Body Weights

Recordings were made twice a week.

In the HD litter, pup body weights were 8 to13% lower than controls from postnatal days (PNDs) 10 to 21 (Table 98). These decreases did not fully resolve in adult animals (-2 to 8%).

Table 98. CGP-TX-15: Summary of Litter Mean Pup Body Weights

	Postnatal Day					
Dose mg/kg	**4**	**7**	**10**	**14**	**17**	**21**
0	10 g	16 g	24 g	32 g	37 g	46 g
125	11 g	16 g	22 g*	28 g*	33 g*	42 g*
%Difference	10%	0%	-8%	-13%	-11%	9%

Source: Reviewer
* p≤0.05
Abbreviations: GD, gestation day

Food Consumption

Recordings were made continuously over 3-day intervals.

There were no drug-related findings.

Visual Function

Pupillary closure and visual placing responses were tested on PND 21.

There were no drug-related findings.

Physical Development

Observations were made daily for vaginal opening (from PND 26) or preputial separation (from PND 35).

There were no drug-related findings.

Neurological Assessment

Motor activity assessed on PND 52.

Cincinnati Water Maze conducted on PND 55 and 75.

There were no drug-related findings.

Reproduction

The cohabitation period was 14 days from PND 85. Corpora lutea, implantation sites, placental abnormalities, live and dead embryos, and early resorptions were assessed.

There were no drug-related findings.

Other

Necropsy

There were no drug-related findings at necropsy.

Epididymis, prostate, seminal vesicles, ovaries, and testis were weighed.

There were no drug-related findings.

13.2.5. Special Toxicology Studies

Computational modeling of in vitro experiments assessing bile acid transporter inhibition, mitochondrial dysfunction, and oxidative stress suggested atogepant may have a reduced risk of causing hepatotoxicity in humans compared to the predecessor small molecule CGRP receptor antagonists, telcagepant and MK-3207.

A 3-day phototoxicity study of atogepant (up to 40 mg/kg/day followed by a single 90-minute ultraviolet ray exposure) in 8 female pigmented rats showed no drug-related skin reactions or ocular findings.

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

14.1.1. Plasma Protein Binding

The binding of atogepant to human plasma proteins was determined by equilibrium dialysis. In Study MK-8031 PK003, atogepant at 0.1, 1, and 10µM was incubated for 4 hours in human plasma and the unbound fraction was determined. The mean unbound fraction ranged from 4 to 6% across all atogepant concentrations.

In clinical Study CGP-PK-01, plasma protein binding was determined by equilibrium dialysis using plasma samples collected from subjects with different degrees of hepatic impairment. In participants with no, mild, moderate, or severe hepatic impairment administered a single oral dose of 60 mg atogepant, the percentage of unbound atogepant was found to be 1.8%, 2.6%, 2.9%, and 4.7%, respectively.

14.1.2. Metabolism of Atogepant

In Study MK-8031 PK003, the in vitro metabolism of [^{14}C]-atogepant was assessed using rat, monkey, and human liver microsomes and mouse, rat, monkey, and human hepatocytes to compare species-specific metabolism. Metabolites M1 (N-oxide on the azaoxindole moiety) and M2 (5-hydroxylation on the azaoxindole moiety) were found following liver microsome incubation. All human metabolites were observed in mouse, rat, and/or monkey hepatocytes, the preclinical toxicology species.

In study MK-8031 PK007, circulating metabolites of atogepant in human plasma were characterized using pooled clinical samples from Study MK-8031 P002. With a semi-quantitative Liquid Chromatography-High Resolution Mass Spectrometry method, results showed that atogepant was the predominant circulating component (97.8% of total exposure) and metabolite M1 was a minor circulating metabolite (2.2% of total exposure) with no apparent accumulation following multiple doses of atogepant. M2 was not found in the pooled clinical samples.

In the clinical mass balance study of Study CGP-PK-03, the only two radiometric peaks detected in plasma were atogepant and metabolite M23, together representing 15.3% of the circulating radioactivity exposure. Characterization of M23 in Study 3101-N02-050 indicated that M23 is

not an acyl-glucuronide metabolite. Following a single dose of 50 mg atogepant, the AUC of M23 was found to be 3 times lower than that from monkeys dosed with a single dose of atogepant at 10 mg/kg in Study PK002.

In study MK-8031 PK003, cytochrome P450 (CYP) reaction phenotyping was conducted using human liver microsomes incubated with inhibitory antibodies for CYP3A4/5, 2C, and 2D6 and with recombinant CYP enzymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The results showed that the oxidative metabolism of atogepant occurred almost predominantly via CYP3A4 with minor involvement of CYP2D6.

14.1.3. Inhibition and Induction of CYP Isozymes by Atogepant

Results from in vitro studies showed that atogepant is not anticipated to inhibit CYP enzymes, monoamine oxidase A, or UGT1A1.

Table 99. Studies MK-8031 PK003, 110337: Effect of Atogepant on Cytochrome P450 Marker Enzyme Activities in Human Liver Microsomes

Isoenzyme	Reaction	IC_{50} (µM)[a]	
		Control Inhibitor	Atogepant
CYP1A2	Phenacetin *O*-Deethylation	0.010 (α-Naphthoflavone)	>100 (0%)[b]
CYP2B6	Bupropion Hydroxylation	0.44 (Ticlopidine)	83
CYP2C8	Amodiaquine *N*-Deethylation	0.33 (Montelukast)	41
CYP2C9	Diclofenac 4′-Hydroxylation	0.79 (Sulfaphenazole)	16
CYP2C19	S-Mephenytoin 4′-Hydroxylation	0.20 (Benzylnirvanol)	59
CYP2D6	Dextromethorphan *O*-Demethylation	0.18 (Quinidine)	34
CYP3A4	Midazolam 1′-Hydroxylation	0.035 (Ketoconazole)	>100 (41 ± 0.39%)
	Testosterone 6β-Hydroxylation	0.036 (Ketoconazole)	>100 (26 ± 0.12%)

[a] The absolute IC_{50} is represented as the inhibitor concentration that yields 50% of the mean control activity.
[b] The values in parentheses represent the percent inhibition (mean ± standard deviation) observed at 100 µM.
Source: Module 4.2.2.4, Study MK-8031 PK003, Table 3

In Study PK003, atogepant was found to have no inhibition potential on monoamine oxidase A and UGT1A with a half maximal inhibitory concentration of >122µM and 83µM, respectively.

In Study PK003, atogepant up to 20µM was found to have no induction potential on CYP1A2 or CYP2B6. At 5 to 20µM, atogepant was found to increase by more than 2-fold the messenger RNA activity of CYP3A4 compared to the vehicle control. However, atogepant is not expected to have induction potential on CYP3A4 at clinically relevant concentrations.

Table 100. Evaluation of Drug Transporters Involved in the Disposition of Atogepant

Transporter	Results	Conclusion	Test System	Positive Control	Study
P-gp	Efflux ratio (ER) of 16.6 at 0.5µM	Is a substrate	Caco-2 cells	Verapamil	MK-8031 PK003
BCRP	ER of 27.9 at 0.5µM	Is a substrate	MDCKII-BCRP cells	Prazosin	CGP-PH-03
OAT3	Uptake ratio <2 at 0.2-20µM	Not a substrate	HEK293-OAT3 cells	[^{3}H]-estrone-3-sulfate	

Transporter	Results	Conclusion	Test System	Positive Control	Study
OCT2	Uptake ratio <2 at 0.2-20µM	Not a substrate	HEK293-OCT2 cells	[^{14}C]-Metformin	
MATE1	Uptake ratio <2 at 0.2-20µM	Not a substrate	HEK293-MATE1 cells	[^{14}C]-Metformin	
OATP1B1	Greater uptake in MDCKII-OATP1B1 cells, compared to parental MDCKII cells at 1µM	Is a substrate	MDCKII-OATP1B1 cells	[^{3}H] Estradiol-17β-glucuronide	MK-8031 PK008
OATP1B3	Greater uptake in MDCKII-OATP1B3 cells, compared to parental MDCKII cells at 1µM	Is a substrate	MDCKII-OATP1B3 cells	[^{3}H] cholecystokinin-8	
OAT1	Greater uptake in MDCKII-OAT1 cells, compared to parental MDCKII cells at 1µM	Is a substrate	MDCKII-OAT1 cells	P-aminohippurate	

Source: Study MK-8031 PK003, CGP-PH-03, and MK-8031 PK008 reports
Abbreviations: BCRP, breast cancer resistance protein; ER, efflux ratio; MATE, multidrug and toxin extrusion; OAT, organic anion transporter; OCT, organic cation transporter; P-gp, P-glycoprotein;

Table 101. Evaluation of Inhibition of Drug Transporters by Atogepant

Transporter	IC_{50}	Conclusion	Test System	Positive Control	Study
P-gp	No inhibition up to 100µM	Not an inhibitor	[^{3}H] Digoxin in LLC-PK1 and LLC-MDR1 Cell Monolayers	Cyclosporine	MK-8031 PK 003
BCRP	>10µM	Not an inhibitor at clinically relevant concentration	[^{3}H] Methotrexate in membrane vesicles containing BCRP	KO143	MK-8031 PK 008
OATP1B1	3.3µM	Not an inhibitor at clinically relevant concentration	[^{3}H] pitavastatin in OATP1B1 stably transfected MDCKII cells	Cyclosporine A	
OATP1B3	8.4µM	Not an inhibitor at clinically relevant concentration	[^{3}H] BSP in OATP1B3 stably transfected MDCKII cells	Cyclosporine A	
OAT1	No inhibition up to 10µM	Not an inhibitor	[^{3}H] cidofovir in OAT1 stably transfected MDCKII cells	Probenecid	
OAT3	No inhibition up to 10µM	Not an inhibitor	[^{3}H] Estrone sulfate in OAT3 stably transfected MDCKII cells	Probenecid	
OCT2	>10µM	Not an inhibitor at clinically relevant concentration	[^{14}C] metformin in OCT2 stably transfected CHO-K1 cells	Quinidine	

Transporter	IC_{50}	Conclusion	Test System	Positive Control	Study
BSEP	>15µM	Not an inhibitor at clinically relevant concentration	BSEP-mediated transport of Taurocholate	Cyclosporin A	3101-N01-050
MRP3	>15µM	Not an inhibitor at clinically relevant concentration	MRP3-mediated transport of Estradiol-17-β-glucuronide	Sulfasalazine	
NTCP	>20µM	Not an inhibitor at clinically relevant concentration	NTCP-mediated transport of Taurocholate	TCDC	
MRP4	No inhibition up to 15µM	Not an inhibitor	MRP4-mediated transport of Dehydroepiandrosterone sulfate	MK571	
OCT1	1.23µM	Not a potential inhibitor at clinically relevant concentration	OCT1-mediated transport of [^{14}C]-tetraethylammonium bromide	Quinidine and verapamil	CGP-PH-03
MATE1	2.24µM	Not a potential inhibitor at clinically relevant concentration	MATE1-mediated transport of [^{14}C]-metformin	Cimetidine and pyrimethamine	
MATE2-K	No inhibition up to 20µM	Not an inhibitor	MATE2-K-mediated transport of [^{14}C]-metformin	Cimetidine and pyrimethamine	

Source: Study MK-8031 PK003, CGP-PH-03, 3101-N01-050, and MK-8031 PK008 reports
Abbreviations: BCRP, breast cancer resistance protein; BSEP, bile salt export pump; BSP, sulfobromophthalein; IC_{50}, half inhibitory concentration; MATE, multidrug and toxin extrusion; MRP, multidrug resistance associated protein; NTCP, Na^+-taurocholate cotransporting polypeptide; OAT, organic anion transporter; OCT, organic cation transporter; P-gp, P-glycoprotein; TCDC, taurochenodeoxycholic acid

14.2. In Vivo Studies

Mass Balance of Atogepant Following Administration of [^{14}C]-Atogepant (Study CGP-PK-03)

Study Design

Under fasting conditions, healthy male subjects (N=6) were administered 50 mg total (~200 µCi) of a ^{14}C-atogepant oral solution.

Blood samples were collected at predose through 168 hours, and up to Day 29, to measure total radioactivity, atogepant concentration, and metabolite profiling. Urine and fecal samples were collected to measure the levels of atogepant and metabolites, and total radioactivity from predose through up to Day 29, if discharge criteria were met. If discharge criteria were not met, urine and fecal sampling continued beyond Day 29 postdose.

Results and Conclusion

- Based on the AUC ratio of atogepant and total radioactivity in plasma, atogepant contributed approximately 75% of the total radioactivity exposure and metabolite M23 contributed approximately 15%.
- The total recovery of radioactivity in urine and feces 336 hours after dosing was approximately 89%, with 8% from urine, and 81% from feces.
  - In urine, atogepant represented approximately 5% of the radioactive dose and was the only peak detected that was greater than 1% of the radioactive dose
  - In feces, atogepant represented approximately 42% of the radioactive dose. At least 11 metabolites were detected in feces and each represented less than 10% of the radioactive dose.

Reviewer's Comments*: The reviewer agrees with the Applicant's assessments.*

Food Effect of Atogepant (Study 3101-105-002)

Study Design

The study was a randomized, open-label, single-dose, 2-period crossover study conducted in 20 healthy subjects.

Intervention A: Single dose of 60 mg atogepant, hot melt extrudate oral compressed tablet (HME-OCT) formulation, following a high fat and high calorie meal (with a total of approximately 800 to 1,000 calories; approximately 150 calories derived from protein, 250 from carbohydrates, and 500 to 600 from fat) consumed within 30 minutes before dosing.

Intervention B: Single dose of 60 mg atogepant, HME-OCT formulation, following a 10-hour overnight fast.

The pharmacokinetics (PK) blood samples were collected starting on Days 1 (Period 1) and 8 (Period 2); at 0 hour (predose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours postdose.

Results

Table 102. Statistical Analysis of Food Effect on Atogepant PK

Parameter (units)	Fed (Test) N	Fed (Test) GLSM	Fasted (Ref) N	Fasted (Ref) GLSM	Ratios of GLSMs (%) Test/Ref	90% CIs	Intra-CV% A (Test)	Intra-CV% B (Ref)	Inter-CV%
AUC_{0-t} (h*ng/mL)[a]	19	2558.05	20	3130.99	81.70	71.57 – 93.26	23.80[a]		50.29
AUC_{0-inf} (h*ng/mL)	18	2606.55	20	3158.38	82.53	71.77 – 94.89	34.50	3.62	49.89
C_{max} (ng/mL)	19	527.40	20	677.01	77.90	64.14 – 94.62	40.75	29.73	30.32

Parameter (units)	Fed (Test) N	Fed (Test) Median	Fasted (Ref) N	Fasted (Ref) Median	Median of Paired Differences (Test Minus Reference)
T_{max} (h)	19	2.01	20	2.01	0.50

[a] Results for AUC_{0-t} were provided from a model without the repeated statement (which allowed the variance of the response to vary across different study interventions), because the model did not converge.

Source: Study 3101-105-002, Table 11-2
Abbreviations: AUC, area under the plasma concentration-time curve; CI, confidence interval; C_{max}, maximum concentration; CV, coefficient of variation; GLSM, geometric least squares mean; N, number of subjects; PK, pharmacokinetics; Ref, reference; T_{max}, time to maximum concentration

Conclusion

A high-fat, high-calorie meal reduced the atogepant AUC and maximum concentration (C_{max}) by 18% and 22%, respectively, while the median time to maximum concentration was unaffected. These changes in exposures are not expected to be clinically relevant.

Reviewer's Comments: *The reviewer agrees with the Applicant's assessments.*

Atogepant PK in Subjects With Hepatic Impairment (Study CGP-PK-01)

Study Design

Study CGP-PK-01 was a multicenter, nonrandomized, open-label, parallel-group, single-dose study. Participants with normal hepatic function (healthy controls) and subjects with hepatic impairment (mild, moderate, or severe according to the Child-Pugh classification) received a single, oral, 60 mg tablet of atogepant under fasting conditions. A total of 32 subjects were enrolled with 8 subjects for each group based on the hepatic function.

PK blood samples were collected at predose through 72 hours postdose. Plasma samples were also collected for evaluation of protein binding at predose and two hours postdose.

Results

Table 103. Summary of Statistical Analysis of Plasma Atogepant PK Parameters Following a Single Dose Oral Administration of 60 mg Atogepant in Participants With Mild, Moderate, or Severe Hepatic Impairment as Compared With Participants With Normal Hepatic Function

Hepatic Group	PK Parameter	Geometric Least Squares Mean		Ratio of Geometric Means	90% Lower CI	90% Upper CI
		Test	Reference	Test/Reference		
Mild impairment	C_{max} (ng/mL)	586.89	538.55	108.97	72.72	163.31
	AUC_{0-t} (ng•h/mL)	3249.63	2612.14	124.40	89.78	172.38
	AUC_{0-inf} (ng•h/mL)	3273.58	2633.43	124.31	89.93	171.83
Moderate impairment	C_{max} (ng/mL)	474.85	538.55	88.17	58.83	132.14
	AUC_{0-t} (ng•h/mL)	2976.87	2612.14	113.96	82.25	157.91
	AUC_{0-inf} (ng•h/mL)	3028.57	2633.43	115.00	83.20	158.97
Severe impairment	C_{max} (ng/mL)	515.45	538.55	95.71	63.86	143.44
	AUC_{0-t} (ng•h/mL)	3601.63	2612.14	137.88	99.51	191.05
	AUC_{0-inf} (ng•h/mL)	3633.22	2633.43	137.97	99.81	190.71

Source: Study CGP-PK-01, Table 11-2
Abbreviations: AUC, area under the plasma concentration-time curve; CI, confidence interval; C_{max}, maximum concentration; PK, pharmacokinetics

Table 104. Summary of Atogepant Plasma Protein-Binding (Expressed as Percent Bound) Following Single Dose Oral Administration of 60 mg Atogepant

Hepatic Group	0 hr (Predose)	2 hr
Mild-impaired (N=8)	97.03 ± 0.75	97.36 ± 0.70
Moderate-impaired (N=8)	96.60 ± 0.94	97.05 ± 0.62
Severe-impaired (N=8)	94.48 ± 1.21	95.34 ± 0.85
Normal Hepatic Function (N=8)	97.89 ± 0.54	98.21 ± 0.46

Source: Study CGP-PK-01, Table 11-3
Abbreviations: hr, hour; N, number of subjects

Conclusion

Subjects with mild, moderate, or severe hepatic impairment generally had C_{max} of total atogepant comparable to that of healthy controls. The AUC of total atogepant was 14% to 38% higher in subjects with mild, moderate, or severe hepatic impairment compared with subjects with normal hepatic function.

Unbound atogepant following a single oral dose of 60 mg was 1.8%, 2.6%, 2.9%, and 4.7%, respectively, in subjects with no, mild, moderate, or severe hepatic impairment.

Reviewer's Comments: *The protein binding data obtained from predose and 2 hours postdose subject samples from study CGP-PK-01 showed minimal difference in atogepant protein binding.*

Based on the unbound atogepant % (calculated as: 1-%bound) at 2 hours postdose and PK parameters (AUC and C_{max}) of total atogepant, the reviewer performed the statistical comparison of unbound plasma atogepant PK exposures between subjects with mild, moderate, or severe hepatic impairment and those with normal hepatic function. The results showed that the exposure of unbound atogepant increased by 84%, 91%, and 266% in subjects with mild, moderate, or severe hepatic impairment, respectively as compared with those in subjects with normal hepatic function. However, there are two limitations with the analysis on unbound atogepant PK: 1) the method validation for the equilibrium dialysis assay using the rapid equilibrium dialysis was not validated for protein binding analysis of samples from CGP-PK-01; and 2) unbound atogepant PK was characterized based on the protein binding data obtained from two time points, predose and 2 hours postdose, instead of multiple time points covering the PK profile. Therefore, the unbound atogepant data should be interpreted as supportive information.

Table 105. Summary of Statistical Analysis of Unbound Plasma Atogepant PK Parameters in Participants With Mild, Moderate, or Severe Hepatic Impairment as Compared With Participants With Normal Hepatic Function

Hepatic Function	Protein Binding % (2 hr postdose)	Unbound Atogepant C_{max} (ng/mL)	Unbound Atogepant AUC_{0-t} (ng*h/mL)	Unbound Atogepant C_{max} GMR (90% CI)	Unbound Atogepant AUC_{0-t} GMR (90% CI)
Normal	98.21	9.3	45.1	NA	NA
Mild HI	97.36	15	83.2	1.62 (1.08-2.41)	1.84 (1.35-2.52)
Moderate HI	97.05	13.7	86.2	1.48 (0.99-2.20)	1.91 (1.40-2.61)
Severe HI	95.34	23.6	165.2	2.54 (1.71-3.78)	3.66 (2.68-5.00)

Source: Reviewer's analysis from datasets from Study CGP-PK-01
Abbreviations: AUC, area under the plasma concentration-time curve; CI, confidence interval; C_{max}, maximum concentration; GMR, geometric mean ratio; HI, hepatic impairment; hr, hour; NA, not applicable; PK, pharmacokinetics

Drug-Drug Interaction: Effect of Itraconazole on Atogepant PK (Study CGP-PK-02)

Study Design

Study CGP-PK-02 used a fixed-sequence, open-label, single-sequence design to assess the effect of itraconazole, a strong CYP3A4 inhibitor, on the PK of atogepant in healthy subjects. A 7-day washout period was used between treatments.

Treatment A: Single oral 60 mg dose of atogepant under fasted conditions on Day 1.

Treatment B: On Days 8 to 14, 200 mg itraconazole was taken orally once daily under fed conditions; on Day 15, 200 mg itraconazole was co-administered with 60 mg atogepant under fasted conditions; on Days 16 to 17, 200 mg itraconazole was taken once daily under fed conditions.

PK blood samples were collected at predose through 72 hours postdose on Day 1 and Day 15 to determine atogepant concentration in plasma. Blood samples were also collected on Day 1 at 2, 4, 8, 12, and 24 hours postdose to compare atogepant concentrations determined in Dry Blood Spot analysis. Blood samples were taken at predose on Day 8, 13, 14, and 15 to determine itraconazole plasma concentration.

Results

Table 106. PK Parameters of Atogepant Following Treatment A and Treatment B in Healthy Subjects

PK Parameter	Atogepant Alone (Treatment A; N=40)	Atogepant + Itraconazole (Treatment B; N=40)	GM Ratio (%) Treatment B/ Treatment A	90% CI
C_{max} (ng/mL)	740 (231)	1580 (469)	215.11	195.25, 236.99
AUC_{0-t} (ng.h/mL)	3440 (1030)	18500 (4860)	543.26	501.54, 588.45
$AUC_{0-\infty}$ (ng.h/mL)	3470 (1040)	18900 (4990)	550.78	508.64, 596.42
T_{max} (h)	2.0 (1.0 – 3.0)*	3.0 (1.5 – 4.0)*	1.0**	-
λ_z (1/h)	0.0825 (0.0412)	0.0496 (0.0122)	-	-
$T_{1/2}$ (h)	11.2 (7.78)	14.9 (3.96)	-	-
CL/F (L/h)	19.2 (7.49)	3.46 (1.18)	-	-
V_z/F (L)	292 (175)	73.8 (34.4)	-	-

Treatment A: single dose 60 mg atogepant alone on Day 1; Treatment B: 200 mg itraconazole once daily on Days 8 to 14, single dose 60 mg atogepant with 200 mg itraconazole on Day 15, 200 mg itraconazole once daily on Days 16 to 17.
AUC_{0-t} = area under the plasma concentration versus time curve from time 0 to time t; $AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 to infinity; CI = confidence interval; CL/F = apparent total body clearance of drug from plasma after extravascular administration; C_{max} = maximum plasma drug concentration; GM = geometric mean; λz = terminal elimination rate constant; $T_{1/2}$ = terminal elimination half-life; T_{max} = time to reach maximum plasma drug concentration; V_z/F = apparent volume of distribution during the terminal phase after extravascular administration.
* Median (Min-Max)
** Difference of medians

Source: Study CGP-PK-01, Table 11-1

Conclusion

The C_{max} and AUC of atogepant increased by 2.15-fold and 5.5-fold, respectively, following co-administration of atogepant with itraconazole, a strong CYP3A4 inhibitor.

Reviewer's Comments: *The reviewer agrees with the Applicant's assessments.*

Drug-Drug Interaction: Effect of Single and Multiple Dose Rifampin on PK of Atogepant (Study CGP-PK-12)

Study Design

Study CGP-PK-12 was an open-label, 2-treatment, 2-period, single-sequence, nonrandomized, crossover interaction study conducted in healthy subjects. Rifampin is an inducer of both CYP3A4 and P-glycoprotein (P-gp), and an inhibitor of organic anion transporting polypeptides (OATPs). All subjects received the following treatments with a sequence of A, B1, and B2 as described below:

Treatment A (atogepant alone): A single dose of 60 mg atogepant was administered orally on Day 1.

Treatment B1 (Co-administration of atogepant with a single dose of rifampin): A single dose of 60 mg atogepant was co-administered with 600 mg rifampin (2 × 300 mg capsules) on Day 7, followed by 600 mg once daily, rifampin alone, on Days 8, 9, 10, and 11.

Treatment B2 (Co-administration of atogepant after multiple doses of rifampin): A single dose of 60 mg of atogepant was co-administered with 600 mg rifampin on Day 12, followed by 600 mg rifampin alone on Day 13.

On Days 1, 7, and 12, atogepant, either alone or co-administration with rifampin, was administered under fasting conditions. When rifampin was administered alone (on Days 8, 9, 10, 11, and 13), subjects were not allowed to take food for 1 hour before and 1 hour after dosing.

Blood samples were collected at predose through 48 hours and postdose on Days 1 and 12. On Day 7, blood samples were collected at predose through 24 hours postdose. Blood samples at predose were collected on Days 11 and 12 to determine rifampin concentration.

Results

Table 107. Summary of Statistical Analysis Results of Plasma Atogepant Pharmacokinetic Parameters Following A Single Dose of 600 mg Rifampin in Combination With 60 mg Atogepant (Treatment B1, Test) in Comparison to 60 mg Atogepant Administered Alone (Treatment A, Reference)

	Geometric LSM		Ratio of Geometric Means (%)	90% Lower Confidence Interval	90% Upper Confidence Interval
PK Parameter	Test	Reference	Test/Ref		
AUC_{0-24} (ng•h/mL)	7631.86	2679.39	284.84	260.29	311.69
C_{max} (ng/mL)	1444.14	648.61	222.65	198.55	249.68

CI = confidence interval; LSM = least squares mean
Source: Study CGP-PK-12, Table 11-2
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; LSM, least squares mean; PK, pharmacokinetics; Ref, reference

Table 108. Summary of Statistical Analysis Results of Plasma Atogepant Pharmacokinetic Parameters Following Oral Administration of Multiple Dose 600 mg Rifampin in Combination With 60 mg Atogepant (Treatment B2, Test) in Comparison to 60 mg Atogepant Administered Alone (Treatment A, Reference)

	Geometric LSM		Ratio of Geometric Means (%)	90% Lower Confidence Interval	90% Upper Confidence Interval
PK Parameter	Test	Reference	Test/Ref		
$AUC_{0-\infty}$ (ng*h/mL)	1091.54	2809.41	38.85	34.56	43.68
AUC_{0-t} (ng*h/mL)	1121.66	2772.16	40.46	36.16	45.28
C_{max} (ng/mL)	454.44	648.61	70.06	60.27	81.44

CI = confidence interval; LSM = least squares mean
Source: Study CGP-PK-12, Table 11-3
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; LSM, least squares mean; PK, pharmacokinetics; Ref, reference

Conclusion

Co-administration of a single dose of atogepant with a single dose of rifampin resulted in increases in atogepant C_{max} and AUC by 2.85-fold and 2.23-fold, respectively.

Co-administration of a single dose of atogepant after multiple doses of rifampin resulted in decreases in atogepant C_{max} and AUC by 30% and 60%, respectively.

Reviewer's Comments: *The drug-drug interaction (DDI) of rifampin with atogepant is mediated via multiple mechanisms. When rifampin was administered as a single dose, rifampin's effect on atogepant PK is likely to be predominantly mediated by inhibition of OATP. When rifampin was administered at multiple doses, rifampin's effect on atogepant PK is likely a composite interaction mediated by induction of CYP3A4, inhibition of OATPs, induction of OATPs, and induction of P-gp. Refer to Sections 8.2 and 14.4 for detailed discussion. Statistical comparison of atogepant PK exposure between Treatment B1 and Treatment A did not include the statistical analysis for* $AUC_{0\text{-}inf}$*. Since* $AUC_{extrapolated}$ *contributed to only a small percentage (less than 5%), the conclusions based on the* $AUC_{0\text{-}24h}$ *values are acceptable.*

14.3. Pharmacometrics Review

14.3.1. Summary of Findings

14.3.1.1. Key Review Question: Do Any of the Factors, Including Age, Renal Function (Mild and Moderate Renal Impairment), Sex, Race, and Body Weight, Affect the Pharmacokinetics Profile of Atogepant?

No. Based on population PK analysis, none of the factors, including age, renal function (mild and moderate renal impairment), sex, race, and body weight, affect the pharmacokinetics profile of atogepant.

14.3.2. Label Statements

8.5 Geriatric Use

Population pharmacokinetic modeling suggests no significant pharmacokinetic differences between elderly and younger subjects. Clinical studies of QULIPTA did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

12.3 Specific Populations

Patients with Renal Impairment

The renal route of elimination plays a minor role in the clearance of atogepant. Based on a population pharmacokinetic analysis, there is no significant difference in the pharmacokinetics of atogepant in patients with mild or moderate renal impairment (CLcr 30-89 mL/min) relative to those with normal renal function (CLcr >90 mL/min). As patients with severe renal impairment

or end-stage renal disease (ESRD; CLcr <30 mL/min) have not been studied, use of the lowest effective dosage of atogepant (10 mg) is recommended in those patients

Other Specific Populations

Based on a population pharmacokinetic analysis, age, sex, race, and body weight did not have a significant effect on the pharmacokinetics (C_{max} and AUC) of atogepant. Therefore, no dose adjustments are warranted based on these factors.

***Reviewer's Comment**: We agree with the label statement.*

14.3.3. Pertinent Regulatory Background

Atogepant is a potent, selective, orally administered, CGRP receptor antagonist in development for the preventive treatment of migraine in adults with <15 migraine days per month. The proposed dose regimens are:

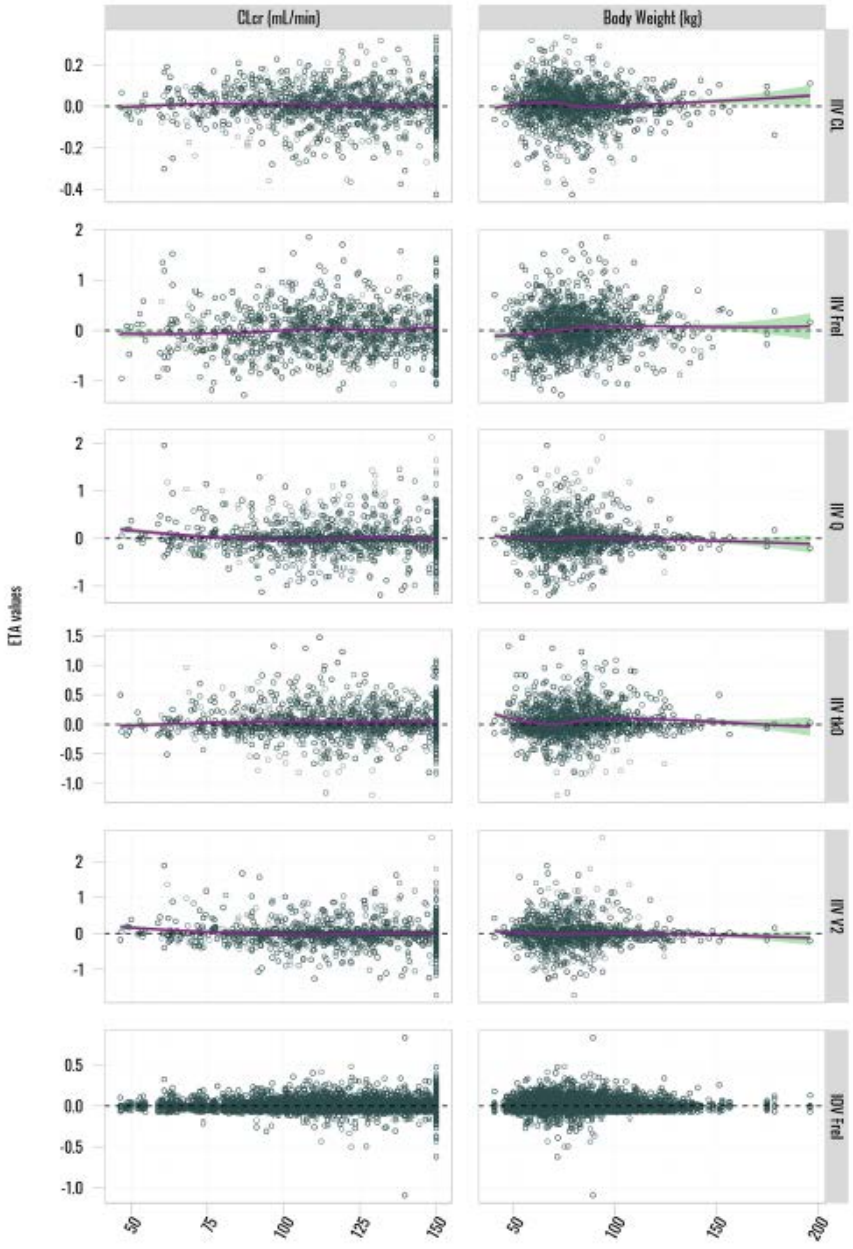
- 30 mg or 60 mg once daily
- Severe renal impairment: 10 mg (b) (4) once daily
- End-stage renal disease: 10 mg once daily

14.3.4. Results of Applicant's Analysis

A dataset composed of 11,763 observations from 1,356 patients was used to develop the final population pharmacokinetic (PopPK) model. The overall PK profile was best described by a three-compartment model with a sequential zero-/first-order lag time absorption model and linear elimination from the central compartment. Formulation, dose, food status, liver function, concomitant medication and body weight were each found to have a statistically significant influence on the atogepant PK.

Healthy volunteers and patients with migraine shared the same PopPK model parameters, except for apparent clearance, which was 22.9 L/h in healthy volunteers, while it was 23.7% lower in patients with episodic migraines (17.4 L/h). The apparent central volume of distribution was 86.1 L and blood concentrations were predicted to be 57.3% of those in plasma. Median terminal elimination half-lives were comparable between healthy volunteers (8.3 hours) and patients (8.5 hours); the overall median estimate was 8.5 hours. Approximately 69% of the orally bioavailable dose was absorbed through a zero-order process. The derived first-order absorption rate constant estimate was 2.48 1/h. The influence of covariates, including age, renal function, sex, race, and body weight, were not clinically relevant. The tested continuous and categorical covariates over Etas profiles were plotted in Figure 22 and Figure 23, respectively. Continuous covariates, such as creatinine clearance and body weight, have no influence on the PK parameters, including the inter-individual variabilities of bioavailability, apparent clearance), inter-compartmental clearance, duration of zero-order absorption, apparent rapid peripheral volume of distribution, and the inter-occasional variability of bioavailability (Figure 22). The PK parameters after single dose and during steady state were simulated with the final PopPK model (Table 109 and Table 110).

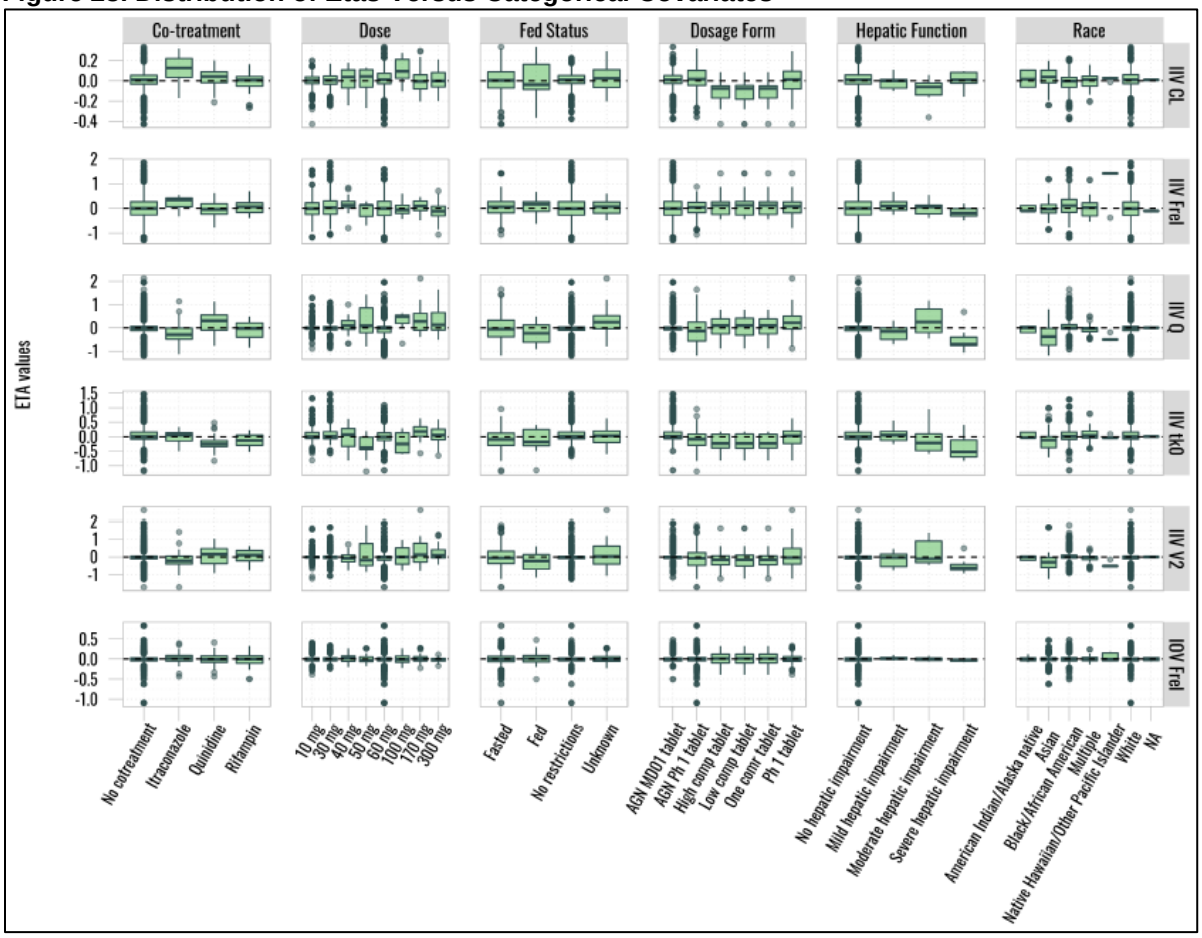
Figure 22. Distribution of Etas Versus Continuous Covariates



Circles: Observed values; **Dashed Line**: zero line; **Solid Magenta Line and Shaded Area**: smoother with the 95% CI; **CLcr**: creatinine clearance, capped at 150 mL/min

Source: cgp-ms-03 Figure 28
Abbreviations: CI, confidence interval; CL, apparent clearance; Frel, inter-individual variability of bioavailability; IIV, inter-individual variation; IOV, inter-occasional variability of bioavailability; Q, inter-compartmental clearance; tk0, zero-order absorption; V2, apparent rapid peripheral volume of distribution

Figure 23. Distribution of Etas Versus Categorical Covariates



Source: cgp-ms-03 Figure 29
Abbreviations: CI, confidence interval; CL, apparent clearance; Frel, inter-individual variability of bioavailability; IIV, inter-individual variation; IOV, inter-occasional variability of bioavailability; NA, not applicable; Q, inter-compartmental clearance; tk0, zero-order absorption; V2, apparent rapid peripheral volume of distribution

Table 109. Simulated Pharmacokinetics Parameters by Dose After a Single Dose

	C_{min} (ng/mL)		C_{avg} (ng/mL)		C_{max} (ng/mL)		t_{max} (hr)		$t_{1/2}$ (hr)		AUC_{24} (ng*h/mL)		
Dose	Median	90% CI	Median	90% CI	Median	90% CI	Median	90% CI	Median	90% CI	Median	90% CI	n
10	2.0	(0.6-7.2)	14.4	(5.1-40.3)	57.2	(20.1-160.0)	1.4	(0.6-3.4)	8.6	(6.3-15.4)	345.7	(122.4-965.6)	1000
30	7.5	(2.1-26.6)	52.3	(19.3-135.4)	191.5	(68.1-518.4)	1.6	(0.8-4.1)	8.5	(6.3-15.9)	1253.0	(461.9-3245.9)	1000
60	16.2	(4.5-53.9)	111.4	(40.9-284.6)	396.5	(143.2-1062.9)	1.8	(0.8-4.2)	8.5	(6.2-15.1)	2671.4	(980.4-6823.8)	1000

Simulated atogepant concentration were calculated every 10 minutes, from the time of the last dose up to 24 hours post dose. **C_{min}:** Minimum concentration; **C_{avg}:** Average concentration; **C_{max}:** Maximum concentration; **t_{max}:** Time at maximum concentration; **$t_{1/2}$:** Half-life in terminal elimination phase; **AUC_{24}:** 24 hours area under the concentration vs time curve after a single dose; **CI:** Confidence interval; **n:** Number of simulated individuals.

Source: cgp-ms-03 Table 21

Table 110. Simulated Pharmacokinetics Parameters by Dose at Steady State

	C_{min} (ng/mL)		C_{avg} (ng/mL)		C_{max} (ng/mL)		t_{max} (hr)		$t_{1/2}$ (hr)		AUC_{24} (ng*h/mL)		
Dose	Median	90% CI	Median	90% CI	Median	90% CI	Median	90% CI	Median	90% CI	Median	90% CI	n
10	1.4	(0.4-5.2)	13.3	(4.8-37.5)	55.3	(19.3-155.3)	1.4	(0.7-3.4)	7.3	(5.8-11.7)	319.8	(115.0-900.3)	1000
30	5.4	(1.5-18.0)	47.8	(17.5-122.0)	183.1	(65.0-500.2)	1.6	(0.8-4.1)	7.2	(5.6-11.7)	1147.6	(418.8-2927.1)	1000
60	11.4	(3.4-36.6)	101.0	(38.2-259.6)	381.8	(135.7-1035.7)	1.8	(0.8-4.2)	7.2	(5.7-11.4)	2424.2	(917.3-6228.1)	1000

Simulated atogepant concentration were calculated every 10 minutes, from the time of the first dose up to 24 hours post dose. **C_{min}:** Minimum concentration; **C_{avg}:** Average concentration; **C_{max}:** Maximum concentration; **t_{max}:** Time at maximum concentration; **$t_{1/2}$:** Half-life in terminal elimination phase; **AUC_{24}:** 24 hours area under the concentration vs time curve after a single dose; **CI:** Confidence interval; **n:** Number of simulated individuals.

Source: cgp-ms-03 Table 22

***Reviewer's Comment**: The PopPK model was successfully reproduced. Please see more details in Reviewer's Analysis below.*

14.3.5. Reviewer's Analysis

14.3.5.1. Introduction

Atogepant (also known as AGN-241689 and MK-8031) is a potent, selective, oral calcitonin gene-related peptide (CGRP) receptor antagonist being developed for preventive treatment of migraine. The proposed dose regimens are: (1) 30 mg or 60 mg once daily for patients with normal renal function, or and mild to moderate renal impairment; (2) 10 mg (b) (4) once daily for patients with severe renal impairment; and (3) 10 mg once daily for patients with end-stage renal disease.

To support the recommended dose regimen, the Applicant developed a population PK model. The overall PK profile was best described by a three-compartment model with a sequential zero-/first-order lag time absorption model and linear elimination from the central compartment. The factors, including age, renal function (mild and moderate renal impairment), sex, and race, were not significant covariates for PK parameters. Body weight was found to be statistically significant for central volume of distribution, however, with a mild relationship. In this analysis, the reviewers adopted the Applicant's population PK model to estimate the individual atogepant exposure at steady states and confirmed the Applicant's findings.

The exposure-efficacy relationship was best described by a zero-inflated Poisson model. The treatment effect was comparable and independent of atogepant exposures across the evaluated dose groups ranging from 10 mg QD to 60 mg BID.

14.3.5.2. Objectives

The analysis objective was to evaluate the influence of age, renal function (mild and moderate renal impairment), sex, race, and body weight, on the pharmacokinetics of atogepant

14.3.5.3. Methods

Data Sets

Data sets used are summarized in Table 111.

Table 111. Analysis Data Sets

Study Number	Name	Link to EDR
CGP-PK-02, 3101-101-002, CGP-PK-03, CGP-MD-01, CGP-PK-12, CGP-PK-01, CGP-PK-04, 3101-103-002, 3101-105-002, MK-8031-P001, MK-8031-P002, MK-8031-P003, MK-8031-P004, MK-8031-P008, 3101-301-002	nm_pk_ph1_ph3_pkocc_all_k0ka.csv	\\CDSESUB1\evsprod\nda215206\0001\m5\datasets\cgp-ms-03\analysis\legacy\datasets\

Source: Reviewer analysis

Software

Population PK model fitting was performed in NONMEM 7.3 and Pirana 2.9.4. Efficacy analysis and plotting were performed in R 4.0.3.

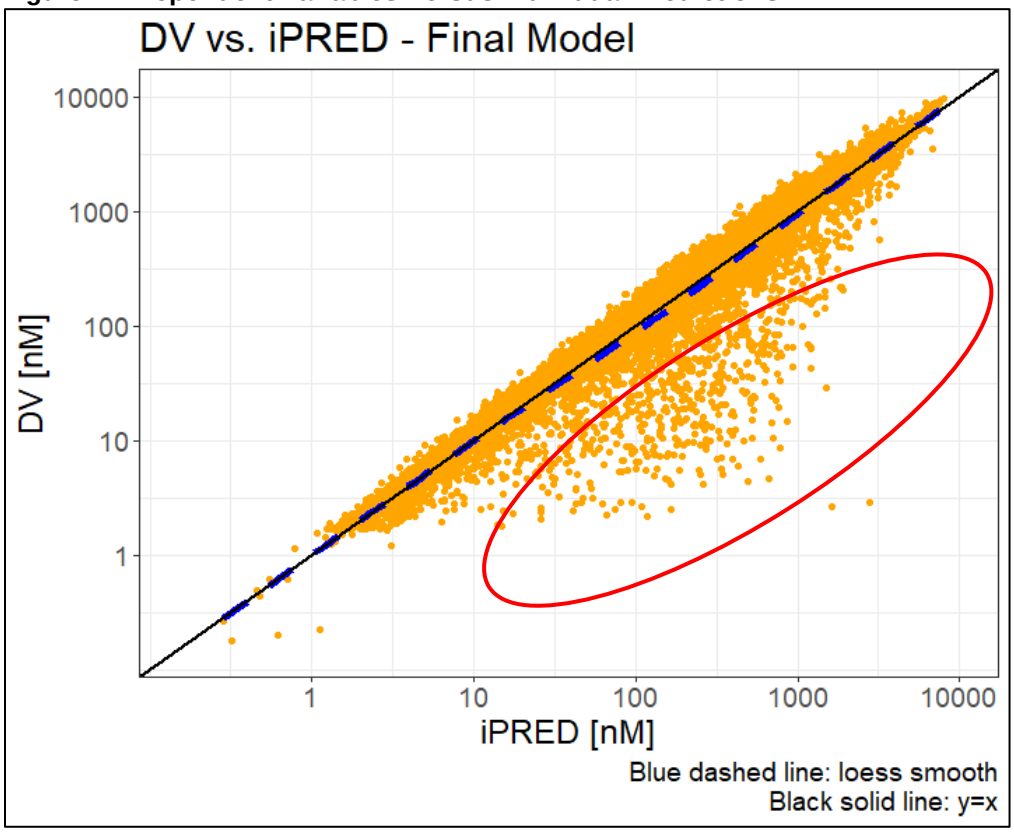
Models

The reviewers adopted the Applicant's final population PK model, which was a three-compartment model with a sequential zero-/first-order lag time absorption model and linear elimination from the central compartment. The individual predicted PK parameters were used to estimate the steady state exposure.

14.3.5.4. Results

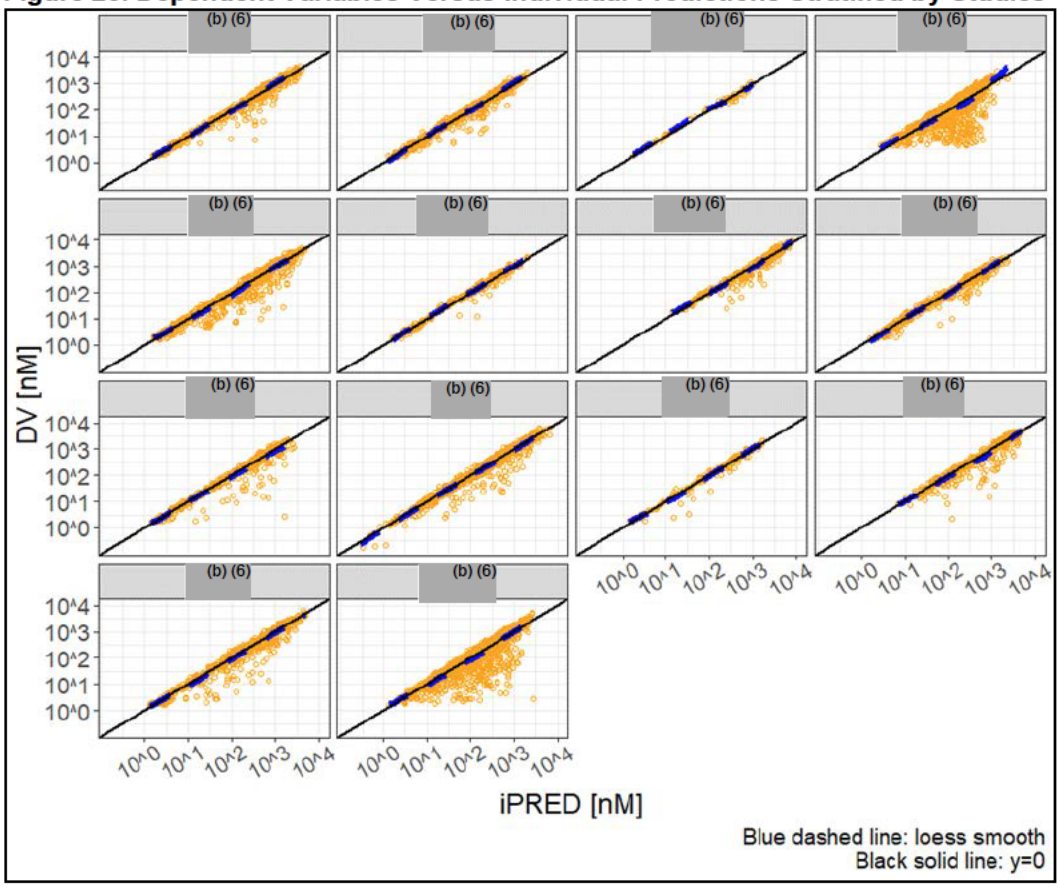
The goodness-of-fit, dependent variables versus individual predictions, are shown in Figure 24. Part of the observations in the red circle were overestimated by the PopPK model. In individual study goodness-of-fit, this overestimation was identified in a majority of the trials (Figure 25). The reviewers further plotted concentration over time profile of 20 subjects with the top ranked deviations calculated by individual prediction over observation (Figure 26). This plot indicated that the deviation of individual prediction and observation was in the absorption phase. In addition to the PopPK model prediction, the reviewer team considered the observed data along with the clinical pharmacology aspect of atogepant to make conclusion on the acceptability of proposed labeling statements.

Figure 24. Dependent Variables Versus Individual Predictions



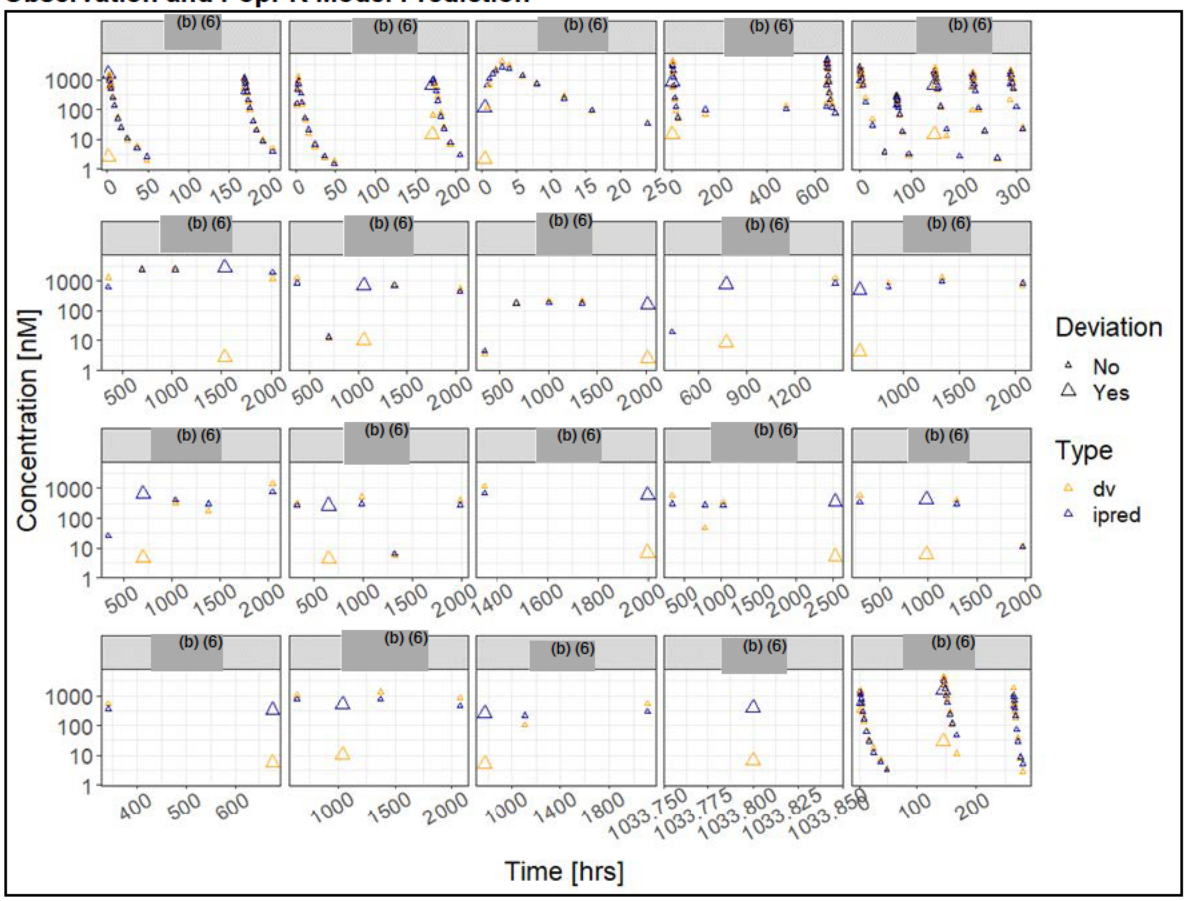
Source: Reviewer analysis
Abbreviations: DV, dependent variable; iPRED, individual prediction

Figure 25. Dependent Variables Versus Individual Predictions Stratified by Studies



Source: Reviewer analysis
Abbreviations: DV, dependent variable; iPRED, individual prediction

Figure 26. Concentration Over Time for Subjects With Top-Ranked Deviations Between Observation and PopPK Model Prediction

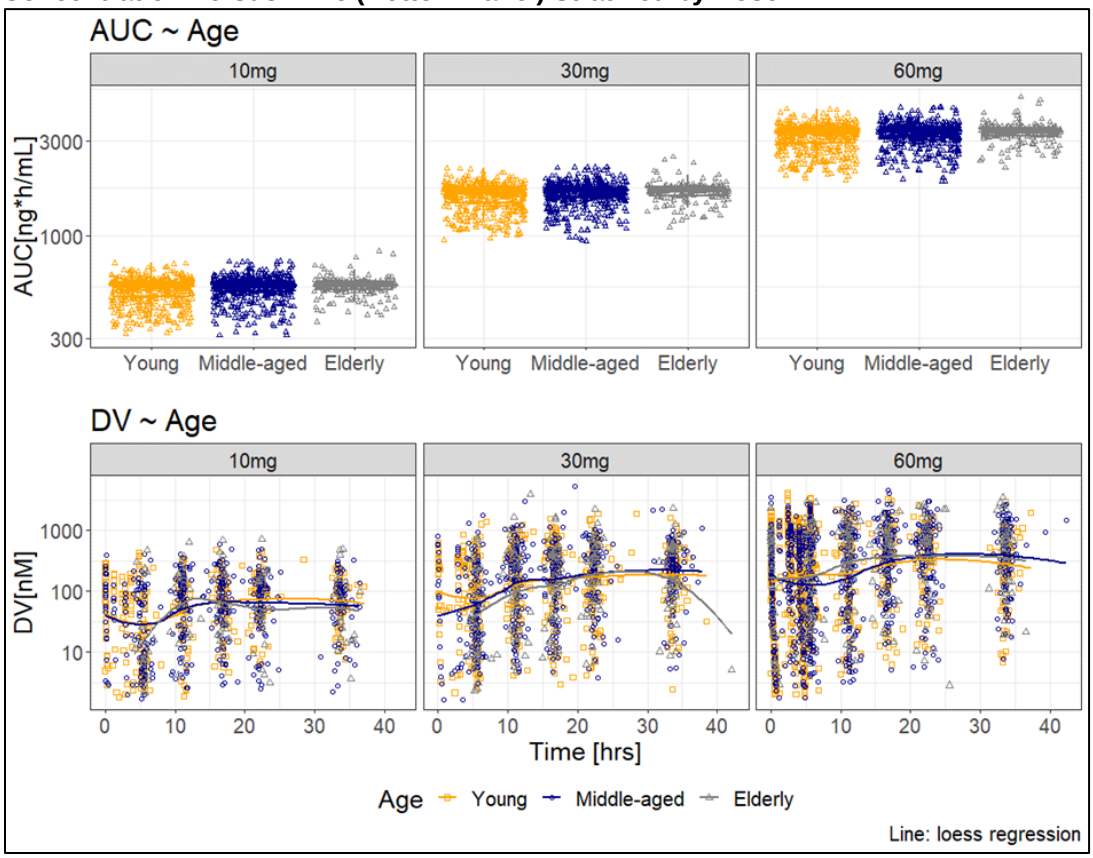


Source: Reviewer analysis
Abbreviations: hrs, hours; PopPK, population pharmacokinetics

The individual predicted PK parameters were then used to calculate the steady state AUC for the studied subjects, which were used to evaluate the effect of covariates, including age, renal function (mild and moderate renal impairment), sex, race, and body weight.

The individuals were categorized by age into young adults (18 to 35y, n=554), middle-aged adults (36 to 55y, n=620), and elderly adults (>55y, n=182). The steady state AUC largely overlapped between the three age populations (Figure 27 and Table 112).

Figure 27. PopPK Model Predicted Steady State AUC Versus Age Group (Top Panel) and Plasma Concentration Versus Time (Bottom Panel) Stratified by Dose



Source: Reviewer analysis
Abbreviations: AUC, area under the plasma concentration-time curve; DV, dependent variable; hrs, hours; PopPK, population pharmacokinetics

Table 112. PopPK Model Predicted Steady State AUC Versus Age Group

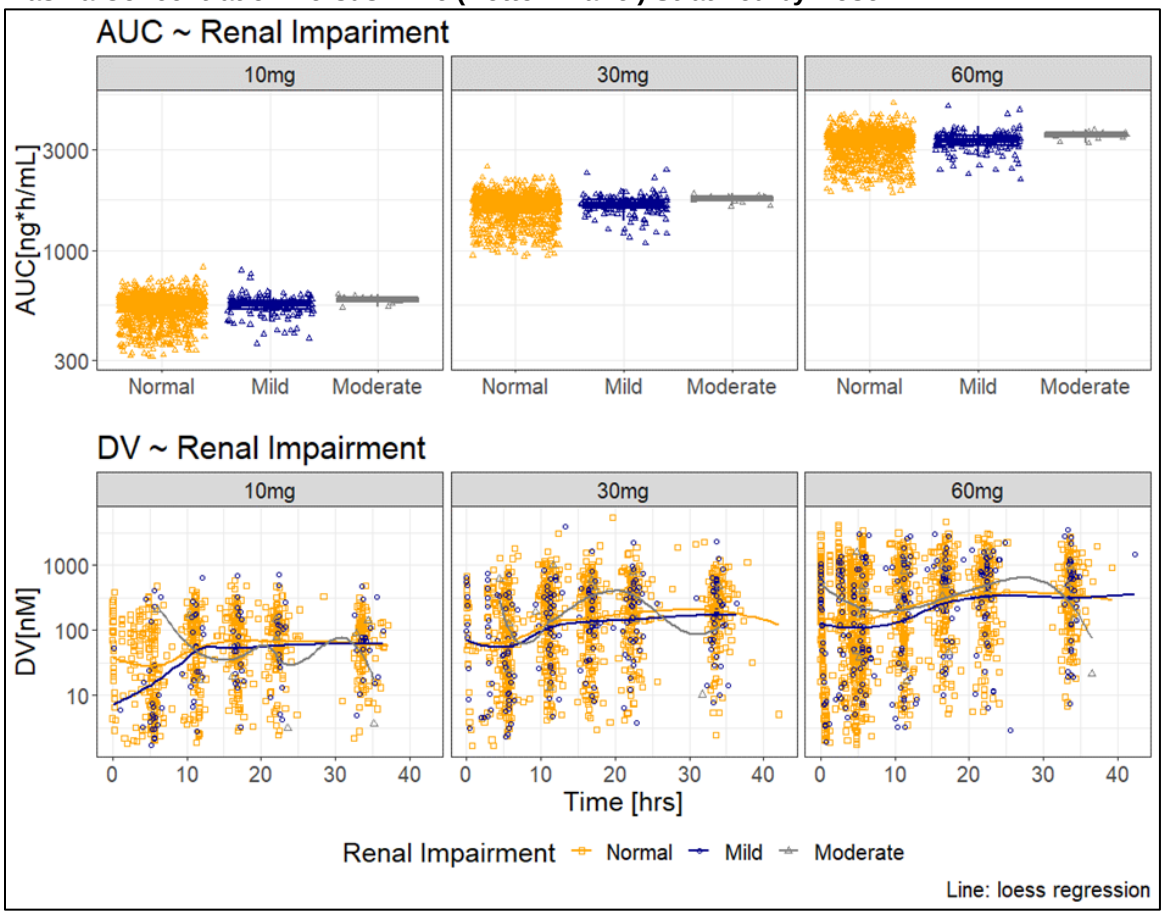
Estimated AUC (ng*h/mL) vs. Age					
Dose	**Age**	**Mean**	**Median**	**95% CI**	**5-95% Quantile**
10mg	Young	530.3	554.8	(523.9 , 536.7)	(370.7 , 628.3)
	Middle-aged	548.3	565.6	(542.8 , 553.8)	(403 , 638.6)
	Elderly	554.3	562.7	(544.9 , 563.7)	(436.7 , 640.5)
30mg	Young	1590.8	1664.5	(1571.7 , 1609.9)	(1112.2 , 1884.9)
	Middle-aged	1645	1696.8	(1628.6 , 1661.4)	(1209 , 1915.7)
	Elderly	1662.9	1688	(1634.7 , 1691.1)	(1310 , 1921.4)
60mg	Young	3181.7	3329.1	(3143.5 , 3219.9)	(2224.3 , 3769.7)
	Middle-aged	3290.1	3393.7	(3257.3 , 3322.9)	(2418 , 3831.4)
	Elderly	3325.8	3375.9	(3269.4 , 3382.2)	(2619.9 , 3842.7)

Source: Reviewer analysis
Abbreviations: AUC, area under the plasma concentration-time curve; CI, confidence interval; PopPK, population pharmacokinetics

Based on creatinine clearance (CLcr) estimated by the Cockcroft-Gault equation, the subjects were categorized into normal (CLcr ≥90 mL/min, n=1,182), mild (90>CLcr ≥60 mL/min,

n=161), and moderate (60>CLcr ≥30 mL/min, n=13) renal impairment. The AUC values showed a substantial overlap across various renal impairment categories. (Figure 28 and Table 113).

Figure 28. PopPK Model Predicted Steady State AUC Versus Renal Impairment (Top Panel) and Plasma Concentration Versus Time (Bottom Panel) Stratified by Dose



Source: Reviewer analysis
Abbreviations: AUC, area under the plasma concentration-time curve; DV, dependent variable; hrs, hours; PopPK, population pharmacokinetics

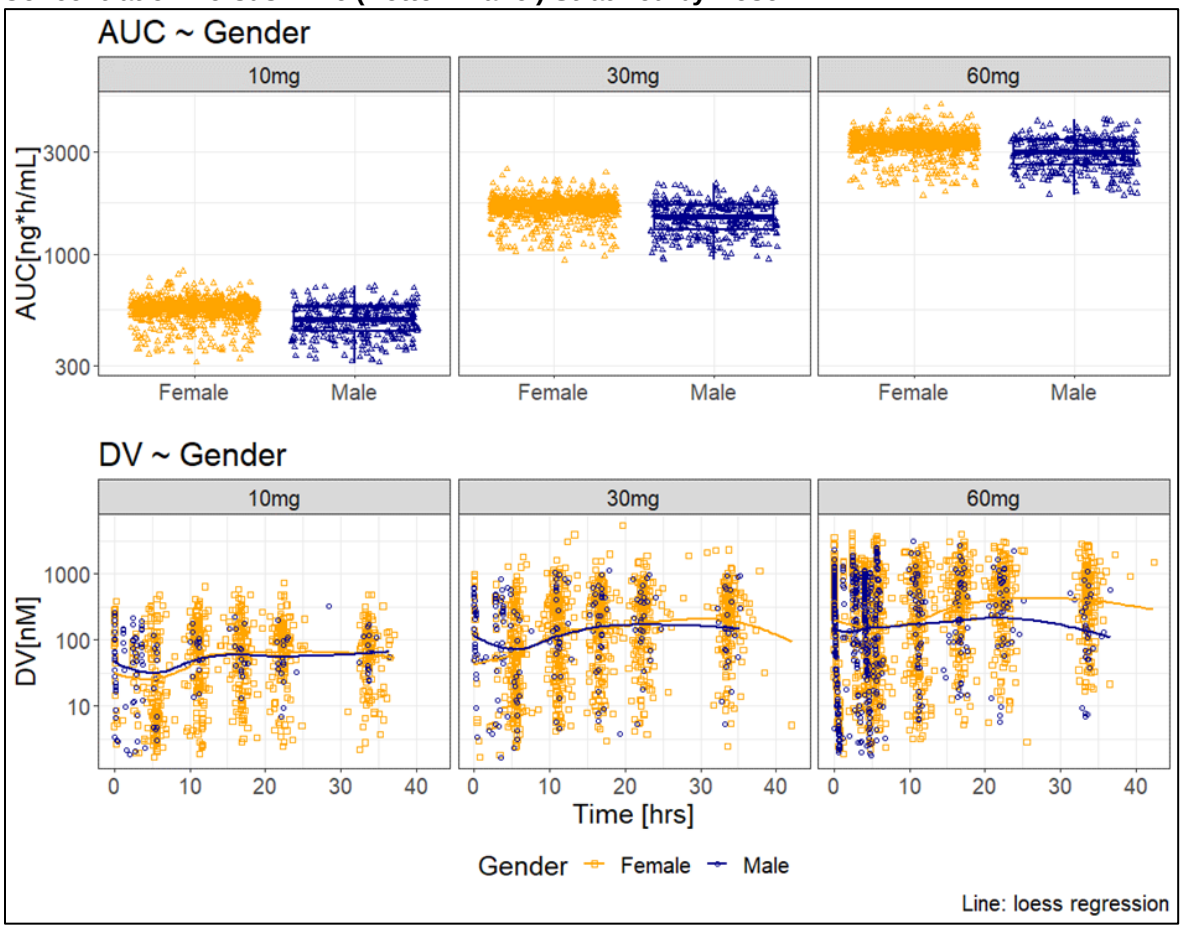
Table 113. PopPK Model Predicted Steady State AUC Versus Renal Impairment

Estimated AUC (ng*h/mL) vs. Renal Impairment					
Dose	RI	Mean	Median	95% CI	5-95% Quantile
10mg	Normal	540.3	562.9	(536.1 , 544.5)	(389.3 , 637)
	Mild	549.3	555.2	(540 , 558.6)	(445.3 , 625.1)
	Moderate	582.4	587.3	(569 , 595.8)	(540.4 , 613.8)
30mg	Normal	1620.9	1688.6	(1608.2 , 1633.6)	(1167.8 , 1911.1)
	Mild	1647.9	1665.6	(1620 , 1675.8)	(1335.8 , 1875.2)
	Moderate	1747.3	1761.9	(1707.1 , 1787.5)	(1621.2 , 1841.3)
60mg	Normal	3241.7	3377.2	(3216.4 , 3267)	(2335.5 , 3822.2)
	Mild	3295.9	3331.3	(3240.2 , 3351.6)	(2671.7 , 3750.5)
	Moderate	3494.5	3523.8	(3414.1 , 3574.9)	(3242.4 , 3682.7)

Source: Reviewer analysis
Abbreviations: AUC, area under the plasma concentration-time curve; CI, confidence interval; PopPK, population pharmacokinetics; RI, renal impairment

The estimated mean steady state AUC of male subjects (n=1,013) was lower compared to that of females (n=343) (Table 114). Overlap in the AUC values between male and female subjects is shown in Figure 29.

Figure 29. PopPK Model Predicted Steady State AUC Versus Sex (Top Panel) and Plasma Concentration Versus Time (Bottom Panel) Stratified by Dose



Source: Reviewer analysis
Abbreviations: AUC, area under the plasma concentration-time curve; DV, dependent variable; hrs, hours; PopPK, population pharmacokinetics

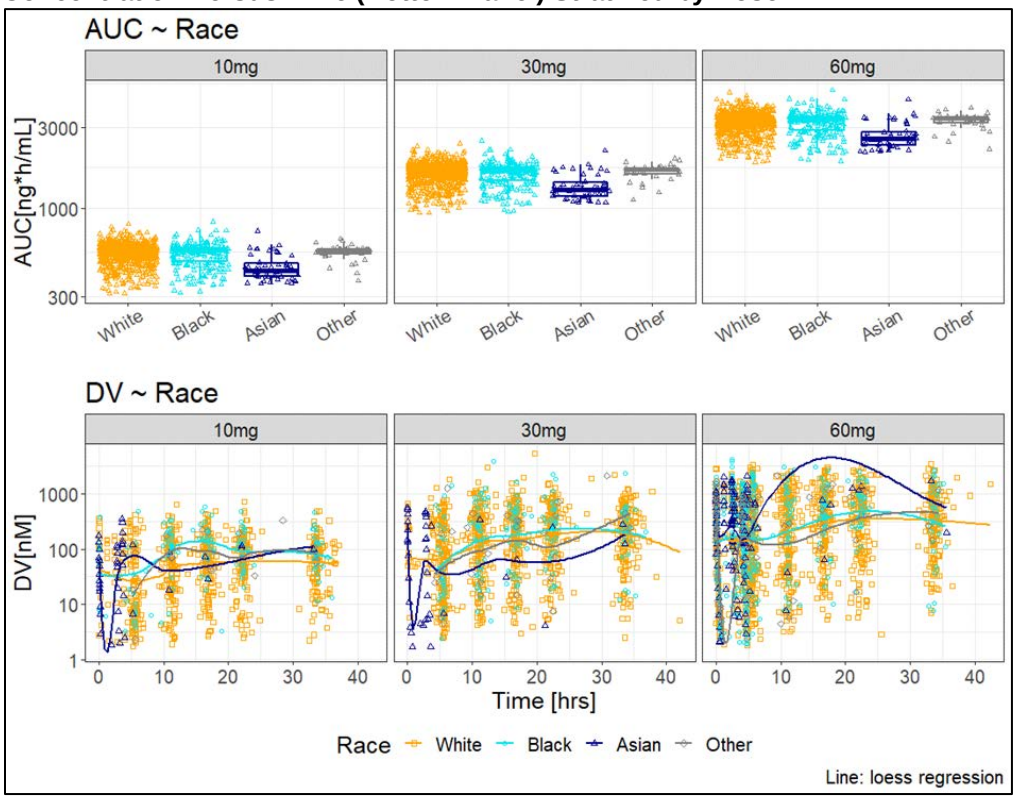
Table 114. PopPK Model Predicted Steady State AUC Versus Sex

Estimated AUC (ng*h/mL) vs. Gender					
Dose	Gender	Mean	Median	95% CI	5-95% Quantile
10mg	Female	556.8	568	(553 , 560.6)	(426.8 , 635.5)
	Male	497.5	496.7	(488.6 , 506.4)	(364.8 , 629.9)
30mg	Female	1670.3	1704	(1659 , 1681.6)	(1280.3 , 1906.5)
	Male	1492.4	1490.2	(1465.7 , 1519.1)	(1094.5 , 1889.7)
60mg	Female	3340.5	3407.9	(3317.9 , 3363.1)	(2560.5 , 3812.9)
	Male	2984.9	2980.3	(2931.5 , 3038.3)	(2189 , 3779.4)

Source: Reviewer analysis
Abbreviations: AUC, area under the plasma concentration-time curve; CI, confidence interval; PopPK, population pharmacokinetics

Substantial overlap in the AUC values across Asian, white (n=1,031), black (n=243), and other race (n=34) subjects (n=48) was observed. (Figure 30 and Table 115).

Figure 30. PopPK Model Predicted Steady State AUC Versus Race (Top Panel) and Plasma Concentration Versus Time (Bottom Panel) Stratified by Dose



Source:
Abbreviations: AUC, area under the plasma concentration-time curve; DV, dependent variable; hrs, hours; PopPK, population pharmacokinetics

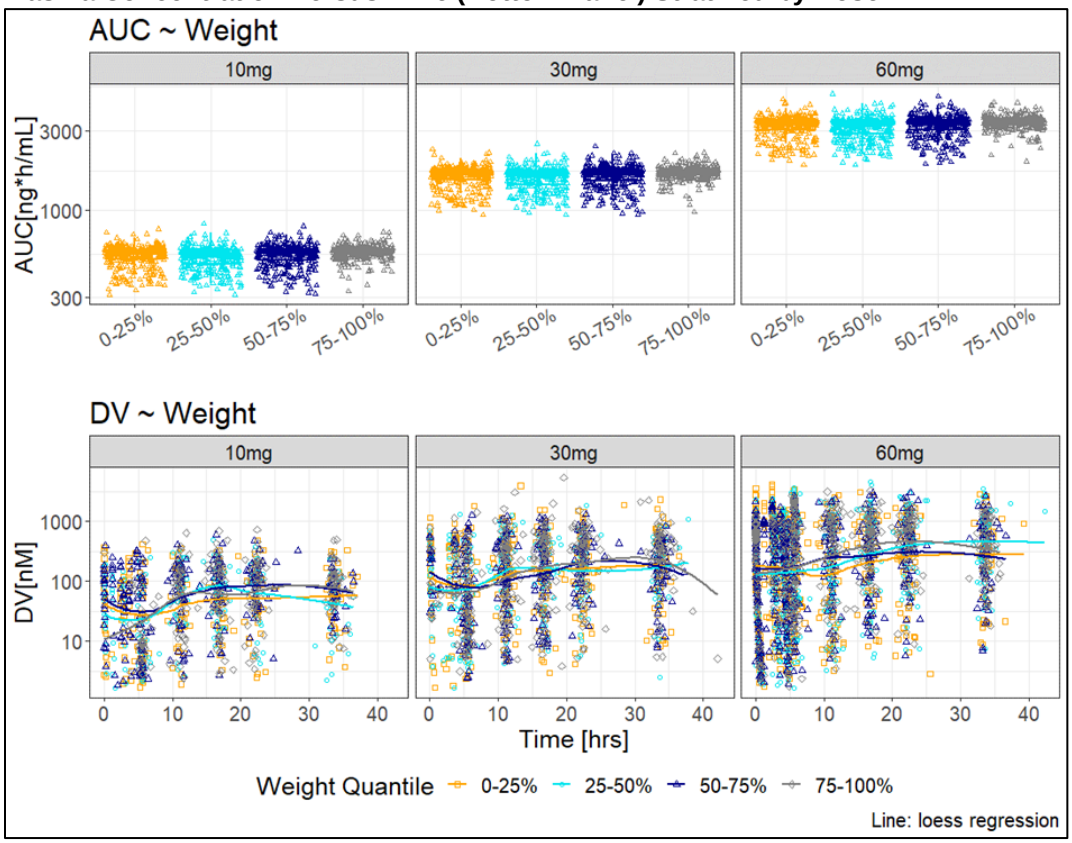
Table 115. PopPK Model Predicted Steady State AUC Versus Race

Estimated AUC (ng*h/mL) vs. Race					
Dose	**Race**	**Mean**	**Median**	**95% CI**	**5-95% Quantile**
10mg	White	547.4	564	(543.3 , 551.5)	(404.4 , 635.4)
	Black	535.3	561.6	(524.9 , 545.7)	(375.8 , 640.1)
	Asian	449.7	428.9	(426.7 , 472.7)	(362.7 , 580.4)
	Other	547.7	565.1	(527.6 , 567.8)	(432.3 , 630.7)
30mg	White	1642.1	1692	(1629.9 , 1654.3)	(1213.2 , 1906.3)
	Black	1606	1684.8	(1574.9 , 1637.1)	(1127.5 , 1920.2)
	Asian	1349	1286.7	(1279.9 , 1418.1)	(1088.2 , 1741.2)
	Other	1643	1695.4	(1582.6 , 1703.4)	(1297 , 1892)
60mg	White	3284.2	3383.9	(3259.8 , 3308.6)	(2426.3 , 3812.7)
	Black	3212.1	3369.7	(3149.8 , 3274.4)	(2255.1 , 3840.4)
	Asian	2698	2573.4	(2559.8 , 2836.2)	(2176.4 , 3482.4)
	Other	3285.9	3390.9	(3165 , 3406.8)	(2593.9 , 3784)

Source: Reviewer analysis
Abbreviations: AUC, area under the plasma concentration-time curve; CI, confidence interval; PopPK, population pharmacokinetics

Substantial overlap for the steady-state AUC was observed across the four body weight quantiles (0 to 25%, 25 to 50%, 50 to 75%, and 75 to 100%) (Figure 31 and Table 116).

Figure 31. PopPK Model Predicted Steady State AUC Versus Weight Quantile (Top Panel) and Plasma Concentration Versus Time (Bottom Panel) Stratified by Dose



Source: Reviewer analysis
Abbreviations: AUC, area under the plasma concentration-time curve; DV, dependent variable; hrs, hours; PopPK, population pharmacokinetics

Table 116. PopPK Model Predicted Steady State AUC Versus Weight Quantile

Estimated AUC (ng*h/mL) vs. Weight					
Dose	WT Quantile	Mean	Median	95% CI	5-95% Quantile
10mg	0-25%	536.2	559.5	(528.3 , 544.1)	(379.1 , 627.9)
	25-50%	525.6	548.7	(517.3 , 533.9)	(380.5 , 630.7)
	50-75%	541.9	565.1	(533.6 , 550.2)	(389.9 , 639.7)
	75-100%	563.4	570.5	(558 , 568.8)	(478.8 , 641.3)
30mg	0-25%	1608.5	1678.4	(1584.7 , 1632.3)	(1137.3 , 1883.7)
	25-50%	1576.9	1646.1	(1552.1 , 1601.7)	(1141.6 , 1892.1)
	50-75%	1625.8	1695.2	(1600.9 , 1650.7)	(1169.6 , 1919.1)
	75-100%	1690.3	1711.5	(1674.2 , 1706.4)	(1436.4 , 1923.8)
60mg	0-25%	3216.9	3356.8	(3169.3 , 3264.5)	(2274.6 , 3767.4)
	25-50%	3153.9	3292.2	(3104.2 , 3203.6)	(2283.3 , 3784.2)
	50-75%	3251.7	3390.3	(3201.9 , 3301.5)	(2339.2 , 3838.3)
	75-100%	3380.6	3423.1	(3348.4 , 3412.8)	(2872.8 , 3847.6)

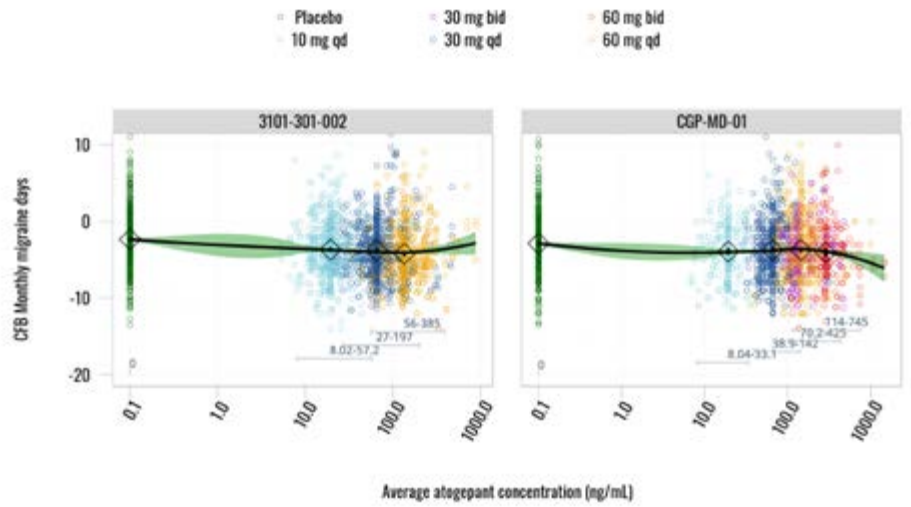
Source: Reviewer analysis
Abbreviations: AUC, area under the plasma concentration-time curve; CI, confidence interval; PopPK, population pharmacokinetics; WT, weight

In conclusion, we agree with the Applicant's conclusion that the influence of age, renal impairment (mild and moderate), sex, race, and body weight on atogepant PK is not clinically relevant.

Exposure-Response Analysis

The Applicant conducted exposure-response modeling analysis. A total of 6,471 monthly migraine days observations from 1,668 subjects were used for model building. Individual atogepant steady-state exposures for exposure-response modeling analysis were predicted using the post hoc estimates from the final PopPK model. The change from baseline monthly migraine days over average atogepant concentration plot suggested a flat exposure-response relationship within the subjects exposed to atogepant (Figure 32). The migraine days data were well described by a zero-inflated Poisson model. Typical exposure metrics were simulated and the individual C_{max}, AUC, average concentration, and daily time above specified threshold levels were calculated for each patient in the Phase 2/3 study. These exposure summaries were used to test the exposure-response modeling in the efficacy models. The introduction of a treatment effect generally provided an improvement of the model. However, a model which described the treatment effect as being of equal magnitude, irrespective of atogepant exposure, performed better than any model that took individual exposure into account. The final model showed relatively good predictive capability to the observed efficacy data (Figure 33).

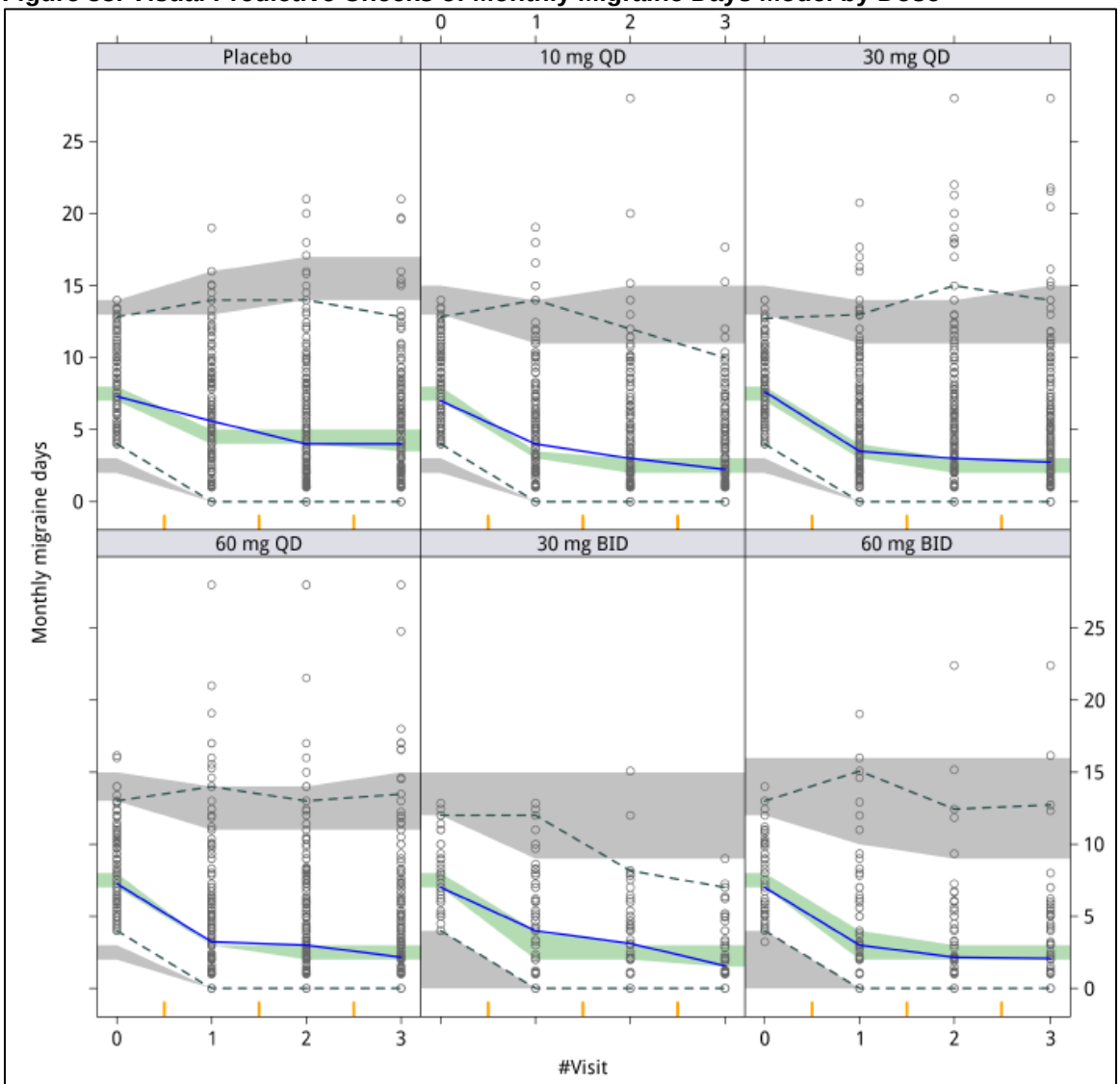
Figure 32. Change From Baseline Monthly Migraine Days by Dose, Study, and Average Atogepant Concentration



Diamonds: Median concentration at each dose level; **Bars:** 95% CI of exposures; **Black line:** smoother line with uncertainty. Colored by dose.

Source: cgp-ms-03 Figure A.3.4
Abbreviations: BID, twice daily; CFB, change from baseline; CI, confidence interval; QD, once daily

Figure 33. Visual Predictive Checks of Monthly Migraine Days Model by Dose



Circles: Observations, **Solid Blue Line**: Median of the observed monthly migraine days, **Dashed Lines**: 2.5^{th} and 97.5^{th} percentiles of the observed monthly migraine days, **Shaded Area**: The shaded areas indicate the 95% CI around the prediction-corrected median (green area), and 2.5^{th} and 97.5^{th} percentiles of the simulated monthly migraine days (gray areas).

Source: cgp-ms-03 Figure 35
Abbreviations: BID, twice daily; CI, confidence interval; QD, once daily

14.3.6. Listing of Analyses Codes and Output Files

Table 117. Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
run61-mod.txt	Final PopPK model for NONMEM	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Atogepant_NDA215206_YY\PPK Analyses\Final Model
cgs-ms-003-final.R	GOF of final PopPK model, individual PK exposure calculation	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Atogepant_NDA215206_YY\PPK Analyses\Final Model

Source: Reviewer analysis
Abbreviations: GOF, goodness-of-fit; PopPK, population pharmacokinetics

14.4. Physiologically Based Pharmacokinetic Modeling Review

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetics (PBPK) report, entitled "Development of a mechanistic physiologically based pharmacokinetic (PBPK) model for atogepant and subsequent evaluation of drug-drug interaction potential as a victim of CYP3A4- and transporter-mediated interactions in healthy adult volunteers" for the following intended purposes.

- To predict the effect of a strong CYP3A inhibitor or a strong CYP3A inducer on the PK of atogepant if only considering CYP-mediated DDI in healthy subjects.
- To predict the effect of a moderate CYP3A inhibitor (i.e., fluconazole) and a weak CYP3A inhibitor (i.e., cimetidine) on the PK of atogepant in healthy subjects.
- To predict the PK of atogepant with and without complete knockout of P-gp or breast cancer resistance protein (BCRP) transporter function in healthy subjects.

The Division of Pharmacometrics has reviewed the submitted PBPK reports and supporting modeling files. FDA reviewers conducted additional PBPK analyses and concluded the following:

- The atogepant PBPK models were able to capture the observed atogepant PK following a single oral dose (50, 60, 100, and 170 mg) and multiple oral dose administration (QD: 50, 100, and 170 mg; BID: 30 and 60 mg) in healthy subjects.
- The atogepant PBPK models are adequate to predict the effect of fluconazole and cimetidine on the PK of atogepant in healthy subjects. The model predicted a 69% and 8% increase in atogepant AUC with fluconazole (loading dose of 400 mg followed by 200 mg QD) and cimetidine (400 mg BID), respectively.
- Atogepant exposure may be reduced by approximately 50% if co-administered with a strong CYP3A inducer but not an inducer of any transporter.
- Atogepant exposure may be increased by approximately 140% if co-administered with a strong CYP3A inhibitor but not an inhibitor of any transporter.
- The DDI potential of atogepant with a selective P-gp or BCRP inhibitor was low.

14.4.1. Applicant's PBPK Modeling Effort

PBPK software

Simcyp V17 (Simcyp Ltd, United Kingdom) was used to develop the atogepant PBPK models and predict the PK of atogepant with and without CYP3A and transporter modulators.

Model development

Atogepant

The Advanced Dissolution Absorption and Metabolism model was used to model atogepant absorption. Atogepant was rapidly absorbed following administration of the tablet formulation with a time to maximum concentration of 1.00 to 1.50 hours under fasting conditions. Single- and multiple-dose PK data indicated that the AUC and C_{max} of atogepant increased in a roughly dose-proportional manner over the dose range of 1 to 170 mg in healthy subjects, suggesting solubility does not limit the absorption in vivo over this dose range. Thus, the Applicant assumed the drug is absorbed in the form of a solution. The atogepant jejunal passive permeability value of 2.85×10^{-4} cm/s was derived from Caco-2 apparent permeability data. The kinetic parameters for intestinal P-gp and BCRP were obtained from transport study data in Caco-2 and MDCKII-BCRP cell lines. Relative activity factor values for intestinal P-gp and BCRP were optimized based on the clinical PK data (Study CGP-PK-12) and excretion data in feces (Study CGP-PK-03).

The fraction unbound in plasma was estimated to be 0.047 and applied in all simulations assuming albumin as the main binding protein. The blood to plasma ratio was 0.77. A full PBPK model was used to simulate the distribution phase of atogepant PK profile. A steady-state volume of distribution value of 0.306 L/kg with a ratio of total concentration of compound in the tissue to total concentration of compound in the plasma at steady-state scalar of 0.403 was optimized using clinical PK data (Study CGP-PK-12 control arm). Based on the in vitro immunoinhibition, chemical inhibition, and phenotyping study results, all metabolism of atogepant was assigned to CYP3A4 in the PBPK model. The hepatic intrinsic clearance value (22.8 L/hr) was optimized based on clinical PK data (Study CGP-PK-12). Atogepant was minimally excreted in urine, with only 5% of the total radioactivity excreted in urine as the unchanged parent drug. In feces, 42% of the dose was recovered as parent drug due to unabsorbed drug, intestinal secretion and biliary excretion or a combined effect of these processes. Renal clearance (1.11 L/h) was obtained from study CPG-PK-03.

OATP1B1/1B3, P-gp, and BCRP were incorporated within the "permeability-limited liver" model to simulate hepatic transport processes. The kinetic parameter values for hepatic P-gp and BCRP, and the intrinsic clearance value for OATP1B1/1B3-mediated active transport processes in the liver were defined based on the transport data in Caco-2 cells, MDCKII-BCRP and MDCKII-control cells, and MDCKII-OATP1B3 and MDCKII control cells, respectively. The relative expression factor values for hepatic OATP1B1, OATP1B3, P-gp, and BCRP were obtained from experimental data for transporter abundance in in vitro cell culture systems and liver tissue. Multiple transporter-related processes (gut secretion, hepatic uptake, and biliary secretion) with CYP3A4-mediated metabolism and renal clearance components incorporated in the model allowed recovery of the systemic PK and the amount of drug excreted unchanged in urine (4.84%) and feces (42%).

Victim Drug Models

The default PBPK models of itraconazole, rifampin, fluconazole, and cimetidine in Simcyp V17 were used for DDI prediction.

With respect to the interaction parameter values, the in vitro obtained itraconazole inhibitory constant (Ki) values for P-gp and BCRP (Kishimoto et al. 2014) were scaled down 15-fold and used in the simulations (itraconazole Ki values for P-gp and BCRP are 0.054 and 0.054µM, respectively). The in vitro obtained hydroxyitraconazole Ki values for P-gp and BCRP (Lempers et al. 2016) were scaled down 37-fold and used in the simulations (hydroxyitraconazole Ki values for P-gp and BCRP are 0.135 and 0.324µM, respectively). In addition, in vitro obtained hydroxyitraconazole Ki values for OATP1B1 and OATP1B3(Lempers et al. 2016; Vermeer et al. 2016) were scaled down 15-fold and used in the simulations (hydroxyitraconazole Ki values for OATP1B1 and OATP1B3 are 0.016 and 0.007µM, respectively).

14.4.2. FDA's Assessment

FDA agreed with the Applicant's assessment and all metabolism of atogepant was assigned to CYP3A4 in the PBPK model. Given the renal clearance of 1.11 L/h, the contribution of CYP3A to the overall atogepant clearance is about 0.75. Using the default itraconazole PBPK model in Simcyp, the model predicted a 140% increase in atogepant exposure (AUC ratio [AUCR] is 2.43) without considering the effect of itraconazole on transporters. As the contribution of CYP3A to the total metabolism of atogepant has been confirmed using in vitro and in vivo data, the observed DDI effect with itraconazole (AUCR of 5.5) is likely partially contributed by nonCYP mediated DDI mechanisms. Since in vitro study showed that atogepant is an OATP1B1/1B3, P-gp, and BCRP substrate, the Applicant conducted additional DDI simulations by incorporating the inhibition potential of itraconazole on OATP1B1/1B3, P-gp, and BCRP as described in the method section. The simulated AUCR with itraconazole is consistent with the observed data as shown in Table 118. The reviewer agreed that the observed atogepant DDI effect with itraconazole might be contributed by both CYP and nonCYP-mediated DDI mechanisms.

Rifampin may cause DDIs via multiple mechanisms. In the PBPK analysis, the rifampin-mediated CYP3A4 competitive inhibition, P-gp and BCRP inhibition, and OATP1B1/1B3 inhibition effects were incorporated in the model to simulate the effect of a single dose of rifampin on the PK of atogepant. It was reported that the competitive inhibition of CYP3A4 by rifampin has minimal impact on the drug PK in vivo (Varma et al. 2013; Asaumi et al. 2019). The impact of P-gp inhibition by rifampin on atogepant PK was likely low given the clinically insignificant exposure change of atogepant with quinidine (1.25-fold, Study 3101-103-002). Additionally, the Applicant's worst-case scenario analysis showed that the DDI potential of atogepant with BCRP inhibitors was weak. Therefore, the observed exposure change of atogepant (AUCR 2.77) with a single dose of rifampin was most likely caused by the inhibition of hepatic uptake transporters OATP1B1/1B3 by rifampin.

To simulate the impact of multiple doses of rifampin on the PK of atogepant, the rifampin-mediated CYP3A4 induction, CYP3A4 competitive inhibition, and the P-gp induction effect were incorporated in the default rifampin model. Intestinal P-gp induction by rifampin (600 mg QD) was defined as a 3.5-fold increase in P-gp expression whereas the negligible induction effect of rifampin (600 mg QD) on hepatic P-gp was assumed (Greiner et al. 1999).

The rifampin-mediated OATP1B1/1B3 inhibition effect was not incorporated in the Applicant's model. The reviewer simulated the effect of multiple doses of rifampin on the atogepant PK after incorporation of the rifampin-mediated OATP1B1/1B3 inhibition effect (observed in Study CGP-PK-12). The simulation results showed that the reduction in hepatic uptake via inhibition of OATP1B1 caused a significant increase in the atogepant AUC as compared to that without considering the rifampin-mediated OATP1B1/1B3 inhibition effect (AUCR 1.32 versus 0.44). After incorporation of the rifampin-mediated possible BCRP induction effect (assumed to be the same magnitude of induction as intestinal P-gp) in the model, the simulated AUCR (1.06) was still not able to match the observed AUCR (0.41). Thus, the induction potential of rifampin on OATP1B1/1B3 cannot be excluded and could explain, at least partially, the reduction in atogepant exposure. The combined effect of rifampin-mediated OATP1B1/1B3 inhibition and induction would not be expected to cause significant change in the systemic exposure of atogepant as evidenced by the similar simulated AUCR (0.44) in the scenario without considering rifampin-mediated OATP1B1/1B3 inhibition and induction effect to the observed AUCR (0.41) (Table 118).

Table 118. Comparison of the Simulated Geometric Means for Atogepant Plasma C_{max} and AUC Ratios in the Absence and Presence of Multiple Doses of Rifampin or Itraconazole With Different Scenarios of Induced or Inhibited Pathways Included in the Rifampin or Itraconazole Models

Drug	$C_{max}R$	AUCR
Rifampin (600 mg QD)		
CYP3A4 induction P-gp induction	0.536	0.441
CYP3A4 induction P-gp induction BCRP induction	0.399	0.349
CYP3A4 induction	0.809	0.629
CYP3A4 induction P-gp induction OATP1B1/1B3 inhibition	1.18[a]	1.32[a]
CYP3A4 induction P-gp induction OATP1B1/1B3 inhibition BCRP induction	0.92[a]	1.06[a]
Itraconazole (200 mg QD)		
CYP3A4 inhibition P-gp inhibition BCRP inhibition OATP1B1/1B3 inhibition	2.09	4.50
CYP3A4 inhibition	1.36[a]	2.43[a]

Source: a: Reviewer's simulation results using Applicant's model; all other simulated results were obtained from PBPK report 3101-S04-000.
Abbreviations: AUC, area under the plasma concentration-time curve; AUCR, ratio of areas under the plasma concentration-time curves; C_{max}, maximum concentration; $C_{max}R$, ratio of maximum concentrations; PBPK, physiologically based pharmacokinetics; QD, once daily

14.4.3. PBPK Model Application

The developed PBPK models were used to simulate the DDI for atogepant in the following scenarios:

- To predict the effect of a strong CYP3A inhibitor or a strong CYP3A inducer on the PK of atogepant if only considering CYP-mediated DDI in healthy subjects.

- To predict the effect of a moderate CYP3A inhibitor (i.e., fluconazole) and a weak CYP3A inhibitor (i.e., cimetidine) on the PK of atogepant in healthy subjects.
- To predict the PK of atogepant with and without complete knockout of P-gp or BCRP transporter function in healthy subjects

Results

(1) Can atogepant PBPK models describe atogepant PK in healthy subjects?

Yes. The atogepant models were able to capture the observed atogepant PK following a single oral dose (50, 60, 100, and 170 mg) and multiple oral dose administration (50, 100, and 170 mg QD; 30 and 60 mg BID) of atogepant in healthy subjects (Figure 34 and Table 119). The atogepant AUC was overpredicted following administration of 50 and 100 mg, presumably due to the high variability in intestinal absorption.

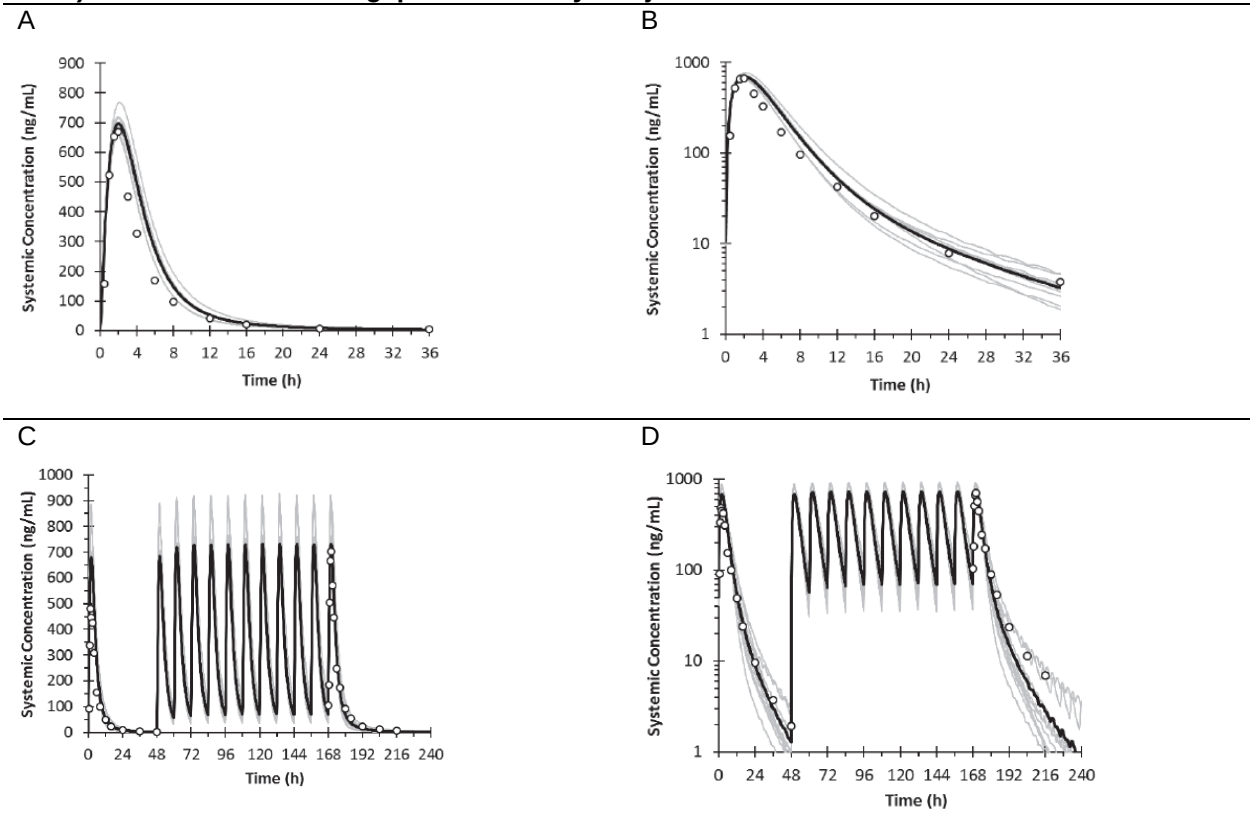
Table 119. Observed and Simulated Atogepant PK Parameters Following a Single and Multiple Oral Doses Administration of Atogepant or a Single Oral Dose Administration of Atogepant in the Presence and Absence of Itraconazole or Rifampin, in Healthy Subjects

	C_{max} (ng/mL)			AUC (ng*h/mL)			C_{max} Ratio		AUC Ratio		
Treatment	***Obs.***	**Pred.**	$R_{P/O}$	***Obs.***	**Pred.**	$R_{P/O}$	***Obs.***	**Pred.**	***Obs.***	**Pred.**	**Sources**
50 mg QD, Day 1[1]	*651*	608[3]	0.93	*2,474*	3,464[3]	1.40					Study MK-8031 P002
50 mg QD, Day 10[1]	*576*	618[3]	1.07	*2,275*	3,582[3]	1.57					
100 mg QD, Day 1[1]	*1,013*	1,237[3]	1.22	*3,729*	6,982[3]	1.87					
100 mg QD, Day 10[1]	*989*	1,257[3]	1.27	*3,965*	7,214[3]	1.82					
170 mg QD, Day 1[1]	*2,021*	2,151[3]	1.06	*10,863*	11,988[3]	1.10					
170 mg QD, Day 10[1]	*1,706*	2,184[3]	1.28	*9,475*	12,373[3]	1.31					
30 mg BID, Day 1[1]	*392*	343[3]	0.88	*1,376*	1,758[3]	1.28					
30 mg BID, Day 10[1]	*444*	366[3]	0.82	*1,442*	1,939[3]	1.34					
60 mg BID, Day 1[2]	*521*	656	1.26	*2,518*	3,522	1.40					Study 3101-101-002
60 mg BID, Day 8[2]	*695*	697	1.00	*3,757*	4,002	1.06					
60 mg w/o itraconazole[2]	*699*	657	0.94	*3,280*	3,613	1.10	*2.15*	2.09	*5.43*	4.50	Study CGP-PK-02
60 mg with itraconazole[2]	*1,500*	1,371	0.91	*17,800*	16,251	0.91					

Treatment	C_{max} (ng/mL)			AUC (ng*h/mL)			C_{max} Ratio		AUC Ratio		Sources
	Obs.	Pred.	$R_{P/O}$	*Obs.*	Pred.	$R_{P/O}$	*Obs.*	Pred.	*Obs.*	Pred.	
60 mg w/o rifampin (SD)[2]	*673*	663	0.99	*2,923*	3,579	1.22	*2.23*	2.51	*2.77*	3.34	Study CGP-PK-12
60 mg with rifampin (SD)[2]	*1,444*	1,661	1.15	*7,853*	11,954	1.52					
60 mg w/o rifampin (MD)[2]	673	663	0.99	2,923	3,556	1.22	*0.70*	0.54	*0.41*	0.44	
60 mg with rifampin (MD)[2]	*454*	355	0.78	*1,159*	1,569	1.35					

Source: PBPK report 3101-S04-00 and FDA reviewer analysis
[1] Arithmetic mean
[2] Geometric mean
[3] Reviewer's simulation results using Applicant's model; all other simulated results were obtained from PBPK report 3101-S04-00
Abbreviations: AUC, area under the plasma concentration-time curve; BID, twice daily; C_{max}, maximum concentration; MD, multiple dose; Obs, observed; PBPK, physiologically based pharmacokinetics; Pred, predicted; QD, once daily; $R_{P/O}$, ratio of predicted to observed; SD, single dose; w/o, without

Figure 34. Observed (Dots or Circles) and Simulated (Lines) Atogepant Plasma Concentration-Time Profiles Following a Single (60 mg) (A and B) or Multiple Oral (60 mg, BID) (C and D) Administration of Atogepant in Healthy Subjects[1]



Sources: Observed data were obtained from Clinical Study CGP-PK-12 (control arm) (A and B) and Clinical study 3101-101-002 (C and D).
[1]A and C: linear scale and B and D: logarithmic scale.
Abbreviations: BID, twice daily; h, hours

(2) Can atogepant PBPK models predict the effect of a strong CYP3A inhibitor or a strong CYP3A inducer on the atogepant PK if only considering CYP-mediated DDI in healthy subjects?

Yes. The contribution of enzyme (CYP3A) and transporters (OATP1B1/1B3, P-gp, and BCRP) in the disposition of atogepant were quantified using clinical PK and DDI data and sensitivity analyses. The maximal contribution of CYP3A to the metabolism of atogepant has already been assigned in the model (the contribution of CYP3A to the total metabolism of atogepant is 100% and the contribution of CYP3A to the total clearance of atogepant is 75%). Thus, the possibility of underestimation of atogepant DDI with a strong CYP3A4 inhibitor or a strong CYP3A4 inducer may be lower. Please refer to Section 14.4.2 for details.

The model predicted an approximately 140% increase (AUC ratio of 2.43) in atogepant exposure after multiple doses of itraconazole if only considering the CYP3A-mediated DDI effect in healthy subjects. The model predicted an approximately 50% reduction (AUCR of 0.63) in atogepant exposure after multiple doses of rifampin if only considering the rifampin-mediated CYP3A4 induction effect in healthy subjects (Table 118).

(3) Can atogepant PBPK models predict the effect of fluconazole (a moderate CYP3A inhibitor) and cimetidine (a weak CYP3A inhibitor) on the PK of atogepant in healthy subjects?

Yes. The atogepant models are adequate to predict the effect of fluconazole and cimetidine on the PK of atogepant in healthy subjects. About 69% increase in atogepant AUC was predicted with fluconazole (loading dose of 400 mg followed by 200 mg QD), whereas the increase in atogepant AUC(8.0%) with cimetidine (400 mg BID) was deemed clinically insignificant.

(4) Can atogepant PBPK models predict the PK of atogepant with or without complete knockout of P-gp or BCRP transporter function in healthy subjects?

Yes. The model simulated atogepant exposure was increased about 20% if completely knocked out of the intestinal and hepatic P-gp or intestinal and hepatic BCRP-mediated transport processes, indicating low DDI potential of atogepant with a selective P-gp or BCRP inhibitor. The prediction was consistent with the clinical finding that the atogepant AUC increased about 25% if coadministered with quinidine (a P-gp inhibitor) (Study 3101-103-002).

14.5. Summary of Bioanalytical Method Validation and Performance

The review team reviewed the bioanalytical method validation reports and sample analysis reports for the quantitation of atogepant in human plasma and whole blood (as Dry Blood Spot). Method validation and sample analysis were acceptable. Validation results for bioanalytical methods are summarized in Table 120.

Table 120. Bioanalytical Method Validation for the Determination of Atogepant in Human Plasma and Whole Blood

Validation Report Identifier	Clinical Studies Supported	Matrix	Method Description	Linear Range	Interday Accuracy for QCs	Interday Precision for QCs
V161101.00	3101-101-002 CGP-PK-01 CGP-PK-03	Plasma	Liquid-liquid extraction followed by LC-MS/MS	1 to 1,000 ng/mL	-1.03%-5.69%	2.2%-4.7%
ARG-W4-431	CGP-PK-02 CGP-PK-12 3101-102-002	Plasma	Protein precipitation followed by LC-MS/MS	1 to 1,000 ng/mL	-4.1%-0.4%	2.6%-8.4%
ARG-W2-648	CGP-PK-06 CGP-PK-13 3101-103-002 3101-105-002 3101-301-002	Plasma	Protein precipitation followed by LC-MS/MS	1 to 1,000 ng/mL	-6.4%-1.9%	3.0%-5.6%
ARG-W2-179	CGP-PK-04	Plasma	Protein precipitation followed by LC-MS/MS	1 to 1,000 ng/mL	-2.9%-2.1%	3.0%-9.6%
BP-0029	MK-8031 P004 MK-8031-008	Plasma	Liquid-liquid extraction followed by LC-MS/MS	1 to 1,000 ng/mL	1.9%-5%	1.1%-2.5%
DM-1007 DM-1007A	MK-8031-001 MK-8031-002 MK-8031-003 MK-8031-005	Plasma	Liquid-liquid extraction followed by LC-MS/MS	1 to 1,000 ng/mL	-2.1%-4%	0.7%-6.7%
ARG-W7-849	CGP-MD-01	Whole Blood (Dry Blood Spot)	Protein precipitation followed by LC-MS/MS	2.5 to 2,500 ng/mL	-4.1%-0%	6.2%-9.5%
V170114	CGP-PK-01	Human Plasma (EDTA) with PBS	Liquid-liquid extraction followed by LC-MS/MS	1 to 1,000 ng/mL	-11.2% to -1.3%	2.9% to 6.1%

Source: 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods
Abbreviations: EDTA, ethylenediaminetetraacetic acid; LC-MS/MS, Liquid chromatography–with tandem mass spectrometry; PBS, phosphate buffered saline; QC, quality control

15. Trial Design: Additional Information and Assessment

Not Applicable.

16. Efficacy: Additional Information and Assessment

16.1. Sensitivity Analyses for Study CGP-MD-01

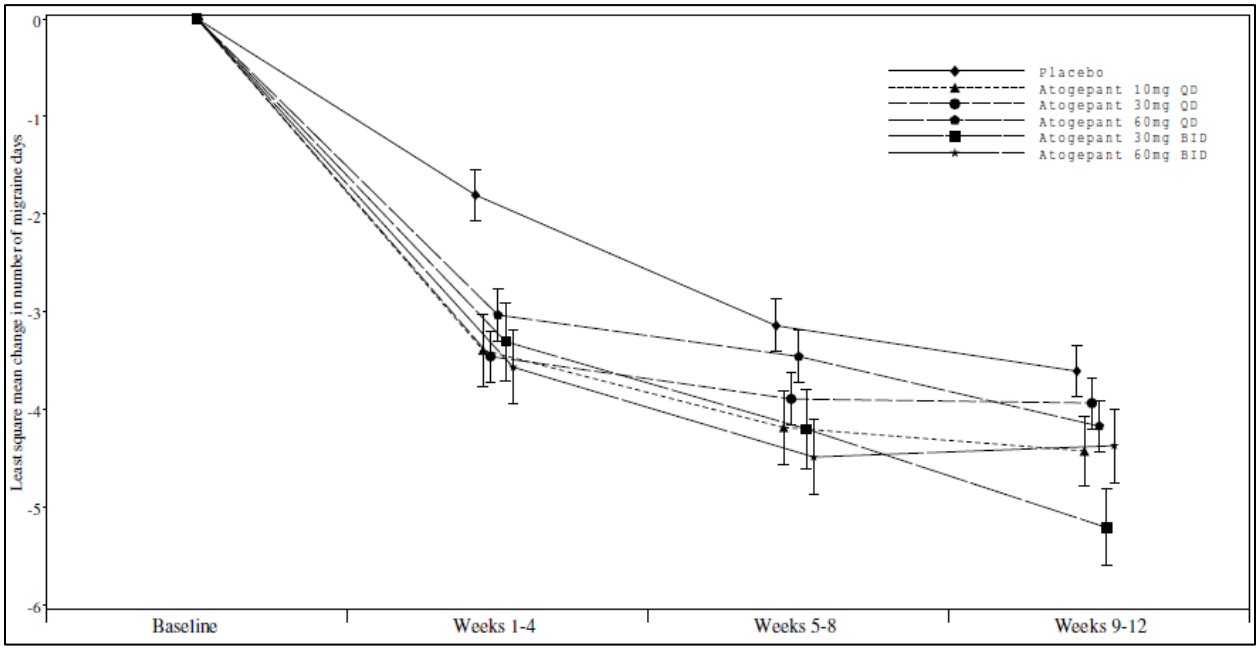
A pattern-mixture model based on nonignorable missing (i.e., missing not at random) was conducted to assess the robustness of the primary mixed-effects model for repeated measures analysis to the possible violation of the missing at random assumption. In the pattern-mixture model, the placebo group was used as reference to impute missing values. Each imputed dataset is analyzed using analysis of covariance with treatment group as a factor and baseline value as a covariate and the estimates and p-values were obtained from combining all the results from each individual analysis. The result of the pattern-mixture model is consistent with the primary analysis (Table 121). As shown in Figure 35, the change in the number of migraine days after the first month has similar trends in the placebo and atogepant groups. Therefore, imputing missing data for the atogepant groups based on the pattern of the placebo group yielded a similar result as the mixed-effects model for repeated measures analysis under missing at random assumption.

Table 121. Study CGP-MD-01: Sensitivity Analysis of Change From Baseline in Mean Monthly Migraine Days Using Pattern-Mixture Model

Statistic	Placebo	Atogepant 10 mg QD	Atogepant 30 mg QD	Atogepant 60 mg QD	Atogepant 30 mg BID	Atogepant 60 mg BID
N	178	92	182	177	79	87
LSMD		-1.16	-0.95	-0.72	-1.35	-1.31
95% CI		-1.93, -0.39	-1.58, -0.31	-1.36, -0.09	-2.16, -0.53	-2.10, -0.52
Nominal p-value		0.0033	0.0034	0.0262	0.0012	0.0012

Source: Study CGP-MD-01 CSR Table 11-3
Abbreviations: BID, twice daily; CI, confidence interval; LSMD, least squares mean difference; N, number; QD, once daily

Figure 35. Study CGP-MD-01: Change From Baseline in Number of Migraine Days During the Treatment Period



Source: Study CGP-MD-01 CSR Figure 14.2-1.1
Note: the estimates are Least Square Means from mixed-effects model for repeated measures (MMRM).
Abbreviations: BID, twice daily; QD, once daily

The reviewer also conducted an analysis of covariance model based on 3-month average of the monthly migraine days. The results were similar to the primary analysis (Table 122).

Table 122. Study CGP-MD-01: Change From Baseline in Mean Monthly Migraine Days Using ANCOVA

Statistic	Placebo	Atogepant 10 mg QD	Atogepant 30 mg QD	Atogepant 60 mg QD	Atogepant 30 mg BID	Atogepant 60 mg BID
N	178	92	182	177	79	87
LSMD		-1.11	-0.95	-0.70	-1.39	-1.36
95% CI		-1.88, -0.32	-1.54, -0.25	-1.31, -0.02	-2.21, -0.56	-2.16, -0.56
Nominal p-value		0.0057	0.0040	0.0337	0.0010	0.0009

Source: Reviewer analysis
Abbreviations: ANCOVA, analysis of covariance; BID, twice daily; CI, confidence interval; LSMD, least squares mean difference; QD, once daily

In study CGP-MD-01, it was required that a minimum of 12 days' diary data during each postbaseline 4-week treatment period be evaluable for that particular period. However, the requirement was updated to "14 days" in study 3101-301-002 as requested by FDA during the End of Phase 2 meeting. Therefore, the statistical reviewer conducted an additional analysis using the "14 days" requirement for study CGP-MD-01. The estimated treatment effects were similar to the primary analysis, although the p-value after adjusting for multiplicity is slightly larger than 0.05 for the atogepant 60 mg QD group, and the atogepant 30 mg QD group (Table 123). The analysis using the evaluable requirement of "12 days" is considered as the primary analysis as that was consistently specified in all versions of the Statistical Analysis Plan.

Table 123. Study CGP-MD-01: Change From Baseline in Mean Monthly Migraine Days Using Updated Evaluable Requirement

Statistic	Placebo	Atogepant 10 mg QD	Atogepant 30 mg QD	Atogepant 60 mg QD	Atogepant 30 mg BID	Atogepant 60 mg BID
N	177	91	179	176	78	86
LSMD		-1.10	-0.89	-0.66	-1.39	-1.36
95% CI		-1.88, -0.32	-1.54, -0.25	-1.31, -0.02	-2.21, -0.56	-2.16, -0.56
Nominal p-value		0.0058	0.0066	0.0436	0.0010	0.0009
Adjusted p-value		0.0350	0.0523	0.0523	0.0033	0.0017

Source: Reviewer analysis
Abbreviations: BID, twice daily; CI, confidence interval; LSMD, least squares mean difference; N, number; QD, once daily

16.2. Sensitivity Analyses for Study 3101-301-002

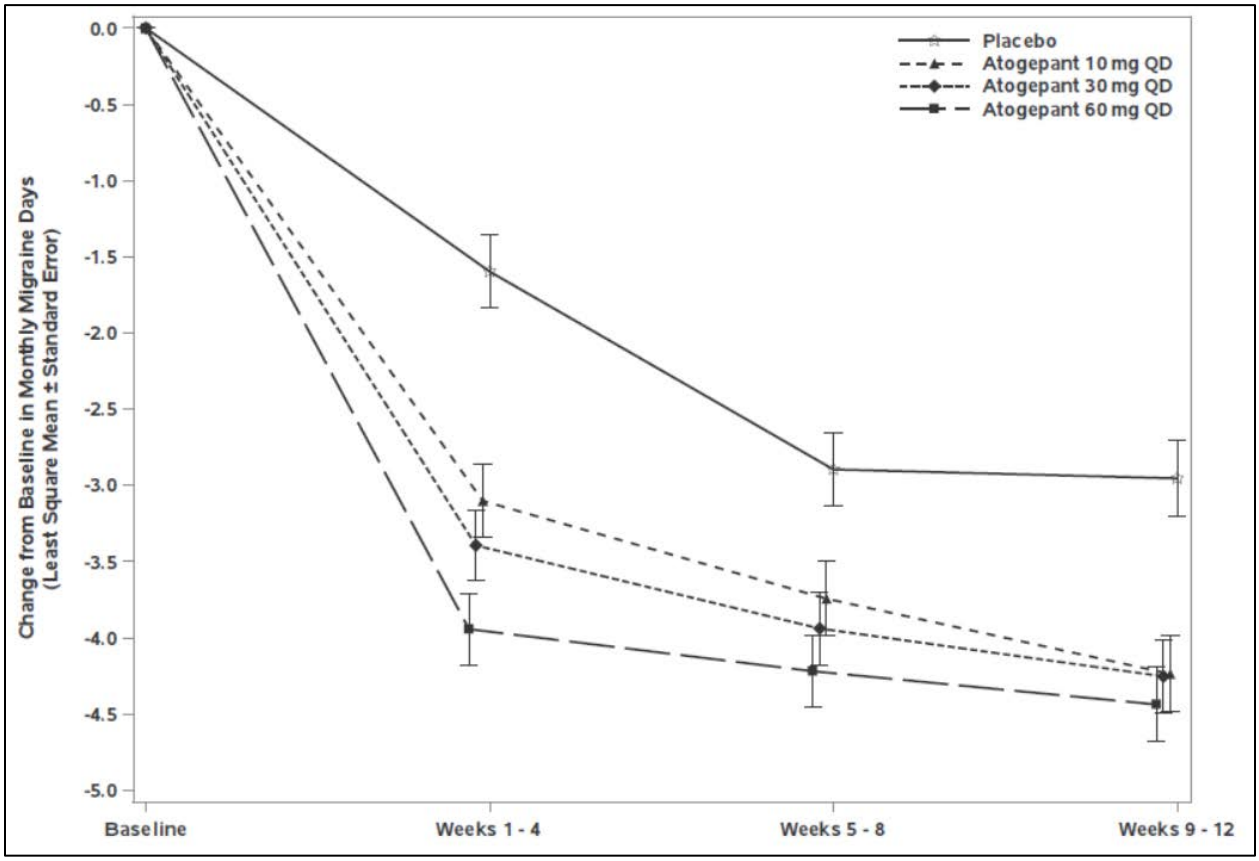
Prespecified sensitivity analyses using various methods for handling missing data assuming missing at random and missing not at random yielded similar results as the primary analysis (results not shown). An additional mixed-effects model for repeated measures was conducted based on primary measures collected during the double-blind and follow-up periods. The result was consistent with the primary analysis (Table 124).

Table 124. Study 3101-301-002: Change From Baseline in Mean Monthly Migraine Days During the Double-Blind and Follow-Up Periods

Statistic	Atogepant 10 mg QD	Atogepant 30 mg QD	Atogepant 60 mg QD
N	216	224	226
LSMD	-1.22	-1.38	-1.66
95% CI	-1.79, -0.65	-1.94, -0.81	-2.23, -1.10
Nominal p-value	<.0001	<.0001	<.0001

Source: Study 3101-301-002 CSR Table 11-14
Abbreviations: CI, confidence interval; LSMD, least squares mean difference; N, number; QD, once daily

Figure 36. Study 3101-301-002: Change From Baseline in Number of Migraine Days During the Treatment Period



Source: Study 3101-301-002 CSR Figure 14.2-1.1.A
Abbreviations: QD, once daily

16.3. Subgroup Analyses for Study CGP-MD-01

Atogepant groups showed consistent reductions from baseline in monthly migraine days when compared with placebo across all subgroups of age, sex, and race, except for groups of small sample size. The treatment effect appears to be larger for patients with prior exposure to a migraine preventive medication.

Table 125. Study CGP-MD-01: Subgroup Analyses of Change From Baseline in Mean Monthly Migraine Days

Subgroup	Atogepant 10 mg QD	Atogepant 30 mg QD	Atogepant 60 mg QD	Atogepant 30 mg BID	Atogepant 60 mg BID
Age group: <40 (N=394)					
n	52	90	82	44	44
LSMD	-1.03	-0.71	-0.83	-1.17	-1.41
95% CI	-2.09, 0.02	-1.62, 0.20	-1.76, 0.09	-2.29, -0.05	-2.52, -0.29
Age group: ≥40 - <65 (N=370)					
n	35	80	92	33	39
LSMD	-1.27	-0.71	-0.44	-1.55	-1.46
95% CI	-2.51, -0.03	-1.67, 0.25	-1.37, 0.48	-2.82, -0.29	-2.65, -0.26

Subgroup	Atogepant 10 mg QD	Atogepant 30 mg QD	Atogepant 60 mg QD	Atogepant 30 mg BID	Atogepant 60 mg BID
Age group: ≥65 (N=23)					
n	4	9	2	1	3
LSMD	0.13	-4.57	-2.25	-1.88	0.31
95% CI	-2.82, 3.08	-7.08, -2.06	-5.90, 1.40	-6.39, 2.63	-2.77, 3.38
Sex: male (N=105)					
n	11	17	29	13	8
LSMD	-2.03	-2.24	-1.44	-2.12	-2.76
95% CI	-4.41, 0.35	-4.28, -0.21	-3.21, 0.32	-4.35, 0.11	-5.40, -0.11
Sex: female (N=682)					
n	80	162	147	65	78
LSMD	-0.94	-0.71	-0.51	-1.25	-1.18
95% CI	-1.76, -0.11	-1.39, -0.03	-1.21, 0.18	-2.14, -0.36	-2.02, -0.34
Race: white (N=607)					
n	68	142	129	66	71
LSMD	-1.08	-0.89	-0.62	-1.32	-1.40
95% CI	-2.02, -0.15	-1.64, -0.13	-1.39, 0.15	-2.26, -0.37	-2.32, -0.47
Race: black (N=151)					
n	19	28	38	10	14
LSMD	-1.27	-1.30	-1.03	-2.44	-1.23
95% CI	-2.78, 0.24	-2.66, 0.05	-2.26, 0.20	-4.39, -0.50	-2.92, 0.47
Race: all other races (N=29)					
n	4	9	9	2	1
LSMD	-0.75	-0.80	-0.29	-0.98	-1.84
95% CI	-4.95, 3.45	-4.57, 2.97	-4.05, 3.48	-6.03, 4.06	-8.35, 4.67
Prior exposure to a migraine preventive medication: Yes (N=225)					
n	29	45	50	24	26
LSMD	-2.33	-1.49	-1.41	-1.87	-3.64
95% CI	-3.71, -0.95	-2.71, -0.27	-2.61, -0.22	-3.36, -0.39	-5.08, -2.19
Prior exposure to a migraine preventive medication: No (N=562)					
n	62	134	126	54	60
LSMD	-0.61	-0.64	-0.37	-1.23	-0.42
95% CI	-1.55, 0.33	-1.40, 0.11	-1.13, 0.39	-2.21, -0.24	-1.37, 0.53

Source: Reviewer analysis
Abbreviations: BID, twice daily; CI, confidence interval; LSMD, least squares mean difference; N, total number of subjects with indicated characteristic; n, number of subjects with indicated characteristic, by study arm; QD, once daily

16.4. Subgroup Analyses for Study 3101-301-002

Atogepant groups showed consistent reductions from baseline in monthly migraine days when compared with placebo across all subgroups of age, sex, and race, except for groups of small sample size. The treatment effect appears to be larger for patients with prior exposure to a migraine preventive medication.

Table 126. Study 3101-301-002: Subgroup Analyses of Change From Baseline in Mean Monthly Migraine Days

Subgroup	Atogepant 10 mg QD	Atogepant 30 mg QD	Atogepant 60 mg QD
Age group: <40 (N=403)			
n	98	96	98
LSMD (SE)	-1.12 (0.437)	-1.44 (0.437)	-1.47 (0.437)
95% CI	-1.98, -0.26	-2.30, -0.58	-2.33, -0.61

Subgroup	Atogepant 10 mg QD	Atogepant 30 mg QD	Atogepant 60 mg QD
Age group: ≥40 - <65 (N=437)			
n	109	119	116
LSMD (SE)	-1.33 (0.400)	-1.31 (0.393)	-2.16 (0.394)
95% CI	-2.12, -0.54	-2.08, -0.54	-2.93, -1.38
Age group: ≥65 (N=33)			
n	7	8	8
LSMD (SE)	-1.08 (1.653)	-1.77 (1.587)	1.43 (1.608)
95% CI	-4.47, 2.32	-5.02, 1.49	-1.87, 4.73
Sex: male (N=100)			
n	21	24	31
LSMD (SE)	-1.63 (0.889)	-1.52 (0.837)	-2.40 (0.795)
95% CI	-3.40, 0.14	-3.18, 0.15	-3.98, -0.82
Sex: female (N=773)			
n	193	199	191
LSMD (SE)	-1.15 (0.310)	-1.36 (0.307)	-1.62 (0.311)
95% CI	-1.75, -0.54	-1.96, -0.76	-2.23, -1.01
Race: white (N=729)			
n	176	181	184
LSMD (SE)	-1.24 (0.299)	-1.61 (0.295)	-1.95 (0.294)
95% CI	-1.83, -0.66	-2.19, -1.03	-2.53, -1.38
Race: black (N=118)			
n	32	37	27
LSMD (SE)	-1.69 (1.048)	-0.80 (1.025)	-0.77 (1.082)
95% CI	-3.76, 0.39	-2.83, 1.23	-2.92, 1.37
Race: all other races (N=25)			
n	6	5	10
LSMD (SE)	-1.54 (2.086)	-2.90 (2.305)	0.36 (1.941)
95% CI	-5.91, 2.83	-7.72, 1.92	-3.70, 4.43
Prior exposure to a migraine preventive medication: Yes (N=608)			
n	145	159	152
LSMD (SE)	-1.38 (0.354)	-1.51 (0.345)	-2.17 (0.349)
95% CI	-2.07, -0.68	-2.19, -0.83	-2.85, -1.48
Prior exposure to a migraine preventive medication: No (N=265)			
n	69	64	70
LSMD (SE)	-0.81 (0.502)	-1.05 (0.510)	-0.66 (0.501)
95% CI	-1.80, 0.18	-2.05, -0.05	-1.65, 0.32

Source: Reviewer analysis
Abbreviations: BID, twice daily; CI, confidence interval; LSMD, least squares mean difference; N, total number of subjects with indicated characteristic; n, number of subjects with indicated characteristic, by study arm; QD, once daily; SE, standard error

17. Clinical Safety: Additional Information and Assessment

Table 127. ISS Group 1: Adverse Events Leading to Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population

System Organ Class FMQ (Narrow)	ATG 10 mg QD N=314 n (%)	ATG 30 mg QD N=411 n (%)	ATG 60 mg QD N=417 n (%)	ATG 30 mg BID N=86 n (%)	ATG 60 mg BID N=91 n (%)	Total ATG N=1,319 n (%)	Placebo N=408 n (%)	Risk Difference (95% CI)
Cardiac disorders								
Palpitations	0	0	0	1 (1.2)	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Systemic hypertension	0	0	0	1 (1.2)	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Ear and labyrinth disorders								
Vertigo	1 (0.3)	0	0	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Gastrointestinal disorders								
Constipation	1 (0.3)	3 (0.7)	2 (0.5)	0	1 (1.1)	7 (0.5)	0	0.5 (0.1, 0.9)
Nausea	1 (0.3)	3 (0.7)	1 (0.2)	0	1 (1.1)	6 (0.5)	0	0.5 (0.1, 0.8)
Vomiting	1 (0.3)	0	0	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Abdominal pain	1 (0.3)	1 (0.2)	0	0	0	2 (0.2)	1 (0.2)	0 (-0.6, 0.4)
General disorders and administration site conditions								
Fatigue	1 (0.3)	0	1 (0.2)	0	3 (3.3)	5 (0.4)	0	0.4 (0, 0.7)
Decreased appetite	0	0	1 (0.2)	0	1 (1.1)	2 (0.2)	0	0.2 (-0.1, 0.4)
Hepatobiliary disorders								
Hepatic injury	0	1 (0.2)	1 (0.2)	0	0	2 (0.2)	0	0.2 (-0.1, 0.4)
Musculoskeletal and connective tissue disorders								
Myalgia	0	1 (0.2)	0	0	0	1 (0.08)	1 (0.2)	-0.1 (-0.7, 0.3)
Nervous system disorders								
Dizziness	1 (0.3)	2 (0.5)	0	0	2 (2.2)	5 (0.4)	0	0.4 (0, 0.7)
Somnolence	1 (0.3)	0	0	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Headache	1 (0.3)	1 (0.2)	1 (0.2)	0	0	3 (0.2)	2 (0.5)	-0.3 (-1, 0.5)
Psychiatric disorders								
Insomnia	0	0	1 (0.2)	0	1 (1.1)	2 (0.2)	0	0.2 (-0.1, 0.4)
Depression	0	1 (0.2)	0	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Irritability	0	0	1 (0.2)	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Mania	0	1 (0.2)	0	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)
Parasomnia	1 (0.3)	0	0	0	0	1 (0.08)	1 (0.2)	-0.1 (-0.7, 0.3)
Skin and subcutaneous tissue disorders								
Rash	1 (0.3)	0	2 (0.5)	0	0	3 (0.2)	0	0.2 (0, 0.5)
Pruritus	0	0	1 (0.2)	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)

System Organ Class FMQ (Narrow)	ATG 10 mg QD N=314 n (%)	ATG 30 mg QD N=411 n (%)	ATG 60 mg QD N=417 n (%)	ATG 30 mg BID N=86 n (%)	ATG 60 mg BID N=91 n (%)	Total ATG N=1,319 n (%)	Placebo N=408 n (%)	Risk Difference (95% CI)
Vascular disorders								
Hemorrhage	1 (0.3)	0	0	0	0	1 (0.08)	0	0.1 (-0.1, 0.2)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that began or worsened (increased in severity or became serious) on or after the date of the first dose of double-blind study treatment and with an onset date before 30 days after the last dose of double-blind study treatment or Visit 8, whichever comes later.
Duration is 12 weeks (median 85 days, range 1-111 days).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
For specific preferred terms under each FMQ, see the table "Adverse Events Leading to Discontinuation by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: ATG, atogepant; BID, twice daily; QD, once daily; CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event

Table 128. ISS Group 2: Adverse Events Leading to Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population

System Organ Class FMQ (Narrow)	Atogepant 60 mg QD N=1,198 n (%)	Standard of Care N=196 n (%)	Risk Difference (%) (95% CI)
Cardiac disorders			
Systemic hypertension	1 (0.08)	0	0.1 (-0.1, 0.2)
Gastrointestinal disorders			
Nausea	5 (0.4)	0	0.4 (0.1, 0.8)
Abdominal pain	4 (0.3)	0	0.3 (0, 0.7)
Vomiting	2 (0.2)	0	0.2 (-0.1, 0.4)
Constipation	1 (0.08)	0	0.1 (-0.1, 0.2)
Dyspepsia	1 (0.08)	0	0.1 (-0.1, 0.2)
General disorders and administration site conditions			
Fatigue	3 (0.3)	0	(0, 0.5)
Decreased appetite	1 (0.08)	0	0.1 (-0.1, 0.2)
Hepatobiliary disorders			
Hepatic injury	2 (0.2)	0	0.2 (-0.1, 0.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Malignancy	4 (0.3)	2 (1.0)	-0.7 (-2.1, 0.8)
Nervous system disorders			
Headache	4 (0.3)	0	(0, 0.7)
Somnolence	2 (0.2)	0	(-0.1, 0.4)
Paresthesia	1 (0.08)	0	(-0.1, 0.2)
Seizure	1 (0.08)	0	(-0.1, 0.2)
Dizziness	3 (0.3)	1 (0.5)	-0.2 (-1.3, 0.8)
Psychiatric disorders			
Self-harm	2 (0.2)	0	(-0.1, 0.4)
Depression	1 (0.08)	0	(-0.1, 0.2)
Insomnia	1 (0.08)	0	0.1 (-0.1, 0.2)
Skin and subcutaneous tissue disorders			
Rash	3 (0.3)	0	(0, 0.5)
Urticaria	1 (0.08)	0	(-0.1, 0.2)
Alopecia	0	1 (0.5)	-0.5 (-1.5, 0.5)

System Organ Class FMQ (Narrow)	Atogepant 60 mg QD N=1,198 n (%)	Standard of Care N=196 n (%)	Risk Difference (%) (95% CI)
Vascular disorders			
Hemorrhage	1 (0.08)	0	0.1 (-0.1, 0.2)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that began or worsened (increased in severity or became serious) on or after the date of the first dose of double-blind study treatment and with an onset date before 30 days after the last dose of double-blind study treatment or Visit 8, whichever comes later.
Duration is mean 32.5 weeks (standard deviation, 18.7; median, 36.1; minimum, 0.1; maximum, 58).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
For specific preferred terms under each FMQ, see the table "Adverse Events Leading to Discontinuation by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; QD, once daily

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

There is no additional information to report.

19. Other Drug Development Considerations: Additional Information and Assessment

Not Applicable.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

OSI inspected the clinical sites of Robin Kroll, M.D. and Brock McConnehey, D.O. covering Protocol CGP-MD-01 and Melvin Helm, M.D. and John Michael Hemphill, M.D. covering Protocol 3101-301-002. All four clinical sites were in the United States. Despite some protocol deviations noted at the sites of Drs. Kroll and McConnehey, the studies appear to have been conducted adequately and the data generated by these sites appear acceptable in support of the respective indication.

21. Labeling Summary of Considerations and Key Additional Information

Significant modifications to the Applicant- proposed Prescribing Information (PI) submitted on January 28, 2021, are described in Table 129. The Highlights, Table of Contents, and Patient Information were revised to reflect edits to the Full Prescribing Information. In addition to the core review team, consultations with respect to labeling were obtained, as described in Table 130.

5 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4864103

22. Postmarketing Requirements and Commitments

(1) A juvenile animal toxicology study of atogepant in rats.

(2) A randomized, double-blind, placebo-controlled efficacy and safety study under the PediatricResearch Equity Act for the preventive treatment of episodic migraine in children 6 through 17 years of age. This efficacy study must be designed to show superiority of atogepant over placebo and is to be submitted as a special protocol assessment (SPA). A pharmacokinetics evaluation needs to be conducted in children 6 through 11 years of age to determine the appropriate dosing in the efficacy portion of the study in this age group.

(3) A study under the Pediatric Research Equity Act to evaluate the long-term safety of preventive treatment of episodic migraine in patients 6 through 17 years of age. This study should be a minimum of one year in length.

(4) A prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with migraine exposed to atogepant during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to atogepant before and during pregnancy and the other consisting of women without migraine. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. 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.

(5) A pregnancy outcomes study using a different study design than provided for in the pregnancy registry postmarketing requirement above (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to atogepant during pregnancy compared to an unexposed control population.

(6) A dose range-finding study of orally administered atogepant in female CD-1 mouse.

(7) A 2-year carcinogenicity study of orally administered Qulipta in female mouse.

Enhanced pharmacovigilance is recommended for liver toxicity, cardiovascular (including hypertension), cerebrovascular, and serious gastrointestinal events.

23. Financial Disclosure

Table 131. Study CGP-MD-01: Covered Clinical Study

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 78		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
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: 6 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator: 2 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 3		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

There were three investigators in CGP-MD-01 who did not provide financial disclosure forms. One site subsequently submitted the required forms. Two other sites did not submit forms, but only two subjects were enrolled in the study during the time these investigators were active in the study. The number of patients enrolled by these sites was minimal compared with the overall number of patients in the study. Removing these sites did not affect the p-value on the primary endpoint.

Table 132. Study 3101-301-002: Covered Clinical Study

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 128		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 7		
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: 7 Significant payments of other sorts: 7 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 54		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

There were 54 sites noted to not have financial disclosure documents for some of the staff (associate investigators and/or site coordinators). The Applicant made an effort to obtain this information that is assessed as adequate. Each site was removed individually for the statistical analysis of the primary endpoint, and no site when removed resulted in reducing the p-value for this analysis such that it was not statistically significant in Study 3101-301-002.

There were several investigators with financial interests. Removing the individual sites, as stated previously, did not affect the primary endpoint negatively.

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Vivus, see Qsymia, https://www.accessdata.fda.gov/scripts/cder/daf/.

25. Review Team

Table 133. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Daniel Ngembus
Nonclinical Reviewer	Edmund Nesti
Nonclinical Team Leader	Lois Freed
Office of Clinical Pharmacology Reviewer(s)	Xiaohan Cai; Ye Yuan; Jianghong Fan; Hobart Rogers
Office of Clinical Pharmacology Team Leader(s)	Yuching Yang; Atul Bhattaram; Gopichand Gottipati; Sreedharan Sabarinath
Clinical Reviewer	Viveca Livezey
Clinical Team Leader	Heather Fitter
Statistical Reviewer	Xiang Ling
Statistical Team Leader	John P. Lawrence
Division of Clinical Outcomes Assessment	Jing (Julia) Ju
Deputy Director , Clinical Outcomes Assessment	David Reasner
Associate Director for Labeling	Tracy Peters
Cross-Disciplinary Team Leader	Heather Fitter
Division Director (pharm/tox)	Lois Freed
Division Director (OCP)	Mehul Mehta
Division Director (OB)	Hsien Ming James Hung
Division Director (clinical)	Nick Kozauer
Office Director (or designated signatory authority)	Eric Bastings

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 134. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Martha Heimann (Team Leader) & Erica Keafer (RPM)
Drug Product	Eric Bow; Julia Pinto
Drug Substance	Sharon Kelly; Donna Christner
OPMA-Manufacturing	Pratibha Bhat; Shujun Chen
Environmental Assessment	James Laurenson
OPDP	Sapna Shah
OSI	Cara Alfaro; Philip Kronstein
OSE/DPV	Suprat Saely
OSE/DMEPA	John C. Morris; Celeste A. Karpow
OSE/DRM	Ingrid Chapman; Jacqueline Sheppard
CSS	Chad Reissig; Sandy Saltz
DHN	Paul (Skip) Hayashi
DAI	Edward Weinstein
DCN	Devi Kozeli
DMPP	Lonice Carter; Marcia Williams
Medical Editors	Erica Boehm; Megan Young

Abbreviations: CSS, Controlled Substance Staff; DAI, Division of Anti-Infectives; DCN, Division of Cardiology and Nephrology; DHN, Division of Hepatology and Nutrition; DMEPA, Division of Medication Error Prevention and Analysis; DMPP: Division of Medical Policy Programs; DRM, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPMA, Office of Pharmaceutical Manufacturing Assessment OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; RPM, regulatory project manager

Table 135. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Cross-Disciplinary	Heather Fitter, MD	OND/DN2	Sections 2.1 ☒ Authored Section II. IA ☒ Contributed Section II. IA ☒ Approved
Cross-Disciplinary Team Lead	**Signature:** Heather Fitter -S Dig tally signed by Heather Fitter -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Heather Fitter -S, 0.9.2342.19200300.100.1.1=2000244097 Date: 2021.09 27 15:14 40 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Viveca, Livezey, MD	OND/DN2	Sections 3, 6, 7, 17, 22, 23, 24 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Viveca B. Livezey -S Digitally signed by Viveca B. Livezey -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9 2342.19200300.100.1.1=2001420639, cn=Viveca B. Livezey -S Date: 2021.09.27 08:38:08 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Cross-Disciplinary	Tracy Peters, PharmD	OND/DN2	Section 21 ☒ Authored ☐ Contributed ☐ Approved
Associate Director for Labeling	**Signature:** Tracy Peters -S Digitally signed by Tracy Peters -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Tracy Peters -S, 0.9.2342.19200300.100.1.1=2000625319 Date: 2021.09.28 09:03:59 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Lois Freed, PhD	OND/DPT-N	Sections 5, 5.1, 7.1, 8.6, 13.1, 13.2, 22 ☐ Authored ☒ Contributed ☒ Approved
Division Director	**Signature:** Lois M. Freed -S Dig tally signed by Lois M Freed S DN: c=US o=U S Government ou=HHS ou=FDA ou=Peop e cn=Lois M Freed S 0 9 2342 19200300 100 1 1=1300076414 Date: 2021 09 28 11:01:06 04 00		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Continued: Table 135. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Edmund Nesti, PhD	OND/DPT-N	Sections 5, 5.1, 7.1, 8.6, 13.1, 13.2, 22 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Edmund D. Nesti -S Digitally signed by Edmund D. Nesti -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001732219, cn=Edmund D. Nesti -S Date: 2021.09.27 13:27:43 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Xiang Ling, PhD	OB/DBI	Sections 6 and 16 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Xiang Ling -S Digitally signed by Xiang Ling -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiang Ling -S, 0.9.2342.19200300.100.1.1=2000343063 Date: 2021.09.24 17:16:48 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	John Lawrence, PhD	OB/DBI	Sections 6 and 16 ☐ Authored ☒ Contributed ☐ Approved
Team Leader	**Signature:** John P. Lawrence -S Digitally signed by John P. Lawrence -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300144280, cn=John P. Lawrence -S Date: 2021.09.24 15:31:09 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Hsien Ming James Hung, PhD	OB/DBI	Sections 6 and 16 ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Hsienming J. Hung -S Digitally signed by Hsienming J. Hung -S Date: 2021.09.27 12:12:33 -04'00'		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Regulatory Project Management	Daniel Ngembus, PharmD	OND/ORO/DN2	Section 12 ☒ Authored ☐ Contributed ☐ Approved
Regulatory Project Manager	**Signature:** Daniel E. Ngembus -S	Digitally signed by Daniel E. Ngembus -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002922767, cn=Daniel E. Ngembus -S Date: 2021.09.24 15:16:49 -04'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Xiaohan Cai, Ph.D.	OTS/OCP/DNP	Sections 5, 8.1, 8.2, 14.1, 14.2, and 14.5 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Xiaohan Cai -S	Digitally signed by Xiaohan Cai -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiaohan Cai -S, 0.9.2342.19200300.100.1.1=2001746349 Date: 2021.09.25 09:30:26 -04'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Ye Yuan, Ph.D.	OTS/OCP/DPM	Section 14.3 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Ye Yuan -S	Digitally signed by Ye Yuan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ye Yuan -S, 0.9.2342.19200300.100.1.1=2002006018 Date: 2021.09.27 11:08:27 -04'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Atul Bhattaram, PhD	OTS/OCP/DPM	Section 14.3 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Venkatesh A. Bhattaram -S	Dig tally signed by Venkatesh A Bhattaram S DN: c US o U S Government ou HHS ou FDA ou People 0 9 2342 19200300 100 1 1 1300212823 cn Venkatesh A Bhattaram S Date: 2021 09 26 08:46:09 04'00'	

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Jianghong Fan, Ph.D.	OTS/OCP/DPM	Section 14.4 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Jianghong Fan -S Digitally signed by Jianghong Fan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jianghong Fan -S, 0.9.2342.19200300.100.1.1=2001454698 Date: 2021.09.24 21:13:07 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Yuching Yang, PhD	OTS/OCP/DPM	Section 14.4 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Yuching Yang -S Digitally signed by Yuching Yang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yuching Yang -S, 0.9.2342.19200300.100.1.1=2000846164 Date: 2021.09.27 10:28:57 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Gopichand Gottipati, Ph.D.	OTS/OCP/DNP	Sections 5, 8.1, 8.2, and 14 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Gopichand Gottipati -S Digitally signed by Gopichand Gottipati -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002119040, cn=Gopichand Gottipati -S Date: 2021.09.25 12:32:06 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Sabarinath Sreedharan, Ph.D.	OTS/OCP/DNP	Sections 5, 8.1, 8.2, and 14 ☐ Authored ☐ Contributed ☒ Approved
Associate Director	**Signature:** Sreedharan N. Sabarinath -S Digitally signed by Sreedharan N. Sabarinath -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000494325, cn=Sreedharan N. Sabarinath -S Date: 2021.09 25 20:51:02 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Mehul Mehta, Ph.D.	OTS/OCP/DNP	Sections 5, 8.1, 8.2, and 14 ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Mehul U. Mehta -S Digitally signed by Mehul U. Mehta -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mehul U. Mehta -S, 0.9.2342.19200300.100.1.1=1300039057 Date: 2021.09.28 10:40:57 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Product Quality	Martha Heimann, PhD	OPQ/ONDP/DNDP2	Section 9 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Martha R. Heimann -S Digitally signed by Martha R. Heimann -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300091527, cn=Martha R. Heimann -S Date: 2021.09.27 17:16:40 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Cross-Disciplinary	Cara Alfaro, PharmD, BCCP	OSI	Section 20 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Cara L. Alfaro -S Digitally signed by Cara L. Alfaro -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Cara L. Alfaro -S, 0.9.2342.19200300.100.1.1=1300174859 Date: 2021.09.27 20:07:35 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Nicholas Kozauer, MD	OND/DN2	Section 2.2 ☒ Authored Section II. IA ☒ Contributed Section II IA ☒ Approved
Division Director	**Signature:** Nicholas Kozauer -S Digitally signed by Nicholas Kozauer -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000427865, cn=Nicholas Kozauer -S Date: 2021.09.27 10 46:03 -04'00'		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Jing Ju, PharmD, PhD	OND/DCOA	Section 6.3.3 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Jing Ju -S Digitally signed by Jing Ju -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jing Ju -S, 0.9.2342.19200300.100.1.1=2000337132 Date: 2021.09.28 09:57:21 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	David Reasner, PhD	OND/DCOA	Section 6.3.3 ☐ Authored ☒ Contributed ☒ Approved
Division Director	**Signature:** David Reasner -S Digitally signed by David Reasner -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=David Reasner -S, 0.9.2342.19200300.100.1.1=2003187028 Date: 2021.09.24 16:36:05 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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/s/

DANIEL E NGEMBUS
09/28/2021 12:09:15 PM

ERIC P BASTINGS
09/28/2021 12:23:50 PM

Division of Hepatology and Nutrition
DILI Team Consultation

NDA	215206
Consultation Issue	Drug-induced liver injury (DILI)
Drug	Atogepant (calcitonin gene related peptide receptor antagonist)
Indication	Migraine headache prevention
Applicant	AbbVie, Inc
Requesting Division	Division of Neurology 2 Daniel Ngembus, RPM Viveca Livezey, MD Heather Fitter, Clinical Team Lead
Primary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Reviewer **Office of Pharmacoepidemiology**	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Joseph Toerner, MD, MPH Director, OND/DHN
Assessment Date	Aug 25, 2021

Context:
Atogepant is an oral small molecule antagonist of the calcitonin gene related peptide (CGRP) receptor. It is under NDA review for the prevention of migraine headaches in adults with more than 15 migraine days per month. Other agents in this class have had problems with drug-induced liver injury (DILI). We are asked by the Division of Neurology 2 (DN2) to review "patients with abnormal LFTs for potential liver toxicity" associated with Atogepant with particular attention to a severe adverse event that resulted in fatality. We are asked to give opinion on whether atogepant "carries a risk of potential liver toxicity and, if so, how this may inform labeling."

Executive Summary:
We do not see significant liver toxicity that threatens approval of this drug. There were no cases that met Hy's Law criteria in the registration trials in which over 1300 patients were given Atogepant. Patients were treated for 12 weeks in the placebo-controlled trials and up to 52 weeks in the long-term open label studies. There was no significant imbalance in transaminase elevations between placebo and treatment arms. The fatal case of particular concern did not involve DILI (see Section 4.6.2). Nevertheless, other agents in this class have had significant liver injury issues in development, and there were 5 cases of probable DILI without jaundice overall. All cases did well with holding the Atogepant. We do not recommend monitoring for liver injury with blood tests, but we suggest discussing potential for liver injury in the label because rare cases of severe liver injury could arise in the larger post-market population. Avoidance of use in patients with severe hepatic impairment should be considered. We have full recommendations including comments for labeling in Section 5.0

Reference ID: 4848947

Consultation Sections:

Section 1.0 – Rationale and DILI risk
Section 2.0 - Pharmacokinetic data pertinent to DILI
Section 3.0 - Non-clinical data pertinent to DILI.
Section 4.0 - Clinical data
Section 5.0 – Summary & Recommendations
Section 6.0 – Addendum 1: 120 Day Safety Report Review
Section 7.0 – Addendum 2: Review of response to information request

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Abbreviations:
ALP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
AGPT: Atogepant
CGRP: calcitonin gene related peptide
DILI: drug-induced liver injury
IV: intravenous
SC: subcutaneous
ULN: Upper limit of normal

1.0 Rationale:

1.1 Disease: Migraine headaches effect over 1 billion people worldwide with substantial morbidity and disability. Persons aged 25 to 35 carry the highest incidence rates with more women than men by a 2:1 ratio (23 versus 10 per 1000 person-years).[1],[2] Theories on pathophysiology have moved away from the idea that vascular constriction leads to migraines. Nowadays, theory on migraine pathophysiology is based on cortical spreading by a propagating wave of neuronal and glial depolarization (cortical spreading depression of Leao).[3] This wave helps to explain the migraine aura. This wave of depolarization reaches the trigeminal vascular system which is felt to be central to the subsequent pain and other manifestations of a migraine attack.

Stimulation of the trigeminal system leads to release of several neuropeptides including calcitonin gene related peptide (CGRP). These peptides then lead to neurogenic inflammation by vasodilation and protein extravasation. CGRP and its receptor are widely expressed in the peripheral and central nervous systems. CGRP may also play a role in pain transmission. It is increased in cerebral spinal fluid and cranial circulation during migraine headaches and can trigger migraine attacks.

---

[1] Ashina M, et al. Lancet 397:1485-95 (2021)
[2] Lyngberg AC, et al. Am J Epidemiol 161:1066-73 (2005)
[3] Cutrer, FM. Pathophysiology, clinical manifestations, and diagnosis of migraine in adults. UpToDate.com (accessed May 14, 2021)

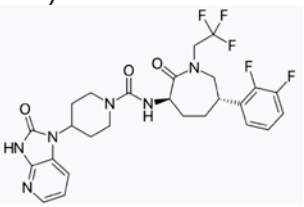
Reference ID: 4848947

1.2 Mechanism of action: Because of CGRP's significant role, it became a primary therapeutic target, and blocking of the CGRP receptor has been shown to prevent migraine headaches. Both small molecules and monoclonal antibodies aimed at blocking the CGRP receptor are approved or in development. Atogepant (AGPT) is a small molecule antagonist similar to two agents approved for migraine prevention.

1.3 CGRP receptor antagonists and DILI risk: Telcagepant is in the same class as AGPT. Telcagepant development was stopped by another sponsor due to liver injury signals in Phase III studies, primarily when given daily for more than 7 days.[4] Elevated transaminases occurred at a rate too high and severe to warrant further development. Similarly, development of another agent, MK-3207 was also stopped due to liver injury concerns. The mechanism of liver injury for these agents is postulated to be a combination of bile acid accumulation (transport inhibition) and oxidative stress (reactive metabolite formation), and less so from mitochondrial toxicity.[5] In vitro and in silico testing have led to development of other CGRP receptor antagonists with less hepatotoxicity. Since the abandonment of telcagepant and MK-3207, several agents in the same class have successfully made it to market without significant liver injury concerns.

Telcagepant structure (Figure 1):

Figure 1



1.3.1 FDA approved oral, small molecule CGRP antagonists (year of approval): rimegepant (2020) and ubrogepant (2019)

1.3.2 FDA approved parenteral, monoclonal antibody CGRP antagonists: Eptinezumab (IV), Galcanezumab (SC), Fremanezumab (SC), Erenumab (SC)

2.0 **Pharmacokinetics**:

2.1 Chemical structure of MK-8031 (now Atogepant) and metabolites (Figure 2):

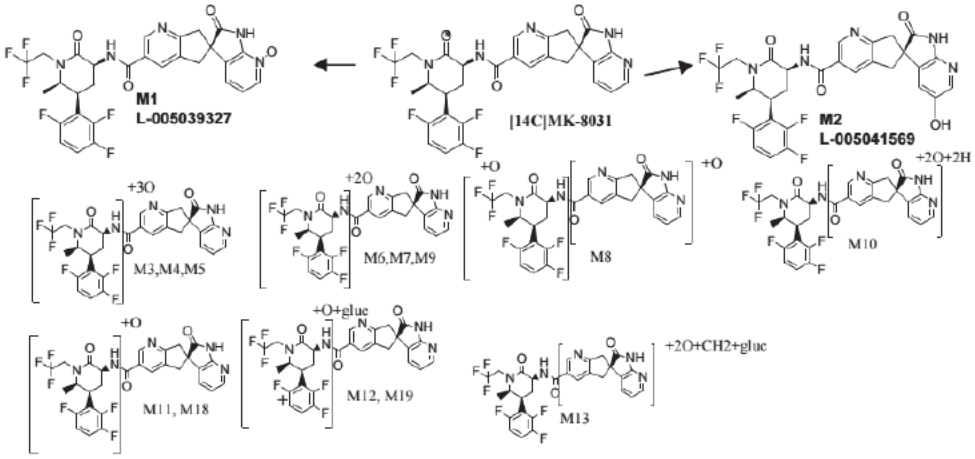
[4] Holland PR, et al. Neurotherapeutics 15:304-312 (2018)

[5] Smith, B, et al. Toxicological Sciences, 177:84-93 (2020)

Reference ID: 4848947

Figure 2

Proposed Metabolites of MK-8031



2.2 AGPT is absorbed quickly (median Tmax =1-2 hrs). Volume of distribution is estimated at 73 to 86.1 L. It is metabolized via CYP3A4 primarily. It is predominantly (81%) hepatically eliminated via metabolites in bile and feces. Renal clearance is minor (<10%). AGPT is a substrate for P-gp, BCRP, OATP1B1, OATP1B3, OAT1.

2.3 Hepatic impairment studies: Cmax is +9, -12% and -4% for mild, moderate and severe impairment compared to normal function (Table 1, Figure 3). However, AUCs were higher in "subjects with hepatic impairment" (14-38% increase). While AUCs were similar between mild and moderate impairment, the highest AUCs at 0-4 hours and overall were for severe impairment (38% increase compared to normal) (Table 1).

Table 1

Arithmetic Mean (SD) Atogepant PK Parameters Following Single Dose Oral Administration of Atogepant 60 mg in Subjects with Hepatic Impairment and Normal Hepatic Function (PK Population; CGP-PK-01)

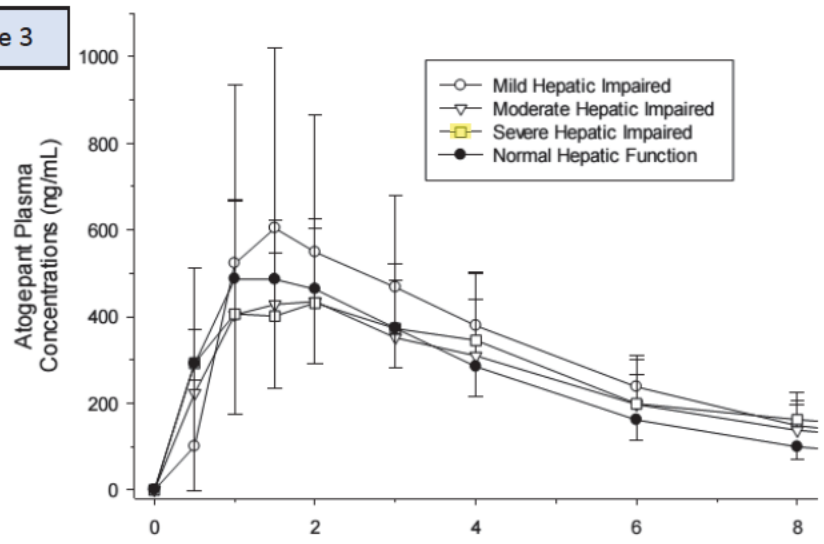
PK Parameter	Mild Hepatic Impairment (N = 8)	Moderate Hepatic Impairment (N = 8)	Severe Hepatic Impairment (N = 8)	Normal Hepatic Function (N = 8)
C_{max} (ng/mL)	666.30 (372.13)	528.60 (227.13)	542.87 (197.18)	588.65 (248.49)
T_{max} (h)[a]	1.76 (1.00 - 4.00)	1.50 (1.00 - 6.00)	1.00 (0.50 - 3.00)	1.75 (1.00 – 3.00)
AUC_{0-t} (ng.h/mL)	3472.65 (1424.90)	3270.13 (1693.04)	3797.07 (1397.20)	2757.92 (918.96)
$AUC_{0-\infty}$ (ng.h/mL)	3495.31 (1425.30)	3313.94 (1684.18)	3836.32 (1439.69)	2779.79 (924.38)
AUC%	0.73 (0.42)	1.70 (1.44)	0.87 (0.65)	0.81 (0.23)
λ_z (1/h)	0.09 (0.03)	0.08 (0.04)	0.10 (0.02)	0.08 (0.03)
$t_{1/2}$ (h)	8.70 (4.06)	11.90 (7.60)	7.54 (2.95)	9.40 (3.24)
CL/F (L/h)	19.42 (6.60)	21.33 (8.06)	17.33 (5.40)	24.20 (9.42)
V_z/F (L)	249.10 (161.40)	404.03 (405.78)	176.59 (47.48)	301.18 (77.01)

[a] Median (range)

Source: Module 5.3.3.3, CGP-PK-01 CSR, Table 11-1

Reference ID: 4848947

Figure 3



3.0 **Non-clinical data related to DILI**:

3.1 Animal studies: The sponsor did rat, mouse and monkey studies for 3 months (100 mg/kg/d), 6 months (200 mg/kg/d) and 9 months (300 mg/kg/d), respectively. No liver injury was found. Three-month and 9-month necropsy studies in Rhesus monkeys did not show any liver abnormalities.

3.2 In vitro testing: The sponsor did bile acid transporter inhibition, oxidative stress and mitochondrial dysfunction studies for AGPT, telcagepant and MK-3207. AGPT is an inhibitor of OCT1 and MATE1 but not BCRP. There is no mention of BSEP inhibition. AGPT is oxidized predominantly by CY3A4 and inhibits it as well. There is no mention of mitochondrial toxicity.

3.3 Quantitative systems toxicology (DILISym®) studies suggest a "reduced risk of hepatotoxicity" for AGPT compared to telcagepant based on in vitro studies outlined. (Seq 001, 4.2.3.7.3). No ALT elevations were predicted at the 60 mg BID dosing. Mild elevations were predicted at 120 mg BID and "more significant" elevations at 180 mg BID.

4.0 **Clinical Data**:

4.1 Registration Trials

4.1.1 Group 1: Short term trials, CGP-MD-1 and 3101-301-002

4.1.2 Group 2: Long term (40-52 weeks) trials, 3101-302-002 and 3101-309-002 (open label extension of Group 1 trials)

4.1.3 Dosing of AGPT ranged from 10mg daily to 60 mg twice daily.

4.2 Total Exposed numbers across all trials:

4.2.1 2467 got at least one dose (509 Healthy controls and 1958 with migraine).

4.3 Summary of clinical studies are shown in Table 2:

Table 2

ID	Phase	Design	Subjects	#
3101-105-002	1	Open label; single dose	(b) (4)	20

Reference ID: 4848947

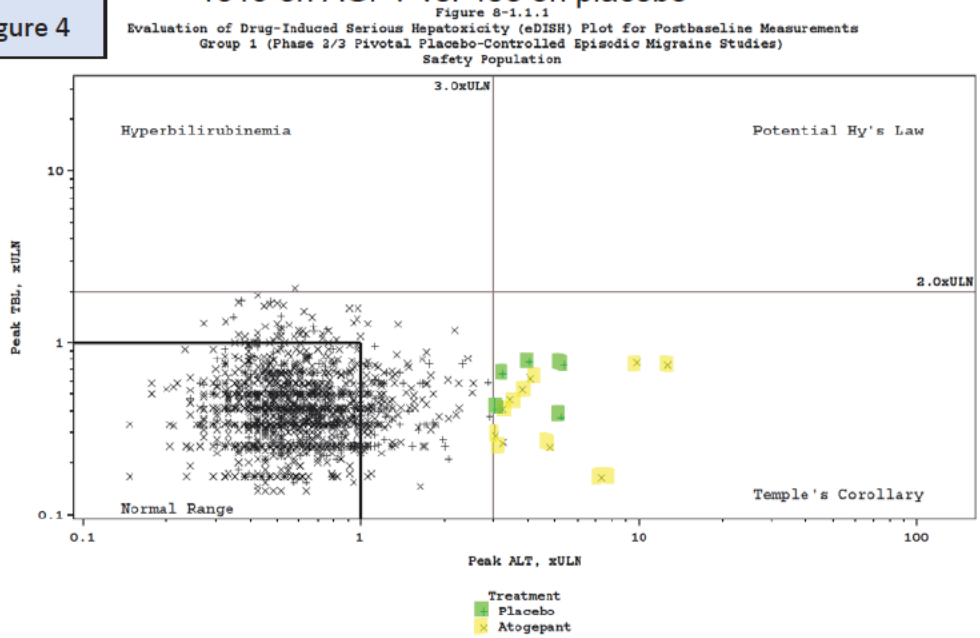
				(b) (4)	
	MK-8031-008	1	Open label; single dose		15
	MK-8031-001	1	RDB, PC; single dose		42
	MK-8031-002	1	RDB, PC; single & multiple dose		40
	MK-8031-004	1	RDB, PC; multi-dose		34
	CGP-PK-03	1	Open label, single dose (14-C)		6
	MK-8031-003	1	RDB, PC		16
	CGP-PI-01	1	Open label; single dose		24
	3101-202-002	1	RDB, PC; single dose		50
	CGP-PK-002	1	DDI; single dose (itraconazole)		40
	CGP-PK-06	1	DDI; single dose (APAP; naproxen)		40
	CGP-PK-12	1	DDi; single dose (rifampin)		32
	CGP-PK-13	1	DDI; single dose (sumatriptan)		30
	31030-102-002	1	DDI; single dose (esomeprazole)		32
	3101-103-002	1	DDI; single dose (quinidine)		33
	MK-8031-005	1	DDI; single dose/multiple (OCP)		26
	CGP-PK-04	1	RDB; PC; TQT study		60
Group 1	**CGP-MD-01**	**2/3**	**RDB, PC (~1:4; placebo:IP) x 12 w**	**Migraine HA pts**	**825**
	3101-301-002	**3**	**RDB, PC (1:3; placebo:IP) x 12 w**	**Migraine HA pts**	**902**
Group 2	**3101-302-002**	**3**	**Open label long term extension (40 w)**	**Migraine HA pts**	**739**
	3101-309-002	**3**	**Open label long term extension (52 w)**	**Migraine HA pts**	**655**

4.4 Group 1 Safety Population: Studies CGP-MD-01 and 3101-301-002

4.4.1 Hepatocellular injury plot: eDISH—ALT only (Figure 4).

Figure 4

1319 on AGPT vs. 408 on placebo



Notes: Based on Group 1 Pivotal Placebo-Controlled Episodic Migraine Studies (CGP-MD-01 and 3101-301-002).

4.4.2 Elevations in transaminases for the 1319 exposed in Group 1 (Table 3).

Reference ID: 4848947

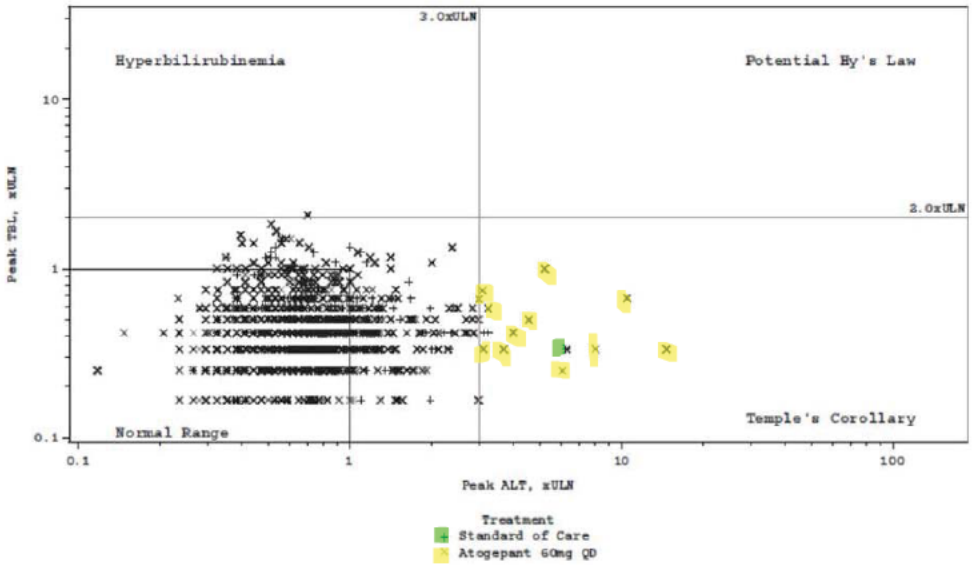
Table 3 **Number (%) of Participants with Postbaseline Hepatic-related Laboratory Values of Clinical Interest: Group 1 - Pivotal Placebo-controlled Studies (Safety Population)**

Hepatic laboratory parameter (Unit)	Criterion	Placebo (N=408) n/N1 (%)	Atogepant 10 mg QD (N=314) n/N1 (%)	Atogepant 30 mg QD (N=411) n/N1 (%)	Atogepant 60 mg QD (N=417) n/N1 (%)	Atogepant 30 mg BID (N=86) n/N1 (%)	Atogepant 60 mg BID (N=91) n/N1 (%)
ALT or AST (U/L)	≥ 1.0 × ULN	63/399 (15.8)	36/312 (11.5)	50/405 (12.3)	53/409 (13.0)	11/84 (13.1)	9/88 (10.2)
	≥ 1.5 × ULN	22/399 (5.5)	7/312 (2.2)	20/405 (4.9)	15/409 (3.7)	2/84 (2.4)	1/88 (1.1)
	≥ 2.0 × ULN	11/399 (2.8)	6/312 (1.9)	8/405 (2.0)	9/409 (2.2)	2/84 (2.4)	1/88 (1.1)
	≥ 3.0 × ULN	7/399 (1.8)	4/312 (1.3)	3/405 (0.7)	4/409 (1.0)	1/84 (1.2)	1/88 (1.1)
	≥ 5.0 × ULN	4/399 (1.0)	1/312 (0.3)	1/405 (0.2)	2/409 (0.5)	0/84 (0)	0/88 (0)
	≥ 10.0 × ULN	0/399 (0)	1/312 (0.3)	0/405 (0)	0/409 (0)	0/84 (0)	0/88 (0)
	≥ 20.0 × ULN	0/399 (0)	0/312 (0)	0/405 (0)	0/409 (0)	0/84 (0)	0/88 (0)

4.5 Group 2 Safety Population: Studies 3101-302-002 and 3101-309-002 (open label, long term)

4.5.1 Hepatocellular injury plot: eDISH—ALT only (Figure 5)
1198 on AGPT versus 196 on standard of care.

Figure 5 **eDISH Plot for Postbaseline Measurements: Group 2 - Long-term Safety Studies (Safety Population)**



4.5.2 Elevations in transaminases for the 1198 exposed in Group 2.

Table 4

Hepatic laboratory parameter (Unit)	Criterion	Standard of Care (N=196) n/N1 (%)	Atogepant 60 mg QD (N=1198) n/N1 (%)
ALT or AST (U/L)	≥ 1.0 × ULN	55/190 (28.9)	179/1137 (15.7)
	≥ 1.5 × ULN	16/190 (8.4)	67/1137 (5.9)
	≥ 2.0 × ULN	11/190 (5.8)	37/1137 (3.3)
	≥ 3.0 × ULN	6/190 (3.2)	16/1137 (1.4)
	≥ 5.0 × ULN	1/190 (0.5)	8/1137 (0.7)
	≥ 10.0 × ULN	0/190 (0)	3/1137 (0.3)
	≥ 20.0 × ULN	0/190 (0)	0/1137 (0)

4.6 Case level analyses: There were 29 patients on AGPT (13 from Group 1; 16 from Group 2) who had transaminases (ALT or AST) greater than 3x ULN

Reference ID: 4848947

during the study. All 29 had narratives and were assessed. No cases met transaminase, ALP and bilirubin criteria for potential Hy's Law. Twenty-three cases were assessed as unlikely DILI due to AGPT. The most common alternative diagnosis amongst these 23 was myopathy or myositis (9 cases). Three cases had elevations in transaminases related to infection (e.g. EBV, enteritis). Four had elevations more likely due to another drug or herbal product. Autoimmune hepatitis was assessed more likely in 2 patients. No identifiable alternative was found for 5, but DILI due to AGPT was still felt unlikely for other reasons (e.g. latency, dechallenge while still on AGPT). Therefore, only 6 of the 29 were considered at least possible DILI due to AGPT.

4.6.1 Six cases of at least possible DILI due to AGPT: We summarize data on these 6 cases in the table below in Table 5.

Table 5

ID	Study	Causality Score*	Alternate diagnosis	Age (y)	Sex	Race	Hy's Law	Latency from start drug (d)	Latency from stop drug (d)	Symptoms	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak	R value peak (AST)	Washout 50% ALT (d)	Washout ALT normal (d)
(b) (6)	CGP-MD-01	4	APAP	46	F	Black	No	42	-42	No	125	90	115	0.6	3.79	2.50	14	NA
	CGP-MD-01	4	Myostitis, APAP	33	F	Black	No	113	29	No	107	76	115	0.3	3.24	2.11	9	NA
	CGP-MD-01	3	?APAP	39	F	White	No	12	-5	No	324	237	115	0.5	9.82	6.58	16	41
	CGP-MD-01	4	Azithromycin, infection	62	F	Black	No	84	0	No	113	77	115	0.5	3.42	2.14	8	27
	3101-301-002	3		39	F	White	No	21	-35	No	249	107	169	0.2	5.13	2.02	2	9
	3101-302-002	*4*	AIH, parital tolerance	56	F	White	No	169	-197	No	177	93	106	1.2	5.11	2.68	153	248
			Mean	45.8				74	-42		183	113	123	0.6	5.1	3.0	34	81
			Std Dev	10.2				55	73		80	56	21	0.3	2.2	1.6	54	97
			Median	42.5				63	-20		151	92	115	0.5	4.4	2.3	12	34
			Max	62				169	29		324	237	169	1.2	9.8	6.6	153	248
			Min	33				12	-197		107	76	106	0.2	3.2	2.0	2	9

***DILI likelihood score**
1 = Definte
2 = Highly likely
3 = Probable
4 = Possible
5 = Unlikely
6 = Indeterminate

NA = not applicable or not available
APAP = acetaminophen
CMV = cytomegalovirus

We describe 1 unlikely, 2 probable and 1 possible case in detail.

4.6.2 *Case* (b) (6) *(Study 3101-302-002)*: Unlikely DILI due to AGPT. We discuss this case because the patient died, and the consulting Division specifically requested that we assess this case in detail.

<u>Summary</u>: This is a 26-year-old black woman who developed elevated transaminases without jaundice 4 weeks after drug start (Atogepant 60mg QD)

Her only baseline medication was ibuprofen. There is no mention of underlying liver disease. Liver tests were normal at baseline but CPK was mildly up at 213 U/L. She started study drug on (b) (6) and started sertraline 50 mg/d one day later. She had a flu-like illness (b) (6) taking 2 over the counter medications that contained acetaminophen (APAP). She stayed on study drug.

Elevated liver tests were noted on routine follow-up (b) (6) (ALT 141, AST 491, normal ALP and bilirubin), but her CPK was also elevated at 28,210 U/L. Study drug was stopped. She had been exercising with a

Reference ID: 4848947

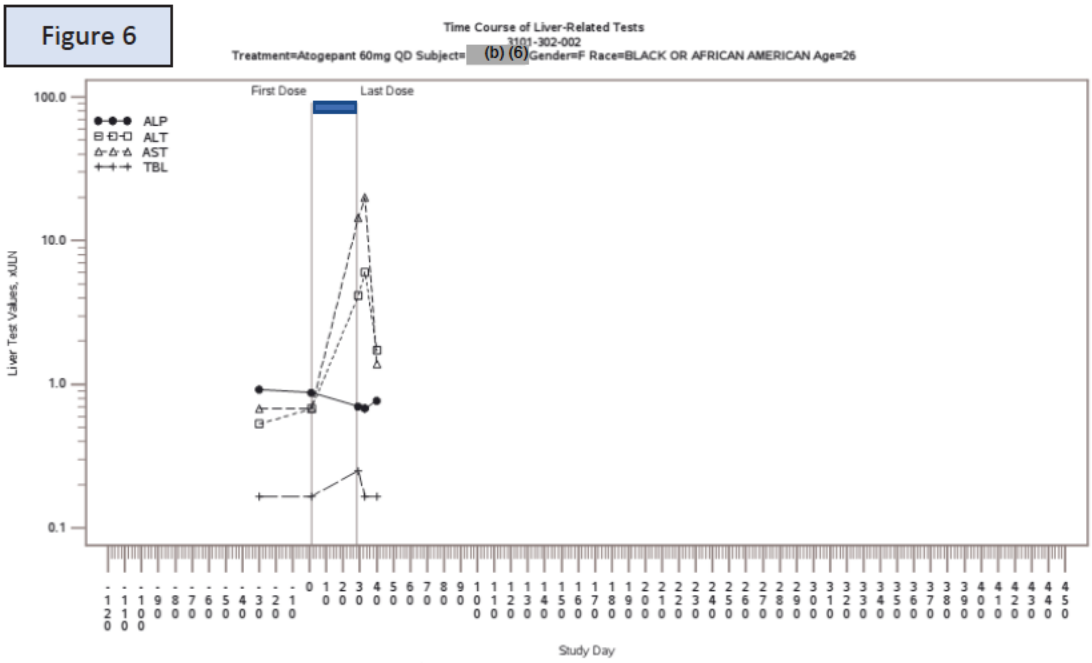
trainer but was asymptomatic. On [redacted] (b) (6), her CPK and liver tests were higher (ALT 205, AST 677, CPK = 38,607), but ALP and bilirubin remained normal. She was advised to go to the ER, but she did not go until [redacted] (b) (6) at which time the CPK was down to the 400s. ALT and AST had fallen by 50%. These are the last set of labs available.

She still felt well through [redacted] (b) (6), but in the early morning of [redacted] (b) (6) she had chest pain and SOB. She was being taken by ambulance to the ER, when she had a cardiac arrest. CPR was in progress on arrival. ACLS measures recovered vital signs, but she had another cardiac arrest the same morning from which she did not recover. No labs available after [redacted] (b) (6) No mention of fever or elevated WBC.

Autopsy diagnosed Group A beta hemolytic strep in the liver, blood and spleen. No primary source. Toxicology showed only doxylamine (ant-histamine) and dextromethorphan. No study drug detected. No illicit drugs or alcohol mentioned.

Assessment: This is unlikely DILI. Even before the cardiac arrest, myositis or myopathy is a better explanation for the elevated AST and ALT. CPK was over 25,000. Myopathy may have been related to sertraline which has been reported with this drug. It was started at 50 mg/d, one day after study drug start. There is no mention of sertraline thereafter, but gradual dose increase is typical. An increasing dose may have played a role in her myopathy. The shock and death are unrelated. Her CPK and liver enzymes had fallen by >50% before the onset of shock (Figure 6).

Figure 6



4.6.3 *Case* [redacted] (b) (6) *(Study 3101-301-002)*: Probable DILI due to AGPT

Reference ID: 4848947

Summary: This is a 39-year-old white woman who had elevated transaminases without jaundice 3 weeks after starting Atogepant 30mg/d.

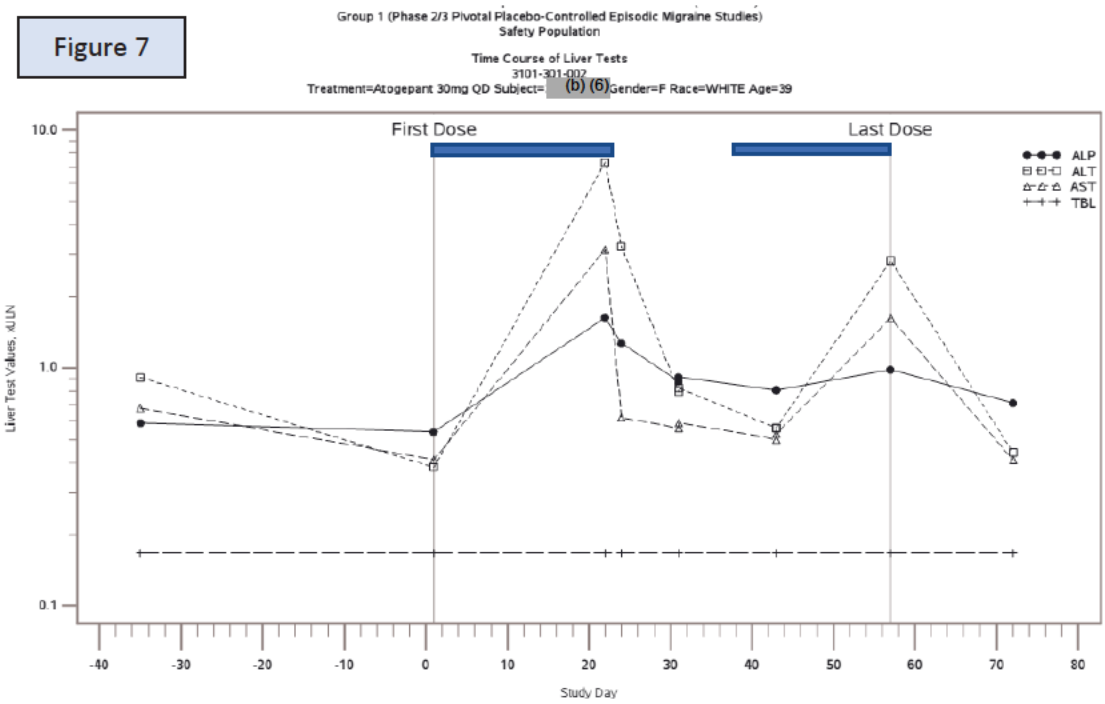
At baseline, she was on an acetaminophen (APAP) medication, but AST, ALT and CPK were normal at baseline. She was asymptomatic when elevated liver enzymes were noted on routine follow-up (ALT 249, AST 107, ALP 169, Bilirubin 0.2). Although, she did not meet interruption criteria, study drug was held from [redacted] (b) (6) (day after onset) to [redacted] (b) (6) While study drug was held, her liver tests returned to normal within 9 days.

However, on [redacted] (b) (6) 18 days after restarting study drug, her ALT and AST rose again (ALT 96, AST 55). ALP remained normal on this second rise. She remained asymptomatic throughout. Study drug was stopped on that day [redacted] (b) (6) She had one more follow-up set of labs 15 days later and ALT & AST were normal again at 15 and 14. She was last lost to follow-up thereafter.

HAV "antibody", HBV surface antibody and HCV antibody negative. EBV antibody also negative. No other evaluation noted. No mention of new medications or herbal/dietary supplements.

Assessment: This appears to be a DILI due to the study drug. Though evaluation testing was sparse, this appears to be a positive re-challenge (Figure 7).

Figure 7



Reference ID: 4848947

4.6.4 *Case* (b) (6) *(Study CGP-MD-01)*: Probable DILI due to AGPT

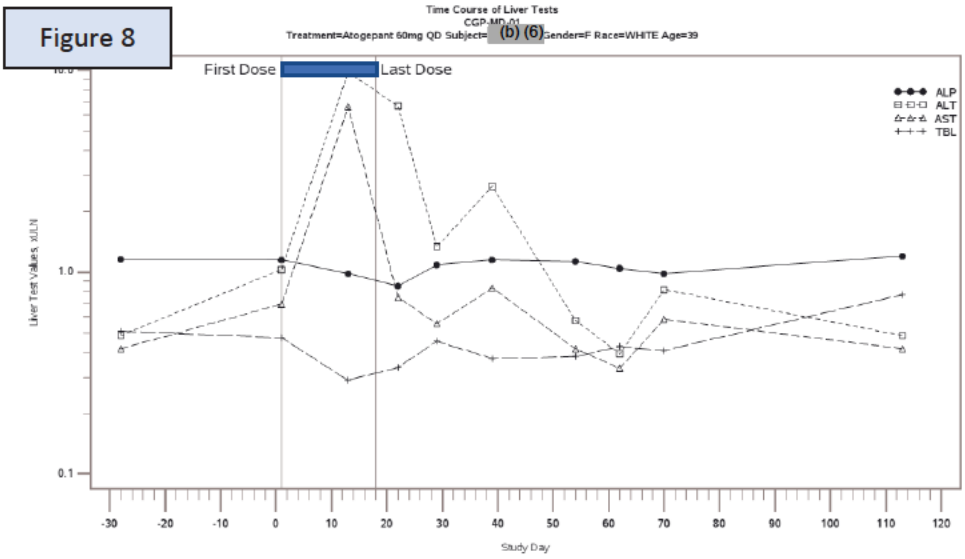
Summary: This is a 39 year-old white woman who developed elevated transaminases w/o jaundice 12 days after starting Atogepant 60mg QD.

No mention of pre-existing liver disease. She drinks one alcoholic beverage per week. Liver tests were normal at Day 0, but they had climbed during screening. She had no symptoms when ALT and AST rose on Day 12. No ALP or bilirubin rise. Drug was stopped 5 days after DILI onset. Viral hepatitis serology testing was "negative". Autoimmune hepatitis (AIH) markers negative. Ultrasound (US) unrevealing.

Patient was taking Excedrin Migraine "frequently" (every other day) but precise dosing was not provided. This over the counter was continued through the washout after stopping study drug.

Assessment: This case is a weak probable DILI due to the study drug. APAP (acetaminophen) use competes some, but use continued through the washout. It was also part of her baseline medications. Unclear if APAP dosing changed. The sponsor suggests NAFLD, but that disease would not present with such an acute rise and fall of ALT (peak of >9x ULN). Sponsor notes inadvertent double dosing of IP, but this occurred the day of DILI onset when ALT was already >300. The main argument against DILI is that her ALT and AST had increased by 2.1x and 1.67x her baseline even before drug start, so something else may have been brewing (Figure 8). No other prior baseline liver enzyme data provided.

Figure 8



Notes: Based on Group 1 Pivotal Placebo-Controlled Episodic Migraine Studies (CGP-MD-01 and 3101-301-002).

4.6.5 *Case* (b) (6) *(Study 3101-302-002)*: Possible DILI due to AGPT

Reference ID: 4848947

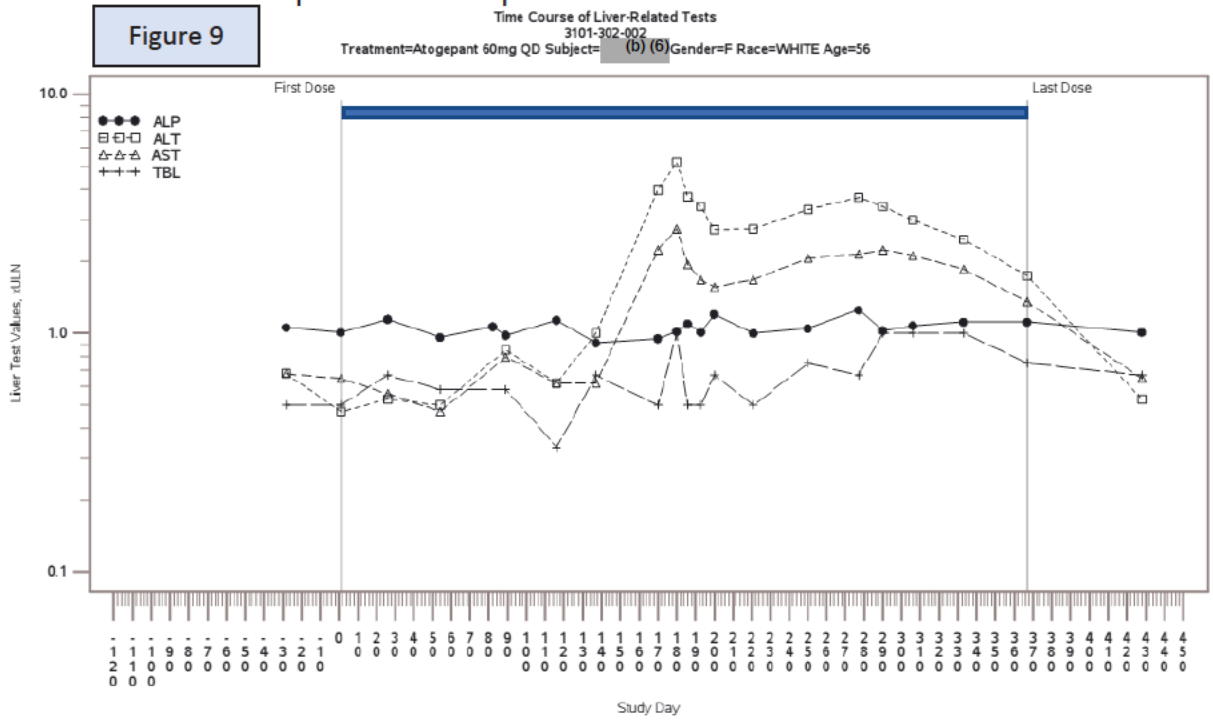
Summary: This is a 56-year-old white woman who developed elevated transaminases without jaundice 24 weeks after drug start (Atogepant 60mg QD)

On acetaminophen (APAP) at baseline. ALP mildly elevated at baseline. Other LFTs and CPK normal. She developed asymptomatic elevation in transaminases 24 weeks after study drug start, which peaked a week later (ALT 177, AST 83). Evaluaton showed a (+) CMV IgM. She had a flu-like illness but this came on after injury onset. Estrogen and rosuvastatin was started just prior to injury but these were held and washout did not occur. Study drug continued and her liver enzymes did decline by 50% from peak. However, they stayed elevated over baseline for 22-27 weeks while on drug. They were gradaully declining but then returned to normal 9 weeks after stopping study drug.

Other viral serologies negative. ANA was (+) at 1:160. Malar rash and chelosis mentioned. No immunosuppression treatments mentioned. No liver biopsy. Imaging negative.

Assessment: This case is of some interest because it may be a case of chronic DILI while on AGPT with partial or slow adaptation (Figure 9). Autoimmune hepatitis (AIH) competes but injury did resolve without immunosuppression and after drug stop. Latency is long for DILI at 24 weeks compared to the 2 probable DILI cases outlined above.

Figure 9



Reference ID: 4848947

5.0 **Assessment**: While the development of two CGRP antagonists, telcagepant and MK-3207, stopped due to hepatotoxicity, we see little evidence of DILI in this NDA for Atogepant. Two other in-class agents (rimegepant and ubrogepant) were approved without significant liver injury concerns. These later generation agents may carry a lower DILI risk. However, the two approvals were recent (2019 and 2020).

In vitro, in silico, and animal studies in this NDA did not raise significant liver injury concerns. Three animal models (mouse, rat and monkey) dosing Atogepant for 3, 6 and 9 months respectively did not show histopathologic liver injury. Using in vitro data, quantitative systems toxicology studies (in silico) predicted less injury risk compared to telcagepant and MK-3207. The in silico and in vitro modeling predicted an increased risk of mild ALT elevation beginning at twice the highest Atogepant dosing used in the registration trials.

Avoiding the use of Atogepant in patients with severe hepatic impairment may be prudent because the in-silico data suggest a dose response for DILI. Hepatic impairment studies showed a 38% increase in systemic exposure in severe hepatic impairment. Also, patients with severe impairment have less tolerance of DILI.

Registration trial data for this NDA did not suggest significant liver injury risk. Treatment duration ranged from 12 to 52 weeks and dosing from 10 mg daily to 60 mg twice daily. Total number of patients exposed was large at over 1300. There were no obvious imbalances in elevation of ALT or AST elevations between placebo and treatment arms. There were no cases meeting Hy's Law criteria. Case level analyses found just 2 patients with probable DILI due to Atogepant and 4 possible cases. No cases had abnormal bilirubin levels. The 4 possible cases had competing etiologies to explain the liver enzyme elevations. Both patients with probable DILI had short latencies, were asymptomatic and had quick resolution in enzyme elevations after drug stop. The patient who died with prior elevations in ALT and AST, had a myopathy causing these elevations, not DILI. These elevations were resolving when she died of sepsis.

Therefore, we did not find a liver injury risk that should prevent approval, but the risk is not zero. While the registration trials were large, wider use in the market can uncover a rare risk of significant DILI not captured in these trials. We do not recommend routine monitoring of liver enzymes, but we suggest mentioning potential for ALT or AST elevation in the label. It may be prudent to avoid use in patients with severe hepatic impairment.

5.1 Recommendations

a. Routine blood tests for liver enzyme monitoring is not necessary.
b. Consider avoiding use of Atogepant in patients with severe hepatic impairment.
c. Consider the wording below for labeling:
   Liver Enzyme Elevations – (b) (4)

Reference ID: 4848947

(b) (4)

6.0 **Addendum 1:** After completing this consultation on May 16, 2021, the sponsor sent a 120-Day Safety Report (Sq 17, SDN 17, 1.11.3) on May 19, 2021. The report covered safety data through Jan 31, 2021.

Report Review Summary: After review of the report, our assessment and recommendations in Section 5.0 are largely unchanged. However, the report raises questions about an increased DILI risk in Japanese, or Asians in general. It appears that the proportion of patients with elevation in transaminases is higher in Japanese in a Phase 3 study that is not included in the ISS Group 1 or 2 of the NDA. Precise proportions of patients with elevated transaminases by race are not provided, and we would like such data in this Phase 3 and the ISS. Details of our report review are below. Upon our suggestion, DN2 sent an information request on Jun 2, 2021.

Full Report Review: The Safety Report has two areas of interest: (1) Updated data for the ISS Group 2 and (2) New cases of liver enzyme elevations in 2 studies outside the ISS Groups.

6.1 ISS Group 2 OLE Studies: Updated eDISH plot did not find any cases in Hy's Law quadrant. Proportions of patients with transaminases over 3x ULN and higher were not significantly changed from earlier data sent with the NDA. Just 1 new case ((b) (6), Study 3101-309-002) required review with AST elevation over 3x ULN. We reviewed the case narrative and graphic. This was not DILI. AST elevation occurred 324 days after AGPT start (60 mg/d). The rise was concurrent with increased physical activity and CPK of 4806 U/L. ALT was 38 U/L and bilirubin 0.2 mg/dL. Patient also reported recent increase in alcohol intake. CPK and AST fell to normal within 30 days. AGPT was continued without dose change.

6.2 Cases from Studies Not Included in Group 2 OLE Studies: The report describes 5 new case of liver enzyme elevations. No cases met Hy's Law liver test elevation criteria. No case developed jaundice. All recovered.

6.2.1 Study CGP-PK-14 (Phase 1 study of PK in health volunteers, IND 114780, Sq 172, 5.3.3.4): One case had elevation in ALT and AST more that 3x ULN after taking AGPT, 60 mg/d, for 7 days. This

Reference ID: 4848947

case's narrative and graphic data were reviewed and assessed as probable DILI due to AGPT. However, this reviewer could not find overall study safety data. Target enrollment is 50 healthy volunteers of which 25 would get AGPT at varying doses.

6.2.2 Study 3101-306-002 (OLE of Phase 3 RCT, 3101-303-002, IND 114870, Seq 172, 5.3.5.1). Four cases developed elevation in ALT and/or AST greater than 3x ULN. All four were Japanese. We assessed 2 as probable DILI due to AGPT, 1 possible and 1 unlikely. An independent Causality Assessment Committee (CAC) assessed them as 3 probable and 1 unlikely, while the sponsor's internal review assessed them as 3 possible and 1 unlikely. Target enrollment for this Phase 3, 3101-303-002 was 750, randomized 2:1, AGPT to placebo, but this reviewer could not find summary safety information, current enrollment or demographics in this OLE. The sponsor did not provide proportions of patients with elevation in transaminases by race.

6.2.3 Summary of 5 new cases from CGP-PK-14 and 3101-306-002:

Table 6

ID	Study	Causality Score	Alternate diagnosis	Age (y)	Sex	Race	Hy's Law	Latency from start drug	Latency from stop drug	Symptoms	Latency symptoms (da)	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak (ALT)	R value peak (AST)	Washout 50% ALT (da)	Washout ALT normal (da)
(b) (6)	CGP-PK-14	3		30	M	Black	No	6	-1	No		234	154	104	0.7	6.88	4.53	42	NA
	3101-306-002	3		49	F	Asian	No	112	-24	No		309	184	104	0.9	9.09	5.41	26	68
	3101-306-002	3		49	F	Asian	No	141	-31	No		395	265	116	0.5	10.42	6.99	16	37
	3101-306-002	4	Azithromycin liver injury	42	F	Asian	No	193	-39	Yes	-39	238	109	104	0.6	7.00	3.21	23	NA
	3101-306-002	5	Gallstone disease	51	F	Asian	No	91	-1	Yes	1	594	1094	751	1.9	2.42	4.46	7	14

NA = not available

3 = probable DILI, 4 = possible DILI, 5 = Unlikely DILI

6.2.4 Summary of all cases with at least possible DILI due to AGPT in the ISS and *including* the new cases in the 120 Day Safety Report.

Table 7

ID	Study	Causality Score	Alternate diagnosis	Age (y)	Sex	Race	Hy's Law	Latency from start drug (da)	Latency from stop drug (da)	Symptoms	Latency symptoms	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak (ALT)	R value peak (AST)	Washout 50% ALT (da)	Washout ALT normal (da)
(b) (6)	3101-302-002	4	AIH, partial tolerance	56	F	White	No	169	-197	No		177	93	106	1.2	5.11	2.68	153	248
	3101-306-002	3		49	F	Asian	No	112	-24	No		309	184	104	0.9	9.09	5.41	26	68
	3101-306-002	4	Azithromycin	42	F	Asian	No	193	-39	Yes	-39	238	109	104	0.6	7.00	3.21	23	
	3101-306-002	3		49	F	Asian	No	141	-31	No		395	265	116	0.5	10.42	6.99	16	37
	CGP-PK-14	3		30	M	Black	No	6	-1	No		234	154	104	0.7	6.88	4.53	42	
	CGP-MD-01	4	APAP use	46	F	Black	No	42	-42	No		125	90	115	0.57	3.79	2.50	14	
	CGP-MD-01	4	Myositis, APAP use	33	F	Black	No	113	29	No		107	76	115	0.29	3.24	2.11	9	
	CGP-MD-01	3		39	F	White	No	12	-5	No		324	237	115	0.52	9.82	6.58	16	41
	CGP-MD-01	4	Azithromycin, infection.	62	F	Black	No	84	0	No		113	77	115	0.52	3.42	2.14	8	27
	3101-301-002	3		39	F	White	No	21	-35	No		249	107	169	0.2	5.13	2.02	2	9
			mean	*45*				*89*	*-35*			*227*	*139*	*116*	*0.6*	*6.4*	*3.8*	*31*	*72*
			std dev	*9.9*				*67*	*61*			*97*	*68*	*19*	*0.3*	*2.7*	*1.9*	*44*	*89*
			median	*44*				*98*	*-28*			*236*	*108*	*115*	*0.5*	*6.0*	*2.9*	*16*	*39*
			max	*62*				*193*	*29*			*395*	*265*	*169*	*1.2*	*10.4*	*7.0*	*153*	*248*
			min	*30*				*6*	*-197*			*107*	*76*	*104*	*0.2*	*3.2*	*2.0*	*2*	*9*

3 = probable DILI, 4 = possible DILI, 5 = Unlikely DILI

6.2.5 Summary of all cases with at least probable DILI due to AGPT in the ISS and including the new cases in the 120 Day Safety Report.

Reference ID: 4848947

Table 8

At Least Probable DILI Cases

ID	Study	Causality Score	Alternate diagnosis	Age (y)	Sex	Race	Hy's Law	Latency from start drug (da)	Latency from stop drug (da)	Symptoms	Latency symptoms	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak (ALT)	R value peak (AST)	Washout 50% ALT (da)	Washout ALT normal (da)
(b) (6)	3101-306-002	3		49	F	Asian	No	112	-24	No		309	184	104	0.9	9.09	5.41	16	68
	3101-306-002	3		49	F	Asian	No	141	-31	No		395	265	116	0.5	10.42	6.99	16	37
	CGP-PK-14	3		30	M	Black	No	6	-1	No		234	154	104	0.7	6.88	4.53	42	
	CGP-MD-01	3		39	F	White	No	12	-5	No		324	237	115	0.52	9.82	6.58	16	41
	3101-301-002	3		39	F	White	No	21	-35	No		249	107	169	0.2	5.13	2.02	2	9
			mean	*41*				*58*	*-19*			*302*	*189*	*122*	*0.6*	*8.3*	*5.1*	*20*	*39*
			std dev	*8*				*63*	*15*			*64*	*63*	*27*	*0.3*	*2.2*	*2.0*	*15*	*24*
			median	*39*				*21*	*-24*			*309*	*184*	*115*	*0.5*	*9.1*	*5.4*	*16*	*39*
			max	*49*				*141*	*-1*			*395*	*265*	*160*	*0.9*	*10.4*	*7.0*	*42*	*68*
			min	*30*				*6*	*-35*			*234*	*107*	*104*	*0.2*	*5.1*	*2.0*	*2*	*9*

3 = probable DILI, 4 = possible DILI, 5 = Unlikely DILI

6.2.6 Japanese Subgroup Analyses: Because 4 of the 5 new cases were Japanese, the sponsor examined AGPT concentrations by race/nationality (white, black, Asian, Japanese and American Indian). They did not see higher levels that might be explanatory (see Figures 10 and 11). However, we found no summary data of proportions of patients with liver enzyme elevations by Japanese versus other races in study 3101-303-002 or other studies.

Figure 10

Steady-State Plasma Concentrations (ng/mL) of Atogepant by Race of Participants Enrolled in Phase 3 Study 3101-303-002
(Jpn3 represent participants with elevated aminotransferase levels)

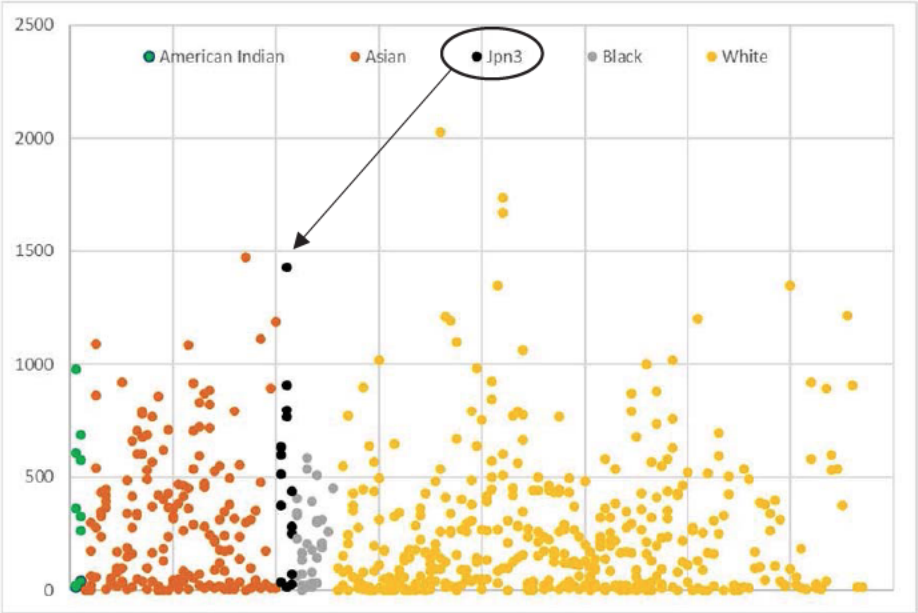
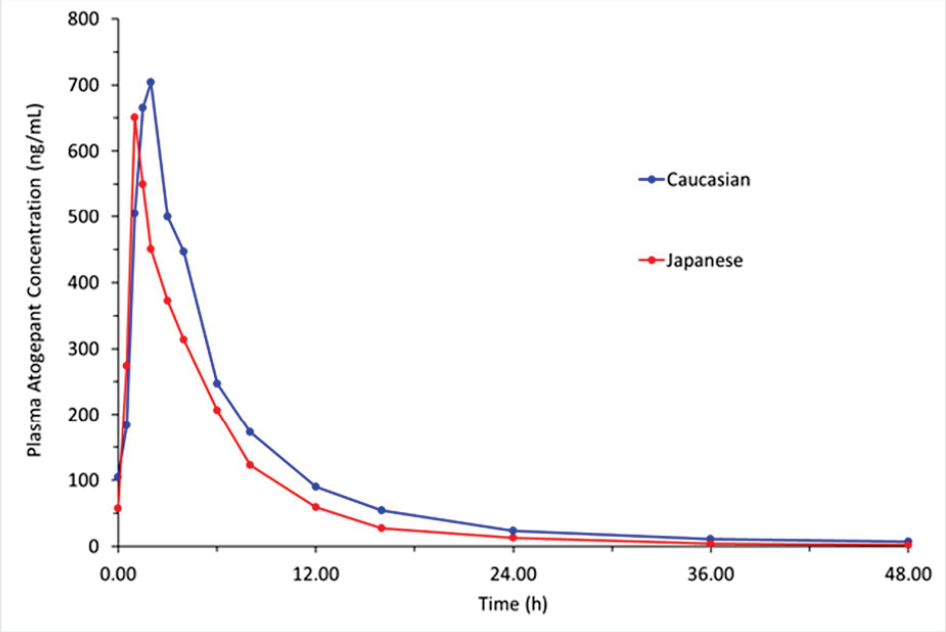


Figure 11

Reference ID: 4848947

Figure 3-3 Mean Steady-state Plasma Concentrations of Atogepant on Day 8 following 60 mg BID Dosing in Healthy Japanese and Caucasian Participants



Because the sponsor is hoping to market AGPT in Japan, a Phase 1 RCT specifically looking at PK in Japanese versus Caucasians was done in 2017 (Study 3101-101-002, Sq 18, 5.3.3.3). 40 Japanese and 10 Caucasians enrolled. The Japanese were randomized 4:1 to varying exposures of AGPT and placebo. There were no cases of transaminase elevations above 3x ULN in any patient, Japanese or Caucasian (Clinical Study Report, page 251).

7.0 **Addendum 2**: After our review of the 120 Day Safety Report (Sq 17, SDN 17) outlined in Section 6.0, an information request (IR) to assess potential increased DILI risk in Japanese and/or Asians in general was sent by email on Jun 2, 2021 with 4 specific requests. The sponsor's response came on Jun 7, 2021 (Seq 19, SDN 19, 1.11.3). Of note, the response had safety data through May 26, 2021, so the same data are also contained in the Safety Report submitted June 30, 2021 (Sq 22, SDN 22, 5.3.5.3).

7.1 Response Review Summary: In totality, the data in the sponsor's response do not warrant labeling a difference in liver injury risk for Japanese or Asians. While the ongoing OLE study of 113 Japanese patients so far enrolled (3101-306-002) indicates a higher rate of transaminase elevation than the overall rate in this NDA's ISS, no such increase is seen for Asians in the ISS nor the RCT from which patients entered 3101-306-002. We acknowledge that the number of Asians in the ISS is too low to draw conclusions. However, the RCT had 248 Asians randomized across 3 arms (placebo, AGPT 30 mg bid,

Reference ID: 4848947

AGPT 60 mg/d) for 12 weeks of treatment. Only 1 of 248 Asians had elevation in transaminases which was unlikely attributable to the IP. The RCT remains blinded. At least 113 of those 248 were Japanese and enrolled in 3101-306-002. This OLE has no comparator arm. Therefore, we cannot definitively assign an increased risk of DILI amongst Japanese, or Asians in general, based on these data.

Similarly, we do not think labeling for a possible difference in DILI risk for blacks is needed. There was a higher rate of transaminase elevations in blacks on AGPT in the Group 2 ISS, but the number of blacks on placebo is small at 38 and may not offer a large enough comparator arm. The number of blacks in the Group 1 ISS was larger (69 placebo vs. 223 AGPT), and no clear differences were seen in transaminase elevations amongst blacks. Therefore, the data are equivocal.

Our detailed review follows (Section 7.2)

7.2 Sponsor Response Review:

7.2.1 Response to request 1: We had requested clarification whether the ongoing, 52-week, open label study 3101-306-002 is restricted to Japanese nationals. The sponsor replied that it is so restricted. Therefore, the overall rates of enzyme elevations and DILI cases for this study reflect Japanese nationality rates and can be compared to other race or nationality groups in the ISS.

7.2.2 Response to request 2: We requested current enrollment status of 3101-306-002. The sponsor replied that 113 patients had enrolled and included in the safety population as of May 26, 2021. Therefore, we presume that all 113 have taken at least one dose of AGPT at 60 mg/d. There is no comparator arm in this study.

7.2.3 Response to request 3: We requested elevation in liver test rates for Study 3101-306-002 in tabular form. The sponsor sent the table below. The rates of ALT and AST elevations are higher compared to ISS Group 2 of 1198 patients also on 60 mg/d (see Section 4.5, Table 4 above). For example, the rate for ALT or AST elevation >3x and >5x ULN were 2.7% to 4.4% and 1.8% to 2.7% for Japanese nationals, respectively. The rates of elevations in ALT *or* AST at the same multiples of ULN were 1.4% and 0.7% for ISS Group 2.

Reference ID: 4848947

Allergan
Protocol FDA Request

Atogepant
Page 1 of 1

Table 9

Table 1-3
Postbaseline Hepatic-Related Laboratory Values of Clinical Interest
Study 3101-306-002
Safety Population

Lab Endpoint Criteria	Open-label Atogepant 60 mg QD for Japanese patients (N=113) (PY [1] = 50.4) n (%)	Incidence rate per 100 patient exposure years [2]
ALT		
>= 1*ULN	9 (8.0)	17.8
>= 3*ULN	5 (4.4)	9.9
>= 5*ULN	3 (2.7)	5.9
>= 10*ULN	1 (0.9)	2.0
>= 20*ULN	1 (0.9)	2.0
AST		
>= 1*ULN	7 (6.2)	13.9
>= 3*ULN	3 (2.7)	5.9
>= 5*ULN	2 (1.8)	4.0
>= 10*ULN	1 (0.9)	2.0
>= 20*ULN	1 (0.9)	2.0
Alkaline Phosphatase		
>= 2*ULN	1 (0.9)	2.0
>= 3*ULN	0 (0.0)	0.0
Total Bilirubin		
>= 2*ULN	0 (0.0)	0.0
>= 5*ULN	0 (0.0)	0.0
>= 8*ULN	0 (0.0)	0.0

Notes: Based on study 3101-306-002 with the data cut as of 26-May-2021.
PY = patient exposure years. PY for a patient is calculated as (Study treatment end date-study treatment start date+1)/365.25.
[1] Total patient exposure years is sum of each patient's exposure years in the safety population.
[2] Incidence rate per 100 patient exposure years = (number of patients with event/total patient exposure years)*100.
N = number of patients in the Safety Population.
n = number of patients within a specific category.
Percentages are alculated as 100 x (n/N).

Program: /RIsas/sasprog/cgp/FDARequest/f20210602/production/programs/tables/t01-03.sas FINAL 2021-06-03 17:17:41

The sponsor also provided an additional case (patient ID: [redacted] (b) (6) Study 3101-306-002) of transaminase elevation over >3x ULN that occurred between Jan 31 and May 26, 2021. This case was not included in the 120-day report reviewed in Section 6.0. We assessed this case as unlikely DILI due to AGPT. Acetaminophen 1-3 grams IV daily x 6 days is a more likely explanation. AGPT was continued without dose reduction through complete dechallenge. ALT rose to 3-5x ULN without hyperbilirubinemia. This case is included in the table above.

7.2.4 Response to request 4: We requested liver enzyme elevation rates by race, particularly Asians, in Groups 1 and 2 of the ISS. We also requested these rates for the blinded, RCT, 3101-303-002, from which Japanese patients entered the open label extension (OLE) study, 3101-306-002. The sponsor provided tables for this request (Seq 19, SDN 19, 1.11.3, pages 11-20).

Group 1 ISS: There were no enzyme elevations in Asians, but there were only 20 Asians out of 1727 total. Nationalities were not recorded. While blacks on AGPT had higher crude occurrence rate and incidence rates per 100-person year exposure compared to

Reference ID: 4848947

whites the difference between blacks on placebo and AGPT was equivocal. (see table x)

Group 1, Table 10 displays crude occurrence rate (%) and incidence rates per 100-patient exposure years (%; incidence rate), for whites and blacks by placebo and atogepant (AGPT) arms. Numbers of patients in each arm are in parentheses.

Table 10	White		Black	
	Placebo (331)	AGPT (1049)	Placebo (69)	AGPT (223)
ALT > 3x	1.2; 5.6	0.5; 2.2	1.4; 7.2	2.2; 11
ALT > 5x	0.3; 1.4	0.3; 1.3	1.4; 7.2	0.0; 0.0
AST >3x	0.9; 4.2	0.6; 2.7	1.4; 7.2	0.9; 4.4
AST >5x	0.6; 2.8	0.2; 0.9	1.4; 7.2	0.4; 2.2

Group 2 ISS: For Group 2, there were similarly very few Asians (n = 26), no nationality data and no cases of enzyme elevations. Again, blacks had higher crude rates and incidence per 100 patient-year exposure compared to whites, but here, the rates amongst blacks on AGPT was higher than blacks on standard of care.

Group 2, Table 11 displays crude occurrence rate (%) and incidence rates per 100-patient exposure years (%; incidence rate), for whites and blacks by standard of care and AGPT arms. Numbers of patients in each arm are in parentheses.

Table 11	White		Black	
	Std of care (145)	AGPT (994)	Std of care (38)	AGPT (186)
ALT > 3x	2.1; 2.7	0.8; 1.1	0.0; 0.0	2.7; 4.2
ALT > 5x	0.7; 0.9	0.4; 0.6	0.0; 0.0	1.1; 1.7
AST >3x	2.8; 3.7	0.7; 1.0	0.0; 0.0	2.7; 4.2
AST >5x	0.0; 0.0	0.3; 0.4	0.0; 0.0	1.6; 2.5

Study 3101-303-002: In this blinded RCT, the rates of transaminase elevations were low across all races. Only one Asian out of 248 had an ALT 3-5x ULN. No unblinded data were provided. A narrative was provided for the one Asian case. We assessed it as possible to unlikely DILI due to AGPT, though if DILI is present than there was partial tolerance with improvement in liver enzymes while still on IP. Otherwise, fatty liver and autoimmune hepatitis compete well. Transaminases rose to 2.6 to 3.5x ULN at day 14. Patient had gained 3.2 kg from screening to day 14. IP was held on Day 16 and

Reference ID: 4848947

then restarted on Day 28. Transaminases fell to 1.0x to 1.7x ULN through day 56 while still on IP. ANA was 1:40. Other serologic evaluations were negative. Imaging showed fatty liver.

Paul H. Hayashi -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002877340, cn=Paul H. Hayashi -S
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Date: 2021.08.27 11:25:06 -04'00'

Joseph Toerner, MD, MPH
Director, Division of Hepatology and Nutrition
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Reference ID: 4848947

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/s/

PAUL H HAYASHI
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA/BLA #:	NDA215206
Drug Name:	Atogepant, tablet
Indication(s):	The preventive treatment of migraine in adults with less than 15 migraine days per month
Applicant:	AbbVie/Allergan International LTD. C/O ALLERGAN SALES LLC, 5 GIRALDA FARMS MADISON, NEW JERSEY 07940, USA Laboratory: Charles River Laboratories Montreal ULC Senneville Site (CR-MTL), 22022 Transcanadienne, Senneville, QC H9X 3R3, Canada
Date(s):	Received 1/28/2021
Documents Reviewed:	Studies cgp-tx-06-a1 (rats) cgp-tx-05-a1 (mice) and the electronic SEND datasets were submitted on 1/28/2021 (via NDA 215206).
Review Priority:	Standard Review
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Feng Zhou, MS
Concurring Reviewers:	Karl Lin, Ph. D., Team Leader
Medical Division:	CDER/ON/Division of Neurology 2
Nonclinical Team:	Edmund M. Nesti, Ph.D; Lois Freed, Ph.D.
Project Manager:	Daniel Ngembus, RPM
Keywords:	Carcinogenicity, Dose response

Reference ID: 4840868

Table of Contents

1 SUMMARY **3**

2 BACKGROUND **5**

3 RAT STUDY- CGP-TX-06-A1 ..... **5**

3.1 SPONSOR'S ANALYSES 6
3.1.1 Survival Analysis *6*
3.1.2 Tumor Data Analysis *6*
3.2 REVIEWER'S ANALYSES 7
3.2.1 Data Quality *7*
3.2.2 Survival Analysis *7*
3.2.3 Tumor Data Analysis *7*

4 MOUSE STUDY- CGP-TX-05-A1 ..... **9**

4.1 SPONSOR'S ANALYSES 10
4.1.1 Survival Analysis *10*
4.1.2 Tumor Data Analysis *10*
4.2 REVIEWER'S ANALYSES 10
4.2.1 Data Quality *10*
4.2.2 Survival Analysis *10*
4.2.3 Tumor Data Analysis *11*

5 CONCLUSION **12**

6 APPENDIX **14**

Table 1A: Intercurrent Mortality Rate in Male Rats *14*
Table 1B: Intercurrent Mortality Rate in Female Rats *14*
Table 2A: Intercurrent Mortality Rate in Male Mice *14*
Table 2B: Intercurrent Mortality Rate in Female Mice *15*
Table 3A: Intercurrent Mortality Comparison in Male Rats *15*
Table 3B: Intercurrent Mortality Comparison in Female Rats *15*
Table 4A: Intercurrent Mortality Comparison in Male Mice *15*
Table 4B: Intercurrent Mortality Comparison in Female Mice *16*
Table 5A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats Compared with Vehicle Control *16*
Table 5B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats Compared with Vehicle Control *20*
Table 6A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice Compared with Vehicle Control *23*
Table 6B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice Compared with Vehicle Control *26*
Figure 1A: Kaplan-Meier Survival Functions for Male Rats *30*
Figure 1B: Kaplan-Meier Survival Functions for Female Rats *30*
Figure 2A: Kaplan-Meier Survival Functions for Male Mice *31*
Figure 2B: Kaplan-Meier Survival Functions for Female Mice *31*

REFERENCES **32**

Reference ID: 4840868

1 Summary

This review evaluates statistically the data of the 2-year oral carcinogenicity study of AGN-241689 in Wistar Han Rats and 2-year oral carcinogenicity study in mice. The review analyzes the dose-response relationship of tumor incidences and mortality (including tumor-related mortality). The analyses results showed that AGN-241689 had no effects on survival or tumor incidence in either species.

Table 1: Tumor Types with Statistically Significant Dose Response Relationships and Pairwise Comparisons of Treated Groups and Control in Rats and Mice

Sex/Animal	Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	25 mg/kg/day Low (L) P - VC vs. L	65 mg/kg/day Mid (M) P - VC vs. M	200 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water C (WC) P - VC vs. WC
Female Rats	Cervix	Polyp, benign	0/59 (50)	0/59 (52)	0/56 (46)	3/58 (50)	1/59 (46)
			0.0154 *	NS	NS	0.1212	0.4792
	Comb_Cervix /Uterus	Polyp, benign	6/59 (50)	8/59 (52)	9/56 (47)	7/58 (51)	10/59 (49)
			0.4939	0.4182	0.2446	0.5155	0.1943
Sex/Animal	**Organ name**	**Tumor name**	**0 mg/kg/day Water C P - Trend**	**5 mg/kg/day Low (L) P - WC vs. L**	**20 mg/kg/day Mid (M) P - WC vs. M**	**75 mg/kg/day High (H) P - WC vs. H**	**0 mg/kg/day Vehicle C (VC) P - WC vs. VC**
Male Mice	Subcutis	Rhabdomyosarcoma	0/60 (44)	0/60 (50)	0/60 (47)	3/60 (49)	1/60 (44)
		malignant	0.0164 *	NS	NS	0.1420	0.5000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant. Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively.

Rat Study: Rats (60/sex/group) were dosed by oral gavage with AGN-241689 once daily for up to 104 weeks. The respective AGN-241689 doses in the water control (WC), vehicle control (VC), low (LD), mid (MD), and high-dose (HD) groups were 0, 0, 10, 20, and 100 mg/kg/day for male rats and 0, 0, 25, 65, and 200 mg/kg/day for female rats.

The survival analyses didn't show any statistically significant dose response relationship in mortality in both males and females. The respective survival rates in the WC, VC, LD, MD, or HD of AGN-241689 at the time they were terminated were 72%, 75%, 70%, 70%, and 72% in males and 62%, 63%, 72%, 62%, and 72% in females.

Tumor analysis results (Table 1) showed that the positive dose response was statistically significant in the incidence of rare benign polyp tumor in the cervix in females when compared with vehicle control group (0.0154 <0.025). For this tumor, the incidence rate of any treated group was not statistically significantly greater than that of the vehicle control group or water control group. For this tumor type in combined organ of cervix and uterus, the positive dose response was not statistically significant.

Mouse Study: Mice (60/sex/group) were dosed by oral gavage with AGN-241689 once daily for up to 104 weeks. The respective AGN-241689 doses in the water control (WC), vehicle control (VC), low (LD), mid (MD), and high-dose (HD) groups were 0, 0, 5, 20, and 75 mg/kg/day for male mice and 0, 0, 5, 30, and 160 mg/kg/day for female mice.

Reference ID: 4840868

The survival analyses didn't show any statistically significant dose response relationship in mortality in both males and females. The respective survival rates in the WC, VC, LD, MD, or HD of AGN-241689 at the time they were terminated were 47%, 50%, 62%, 53%, and 50% in males and 48%, 48%, 57%, 55%, and 58% in females.

Tumor analysis results (Table 1) showed that the positive dose response was statistically significant in the incidence of rare malignant rhabdomyosarcoma tumor in subcutis in male mice ($p=0.0164<0.025$) when compared with water control group. For this tumor type, the incidence rate of any treated group was not statistically significantly greater than that of the vehicle control group or water control group.

Reference ID: 4840868

2 Background

The sponsor, AbbVie Inc., is submitting, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50, a New Drug Application (NDA) for atogepant tablets, 10 mg, 30 mg, and 60 mg. The proposed indication is for the preventive treatment of migraine in adults with < 15 migraine days per month. The sponsor submitted two carcinogenicity study reports: Study cgp-tx-06-a1: "A 2-Year Carcinogenicity Study by Oral Gavage in Wistar Han Rat" and Study cgp-tx-05-a1: "A 2-Year Carcinogenicity Study by Oral Gavage in the Mouse" The study reports and the electronic SEND datasets were submitted on 1/28/2021 (via NDA 215206).

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 dose increases. Results of this review have been discussed with the nonclinical team.

3 Rat Study- cgp-tx-06-a1

Study Report: cgp-tx-06-a1.pdf (statistical report on page 890)
SAS data: SEND datasets

The objective of this study was to evaluate the carcinogenic potential of the test item, AGN-241689, a calcitonin gene-related peptide receptor antagonist, when given by daily oral gavage for a minimum of 104 consecutive weeks to Wistar Han Rats. The respective AGN-241689 doses in the water control (WC), vehicle control (VC), low (LD), mid (MD), high-dose (HD) groups were displayed in following table:

Group No./ Treatment	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	No. of Animals Main Study[b]	
				Males	Females
1/ Water Control	0	2	0	60	60
2/ Vehicle Control	0	2	0	60	60
3/ AGN-241689	10	2	5	60	-
4/ AGN-241689	20	2	10	60	-
5/ AGN-241689	100	2	50	60	-
6/ AGN-241689	25	2	12.5	-	60
7/ AGN-241689	65	2	32.5	-	60
8/ AGN-241689	200	2	100	-	60
9/ Health Screen[a]	-	-	-	10	10

- = Not applicable;
[a] Health Screen animals were used for health-screen evaluations only.
[b] 9/sex/group of Main Study animals were bled for toxicokinetic evaluation.

Assessment of carcinogenicity was based on anatomic pathology to include incidences of masses or tumors and possible effects on survival. Mortality, clinical observations, body weight, and food consumption were also monitored and evaluated.

Reference ID: 4840868

3.1 Sponsor's Analyses

3.1.1 Survival Analysis

Intercurrent mortality data were analyzed using the Kaplan-Meier product-limit method. An overall test comparing all groups was conducted using a log-rank test[12]. Any animal with accidental injury that caused death or unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day. If this overall test was significant ($p < 0.05$) and there were more than two groups, then a follow up analysis was done where each treatment group was compared to the control group using a log-rank test. Results of all pair-wise comparisons are reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's concluded results: No AGN-241689-related causes of death occurred in either sex in this study.

3.1.2 Tumor Data Analysis

The statistical evaluation of tumor data was limited to subcutis and hemolymphoreticular tissue using all study animals, to all non-secondary neoplastic lesions found in Study Plan-required tissues/sites, and to the combination of hemangiosarcoma findings across whole body.

Palpable neoplastic lesions found under skin, subcutis, and study plan-required glands were statistically analyzed in a "mortality independent" context according to Peto's onset rate using all study animals. Whereas, non-palpable neoplastic findings were statistically analyzed in a "mortality dependent" context according to Peto's prevalence and death rate methods.

For each dataset of interest, a one-tailed Peto's survival-adjusted trend test, using dose level scores, was conducted in order to assess significance of tumor rate increase across vehicle control group (Group 2) and test item treated groups. In addition, a two-tailed Peto's was used to compare the incidence rates of Group 2 and water control group (Group 1).

If the result revealed significant difference between Groups 1 and 2, then an upper-tailed Peto's trend test was used in order to assess significance of tumor rate increase in each of the test item treated groups when compared to each of Groups 1 and 2. Otherwise, an upper-tailed Peto's trend test was used in order to assess significance of tumor rate increase in each of the test item treated groups when only compared to Group 2.

As per Lin (Lin, K.K. 1997), the discrete permutation distribution tests for dose responses were used for individual tumor types with 10 or less tumor-bearing animals. As recommended by the FDA (Guidance for Industry, 2001), the overall trend and the pairwise comparison tests were discussed in the main report according to the tumor prevalence classification (common or rare).

The Peto (Peto R, Pike MC, Day NE et al, 1980) scoring system was used and assigned to each neoplasm from all animals examined. Histopathology data was submitted separately in an electronic format to Charles River Laboratories, Montreal, Canada for statistical analysis.

Reference ID: 4840868

Results of the statistical analysis was provided to the study director for inclusion in the toxicology report.

All p-values are reported using upper-tailed test, unless otherwise indicated. Evaluation criteria (levels of significance) were applied differently for rare tumors (background rate of 1% or less) and common tumors (background rate greater than 1%).

Sponsor's concluded results: There were no statistically significant differences between the control and the AGN-241689 treated groups.

3.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of these studies received on 1/28/2021 via NDA 215206. The vehicle control group was compared to each of treated group and water control group for the survival analyses and the tumor analyses.

3.2.1 Data Quality

The sponsor only submitted SEND database on 1/28/2021 via NDA 215206. The data quality was acceptable.

3.2.2 Survival Analysis

The survival distributions of rates in all treatment groups were estimated using the Kaplan-Meier product limit method. For control, low, medium, and high dose groups, the dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions were tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female rats, respectively. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 3A and 3B in the appendix for male and female rats, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the group were 17 (28%), 15 (25%), 18 (30%), 18 (30%), or 17 (28%) in male rats and 23 (38%), 22 (37%), 17 (28%), 23 (38%), or 17 (28%) in female rats in the WC, VC, LD, MD, or HD groups, respectively. The survival analyses didn't show any statistically significant dose response relationship in mortality in males and females.

3.2.3 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the papers of

Reference ID: 4840868

Bailer and Portier [2] and Bieler and Williams [3]. 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 developing the 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 Σs_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 Σs_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 of the tumor type being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) 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 adjusted levels of significance for testing a positive dose response in the 2-year rat study are 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The adjusted levels of significance for the pairwise comparison in the 2-year rat study are 0.01 and 0.05 for a common tumor and a rare tumor, respectively. A rare tumor is defined as one in which the tumor rate is less than 1% in the vehicle control group. The tumor rates and the p-values of the tested tumor types are listed in Tables 5A, and 5B in the appendix for male and female rats, respectively.

This reviewer also performed a separate set of tumor data analyses to test the positive dose responses in tumor incidence rates among the water control group and the low, medium, and high groups, and to test the pairwise comparisons between the water control group and each of the low, medium, high, and vehicle control groups. Since there were no statistically significant positive responses, and statistically significant differences in tumor incidences between the water control group and the vehicle control group in all the tumor types tested, the results of this separate set of tumor data analyses were not included in this reviewer's report.

Reviewer's findings: Following table displays the tumor types showing p-values less than or equal to 0.05 either for dose response relationships or for pairwise comparisons of treated groups and control.

Tumor Types with Statistically Significant (at 0.05 significant level) Dose Response Relationships or Pairwise Comparisons of Treated Groups and Controls in Rats

SEX	Organ name	Tumor name	0 mg/kg/day Control P - Trend	10 mg/kg/day Low (L) P - C vs. L	20 mg/kg/day Mid (M) P - C vs. M	100 mg/kg/day High (H) P - C vs. H	0 mg/kg/day Water C (WC) P - C vs. WC
Male	Brain	C_Oligodendroglioma /Astrocytoma	0/59 (55) 0.0279	0/57 (52) NS	3/57 (50) 0.1046	3/55 (46) 0.0911	0/58 (50) NS
	Gland, adrenal	Pheochromocytoma, benign	0/59 (55) 0.0307	1/58 (53) 0.4907	1/57 (50) 0.4762	3/55 (46) 0.0911	0/58 (50) NS
	Gland thyroid	C_Follicular cell/A+C	4/58 (54)	10/58 (53)	5/57 (50)	10/55 (45)	8/58 (50)

Reference ID: 4840868

			0.0531	0.0698	0.4508	0.0381	0.1439
	Lung	Sarcoma, histiocytic,	0/59 (55)	0/58 (53)	0/57 (50)	2/55 (45)	0/58 (50)
		malignant	0.0483	NS	NS	0.2000	NS
SEX	**Organ name**	**Tumor name**	**0 mg/kg/day Vehicle C P - Trend**	**25 mg/kg/day Low (L) P - VC vs. L**	**65 mg/kg/day Mid (M) P - VC vs. M**	**200 mg/kg/day High (H) P - VC vs. H**	**0 mg/kg/day Water C (WC) P - VC vs. WC**
Female	Cervix	Polyp, benign	0/59 (50)	0/59 (52)	0/56 (46)	3/58 (50)	1/59 (46)
			0.0154 *	NS	NS	0.1212	0.4792
	Comb_Cervix	Polyp, benign	6/59 (50)	8/59 (52)	9/56 (47)	7/58 (51)	10/59 (49)
	/Uterus		0.4939	0.4182	0.2446	0.5155	0.1943
	Gland, mammary	Fibroadenoma, benign	8/59 (51)	4/58 (51)	1/56 (45)	3/57 (49)	15/59 (47)
			0.8994	0.9391	0.9977	0.9700	0.0486
	Hemolymphoreticular	Lymphoma, malignant	0/59 (50)	1/59 (52)	1/57 (46)	3/58 (50)	1/59 (46)
	tissue		0.0429	0.5098	0.4792	0.1212	0.4792

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Based on the criteria of adjustment for multiple testing discussed above, the positive dose response was statistically significant in the incidence of rare benign polyp tumor in the cervix in females (p=0.0154<0.025) when compared with vehicle control group. For this tumor type, the incidence rate of any treated group was not statistically significantly greater than that of the vehicle control group or water control group. For this tumor type in combined organ of cervix and uterus, the positive dose response was not statistically significant.

4 Mouse Study- cgp-tx-05-a1

Study Report: cgp-tx-05-a1.pdf (statistical report on page 726)
SAS data: SEND datasets

The objective of this study was to evaluate the carcinogenic potential of the test item, AGN-241689, a calcitonin gene-related peptide receptor antagonist, when given by daily oral gavage for a minimum of 104 consecutive weeks to mice. The respective AGN-241689 doses in the water control (WC), vehicle control (VC), low (LD), mid (MD), high-dose (HD) groups were displayed in following table:

Group No./ Treatment	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	No. of Main Study Animals	
				Males[a]	Females[a]
1/ Water Control	0	10	0	60	60
2/ Vehicle Control	0	10	0	60	60
3/ AGN-241689	5	10	0.5	60	60
4/ AGN-241689	20	10	2	60	-
5/ AGN-241689	75	10	7.5	60	-
6/ AGN-241689	30	10	3	-	60
7/ AGN-241689	160	10	16	-	60

- = not applicable
[a] 9/sex/group of Main Study animals were bled for toxicokinetic evaluation.

Reference ID: 4840868

Assessment of toxicity was based on dose analysis, morbidity, mortality, injury, body weight, food consumption, clinical observations and masses, ophthalmology, clinical pathology, toxicokinetics, macroscopic observations, and microscopic evaluations.

4.1 Sponsor's Analyses

4.1.1 Survival Analysis

The sponsor used the same survival analysis methods for the rat study in this mouse study.

Sponsor's concluded results: AGN-241689 administered orally to mice for up to 104 weeks had no effect on survival.

4.1.2 Tumor Data Analysis

The sponsor used the same tumor data analysis methods for the rat study in this mouse study.

Sponsor's findings: There were no neoplastic findings attributed to AGN-241689.

4.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of these studies received on 1/28/2021 via NDA 215206. The vehicle control group was compared to each of treated group and water control group for the survival analyses and the tumor analyses.

4.2.1 Data Quality

The sponsor only submitted SEND database on 1/28/2021 via NDA 215206. The data quality was acceptable.

4.2.2 Survival Analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data of all treatment groups are given in Tables 2A and 2B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals for control, low, medium, and high dose groups are given in Tables 4A and 4B in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the group were 32 (53%), 30 (50%), 23 (38%), 28 (47%), or 30

Reference ID: 4840868

(50%) in male mice and 31 (52%), 31 (52%), 26 (43%), 27 (45%), or 25 (42%) in female mice in the WC, VC, LD, MD, or HD groups, respectively. The survival analyses didn't show any statistically significant dose response relationship in mortality in males and females.

4.2.3 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of the water control group and the vehicle control group separately with each of the treated groups using the same method that was used for the rat study. The tumor rates and the p-values of the tested tumor types are listed in Tables 6A, and 6B in the appendix for male and female mice, respectively.

This reviewer also performed a separate set of tumor data analyses to test the positive dose responses in tumor incidence rates among the water control group and the low, medium, and high groups, and to test the pairwise comparisons between the water control group and each of the low, medium, high, and vehicle control groups. Only one tumor type (listed in the following table) of rare malignant rhabdomyosarcoma tumor in subcutis in male mice had a statistically significant positive responses between the water control group and treated group. The results of this separate set of tumor data analyses were not included in this reviewer's report.

Reviewer's findings: Following table displays the tumor types showing p-values less than or equal to 0.05 either for dose response relationships or for pairwise comparisons of treated groups and control.

Tumor Types with Statistically Significant (at 0.05 significant level) Dose Response Relationships or Pairwise Comparisons of Treated Groups and Controls in Mice

SEX	Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	5 mg/kg/day Low (L) P - VC vs. L	20 mg/kg/day Mid (M) P - VC vs. M	75 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water C (WC) P - VC vs. WC
Male	Liver	Carcinoma, hepatocellular,	5/60 (45)	6/60 (51)	6/60 (47)	10/60 (49)	13/60 (44)
		malignant	0.0746	0.5888	0.5312	0.1720	0.0278
		C_hepatocellular_A+C	8/60 (45)	11/60 (51)	14/60 (47)	12/60 (49)	16/60 (44)
			0.2879	0.4376	0.1474	0.2948	0.0470
SEX	**Organ name**	**Tumor name**	**0 mg/kg/day Water C P - Trend**	**5 mg/kg/day Low (L) P - WC vs. L**	**20 mg/kg/day Mid (M) P - WC vs. M**	**75 mg/kg/day High (H) P - WC vs. H**	**0 mg/kg/day Vehicle C (VC) P - WC vs. VC**
Male	Subcutis	Rhabdomyosarcoma	0/60 (44)	0/60 (50)	0/60 (47)	3/60 (49)	1/60 (44)
		malignant	0.0164 *	NS	NS	0.1420	0.5000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Based on the criteria of adjustment for multiple testing discussed above, the positive dose response was statistically significant in the incidence of rare malignant rhabdomyosarcoma tumor in subcutis in males ($p=0.0164<0.025$) when compared with water control group. For this tumor type, the incidence rate of any treated group was not statistically significantly greater than that of the vehicle control group or water control group.

Reference ID: 4840868

5 Conclusion

This review evaluates statistically the data of the 2-year oral carcinogenicity study of AGN-241689 in Wistar Han Rats and 2-year oral carcinogenicity study in mice. The review analyzes the dose-response relationship of tumor incidences and mortality (including tumor-related mortality). The analyses results showed that AGN-241689 had no effects on survival or tumor incidence in either species.

Table 1: Tumor Types with Statistically Significant Dose Response Relationships and Pairwise Comparisons of Treated Groups and Control in Rats and Mice

Sex/Animal	Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	25 mg/kg/day Low (L) P - VC vs. L	65 mg/kg/day Mid (M) P - VC vs. M	200 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water C (WC) P - VC vs. WC
Female Rats	Cervix	Polyp, benign	0/59 (50)	0/59 (52)	0/56 (46)	3/58 (50)	1/59 (46)
			0.0154 *	NS	NS	0.1212	0.4792
	Comb_Cervix	Polyp, benign	6/59 (50)	8/59 (52)	9/56 (47)	7/58 (51)	10/59 (49)
	/Uterus		0.4939	0.4182	0.2446	0.5155	0.1943
Sex/Animal	**Organ name**	**Tumor name**	**0 mg/kg/day Water C P - Trend**	**5 mg/kg/day Low (L) P - WC vs. L**	**20 mg/kg/day Mid (M) P - WC vs. M**	**75 mg/kg/day High (H) P - WC vs. H**	**0 mg/kg/day Vehicle C (VC) P - WC vs. VC**
Male Mice	Subcutis	Rhabdomyosarcoma	0/60 (44)	0/60 (50)	0/60 (47)	3/60 (49)	1/60 (44)
		malignant	0.0164 *	NS	NS	0.1420	0.5000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant. Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively.

Rat Study: Rats (60/sex/group) were dosed by oral gavage with AGN-241689 once daily for up to 104 weeks. The respective AGN-241689 doses in the water control (WC), vehicle control (VC), low (LD), mid (MD), and high-dose (HD) groups were 0, 0, 10, 20, and 100 mg/kg/day for male rats and 0, 0, 25, 65, and 200 mg/kg/day for female rats.

The survival analyses didn't show any statistically significant dose response relationship in mortality in both males and females. The respective survival rates in the WC, VC, LD, MD, or HD of AGN-241689 at the time they were terminated were 72%, 75%, 70%, 70%, and 72% in males and 62%, 63%, 72%, 62%, and 72% in females.

Tumor analysis results (Table 1) showed that the positive dose response was statistically significant in the incidence of rare benign polyp tumor in the cervix in females when compared with vehicle control group (0.0154 <0.025). For this tumor, the incidence rate of any treated group was not statistically significantly greater than that of the vehicle control group or water control group. For this tumor type in combined organ of cervix and uterus, the positive dose response was not statistically significant.

Mouse Study: Mice (60/sex/group) were dosed by oral gavage with AGN-241689 once daily for up to 104 weeks. The respective AGN-241689 doses in the water control (WC), vehicle

Reference ID: 4840868

control (VC), low (LD), mid (MD), and high-dose (HD) groups were 0, 0, 5, 20, and 75 mg/kg/day for male mice and 0, 0, 5, 30, and 160 mg/kg/day for female mice.

The survival analyses didn't show any statistically significant dose response relationship in mortality in both males and females. The respective survival rates in the WC, VC, LD, MD, or HD of AGN-241689 at the time they were terminated were 47%, 50%, 62%, 53%, and 50% in males and 48%, 48%, 57%, 55%, and 58% in females.

Tumor analysis results (Table 1) showed that the positive dose response was statistically significant in the incidence of rare malignant rhabdomyosarcoma tumor in subcutis in male mice ($p=0.0164<0.025$) when compared with water control group. For this tumor type, the incidence rate of any treated group was not statistically significantly greater than that of the vehicle control group or water control group.

Feng Zhou
Mathematical Statistician

Concurring Reviewer: Karl Lin, Ph.D., Team Leader, Biometrics-6
cc:
Dr. Edmund M. Nesti
Dr. Lois Freed
Dr. Yi Tsong
Dr. Karl Lin

Reference ID: 4840868

6 Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

	Vehicle Control		Low Dose		Mid Dose		High Dose		Water Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	.	.	1	1.67	1	1.67	4	6.67	1	1.67
53 - 78	1	1.67	4	8.33	6	11.67	5	15.00	6	11.67
79 - 96	8	15.00	9	23.33	5	20.00	4	21.67	6	21.67
97 - 104	6	25.00	4	30.00	6	30.00	3	26.67	4	28.33
Accidental Death	.	.	.	.	.	.	1	1.67	.	.
Terminal sacrifice	45	75.00	42	70.00	42	70.00	43	71.67	43	71.67
Total	60	.	60	.	60	.	60	.	60	.

Table 1B: Intercurrent Mortality Rate in Female Rats

	Vehicle Control		Low Dose		Mid Dose		High Dose		Water Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	5	8.33	4	6.67	4	6.67	2	3.33	3	5.00
53 - 78	3	13.33	2	10.00	5	15.00	4	10.00	8	18.33
79 - 96	5	21.67	4	16.67	7	26.67	9	25.00	8	31.67
97 - 104	9	36.67	7	28.33	7	38.33	2	28.33	4	38.33
Terminal sacrifice	38	63.33	43	71.67	37	61.67	43	71.67	37	61.67
Total	60	.	60	.	60	.	60	.	60	.

Table 2A: Intercurrent Mortality Rate in Male Mice

	Vehicle Control		Low Dose		Mid Dose		High Dose		Water Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	6	10.00			1	1.67			4	6.67
53 - 78	7	21.67	5	8.33	11	20.00	8	13.33	7	18.33
79 - 96	11	40.00	14	31.67	8	33.33	12	33.33	13	40.00
97 - 104	5	48.33	4	38.33	8	46.67	9	48.33	7	51.67
Accidental Death	1	1.67					1	1.67	1	1.67
Terminal sacrifice	30	50.00	37	61.67	32	53.33	30	50.00	28	46.67
Total	60		60		60		60		60	

Reference ID: 4840868

Table 2B: Intercurrent Mortality Rate in Female Mice

	Vehicle Control		Low Dose		Mid Dose		High Dose		Water Control	
Week / Type of Death	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**
0 - 52	2	3.33	1	1.67	2	3.33	4	6.67	5	8.33
53 - 78	7	15.00	6	11.67	7	15.00	6	16.67	7	20.00
79 - 96	14	38.33	13	33.33	14	38.33	11	35.00	8	33.33
97 - 104	8	51.67	6	43.33	4	45.00	4	41.67	11	51.67
Terminal sacrifice	29	48.33	34	56.67	33	55.00	35	58.33	29	48.33
Total	60		60		60		60		60	

Table 3A: Intercurrent Mortality Comparison in Male Rats

Test	**All Dose Groups**	**VC vs. Low**	**VC vs. Mid**	**VC vs. High**	**VC vs. WC**
Dose-Response (Likelihood Ratio)	0.8651	0.4934	0.4857	0.6254	0.5428
Homogeneity (Log-Rank)	0.8956	0.4910	0.4836	0.6240	0.5414
Test	**All Dose Groups**	**WC vs. Low**	**WC vs. Mid**	**WC vs. High**	**WC vs. VC**
Dose-Response (Likelihood Ratio)	0.8722	0.9532	0.9044	0.9425	0.5428
Homogeneity (Log-Rank)	0.9973	0.9531	0.9043	0.9423	0.5414

Table 3B: Intercurrent Mortality Comparison in Female Rats

Test	**All Dose Groups**	**VC vs. Low**	**VC vs. Mid**	**VC vs. High**	**VC vs. WC**
Dose-Response (Likelihood Ratio)	0.5536	0.3318	0.7769	0.3993	0.7118
Homogeneity (Log-Rank)	0.4979	0.3285	0.7757	0.3981	0.7100
Test	**All Dose Groups**	**WC vs. Low**	**WC vs. Mid**	**WC vs. High**	**WC vs. VC**
Dose-Response (Likelihood Ratio)	0.3967	0.1941	0.9066	0.2243	0.7118
Homogeneity (Log-Rank)	0.3779	0.1917	0.9063	0.2230	0.7100

Table 4A: Intercurrent Mortality Comparison in Male Mice

Test	**All Dose Groups**	**VC vs. Low**	**VC vs. Mid**	**VC vs. High**	**VC vs. WC**
Dose-Response (Likelihood Ratio)	0.7674	0.2005	0.7017	0.7473	0.7509
Homogeneity (Log-Rank)	0.5924	0.1981	0.7001	0.7454	0.7492
Test	**All Dose Groups**	**WC vs. Low**	**WC vs. Mid**	**WC vs. High**	**WC vs. VC**
Dose-Response (Likelihood Ratio)	0.9229	0.0981	0.4837	0.5082	0.7509
Homogeneity (Log-Rank)	0.4134	0.0957	0.4803	0.5049	0.7492

Reference ID: 4840868

Table 4B: Intercurrent Mortality Comparison in Female Mice

Test	All Dose Groups	VC vs. Low	VC vs. Mid	VC vs. High	VC vs. WC
Dose-Response (Likelihood Ratio)	0.6214	0.4206	0.6182	0.4208	0.9381
Homogeneity (Log-Rank)	0.8298	0.4168	0.6164	0.4185	0.9376
Test	**All Dose Groups**	**WC vs. Low**	**WC vs. Mid**	**WC vs. High**	**WC vs. VC**
Dose-Response (Likelihood Ratio)	0.5714	0.3535	0.5204	0.3501	0.9381
Homogeneity (Log-Rank)	0.7465	0.3496	0.5174	0.3477	0.9376

Table 5A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats Compared with Vehicle Control

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	10 mg/kg/day Low (L) P - VC vs. L	20 mg/kg/day Mid (M) P – VC vs. M	100 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water C (WC) P - VC vs. WC
Adipose tissue	Hemangioma, benign	0/59 (55) 0.2217	0/58 (53) NS	0/57 (50) NS	1/55 (45) 0.4500	0/58 (50) NS
Body cavity, abdominal	Mesothelioma, malignant	0/59 (55) 0.2217	0/58 (53) NS	0/57 (50) NS	1/55 (45) 0.4500	0/58 (50) NS
	Schwannoma, malignant	1/59 (55) 1.0000	0/58 (53) 1.0000	0/57 (50) 1.0000	0/55 (45) 1.0000	0/58 (50) 1.0000
Body cavity, nasal	Carcinoma, squamous cell Malignant	0/59 (55) 0.4680	0/58 (53) NS	1/57 (50) 0.4762	0/55 (45) NS	0/58 (50) NS
Body cavity, oral	Carcinoma, squamous cell Malignant	0/59 (55) 0.7291	1/58 (53) 0.4907	0/57 (50) NS	0/55 (45) NS	0/58 (50) NS
Brain	Astrocytoma, malignant	0/59 (55) 0.0817	0/57 (52) NS	3/57 (50) 0.1046	2/55 (45) 0.2000	0/58 (50) NS
	Granular cell tumor, benign	0/59 (55) 0.7277	1/57 (52) 0.4860	0/57 (50) NS	0/55 (45) NS	1/58 (50) 0.4762
	Granular cell tumor, malignant	0/59 (55) 0.7860	2/57 (52) 0.2338	0/57 (50) NS	0/55 (45) NS	0/58 (50) NS
	Meningioma, malignant	0/59 (55) NS	0/57 (52) NS	0/57 (50) NS	0/55 (45) NS	1/58 (51) 0.4811
	Oligodendroglioma, malignant	0/59 (55) 0.2266	0/57 (52) NS	0/57 (50) NS	1/55 (46) 0.4554	0/58 (50) NS
	C_Oligodendroglioma Astrocytoma	0/59 (55) 0.0279	0/57 (52) NS	3/57 (50) 0.1046	3/55 (46) 0.0911	0/58 (50) NS
Duct, bile	Carcinoma, malignant	1/59 (55) 1.0000	0/58 (53) 1.0000	0/56 (49) 1.0000	0/54 (44) 1.0000	0/58 (50) 1.0000
Ear	Adenoma, sebaceous, benign	0/59 (55) NS	0/58 (53) NS	0/57 (50) NS	0/55 (45) NS	1/58 (50) 0.4762
Epididymis	Mesothelioma, malignant	1/59 (55) 0.7854	0/58 (53) 1.0000	1/57 (50) 0.7280	0/55 (45) 1.0000	1/58 (50) 0.7280
	Schwannoma, malignant	1/59 (55) 1.0000	0/58 (53) 1.0000	0/57 (50) 1.0000	0/55 (45) 1.0000	1/58 (51) 0.7332

Reference ID: 4840868

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	10 mg/kg/day Low (L) P - VC vs. L	20 mg/kg/day Mid (M) P – VC vs. M	100 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water C (WC) P - VC vs. WC
Esophagus	Sarcoma, malignant	0/59 (55)	0/58 (53)	1/57 (50)	0/55 (45)	0/58 (50)
		0.4680	NS	0.4762	NS	NS
Gland, adrenal	Adenoma, adrenocortical,	4/59 (55)	3/58 (53)	4/57 (50)	3/55 (45)	2/58 (50)
	Benign	0.5128	0.7657	0.5873	0.6907	0.8739
	Ganglioneuroma, benign	0/59 (55)	1/58 (53)	0/57 (50)	0/55 (45)	0/58 (50)
		0.7291	0.4907	NS	NS	NS
	Pheochromocytoma, benign	0/59 (55)	1/58 (53)	1/57 (50)	3/55 (46)	0/58 (50)
		0.0307	0.4907	0.4762	0.0911	NS
	Pheochromocytoma, complex,	1/59 (55)	0/58 (53)	0/57 (50)	0/55 (45)	0/58 (50)
	benign	1.0000	1.0000	1.0000	1.0000	1.0000
	Pheochromocytoma, malignant	0/59 (55)	1/58 (53)	0/57 (50)	0/55 (45)	0/58 (50)
		0.7291	0.4907	NS	NS	NS
Gland, harderian	Fibrosarcoma, malignant	0/59 (55)	0/58 (53)	0/57 (50)	1/55 (45)	0/58 (50)
		0.2217	NS	NS	0.4500	NS
Gland, parathyroid	Adenoma, benign	5/54 (50)	1/49 (44)	3/54 (47)	3/54 (44)	3/55 (48)
		0.5316	0.9805	0.8449	0.8206	0.8522
Gland, pituitary	Adenoma, pars distalis,	22/59 (57)	17/56 (52)	16/56 (51)	21/55 (48)	17/57 (52)
	Benign	0.1603	0.8000	0.8381	0.3683	0.8000
Gland, prostate	Adenocarcinoma, malignant	2/59 (55)	0/58 (53)	1/57 (50)	0/55 (45)	1/58 (50)
		0.9236	1.0000	0.8601	1.0000	0.8601
Gland, salivary,	Fibrosarcoma, malignant	0/58 (54)	0/58 (53)	1/57 (50)	0/55 (45)	0/58 (50)
Submandibular		0.4703	NS	0.4808	NS	NS
	Sarcoma, malignant	0/58 (54)	0/58 (53)	0/57 (50)	1/55 (45)	0/58 (50)
		0.2228	NS	NS	0.4545	NS
	Schwannoma, malignant	0/58 (54)	0/58 (53)	0/57 (50)	1/55 (46)	0/58 (50)
		0.2266	NS	NS	0.4600	NS
Gland,	Adenocarcinoma, malignant	1/58 (54)	0/58 (53)	1/57 (50)	0/55 (45)	1/58 (50)
seminal vesicle		0.7885	1.0000	0.7328	1.0000	0.7328
Gland, thyroid	Adenoma, C-Cell, benign	7/58 (55)	6/58 (53)	4/57 (50)	4/55 (45)	7/58 (51)
		0.6975	0.6974	0.8666	0.8234	0.5525
	Adenoma, follicular cell,	4/58 (54)	8/58 (53)	5/57 (50)	9/55 (46)	7/58 (50)
	Benign	0.0623	0.1704	0.4508	0.0662	0.2201
	Carcinoma, C-Cell, malignant	0/58 (54)	1/58 (53)	0/57 (50)	0/55 (45)	0/58 (50)
		0.7327	0.4953	NS	NS	NS
	Carcinoma, follicular cell,	0/58 (54)	3/58 (53)	0/57 (50)	1/55 (45)	1/58 (50)
	Malignant	0.4734	0.1180	NS	0.4545	0.4808
	C_Follicular cell/A+C	4/58 (54)	10/58 (53)	5/57 (50)	10/55 (45)	8/58 (50)
		0.0531	0.0698	0.4508	0.0381	0.1439
Heart	Hemangioma, benign	0/59 (55)	1/58 (53)	0/57 (50)	0/55 (45)	0/58 (50)
		0.7291	0.4907	NS	NS	NS
	Schwannoma, malignant	0/59 (55)	0/58 (53)	1/57 (50)	0/55 (45)	0/58 (50)
		0.4680	NS	0.4762	NS	NS
Hemolymphoreticular	Leukemia, malignant	0/59 (55)	1/58 (53)	0/57 (50)	0/55 (45)	0/58 (50)

Reference ID: 4840868

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	10 mg/kg/day Low (L) P - VC vs. L	20 mg/kg/day Mid (M) P – VC vs. M	100 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water C (WC) P - VC vs. WC
tissue		0.7291	0.4907	NS	NS	NS
	Lymphoma, malignant	1/59 (55)	0/58 (53)	3/57 (51)	1/55 (45)	3/58 (52)
		0.3731	1.0000	0.2809	0.7000	0.2880
	Sarcoma, histiocytic,	0/59 (55)	0/58 (53)	0/57 (50)	2/55 (45)	1/58 (51)
	malignant	0.0483	NS	NS	0.2000	0.4811
Kidney	Liposarcoma, malignant	1/59 (55)	0/58 (53)	0/57 (50)	0/55 (45)	0/58 (50)
		1.0000	1.0000	1.0000	1.0000	1.0000
Large intestine,	Lipoma, benign	0/59 (55)	0/58 (53)	0/57 (50)	1/55 (45)	0/58 (50)
Cecum		0.2217	NS	NS	0.4500	NS
Large intestine,	Adenocarcinoma, malignant	1/59 (55)	0/58 (53)	0/57 (50)	0/55 (45)	0/58 (50)
Colon		1.0000	1.0000	1.0000	1.0000	1.0000
Large intestine,	Polyp, benign	0/59 (55)	0/58 (53)	0/56 (49)	1/55 (45)	1/57 (49)
Rectum		0.2228	NS	NS	0.4500	0.4712
Liver	Adenoma, hepatocellular,	0/59 (55)	1/58 (53)	0/57 (50)	0/55 (45)	2/58 (50)
	Benign	0.7291	0.4907	NS	NS	0.2244
	Carcinoma, hepatocellular,	0/59 (55)	1/58 (53)	0/57 (50)	0/55 (45)	0/58 (50)
	Malignant	0.7291	0.4907	NS	NS	NS
	Cholangiocarcinoma,	0/59 (55)	0/58 (53)	1/57 (50)	0/55 (45)	0/58 (50)
	Malignant	0.4680	NS	0.4762	NS	NS
Lung	Adenoma, Benign,	1/59 (55)	2/58 (53)	0/57 (50)	0/55 (45)	0/58 (50)
	bronchioloalveolar	0.9236	0.4860	1.0000	1.0000	1.0000
Lymph node,	Hemangioma, benign	0/58 (54)	0/58 (53)	0/56 (49)	1/55 (45)	0/58 (50)
mandibular		0.2239	NS	NS	0.4545	NS
Lymph node,	Hemangioma, benign	2/59 (55)	4/57 (52)	7/57 (50)	6/55 (46)	4/58 (50)
mesenteric		0.1074	0.3128	0.0600	0.0847	0.2948
	Hemangiosarcoma,	1/59 (55)	0/57 (52)	0/57 (50)	0/55 (45)	1/58 (50)
	malignant	1.0000	1.0000	1.0000	1.0000	0.7280
Muscle, skeletal	Fibroma, benign	0/58 (54)	0/57 (52)	0/57 (50)	0/55 (45)	1/58 (50)
		NS	NS	NS	NS	0.4808
Pancreas	Adenoma, islet cell, benign	2/59 (55)	1/58 (53)	2/57 (50)	4/55 (45)	1/58 (50)
		0.0757	0.8715	0.6542	0.2488	0.8601
	Carcinoma, islet cell,	1/59 (55)	2/58 (53)	1/57 (50)	0/55 (45)	1/58 (50)
	malignant	0.8498	0.4860	0.7280	1.0000	0.7280
Skin	Basal cell tumor, benign	2/59 (55)	0/58 (53)	0/57 (50)	0/55 (45)	0/57 (49)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Carcinoma, squamous cell,	0/59 (55)	0/58 (53)	0/57 (50)	1/55 (45)	0/57 (49)
	malignant	0.2217	NS	NS	0.4500	NS
	Hair follicle neoplasm,	1/59 (55)	0/58 (53)	2/57 (50)	1/55 (45)	0/57 (49)
	benign	0.3582	1.0000	0.4640	0.7000	1.0000
	Papilloma, benign	2/59 (55)	0/58 (53)	0/57 (50)	1/55 (45)	1/57 (49)
		0.5305	1.0000	1.0000	0.8378	0.8559
Small intestine,	Sarcoma, malignant	0/59 (55)	0/57 (52)	1/57 (50)	0/55 (45)	1/58 (50)
jejunum		0.4703	NS	0.4762	NS	0.4762

Reference ID: 4840868

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	10 mg/kg/day Low (L) P - VC vs. L	20 mg/kg/day Mid (M) P – VC vs. M	100 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water C (WC) P - VC vs. WC
Spleen	Hemangiosarcoma, malignant	1/59 (55) 1.0000	0/58 (53) 1.0000	0/57 (50) 1.0000	0/55 (45) 1.0000	1/58 (50) 0.7280
Stomach	Fibrosarcoma, malignant	0/59 (55) 0.5841	1/58 (53) 0.4907	1/57 (50) 0.4762	0/55 (45) NS	0/58 (50) NS
	Leiomyosarcoma, malignant	1/59 (55) 1.0000	0/58 (53) 1.0000	0/57 (50) 1.0000	0/55 (45) 1.0000	0/58 (50) 1.0000
	Sarcoma, malignant	0/59 (55) 0.2217	0/58 (53) NS	0/57 (50) NS	1/55 (45) 0.4500	0/58 (50) NS
Subcutis	Carcinoma, basal cell, malignant	0/59 (55) 0.7291	1/58 (53) 0.4907	0/57 (50) NS	0/55 (45) NS	0/57 (49) NS
	Fibroma, benign	1/59 (55) 0.1502	0/58 (53) 1.0000	1/57 (50) 0.7280	2/55 (45) 0.4245	1/57 (49) 0.7227
	Fibrosarcoma, malignant	0/59 (55) NS	0/58 (53) NS	0/57 (50) NS	0/55 (45) NS	1/57 (50) 0.4762
	Hair follicle neoplasm, benign	1/59 (55) 1.0000	0/58 (53) 1.0000	0/57 (50) 1.0000	0/55 (45) 1.0000	0/57 (49) 1.0000
	Hemangioma, benign	1/59 (55) 1.0000	0/58 (53) 1.0000	0/57 (50) 1.0000	0/55 (45) 1.0000	0/57 (49) 1.0000
	Hemangiosarcoma, malignant	0/59 (55) 0.7291	1/58 (53) 0.4907	0/57 (50) NS	0/55 (45) NS	0/57 (49) NS
	Liposarcoma, malignant	0/59 (55) 0.4680	0/58 (53) NS	1/57 (50) 0.4762	0/55 (45) NS	0/57 (49) NS
	Sarcoma, malignant	1/59 (55) 0.9276	1/58 (53) 0.7430	0/57 (50) 1.0000	0/55 (45) 1.0000	0/57 (49) 1.0000
	Schwannoma, benign	1/59 (55) 1.0000	0/58 (53) 1.0000	0/57 (50) 1.0000	0/55 (45) 1.0000	0/57 (49) 1.0000
Tail	Papilloma, benign	0/59 (55) NS	0/58 (53) NS	0/57 (50) NS	0/55 (45) NS	1/58 (50) 0.4762
Testis	Leydig cell tumor, benign	3/59 (55) 0.3070	0/58 (53) 1.0000	0/57 (50) 1.0000	2/55 (45) 0.7499	0/58 (50) 1.0000
	Seminoma, malignant	0/59 (55) 0.4680	0/58 (53) NS	1/57 (50) 0.4762	0/55 (45) NS	0/58 (50) NS
Thymus	Thymoma, benign	0/57 (53) 0.7001	2/56 (51) 0.2381	1/56 (49) 0.4804	0/55 (45) NS	1/57 (49) 0.4804
	Thymoma, malignant	0/57 (53) 0.7323	1/56 (51) 0.4904	0/56 (49) NS	0/55 (45) NS	0/57 (49) NS
Whole animal	Non-correlating lesion	56/59 (59) 0.8978	53/58 (58) 0.8696	50/57 (56) 0.9306	47/55 (54) 0.9659	53/58 (57) 0.7948
Whole body	Hemangiosarcoma	2/59 (55) 0.9236	1/58 (53) 0.8715	0/57 (50) 1.0000	0/55 (45) 1.0000	2/58 (50) 0.6542

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Reference ID: 4840868

Table 5B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats Compared with Vehicle Control

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	25 mg/kg/day Low (L) P - VC vs. L	65 mg/kg/day Mid (M) P - VC vs. M	200 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water (WC) P - VC vs. WC
Body cavity, nasal	Papilloma, benign	1/59 (50)	0/59 (52)	0/57 (46)	0/58 (49)	0/59 (46)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Sarcoma, malignant	0/59 (50)	1/59 (52)	0/57 (46)	0/58 (49)	0/59 (46)
		0.7462	0.5098	NS	NS	NS
Bone	Osteosarcoma, malignant	0/59 (50)	0/58 (51)	1/57 (47)	0/58 (49)	0/59 (46)
		0.4873	NS	0.4845	NS	NS
Brain	Astrocytoma, malignant	1/59 (50)	0/59 (52)	0/57 (46)	0/58 (49)	1/59 (47)
		1.0000	1.0000	1.0000	1.0000	0.7369
	Granular cell tumor, benign	0/59 (50)	0/59 (52)	0/57 (46)	1/58 (49)	0/59 (46)
		0.2487	NS	NS	0.4949	NS
	Granular cell tumor, malignant	0/59 (50)	1/59 (52)	1/57 (47)	0/58 (49)	1/59 (46)
		0.6154	0.5098	0.4845	NS	0.4792
Cervix	Carcinoma, squamous cell,	1/59 (50)	0/59 (52)	0/56 (46)	1/58 (50)	0/59 (46)
	Malignant	0.4422	1.0000	1.0000	0.7525	1.0000
	Polyp, benign	0/59 (50)	0/59 (52)	0/56 (46)	3/58 (50)	1/59 (46)
		0.0154 *	NS	NS	0.1212	0.4792
Comb_Cervix/Uterus	Polyp, benign	6/59 (50)	8/59 (52)	9/56 (47)	7/58 (51)	10/59 (49)
		0.4939	0.4182	0.2446	0.5155	0.1943
	Schwannoma, benign	1/59 (51)	0/59 (52)	0/56 (46)	0/58 (49)	0/59 (46)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Schwannoma, malignant	1/59 (51)	1/59 (52)	0/56 (46)	1/58 (49)	1/59 (47)
		0.5270	0.7573	1.0000	0.7424	0.7317
Gland, adrenal	Adenoma, adrenocortical,	2/59 (50)	2/59 (52)	1/57 (47)	1/58 (50)	3/59 (46)
	Benign	0.7432	0.7060	0.8671	0.8788	0.4601
	Pheochromocytoma, benign	0/59 (50)	0/59 (52)	1/57 (46)	0/58 (49)	0/59 (46)
		0.4822	NS	0.4792	NS	NS
	Pheochromocytoma, malignant	0/59 (50)	1/59 (52)	0/57 (46)	0/58 (49)	0/59 (46)
		0.7462	0.5098	NS	NS	NS
Gland, mammary	Adenocarcinoma, malignant	4/59 (50)	4/58 (51)	4/56 (46)	1/57 (49)	3/59 (47)
		0.9239	0.6536	0.5947	0.9704	0.7558
	Adenoma, benign	1/59 (51)	1/58 (51)	0/56 (45)	0/57 (49)	0/59 (46)
		0.9333	0.7525	1.0000	1.0000	1.0000
	Fibroadenoma, benign	8/59 (51)	4/58 (51)	1/56 (45)	3/57 (49)	15/59 (47)
		0.8994	0.9391	0.9977	0.9700	0.0486
Gland, parathyroid	Adenoma, benign	0/58 (49)	0/58 (51)	1/56 (45)	1/57 (48)	2/56 (43)
		0.1775	NS	0.4787	0.4948	0.2157
Gland, pituitary	Adenoma, pars distalis, benign	36/59 (53)	36/59 (53)	24/56 (49)	29/58 (52)	26/59 (51)
		0.9128	0.5823	0.9842	0.9312	0.9753
	Carcinoma, pars distalis,	1/59 (51)	1/59 (52)	0/56 (46)	0/58 (49)	1/59 (46)
	Malignant	0.9346	0.7573	1.0000	1.0000	0.7262
Gland, thyroid	Adenoma, c-Cell, benign	4/59 (51)	3/58 (51)	4/57 (46)	2/58 (49)	4/59 (47)
		0.7599	0.7818	0.5830	0.8883	0.5956
	Adenoma, follicular cell, benign	4/59 (51)	1/58 (52)	0/57 (46)	1/58 (49)	4/59 (46)
		0.8557	0.9732	1.0000	0.9688	0.5830
	Carcinoma, c-Cell, malignant	2/59 (50)	0/58 (51)	0/57 (46)	0/58 (49)	0/59 (46)
		1.0000	1.0000	1.0000	1.0000	1.0000

Reference ID: 4840868

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	25 mg/kg/day Low (L) P - VC vs. L	65 mg/kg/day Mid (M) P - VC vs. M	200 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water (WC) P - VC vs. WC
	Carcinoma, follicular cell, Malignant	1/59 (50) 1.0000	0/58 (51) 1.0000	0/57 (46) 1.0000	0/58 (49) 1.0000	1/59 (46) 0.7314
Head	Carcinoma, squamous cell, Malignant	0/59 (50) 0.7462	1/59 (52) 0.5098	0/57 (46) NS	0/58 (49) NS	0/59 (46) NS
Hemolymphoreticular issue	Lymphoma, malignant	0/59 (50) 0.0429	1/59 (52) 0.5098	1/57 (46) 0.4792	3/58 (50) 0.1212	1/59 (46) 0.4792
	Sarcoma, histiocytic, malignant	0/59 (50) 0.6141	1/59 (52) 0.5098	1/57 (46) 0.4792	0/58 (49) NS	0/59 (46) NS
Kidney	Carcinoma, squamous cell, Malignant	0/59 (50) 0.2525	0/59 (52) NS	0/57 (46) NS	1/58 (50) 0.5000	0/59 (46) NS
	Schwannoma, malignant	0/59 (50) NS	0/59 (52) NS	0/57 (46) NS	0/58 (49) NS	1/59 (46) 0.4792
Large intestine, Cecum	Leiomyosarcoma, malignant	0/59 (50) NS	0/59 (52) NS	0/56 (46) NS	0/58 (49) NS	1/59 (46) 0.4792
Liver	Adenocarcinoma, malignant	0/59 (50) 0.0708	0/59 (52) NS	2/57 (46) 0.2270	2/58 (50) 0.2475	0/59 (46) NS
	Adenoma, hepatocellular, Benign	0/59 (50) 0.7462	1/59 (52) 0.5098	0/57 (46) NS	0/58 (49) NS	0/59 (46) NS
	Adenoma, Benign hepatocholangiocellular	0/59 (50) 0.4822	0/59 (52) NS	1/57 (46) 0.4792	0/58 (49) NS	0/59 (46) NS
	Carcinoma, hepatocellular, Malignant	0/59 (50) 0.2525	0/59 (52) NS	0/57 (46) NS	1/58 (50) 0.5000	0/59 (46) NS
	Cholangioma, benign	0/59 (50) 0.2487	0/59 (52) NS	0/57 (46) NS	1/58 (49) 0.4949	1/59 (46) 0.4792
Lung	Adenoma, bronchioloalveolar, benign	0/59 (50) NS	0/59 (52) NS	0/57 (46) NS	0/58 (49) NS	1/59 (46) 0.4792
	Fibroma, benign	0/59 (50) 0.4822	0/59 (52) NS	1/57 (46) 0.4792	0/58 (49) NS	0/59 (46) NS
Lymph node, Mesenteric	Hemangioma, benign	0/59 (50) 0.7462	1/59 (52) 0.5098	0/56 (46) NS	0/58 (49) NS	2/59 (46) 0.2270
Muscle, skeletal	Schwannoma, malignant	0/59 (50) NS	0/59 (52) NS	0/57 (46) NS	0/58 (49) NS	1/59 (46) 0.4792
Ovary	Cystadenocarcinoma, malignant	0/59 (50) 0.7462	1/59 (52) 0.5098	0/56 (46) NS	0/58 (49) NS	0/59 (46) NS
	Granulosa cell tumor, benign	0/59 (50) 0.4902	0/59 (52) NS	2/56 (46) 0.2270	0/58 (49) NS	1/59 (46) 0.4792
	Sex cord stromal tumor, mixed, Benign	8/59 (51) 0.8209	5/59 (52) 0.8900	4/56 (46) 0.9134	4/58 (49) 0.9300	1/59 (46) 0.9979
	Teratoma, malignant	0/59 (50) 0.6141	1/59 (52) 0.5098	1/56 (46) 0.4792	0/58 (49) NS	0/59 (46) NS
	Thecoma, benign	0/59 (50) NS	0/59 (52) NS	0/56 (46) NS	0/58 (49) NS	2/59 (46) 0.2270
Pancreas	Adenoma, islet cell, benign	1/59 (50) 1.0000	0/59 (52) 1.0000	0/56 (46) 1.0000	0/58 (49) 1.0000	0/59 (46) 1.0000

Reference ID: 4840868

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	25 mg/kg/day Low (L) P - VC vs. L	65 mg/kg/day Mid (M) P - VC vs. M	200 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water (WC) P - VC vs. WC
Pharynx	Carcinoma, squamous cell, Malignant	0/59 (50) 0.4848	0/59 (52) NS	1/57 (47) 0.4845	0/58 (49) NS	0/59 (46) NS
Site, uncertain Primary	Adenocarcinoma, malignant	0/59 (50) 0.4822	0/59 (52) NS	1/57 (46) 0.4792	0/58 (49) NS	0/59 (46) NS
Skin	Adenoma, sebaceous, benign	0/59 (50) NS	0/58 (51) NS	0/57 (46) NS	0/58 (49) NS	1/59 (46) 0.4792
	Hair follicle neoplasm, benign	0/59 (50) 0.4847	0/58 (51) NS	1/57 (46) 0.4792	0/58 (49) NS	0/59 (46) NS
Small intestine, Jejunum	Fibroma, benign	0/59 (50) 0.4848	0/59 (52) NS	1/56 (47) 0.4845	0/58 (49) NS	0/59 (46) NS
	Sarcoma, malignant	0/59 (50) 0.2525	0/59 (52) NS	0/56 (46) NS	1/58 (50) 0.5000	0/59 (46) NS
Spinal cord, Cervical	Glioma, mixed, malignant	0/59 (50) NS	0/59 (52) NS	0/57 (46) NS	0/58 (49) NS	1/59 (47) 0.4845
Subcutis	Carcinoma, ceruminous gland, Malignant	1/59 (50) 1.0000	0/59 (52) 1.0000	0/57 (46) 1.0000	0/58 (49) 1.0000	0/59 (46) 1.0000
	Fibroma, benign	1/59 (50) 1.0000	0/59 (52) 1.0000	0/57 (46) 1.0000	0/58 (49) 1.0000	0/59 (46) 1.0000
	Hemangioma, benign	0/59 (50) NS	0/59 (52) NS	0/57 (46) NS	0/58 (49) NS	2/59 (46) 0.2270
	Lipoma, benign	1/59 (50) 1.0000	0/59 (52) 1.0000	0/57 (46) 1.0000	0/58 (49) 1.0000	0/59 (46) 1.0000
	Osteosarcoma, malignant	0/59 (50) 0.7462	1/59 (52) 0.5098	0/57 (46) NS	0/58 (49) NS	0/59 (46) NS
	Sarcoma, malignant	0/59 (50) 0.2487	0/59 (52) NS	0/57 (46) NS	1/58 (49) 0.4949	0/59 (46) NS
Tail	Adenoma, sebaceous, benign	0/59 (50) 0.4848	0/59 (52) NS	1/57 (47) 0.4845	0/58 (49) NS	0/59 (46) NS
Thymus	Thymoma, benign	4/58 (49) 0.8828	2/59 (52) 0.9107	2/56 (45) 0.8774	1/57 (48) 0.9704	2/58 (45) 0.8774
Tongue	Granular cell tumor, benign	0/59 (50) NS	0/58 (51) NS	0/57 (46) NS	0/56 (47) NS	1/59 (47) 0.4845
Uterus	Adenocarcinoma, malignant	5/59 (51) 0.2109	3/59 (52) 0.8716	3/56 (46) 0.8298	6/58 (50) 0.4859	1/59 (46) 0.9818
	Adenoma, benign	0/59 (50) 0.4822	0/59 (52) NS	1/56 (46) 0.4792	0/58 (49) NS	0/59 (46) NS
	Leiomyoma, benign	0/59 (50) 0.1777	0/59 (52) NS	1/56 (46) 0.4792	1/58 (49) 0.4949	0/59 (46) NS
	Leiomyosarcoma, malignant	1/59 (50) 1.0000	0/59 (52) 1.0000	0/56 (46) 1.0000	0/58 (49) 1.0000	0/59 (46) 1.0000
	Pheochromocytoma, complex, Malignant	0/59 (50) 0.7462	1/59 (52) 0.5098	0/56 (46) NS	0/58 (49) NS	0/59 (46) NS
	Polyp, benign	6/59 (50) 0.8334	8/59 (52) 0.4182	9/56 (47) 0.2446	4/58 (50) 0.8411	9/59 (49) 0.2737
	Sarcoma, malignant	0/59 (50)	0/59 (52)	0/56 (46)	0/58 (49)	1/59 (46)

Reference ID: 4840868

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	25 mg/kg/day Low (L) P - VC vs. L	65 mg/kg/day Mid (M) P - VC vs. M	200 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water (WC) P - VC vs. WC
		NS	NS	NS	NS	0.4792
	Schwannoma, malignant	1/59 (51)	0/59 (52)	2/56 (47)	0/58 (49)	0/59 (46)
		0.6725	1.0000	0.4691	1.0000	1.0000
	Stromal sarcoma, endometrial,	0/59 (50)	1/59 (52)	0/56 (46)	0/58 (49)	0/59 (46)
	Malignant	0.7462	0.5098	NS	NS	NS
Vagina	Sarcoma, malignant	1/59 (50)	0/59 (52)	0/57 (46)	1/57 (49)	0/59 (46)
		0.4365	1.0000	1.0000	0.7475	1.0000
Whole animal	No-correlating lesion	50/59 (58)	55/59 (59)	55/57 (57)	51/58 (56)	56/59 (59)
		0.3643	0.1725	0.0499	0.3019	0.0966

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 6A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice Compared with Vehicle Control

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	5 mg/kg/day Low (L) P - VC vs. L	20 mg/kg/day Mid (M) P - VC vs. M	75 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water C (WC) P - VC vs. WC
Adipose tissue	Hemangioma, benign	0/60 (44)	0/60 (50)	0/60 (47)	1/60 (48)	0/60 (44)
		0 2540	NS	NS	0.5217	NS
Body cavity, nasal	Adenocarcinoma, malignant	0/60 (44)	0/59 (49)	0/60 (47)	1/60 (48)	0/60 (44)
		0 2553	NS	NS	0.5217	NS
	Fibroma, benign	0/60 (44)	1/59 (49)	0/60 (47)	0/60 (48)	0/60 (44)
		0.7660	0.5269	NS	NS	NS
	Odontoma, benign	1/60 (44)	0/59 (49)	0/60 (47)	0/60 (48)	0/60 (44)
		1.0000	1.0000	1.0000	1.0000	1.0000
Bone	Hemangiosarcoma,	0/60 (44)	0/60 (50)	0/60 (47)	0/60 (48)	1/60 (44)
	malignant	NS	NS	NS	NS	0.5000
Bone, femur	Hemangiosarcoma,	0/60 (44)	1/59 (50)	0/59 (46)	0/59 (47)	1/60 (44)
	malignant	0.7647	0.5319	NS	NS	0.5000
Brain	Meningioma, malignant	0/60 (44)	0/59 (49)	0/60 (47)	0/60 (48)	1/60 (44)
		NS	NS	NS	NS	0.5000
Esophagus	Carcinoma, squamous cell,	0/60 (44)	0/60 (50)	1/60 (47)	0/60 (48)	0/60 (44)
	malignant	0 5026	NS	0.5165	NS	NS
Gland, adrenal	Adenoma, adrenocortical,	1/60 (45)	0/60 (50)	3/60 (47)	0/60 (48)	2/59 (43)
	benign	0.7240	1.0000	0.3250	1.0000	0.4828
	Adrenal tumor, subcapsular,	6/60 (44)	0/60 (50)	2/60 (47)	4/60 (48)	4/59 (43)
	benign	0 3609	1.0000	0.9767	0.8753	0.8336
	Pheochromocytoma, benign	1/60 (44)	0/60 (50)	1/60 (47)	0/60 (48)	0/59 (43)
		0.7540	1.0000	0.7690	1.0000	1.0000
Gland, harderian	Adenocarcinoma, malignant	0/60 (44)	2/60 (51)	1/60 (47)	0/60 (48)	0/60 (44)
		0.7437	0.2856	0.5165	NS	NS
	Adenoma, benign	7/60 (44)	6/60 (52)	8/60 (48)	8/60 (49)	7/60 (46)
		0 3568	0.8219	0.5739	0.5910	0.6484

Reference ID: 4840868

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	5 mg/kg/day Low (L) P - VC vs. L	20 mg/kg/day Mid (M) P - VC vs. M	75 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water C (WC) P - VC vs. WC
Gland, pituitary	Carcinoma, pars intermedia, malignant	0/60 (44) 0.6317	1/57 (48) 0.5217	2/59 (48) 0.2695	0/56 (44) NS	0/59 (43) NS
Gland, salivary, submandibular	Myoepithelioma, malignant	0/60 (44) 0 2540	0/60 (50) NS	0/59 (47) NS	1/60 (48) 0.5217	0/60 (44) NS
Gland, seminal vesicle	Adenocarcinoma, malignant	0/60 (44) NS	0/60 (50) NS	0/60 (47) NS	0/60 (48) NS	1/60 (44) 0.5000
	Leiomyosarcoma, malignant	0/60 (44) 0 5026	0/60 (50) NS	1/60 (47) 0.5165	0/60 (48) NS	0/60 (44) NS
Gland, thyroid	Adenoma, follicular cell, benign	1/60 (44) 0.7286	0/59 (49) 1.0000	3/60 (48) 0.3420	0/60 (48) 1.0000	0/60 (44) 1.0000
	Carcinoma, follicular cell, malignant	0/60 (44) 0 2553	0/59 (49) NS	0/60 (47) NS	1/60 (48) 0.5217	0/60 (44) NS
Heart	Hemangiosarcoma, malignant	0/60 (44) NS	0/60 (50) NS	0/60 (47) NS	0/60 (48) NS	1/60 (44) 0.5000
Hemolymphoreticular tissue	Lymphoma, malignant	10/60 (46) 0.8990	7/60 (51) 0.9040	9/60 (49) 0.7476	5/60 (49) 0.9667	5/60 (44) 0.9469
	Sarcoma, histiocytic, malignant	0/60 (44) 0 5053	0/60 (50) NS	2/60 (48) 0.2695	0/60 (48) NS	0/60 (44) NS
Kidney	Adenoma, tubular cell, benign	0/60 (44) 0.0635	0/60 (50) NS	0/60 (47) NS	2/60 (48) 0.2695	2/60 (44) 0.2471
Large intestine, cecum	Adenocarcinoma, malignant	0/60 (44) 0 2540	0/60 (50) NS	0/60 (47) NS	1/60 (48) 0.5217	0/60 (44) NS
Liver	Adenoma, hepatocellular, benign	3/60 (44) 0.8413	5/60 (51) 0.4433	8/60 (48) 0.1283	2/60 (48) 0.8454	3/60 (44) 0.6618
	Carcinoma, hepatocellular, malignant	5/60 (45) 0.0746	6/60 (51) 0.5888	6/60 (47) 0.5312	10/60 (49) 0.1720	13/60 (44) 0.0278
	C_hepatocellular_A+C	8/60 (45) 0 2879	11/60 (51) 0.4376	14/60 (47) 0.1474	12/60 (49) 0.2948	16/60 (44) 0.0470
	Hemangiosarcoma, malignant	3/60 (45) 0.6697	0/60 (50) 1.0000	3/60 (49) 0.7013	1/60 (48) 0.9490	2/60 (44) 0.8126
	Osteosarcoma, malignant	0/60 (44) 0 5026	0/60 (50) NS	1/60 (47) 0.5165	0/60 (48) NS	1/60 (44) 0.5000
Lung	Adenoma, bronchioloalveolar, benign	6/60 (46) 0.6195	7/60 (51) 0.5803	10/60 (48) 0.2333	6/60 (49) 0.6649	4/60 (44) 0.8237
	Carcinoma, malignant bronchioloalveolar,	15/60 (46) 0.7362	27/60 (54) 0.0598	17/60 (49) 0.5012	18/60 (51) 0.4749	21/60 (48) 0.1845
	Osteosarcoma, malignant	0/60 (44) NS	0/60 (50) NS	0/60 (47) NS	0/60 (48) NS	2/60 (45) 0.2528
Pancreas	Carcinoma, islet cell, malignant	0/60 (44) 0.7672	1/60 (50) 0.5319	0/60 (47) NS	0/60 (48) NS	0/60 (44) NS
	Hemangiosarcoma, malignant	1/60 (44) 1.0000	0/60 (50) 1.0000	0/60 (47) 1.0000	0/60 (48) 1.0000	0/60 (44) 1.0000
Site, uncertain	Osteosarcoma, malignant	0/60 (44)	0/60 (50)	0/60 (47)	0/60 (48)	1/60 (44)

Reference ID: 4840868

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	5 mg/kg/day Low (L) P - VC vs. L	20 mg/kg/day Mid (M) P - VC vs. M	75 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water C (WC) P - VC vs. WC
primary		NS	NS	NS	NS	0.5000
Skin	Adenoma, sebaceous, benign	0/60 (44)	0/60 (50)	0/60 (47)	0/60 (48)	1/59 (43)
		NS	NS	NS	NS	0.4943
	Carcinoma, basal cell,	1/60 (45)	0/60 (50)	0/60 (47)	0/60 (48)	0/59 (43)
	malignant	1.0000	1.0000	1.0000	1.0000	1.0000
	Papilloma, benign	2/60 (45)	2/60 (51)	0/60 (47)	0/60 (48)	0/59 (43)
		0 9838	0.7373	1.0000	1.0000	1.0000
Small intestine,	Adenocarcinoma, malignant	1/59 (44)	0/59 (50)	0/59 (46)	0/60 (48)	0/59 (43)
duodenum		1.0000	1.0000	1.0000	1.0000	1.0000
	Adenoma, benign	0/59 (44)	0/59 (50)	1/59 (46)	0/60 (48)	0/59 (43)
		0 5000	NS	0.5111	NS	NS
Small intestine, ileum	Hemangiosarcoma, malignant	0/60 (44)	0/60 (50)	1/60 (47)	0/60 (48)	0/60 (44)
		0 5026	NS	0.5165	NS	NS
Small intestine,	Adenoma, benign	0/59 (43)	0/59 (50)	1/60 (47)	0/60 (48)	0/58 (42)
jejunum		0 5053	NS	0.5222	NS	NS
	Hemangiosarcoma, malignant	0/59 (43)	1/59 (50)	0/60 (47)	0/60 (48)	0/58 (42)
		0.7713	0.5376	NS	NS	NS
Spleen	Hemangiosarcoma, malignant	2/60 (45)	1/60 (51)	2/60 (48)	0/60 (48)	2/60 (44)
		0.8853	0.9007	0.7157	1.0000	0.6833
Stomach	Adenocarcinoma, malignant	1/60 (45)	0/60 (50)	0/60 (47)	0/60 (48)	0/60 (44)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Adenoma, benign	4/60 (44)	0/60 (50)	1/60 (47)	1/60 (48)	2/60 (44)
		0.7999	1.0000	0.9766	0.9779	0.8988
	Neuroendocrine cell tumor,	0/60 (44)	0/60 (50)	1/60 (47)	0/60 (48)	0/60 (44)
	Malignant	0 5026	NS	0.5165	NS	NS
	Osteosarcoma, malignant	0/60 (44)	0/60 (50)	0/60 (47)	0/60 (48)	1/60 (44)
		NS	NS	NS	NS	0.5000
Subcutis	Fibrosarcoma, malignant	0/60 (44)	2/60 (50)	2/60 (47)	3/60 (50)	0/60 (44)
		0 1141	0.2803	0.2640	0.1462	NS
	Hemangiosarcoma, malignant	0/60 (44)	0/60 (50)	0/60 (47)	0/60 (48)	1/60 (44)
		NS	NS	NS	NS	0.5000
	Rhabdomyosarcoma,	1/60 (44)	0/60 (50)	0/60 (47)	3/60 (49)	0/60 (44)
	Malignant	0.0534	1.0000	1.0000	0.3502	1.0000
	Schwannoma, malignant	0/60 (44)	0/60 (50)	0/60 (47)	0/60 (48)	1/60 (44)
		NS	NS	NS	NS	0.5000
Testis	Hemangiosarcoma, malignant	0/60 (44)	0/60 (50)	1/60 (47)	0/60 (48)	0/60 (44)
		0 5026	NS	0.5165	NS	NS
	Leydig cell tumor, benign	1/60 (45)	2/60 (50)	0/60 (47)	2/60 (48)	0/60 (44)
		0 3361	0.5399	1.0000	0.5245	1.0000
Urinary bladder	Carcinoma, urothelial,	0/60 (44)	0/60 (50)	1/59 (46)	0/60 (48)	0/60 (44)
	malignant	0 5000	NS	0.5111	NS	NS
	Papilloma, transitional cell,	1/60 (45)	0/60 (50)	0/59 (46)	0/60 (48)	0/60 (44)
	benign	1.0000	1.0000	1.0000	1.0000	1.0000
Whole animal	No-correlating lesion	41/60 (57)	29/60 (55)	43/60 (58)	35/60 (55)	45/60 (55)
		0 5587	0.9893	0.4773	0.8733	0.1550

Reference ID: 4840868

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	5 mg/kg/day Low (L) P - VC vs. L	20 mg/kg/day Mid (M) P - VC vs. M	75 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water C (WC) P - VC vs. WC
Whole body	Hemangiosarcoma	4/60 (45)	3/60 (52)	5/60 (49)	1/60 (48)	7/60 (45)
		0 9018	0.8374	0.5546	0.9765	0.2608

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 6B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice Compared with Vehicle Control

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	5 mg/kg/day Low (L) P - VC vs. L	30 mg/kg/day Mid (M) P - VC vs. M	160 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water C (WC) P - VC vs. WC
Adipose tissue	Hemangiosarcoma, malignant	0/60 (47)	0/60 (49)	0/60 (47)	1/60 (47)	0/60 (45)
		0.2474	NS	NS	0.5000	NS
Body cavity, Abdominal	Hemangiosarcoma, malignant	0/60 (47)	0/60 (49)	1/60 (47)	0/60 (47)	0/60 (45)
		0.4947	NS	0.5000	NS	NS
Body cavity, thoracic	Liposarcoma, malignant	0/60 (47)	0/60 (49)	1/60 (47)	0/60 (47)	0/60 (45)
		0.4947	NS	0.5000	NS	NS
	Lymphoma, malignant	0/60 (47)	1/60 (49)	0/60 (47)	0/60 (47)	0/60 (45)
		0.7526	0.5104	NS	NS	NS
Bone, femur	Hemangioma, benign	0/60 (47)	0/59 (48)	1/60 (47)	0/60 (47)	0/60 (45)
		0.4974	NS	0.5000	NS	NS
	Hemangiosarcoma, malignant	0/60 (47)	0/59 (48)	1/60 (47)	0/60 (47)	1/60 (45)
		0.4974	NS	0.5000	NS	0.4891
Bone, sternum	Osteosarcoma, malignant	0/60 (47)	1/60 (49)	0/60 (47)	0/60 (47)	0/60 (45)
		0.7526	0.5104	NS	NS	NS
Brain	Astrocytoma, malignant	0/60 (47)	0/60 (49)	0/60 (47)	0/60 (47)	1/60 (46)
		NS	NS	NS	NS	0.4946
Cervix	Carcinoma, squamous cell, malignant	0/58 (46)	1/54 (45)	0/59 (46)	0/54 (43)	0/58 (45)
		0.7444	0.4945	NS	NS	NS
	Leiomyosarcoma, malignant	0/58 (46)	0/54 (45)	0/59 (46)	1/54 (43)	0/58 (45)
		0.2389	NS	NS	0.4831	NS
	Polyp, benign	0/58 (46)	1/54 (45)	0/59 (46)	0/54 (43)	0/58 (45)
		0.7444	0.4945	NS	NS	NS
Gland, adrenal	Adenoma, adrenocortical, benign	1/60 (47)	0/59 (48)	0/60 (47)	0/60 (47)	0/60 (45)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Adrenal tumor, subcapsular, benign	1/60 (48)	2/59 (49)	3/60 (48)	0/60 (47)	0/60 (45)
		0.8562	0.5078	0.3085	1.0000	1.0000
	Carcinoma, adrenocortical, malignant	0/60 (47)	0/59 (48)	0/60 (47)	0/60 (47)	1/60 (45)
		NS	NS	NS	NS	0.4891
	Pheochromocytoma, benign	0/60 (47)	0/59 (48)	0/60 (47)	1/60 (47)	0/60 (45)
		0.2487	NS	NS	0.5000	NS
	Pheochromocytoma, malignant	0/60 (47)	1/59 (48)	0/60 (47)	0/60 (47)	1/60 (45)
		0.7513	0.5053	NS	NS	0.4891

Reference ID: 4840868

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	5 mg/kg/day Low (L) P - VC vs. L	30 mg/kg/day Mid (M) P - VC vs. M	160 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water C (WC) P - VC vs. WC
Gland, harderian	Adenocarcinoma, malignant	0/60 (47)	0/60 (49)	1/60 (47)	0/60 (47)	1/60 (45)
		0.4947	NS	0.5000	NS	0.4891
	Adenoma, benign	3/60 (48)	1/60 (49)	2/60 (47)	4/60 (47)	4/60 (45)
		0.1563	0.9438	0.8126	0.4881	0.4636
Gland, mammary	Adenocarcinoma, malignant	0/56 (44)	0/52 (42)	0/58 (46)	1/54 (42)	0/54 (41)
		0.2414	NS	NS	0.4884	NS
Gland, parathyroid	Adenoma, benign	0/51 (41)	0/57 (47)	0/54 (42)	0/49 (40)	1/49 (36)
		NS	NS	NS	NS	0.4675
Gland, pituitary	Adenoma, pars distalis, benign	1/59 (46)	0/57 (47)	1/60 (47)	1/58 (45)	2/60 (45)
		0.3835	1.0000	0.7581	0.7473	0.4917
	Adenoma, pars intermedia, benign	1/59 (47)	1/57 (47)	1/60 (48)	2/58 (46)	1/60 (45)
		0.2521	0.7527	0.7579	0.4918	0.7418
	Carcinoma, pars distalis, malignant	0/59 (46)	0/57 (47)	0/60 (47)	0/58 (45)	1/60 (45)
		NS	NS	NS	NS	0.4945
	Carcinoma, pars intermedia, malignant	0/59 (46)	0/57 (47)	0/60 (47)	2/58 (46)	0/60 (45)
		0.0602	NS	NS	0.2473	NS
Gland, thyroid	Adenoma, follicular cell, benign	0/60 (47)	0/60 (49)	0/60 (47)	1/57 (46)	0/60 (45)
		0.2434	NS	NS	0.4946	NS
	Carcinoma, follicular cell, malignant	0/60 (47)	0/60 (49)	1/60 (47)	0/57 (46)	0/60 (45)
		0.4921	NS	0.5000	NS	NS
Hemolymphoreticular tissue	Leukemia, granulocytic, malignant	0/60 (47)	0/60 (49)	2/60 (48)	0/60 (47)	0/60 (45)
		0.4947	NS	0.2526	NS	NS
	Lymphoma, malignant	18/60 (50)	20/60 (53)	21/60 (51)	20/60 (50)	26/60 (53)
		0.3813	0.5089	0.3709	0.4185	0.1272
	Sarcoma, histiocytic, malignant	5/60 (50)	2/60 (49)	2/60 (48)	4/60 (48)	2/60 (46)
		0.3692	0.9410	0.9376	0.7358	0.9303
Liver	Adenoma, hepatocellular, benign	0/60 (47)	2/60 (49)	1/60 (47)	2/60 (47)	0/60 (45)
		0.1948	0.2579	0.5000	0.2473	NS
	Carcinoma, hepatocellular, malignant	0/60 (47)	0/60 (49)	0/60 (47)	0/60 (47)	1/60 (45)
		NS	NS	NS	NS	0.4891
Lung	Adenoma, benign bronchioloalveolar,	7/60 (47)	7/60 (50)	6/60 (48)	7/60 (48)	9/60 (46)
		0.4659	0.6607	0.7377	0.6298	0.3739
	Carcinoma, malignant bronchioloalveolar	15/60 (49)	10/60 (51)	8/60 (48)	10/60 (48)	7/60 (46)
		0.6671	0.9337	0.9689	0.9091	0.9793
Lymph node	Hemangiosarcoma, malignant	0/59 (47)	0/60 (49)	1/60 (47)	0/60 (47)	0/58 (43)
		0.4947	NS	0.5000	NS	NS
Muscle, skeletal	Hemangiosarcoma, malignant	0/60 (47)	0/59 (48)	0/60 (47)	1/60 (47)	1/60 (45)
		0.2487	NS	NS	0.5000	0.4891
Ovary	Adenocarcinoma, malignant	0/60 (47)	0/59 (48)	0/60 (47)	1/60 (47)	0/60 (45)
		0.2487	NS	NS	0.5000	NS
	Adenoma, benign	0/60 (47)	0/59 (48)	0/60 (47)	0/60 (47)	1/60 (45)
		NS	NS	NS	NS	0.4891
	Carcinoma, adrenocortical, malignant	0/60 (47)	0/59 (48)	0/60 (47)	0/60 (47)	1/60 (45)
		NS	NS	NS	NS	0.4891

Reference ID: 4840868

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	5 mg/kg/day Low (L) P - VC vs. L	30 mg/kg/day Mid (M) P - VC vs. M	160 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water C (WC) P - VC vs. WC
	Cystadenoma, benign	1/60 (47)	4/59 (48)	4/60 (47)	0/60 (47)	2/60 (45)
		0.9409	0.1874	0.1807	1.0000	0.4835
	Granulosa cell tumor, benign	0/60 (47)	0/59 (48)	0/60 (47)	0/60 (47)	1/60 (46)
		NS	NS	NS	NS	0.4946
	Hemangioma, benign	4/60 (48)	1/59 (49)	1/60 (47)	0/60 (47)	0/60 (45)
		0.9828	0.9734	0.9704	1.0000	1.0000
	Hemangiosarcoma,	0/60 (47)	0/59 (48)	0/60 (47)	0/60 (47)	1/60 (45)
	malignant	NS	NS	NS	NS	0.4891
	Luteoma, benign	2/60 (47)	3/59 (49)	4/60 (47)	2/60 (47)	2/60 (45)
		0.6034	0.5199	0.3385	0.6916	0.6750
	Sertoli cell tumor, benign	0/60 (47)	0/59 (48)	0/60 (47)	0/60 (47)	1/60 (45)
		NS	NS	NS	NS	0.4891
	Sex cord stromal tumor,	0/60 (47)	1/59 (48)	0/60 (47)	1/60 (47)	0/60 (45)
	mixed, benign	0.3122	0.5053	NS	0.5000	NS
	Thecoma, benign	1/60 (47)	1/59 (48)	0/60 (47)	1/60 (47)	2/60 (45)
		0.5323	0.7579	1.0000	0.7527	0.4835
Pancreas	Carcinoma, islet cell,	1/60 (48)	0/58 (47)	0/60 (47)	0/60 (47)	0/59 (44)
	malignant	1.0000	1.0000	1.0000	1.0000	1.0000
Skin	Keratoacanthoma, benign	0/60 (47)	1/60 (49)	0/60 (47)	0/60 (47)	0/60 (45)
		0.7526	0.5104	NS	NS	NS
	Mast cell tumor, benign	0/60 (47)	1/60 (49)	0/60 (47)	0/60 (47)	0/60 (45)
		0.7526	0.5104	NS	NS	NS
Spleen	Hemangiosarcoma,	1/60 (48)	1/60 (49)	3/60 (47)	2/60 (47)	2/60 (45)
	malignant	0.2825	0.7577	0.3005	0.4920	0.4755
Stomach	Adenoma, benign	0/60 (47)	0/60 (49)	1/60 (47)	1/60 (47)	0/60 (45)
		0.1832	NS	0.5000	0.5000	NS
	Carcinoma, squamous cell,	1/60 (47)	0/60 (49)	0/60 (47)	0/60 (47)	0/60 (45)
	malignant	1.0000	1.0000	1.0000	1.0000	1.0000
Subcutis	Fibrosarcoma, malignant	1/60 (47)	1/60 (50)	1/60 (47)	0/60 (47)	0/60 (45)
		0.8266	0.7678	0.7527	1.0000	1.0000
	Hemangiosarcoma,	0/60 (47)	0/60 (49)	0/60 (47)	1/60 (47)	0/60 (45)
	malignant	0.2474	NS	NS	0.5000	NS
	Rhabdomyosarcoma,	1/60 (47)	1/60 (49)	0/60 (47)	0/60 (47)	1/60 (45)
	malignant	0.9398	0.7629	1.0000	1.0000	0.7418
	Sarcoma, malignant	0/60 (47)	0/60 (49)	0/60 (47)	1/60 (47)	0/60 (45)
		0.2474	NS	NS	0.5000	NS
	Schwannoma, malignant	1/60 (47)	0/60 (49)	0/60 (47)	0/60 (47)	0/60 (45)
		1.0000	1.0000	1.0000	1.0000	1.0000
Thymus	Hemangioma, benign	0/59 (47)	0/60 (49)	1/60 (47)	0/59 (46)	0/60 (45)
		0.4921	NS	0.5000	NS	NS
	Hemangiosarcoma,	1/59 (47)	0/60 (49)	0/60 (47)	0/59 (46)	0/60 (45)
	malignant	1.0000	1.0000	1.0000	1.0000	1.0000
Tongue	Papilloma, benign	1/60 (47)	0/60 (49)	0/60 (47)	0/60 (47)	0/60 (45)
		1.0000	1.0000	1.0000	1.0000	1.0000
Urinary bladder	Carcinoma, urothelial,	0/59 (47)	0/59 (48)	1/60 (47)	0/60 (47)	0/60 (45)

Reference ID: 4840868

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	5 mg/kg/day Low (L) P - VC vs. L	30 mg/kg/day Mid (M) P - VC vs. M	160 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water C (WC) P - VC vs. WC
	malignant	0.4974	NS	0.5000	NS	NS
Uterus	Adenocarcinoma, malignant	0/60 (47)	0/60 (49)	0/60 (47)	1/60 (47)	1/60 (45)
		0.2474	NS	NS	0.5000	0.4891
	Adenoma, benign	0/60 (47)	0/60 (49)	1/60 (47)	0/60 (47)	0/60 (45)
		0.4947	NS	0.5000	NS	NS
	Hemangioma, benign	1/60 (47)	2/60 (49)	0/60 (47)	1/60 (47)	0/60 (45)
		0.6207	0.5158	1.0000	0.7527	1.0000
	Hemangiosarcoma,	2/60 (48)	2/60 (49)	1/60 (48)	5/60 (47)	3/60 (45)
	malignant	0.0550	0.6992	0.8789	0.2089	0.4691
	Leiomyoma, benign	2/60 (47)	1/60 (50)	2/60 (47)	1/60 (47)	2/60 (46)
		0.6364	0.8900	0.6916	0.8790	0.6834
	Leiomyosarcoma, malignant	2/60 (47)	1/60 (49)	1/60 (47)	0/60 (47)	2/60 (45)
		0.9224	0.8865	0.8790	1.0000	0.6750
	Polyp, benign	2/60 (48)	4/60 (50)	0/60 (47)	2/60 (47)	4/60 (47)
		0.6075	0.3585	1.0000	0.6835	0.3286
	Schwannoma, benign	1/60 (47)	0/60 (49)	0/60 (47)	0/60 (47)	0/60 (45)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Schwannoma, malignant	0/60 (47)	0/60 (49)	1/60 (47)	0/60 (47)	0/60 (45)
		0.4947	NS	0.5000	NS	NS
	Stromal sarcoma,	0/60 (47)	1/60 (49)	0/60 (47)	0/60 (47)	0/60 (45)
	endometrial, malignant	0.7526	0.5104	NS	NS	NS
Vagina	Papilloma, benign	1/58 (46)	0/59 (48)	0/58 (47)	0/58 (45)	0/60 (45)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Polyp, benign	0/58 (46)	0/59 (48)	1/58 (47)	0/58 (45)	0/60 (45)
		0.4946	NS	0.5054	NS	NS
Whole animal	No-correlating lesion	46/60 (56)	41/60 (57)	43/60 (57)	38/60 (56)	38/60 (56)
		0.9071	0.9354	0.8647	0.9758	0.9758
Whole body	Hemangiosarcoma	6/60 (49)	2/60 (49)	5/60 (48)	6/60 (47)	5/60 (45)
		0.2131	0.9704	0.7260	0.5904	0.6867

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Reference ID: 4840868

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

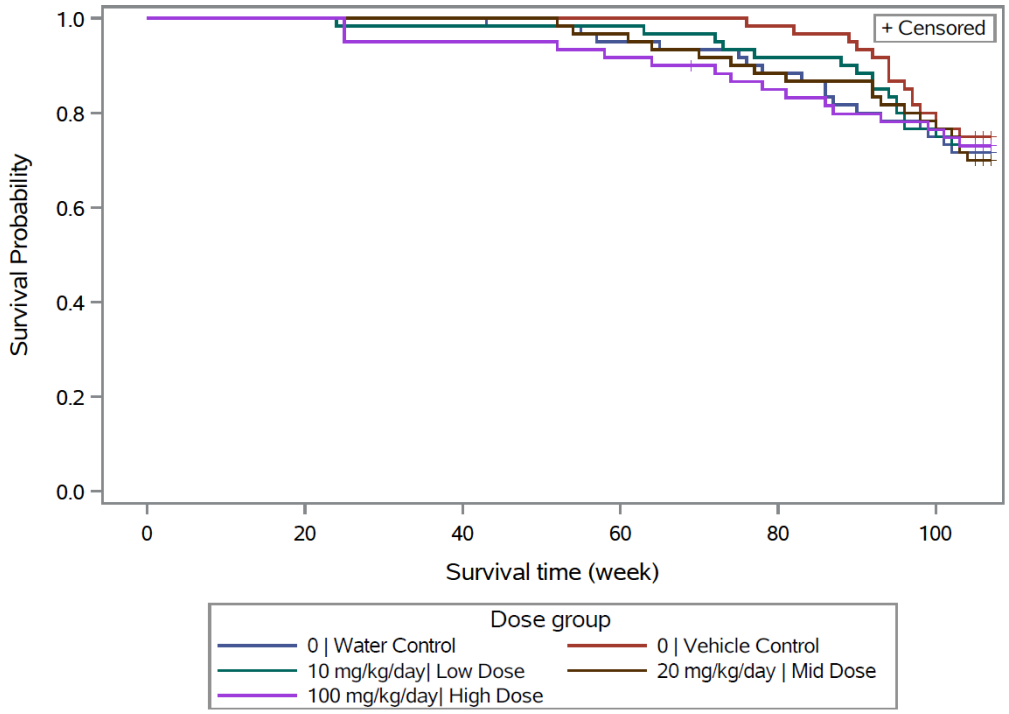

Figure 1B: Kaplan-Meier Survival Functions for Female Rats

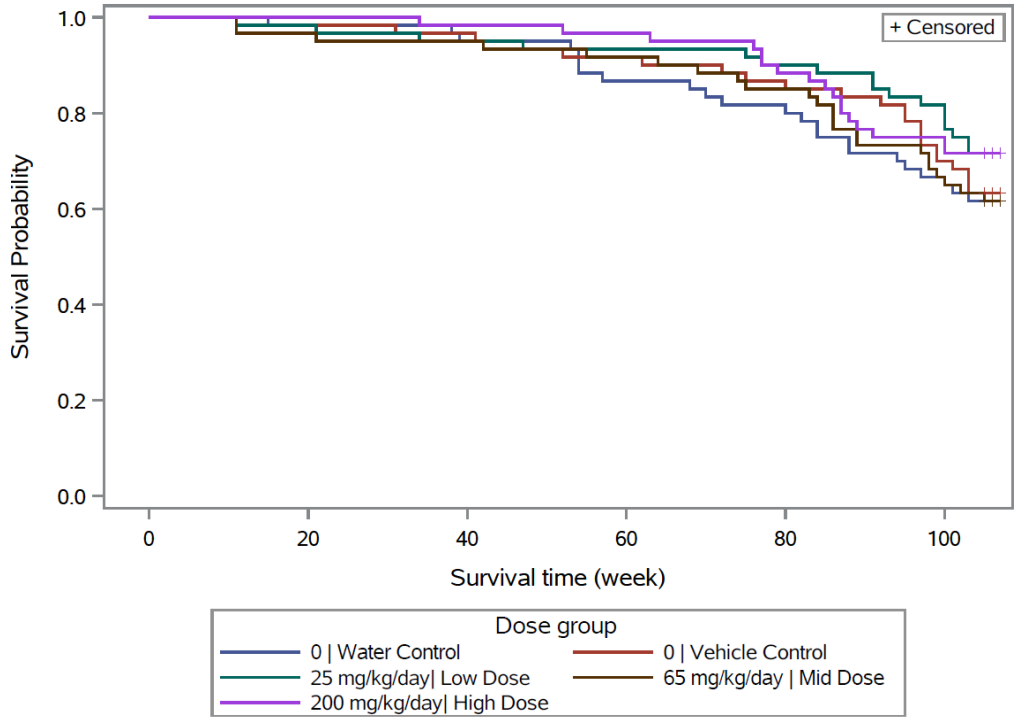

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Figure 2A: Kaplan-Meier Survival Functions for Male Mice

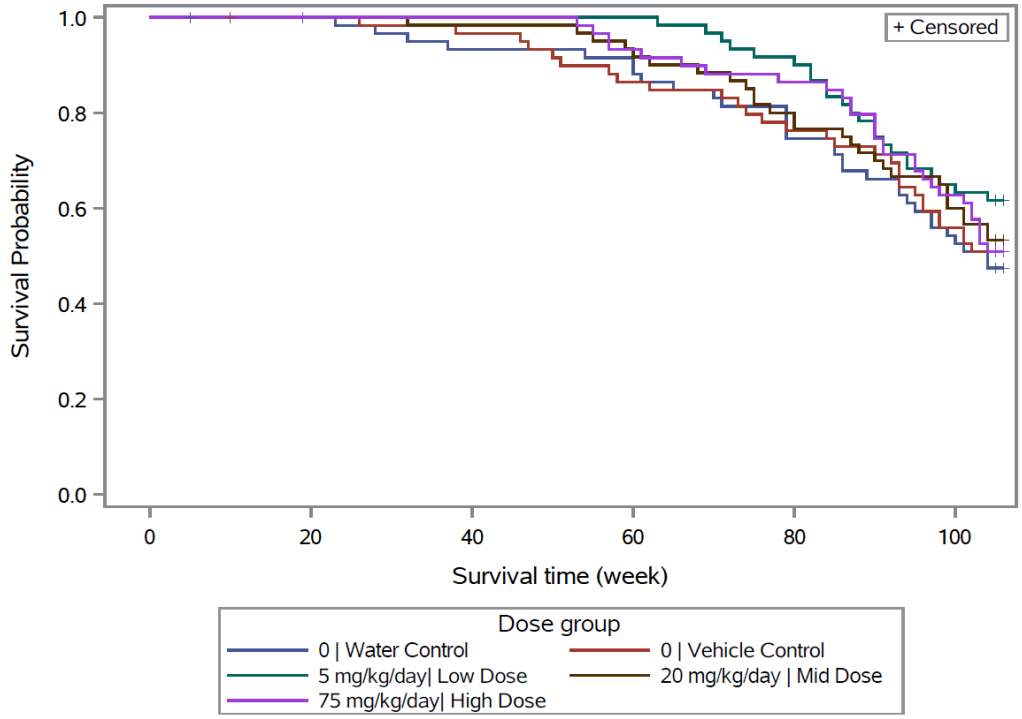
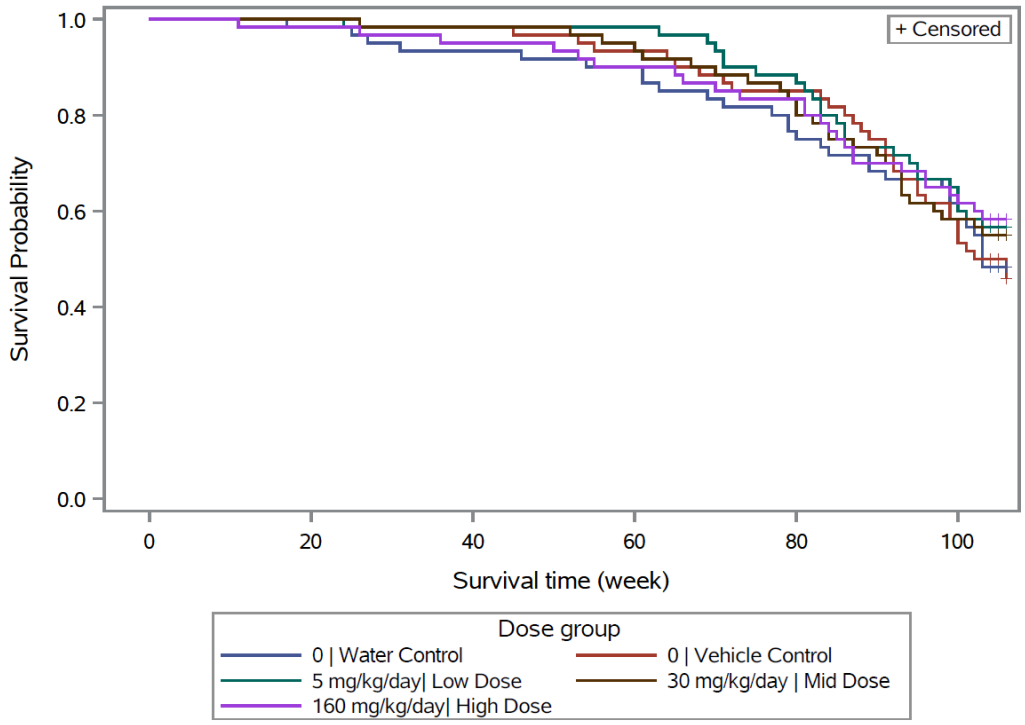


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



Reference ID: 4840868

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/s/

FENG ZHOU
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KARL K LIN
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Concur with review.

Clinical Review Memorandum

Division of Hepatology and Nutrition, Drug-Induced Liver Injury (DILI) Team
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

NDA	*215206*
Drug name	Atogepant
Sponsor	AbbVie, Inc
Review item	*IR Response (SDN 19, SN 19)*
Requesting Division	Division of Neurology-2 (DN2)
Author name	Paul H. Hayashi, MD, MPH
Date	*Jul 7, 2021*

I. OVERALL ASSESSMENT AND RECOMMENDATION(S)

The response data provided by the sponsor does not warrant labeling a difference in liver injury risk for Japanese, or Asians overall. While the ongoing open-label extension (OLE) study (3101-306-002) indicates a higher rate of transaminase elevation than the overall rate in the NDA's Integrated Summary of Safety (ISS), no such increase is seen for Asians in the ISS nor the randomized clinical trial (RCT) from which patients entered 3101-306-002. The rates of transaminase elevations in the OLE are 2.7% for 5x ULN and 1% for >10-20x ULN without any cases of hyperbilirubinemia. The number of Asians in the ISS is too low to draw conclusions. However, the RCT had 248 Asians with only 1 patient having elevation in transaminases which was unlikely attributable to the investigational product (IP). The RCT remains blinded. The OLE has no comparator arm. Therefore, we cannot definitively assign an increased risk of DILI amongst Japanese, or Asians in general, based on these data.

II. BACKGROUND

The DILI team has been helping DN2 with assessing DILI risk in this NDA since February 18, 2021. Atogepant is an oral small molecule antagonist of the calcitonin gene related peptide (CGRP) receptor. It is under NDA review for the prevention of migraine headaches in adults. Other agents in this class have had problems with drug-induced liver injury (DILI). We were asked by the Division of Neurology 2 (DN2) to review "patients with abnormal LFTs for potential liver toxicity" associated with Atogepant with particular attention to a severe adverse event that resulted in fatality. We werw asked to give opinion on whether investigational product (IP) "carries a risk of potential liver toxicity and, if so, how this may inform labeling."

Our full written consult is in process, but thus far we have not seen significant liver toxicity potential that threatens approval. At our suggestion, an IR was sent

Reference ID: 4822400

on Jun 2, 2021 asking for more information about potential increased risk of DILI amongst Japanese in a trial outside the NDA's ISS. The response arrived on Jun 7, 2021 (SDN 19, SN 19). Of note, the response had safety data through May 26, 2021, so the same data are contained in the Safety Report submitted June 30, 2021 (Sq 22, SDN 22, 5.3.5.3).

III. SIGNIFICANT REVIEW FINDINGS

Review of Sponsor Response:

a. Response to request 1: We had requested clarification whether the ongoing, 52-week, open label study 3101-306-002 is restricted to Japanese nationals. The sponsor replied that it is so restricted. Therefore, the overall rates of enzyme elevations and DILI cases for this study reflect Japanese nationality rates and can be compared to other race or nationality groups in the ISS.
b. Response to request 2: We requested current enrollment status of 3101-306-002. The sponsor replied that 113 patients had enrolled and included in the safety population as of May 26, 2021. Therefore, we presume that all 113 have taken at least one dose of AGPT at 60 mg/d. There is no comparator arm in this study.
c. Response to request 3: We requested elevation in liver test rates for Study 3101-306-002 in tabular form. See Table 1. The rates of ALT and AST elevations are higher compared to ISS Group 2 of 1198 patients also on 60 mg/d (see Section 4.5, Table 4 above). For example, the rate for ALT or AST elevation >3x and >5x ULN were 2.7% to 4.4% and 1.8% to 2.7% for Japanese nationals, respectively. The rates of elevations in ALT *or* AST at the same multiples of ULN were 1.4% and 0.7% for ISS Group 2.

Reference ID: 4822400

Allergan
Protocol FDA Request

Atogepant
Page 1 of 1

Table 1

Table 1-3
Postbaseline Hepatic-Related Laboratory Values of Clinical Interest
Study 3101-306-002
Safety Population

Lab Endpoint Criteria	Open-label Atogepant 60 mg QD for Japanese patients (N=113) (PY [1] = 50.4) n (%)	Incidence rate per 100 patient exposure years [2]
ALT		
>= 1*ULN	9 (8.0)	17.8
>= 3*ULN	5 (4.4)	9.9
>= 5*ULN	3 (2.7)	5.9
>= 10*ULN	1 (0.9)	2.0
>= 20*ULN	1 (0.9)	2.0
AST		
>= 1*ULN	7 (6.2)	13.9
>= 3*ULN	3 (2.7)	5.9
>= 5*ULN	2 (1.8)	4.0
>= 10*ULN	1 (0.9)	2.0
>= 20*ULN	1 (0.9)	2.0
Alkaline Phosphatase		
>= 2*ULN	1 (0.9)	2.0
>= 3*ULN	0 (0.0)	0.0
Total Bilirubin		
>= 2*ULN	0 (0.0)	0.0
>= 5*ULN	0 (0.0)	0.0
>= 8*ULN	0 (0.0)	0.0

Notes: Based on study 3101-306-002 with the data cut as of 26-May-2021.
PY = patient exposure years. PY for a patient is calculated as (Study treatment end date-study treatment start date+1)/365.25.
[1] Total patient exposure years is sum of each patient's exposure years in the safety population.
[2] Incidence rate per 100 patient exposure years = (number of patients with event/total patient exposure years)*100.
N = number of patients in the Safety Population.
n = number of patients within a specific category.
Percentages are alculated as 100 x (n/N).

Program: /RIsas/sasprog/cgp/FDARequest/f20210602/production/programs/tables/t01-03.sas FINAL 2021-06-03 17:17:41

The sponsor also provided an additional case (patient ID: [redacted] (b) (6), Study 3101-306-002) of transaminase elevation over >3x ULN that occurred between [redacted] (b) (6). This case was not included in the 120-day report reviewed in Section 6.0. We assessed this case as unlikely DILI due to AGPT. Acetaminophen 1-3 grams IV daily x 6 days is a more likely explanation. AGPT was continued without dose reduction through complete dechallenge. ALT rose to 3-5x ULN without hyperbilirubinemia. This case is included in the table above.

d. We requested liver enzyme elevation rates by race, particularly Asians, in Groups 1 and 2 of the ISS. We also requested these rates for the blinded, RCT, 3101-303-002, from which Japanese patients entered the open label extension (OLE) study, 3101-306-002. The sponsor provided tables for this request (Seq 19, SDN 19, 1.11.3, pages 11-20).

<u>Group 1 ISS</u>: There were no enzyme elevations in Asians, but there were only 20 Asians out of 1727 total. Nationalities were not recorded. While blacks on AGPT had higher crude occurrence rate and incidence rates per 100-person year exposure compared to whites the difference between blacks on placebo and AGPT was equivocal. (see table x)

Reference ID: 4822400

Group 1, table 2 displays crude occurrence rate (%) and incidence rates per 100-patient exposure years (%; incidence rate), for whites and blacks by placebo and atogepant (AGPT) arms. Numbers of patients in each arm are in parentheses.

Table 2	White		Black	
	Placebo (331)	AGPT (1049)	Placebo (69)	AGPT (223)
ALT > 3x	1.2; 5.6	0.5; 2.2	1.4; 7.2	2.2; 11
ALT > 5x	0.3; 1.4	0.3; 1.3	1.4; 7.2	0.0; 0.0
AST >3x	0.9; 4.2	0.6; 2.7	1.4; 7.2	0.9; 4.4
AST >5x	0.6; 2.8	0.2; 0.9	1.4; 7.2	0.4; 2.2

Group 2 ISS: For Group 2, there were similarly very few Asians (n = 26), no nationality data and no cases of enzyme elevations. Again, blacks had higher crude rates and incidence per 100 patient-year exposure compared to whites, but here, the rates amongst blacks on AGPT was higher than blacks on standard of care.

Group 2, table 3 displays crude occurrence rate (%) and incidence rates per 100-patient exposure years (%; incidence rate), for whites and blacks by standard of care and AGPT arms. Numbers of patients in each arm are in parentheses.

Table 3	White		Black	
	Std of care (145)	AGPT (994)	Std of care (38)	AGPT (186)
ALT > 3x	2.1; 2.7	0.8; 1.1	0.0; 0.0	2.7; 4.2
ALT > 5x	0.7; 0.9	0.4; 0.6	0.0; 0.0	1.1; 1.7
AST >3x	2.8; 3.7	0.7; 1.0	0.0; 0.0	2.7; 4.2
AST >5x	0.0; 0.0	0.3; 0.4	0.0; 0.0	1.6; 2.5

Reference ID: 4822400

Study 3101-303-002: In this blinded RCT, the rates of transaminase elevations were low across all races. Only one Asian out of 248 had an ALT 3-5x ULN. No unblinded data were provided. A narrative was provided for the one Asian case. We assessed it as possible to unlikelyDILI due to AGPT, though if DILI is present than there was partial tolerance with improvement in liver enzymes while still on IP. Otherwise, fatty liver and autoimmune hepatitis compete well. Transaminases rose to 2.6 to 3.5x ULN at day 14. Patient had gained 3.2 kg from screening to day 14. IP was held on Day 16 and then restarted on Day 28. Transaminases fell to 1.0x to 1.7x ULN through day 56 while still on IP. ANA was 1:40. Other serologic evaluations were negative. Imaging showed fatty liver.

IV. CONCLUSIONS

The data in the sponsor's response do not warrant labeling a difference in liver injury risk for Japanese or Asians. While the ongoing OLE study of 113 Japanese patients so far enrolled (3101-306-002) indicates a higher rate of transaminase elevation than the overall rate in this NDA's ISS, no such increase is seen for Asians in the ISS nor the RCT from which patients entered 3101-306-002. We acknowledge that the number of Asians in the ISS is too low to draw conclusions. However, the RCT had 248 Asians randomized across 3 arms (placebo, AGPT 30 mg bid, AGPT 60 mg/d) for 12 weeks of treatment. Only 1 of 248 Asians had elevation in transaminases which was unlikely attributable to the IP. The RCT remains blinded. At least 113 of those 248 were Japanese and enrolled in 3101-306-002. This OLE has no comparator arm. The rates of transaminase elevations in the OLE are 2.7% for 5x ULN and 1% for >20x ULN without any cases of hyperbilirubinemia. Therefore, we cannot definitively assign an increased risk of DILI for Japanese, or Asians, based on these data.

Similarly, we cannot assign a difference in DILI risk for blacks. There was a higher rate of transaminase elevations in blacks on AGPT in the Group 2 ISS, but the number of blacks on placebo is small at 38 and may not offer a large enough comparator arm. The number of blacks in the Group 1 ISS was larger (69 placebo vs. 223 AGPT), and no clear differences were seen in transaminase elevations amongst blacks. Therefore, the data are equivocal.

V. RECOMMENDED REGULATORY ACTION(S)

We do not recommend any regulatory action for this IR response currently. We have informed DN2 of our assessment. We will continue to collaborate with them during their NDA review. Our full written consult assessing DILI risk in this NDA is pending our further review and communication with DN2.

Reference ID: 4822400

Abbreviations:
AGPT: atogepant
DILI: drug-induced liver injury
IP: investigational product (AGPT or placebo)
IR: information request
ISS: integrated summary of safety
NDA: new drug application
OLE: open-label extension
RCT: randomized control trial
ULN: upper limit of normal

Paul H. Hayashi -S

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DILI Team Lead, Division of Hepatology and Nutrition
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Reference ID: 4822400

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Clinical Review Memorandum

Division of Hepatology and Nutrition, Drug-Induced Liver Injury (DILI) Team
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

NDA	*215206*
Drug name	Atogepant
Sponsor	AbbVie, Inc
Review item	*120 Day Clinical/Safety Update (SDN 22, SN 22)*
Requesting Division	Division of Neurology-2 (DN2)
Author name	Paul H. Hayashi, MD, MPH
Date	*Jul 7, 2021*

I. OVERALL ASSESSMENT AND RECOMMENDATION(S)

This 120-day Safety Update Report included 4 new cases of elevation in transaminases. We assessed 3 as unlikely and 1 as possible DILI due to investigational product (IP). None had hyper bilirubinemia. The possible DILI case is still on IP with monitoring of improved transaminases. No new cases had transaminase elevations over 8x ULN. These data do not significantly change our ongoing assessment of this NDA's DILI risk. We have no recommendations for this report at this time.

II. BACKGROUND

The DILI team has been helping DN2 with assessing DILI risk in this NDA since February 18, 2021. Atogepant is an oral small molecule antagonist of the calcitonin gene related peptide (CGRP) receptor. It is under NDA review for the prevention of migraine headaches in adults. Other agents in this class have had problems with drug-induced liver injury (DILI). We were asked by the Division of Neurology 2 (DN2) to review "patients with abnormal LFTs for potential liver toxicity" associated with Atogepant with particular attention to a severe adverse event that resulted in fatality. We were asked to give opinion on whether investigational product (IP) "carries a risk of potential liver toxicity and, if so, how this may inform labeling."

Our full written consult is in process, but thus far we have not seen significant liver toxicity potential that threatens approval. Much of the data in this Safety Report submitted June 30, 2021 (Sq 22, SDN 22, 5.3.5.3) appear in the Jun 7, 2021 (SDN 19, SN 19) response to information request (IR), for which we submitted a review also on July 7, 2021. Our full written consultation for regarding DILI risk for this NDA is pending.

Reference ID: 4822597

III. SIGNIFICANT REVIEW FINDINGS

Summary review of 4 cases:

Adequate narrative and tabular lab data were provided for these four cases. We reviewed all four and our Causality Score assessments are shown below along with other data. Only one was considered possibly due to DILI from AGPT. All cases remained blinded to their treatment assignment in the RCT.

ID	Study	Causality Score*	Alternate diagnosis	Age	Gender	Race	Symptoms	Hy's Law	Latency from start drug (da)	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)^	R value peak (ALT)	R value peak (AST)
(b) (6)	3101-303-002	5	Myositis	24	M	White	No	No	14	77	306	115	1	2.33	8.50
	3101-303-002	5	HEV; EBV;	27	F	White	No	No	118	212	167	377	1	1.96	1.42
	3101-303-002	4	NAFLD; AIH	34	F	Asian	No	No	13	116	95	115	1	3.52	2.64
	3101-306-002	5	IV APAP	44	M	Asian	No	No	196	154	67	104	1	4.53	1.97

^all noted as "normal"; imputed 1.0

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

All cases remain blinded to RCT treatment assignment. Only 303615003 entered OLE after RCT.

Liver Test Data for Safety Population.

The Report also contains liver test elevation data for this overall safety population in several tables (Appendix 2). No significant changes were seen. Study 3101-306-002 which is an OLE study outside this NDA's ISS is ongoing in Japan and has 113 patients thus far enrolled. The amount of transaminase elevation is higher than the overall ISS (see Table 14.3-3.3, SDN 22, SN 22, 5.3.5.3). We already reviewed this issue via an information request (IR) and sponsor response. Please see our review of the sponsor's IR response (July 7, 2021) in DARRTs.

IV. CONCLUSIONS

None of the four new cases raise concerns for DILI beyond what we have already seen for this NDA. Tabular data of liver tests elevations for the overall safety population in this report did not have significant changes.

V. RECOMMENDED REGULATORY ACTION(S)

We do not recommend regulatory action for this 120-Day Safety Update Report. We will continue to collaborate with DN2 during their NDA review. Our full written consult assessing DILI risk in this NDA is pending our further review and communication with DN2.

Abbreviations:
AGPT: atogepant
DILI: drug-induced liver injury
IP: investigational product (AGPT or placebo)
IR: information request
ISS: integrated summary of safety
NDA: new drug application
OLE: open-label extension

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RCT: randomized control trial
ULN: upper limit of normal

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Reference ID: 4822597

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