

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761367Orig1s000

INTEGRATED REVIEW

Cross-Discipline Team Leader Memo

Application Type	BLA
Application Number	761367
Applicant	CSL Behring
Date of Submission	December 17, 2024
PDUFA Goal Date	June 17, 2025
Division/Office	DPACC/OII
Review Completion Date	June 03, 2025
Proprietary Name/Established Name	Andembry/ garadacimab
Code Name	CSL312
Pharmacologic Class	Activated Factor XII (FXIIa) inhibitor, monoclonal antibody
Dose and Dosing Regimen	400mg SC loading dose followed by 200mg SC every month
Dosage Form(s)	• 200mg/1.2mL solution in single-dose prefilled autoinjector • 200mg/1.2mL solution in single-dose prefilled syringe with needle safety device
Proposed Indication	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older
Recommended Regulatory Action	Approval

Executive Summary

The Applicant (CSL Behring) provided a Complete Response (CR) resubmission to biologics licensing application (BLA) 761367 for garadacimab, a fully human IgG4 monoclonal antibody that targets the catalytic subunit of Factor XIIa, for the proposed indication of prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and adolescent patients 12 years and older. The proposed recommended dosage of garadacimab is a 400mg subcutaneous (SC) injection loading dose followed by 200mg SC injection every month. HAE is a rare, autosomal dominant genetic condition, caused by reduced or absent functional C1 esterase inhibitor (C1-INH), which is clinically characterized by episodic and unpredictable attacks of angioedema involving the skin and/or submucosal surfaces, including the gastrointestinal tract, genitourinary tract, and/or throat and upper airway, which can be potentially life-threatening. Garadacimab, an FXIIa inhibitor, represents a novel therapeutic target for HAE.

After an initial refusal to file due to unavailability of rabbit pyrogen test results, the original BLA application was resubmitted on October 13, 2023, and filed on December 12, 2023. The submitted clinical program was adequate to support the efficacy and safety of garadacimab for the proposed indication. The BLA included the appropriate preapproval nonclinical and clinical pharmacology studies. The pharmacology/toxicology, clinical

pharmacology, statistical, and clinical review teams did not identify any issues that precluded approval of garadacimab in the initial BLA review cycle.¹ However, the Office of Product Quality (OPQ) and the Office of Pharmaceutical Manufacturing Assessment (OPMA) review teams determined that the data submitted were not sufficient to conclude that the manufacture of garadacimab was well-controlled and would lead to a product that was pure and potent.²

Therefore, the Agency issued a complete response letter (CRL) on October 7, 2024, citing microbiology, product quality, and facility inspection deficiencies.³ The microbiology deficiency was based on inadequate drug product (DP) manufacturing process design to minimize potential contamination of the sterile DP, specifically, (b) (4)

. Multiple product quality deficiencies were also identified including insufficient DP process control to ensure consistent product quality and insufficient DP process validation data to demonstrate consistent process performance. Lastly, a withhold approval was recommended for the DP manufacturing facility, CSL Behring GmbH, Marburg, Germany based on the pre-license inspection and facility compliance review.

In this CR resubmission, the Applicant demonstrated that the manufacturing processes and overall control strategies for garadacimab were appropriately established to ensure consistency and quality of the final product and thus has adequately addressed the deficiencies outlined in the CRL. The Applicant and Agency have reached agreement on the product labeling that includes the carton & container, Prescribing Information (PI), Patient Information, and Instructions for Use. The recommended regulatory action from all members of the multidisciplinary review team is Approval.

Product Quality

In this review cycle, a 704(a)(4) Records Request review was conducted for the DP manufacturing facility (CSL Behring GmbH, Marburg, Germany FEI 3003098680). OPMA determined that the facility inspection deficiencies outlined on Form FDA 483 had been adequately addressed.

To address the microbiology deficiencies, the drug product (DP) manufacturing process (b) (4)

To address the DP quality manufacturing process deficiencies, the Applicant implemented additional process controls and submitted supporting process validation data in the BLA resubmission. The Applicant also provided real time DP shipping validation data, specifically the Container Closure Integrity Testing (CCIT) and critical quality attributes (CQA) data of garadacimab after international transport in shipping containers. After reviewing the BLA resubmission, the OPQ determined that the Applicant adequately addressed the microbiology and product quality deficiencies outlined in the CRL. The

¹ Integrated Assessment of Marketing Application dated October 7, 2024:
<https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af807740bd>

² OPQ Executive Summary dated August 26, 2024:
<https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80764a3e>

³ Complete Response Letter dated October 7, 2024:
<https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af807736c4>

microbial control and sterility assurance strategy of the DP manufacturing process supported consistent manufacture of a sterile product. The product quality data supported adequate control to ensure consistent product quality and process performance. Lastly, the post-approval annual stability protocol and stability commitment were acceptable. CDRH performed a consult review for the device technical engineering and facilities, and recommends approval. The BLA is recommended for approval from the product quality, facility, microbiology, and sterility assurance perspectives. Refer to the OPQ Executive Summary dated May 20, 2025,⁴ for additional information.

Pharmacology/Toxicology

No new nonclinical data were submitted or required in this CR resubmission. The updated proposed PI is acceptable. No pharmacology/toxicology issues preclude approval.

Clinical Pharmacology

No new clinical pharmacology data were provided in this CR resubmission. On resubmission, the Applicant addressed clinical pharmacology comments in the proposed PI. These included changes to Sections 7 (Drug Interactions), 12.2 (Pharmacodynamics), and 12.3 (Pharmacokinetics). The updated proposed PI is acceptable from a clinical pharmacology perspective. As concluded during the initial review cycle, no issues preclude approval from a clinical pharmacology perspective.

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Clinical/Statistics

The initial BLA submission included results from a single, adequate and well-controlled phase 3 trial (Trial 3001). This trial was a 6-month, randomized, double-blind, placebo-controlled trial evaluating 64 adult and adolescent subjects with HAE Type I and II who received either garadacimab 200mg or placebo monthly.

Trial 3001 met its primary endpoint, demonstrating a statistically significant reduction in the time-normalized number of investigator-confirmed HAE attacks per month. This endpoint is an established and clinically meaningful outcome for HAE prophylaxis development programs. The garadacimab group showed a mean of 0.27 attacks per month (95% CI: 0.05, 0.49) compared to 2.01 attacks per month (95% CI: 1.44, 2.57) in the placebo group. Substantial evidence of effectiveness of garadacimab in patients with HAE was established using data from Trial 3001 and confirmatory evidence based on mechanistic data. The available safety data demonstrated that garadacimab is safe for its intended use.

In the BLA resubmission, no new efficacy data were required or submitted. The Applicant provided updated exposure and safety datasets through June 15, 2024 (previous data cutoff was May 22, 2023). The clinical review team analyzed the updated datasets and modified the drug exposure and frequency of injection site reactions in Section 6 of the PI, accordingly. Section 14 of the updated proposed PI is acceptable from the statistical and

⁴ OPQ Executive Summary dated May 20, 2025:
<https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af807ba780>

clinical perspective. No clinical or statistical issues preclude approval. The benefit-risk assessment of garadacimab for the prophylaxis of HAE attacks in adults and pediatric patients 12 years of age and older remains favorable.

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Integrated Review

Table 1. Application Information

Application type	BLA
Application number(s)	761367
Priority or standard	STANDARD
Submit date(s)	10/13/2023
Received date(s)	10/13/2024
PDUFA goal date	10/12/2024
Division/office	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Review completion date	10/3/2024
Established/proper name	garadacimab
(Proposed) proprietary name	Andembry
Pharmacologic class	Activated Factor XII (FXIIa) inhibitor (monoclonal antibody)
Other product name(s)	CSL312
Applicant	CSL Behring LLC
Dosage form(s)/formulation(s)	Subcutaneous injection
Dosing regimen	400 mg SC loading dose followed by 200 mg SC every month
Applicant-proposed indication(s)/ population(s)	prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older
SNOMED CT code for proposed indication disease term(s)¹	82966003 Hereditary angioedema
Regulatory action	Complete response
Approved dosage (if applicable)	N/A
Approved indication(s)/ population(s) (if applicable)	N/A
SNOMED CT code for approved indication disease term(s)¹	N/A

¹ For internal tracking purposes only.

Abbreviations: N/A, not applicable; PDUFA, Prescription Drug User Fee Act; SC, subcutaneous; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

Table of Contents

Table of Tables	ix
Table of Figures	xv
Glossary	1
I. Executive Summary.....	3
1. Summary of Regulatory Action	3
2. Benefit-Risk Assessment.....	4
2.1. Benefit-Risk Framework	4
2.2. Conclusions Regarding Benefit-Risk	6
II. Interdisciplinary Assessment.....	8
3. Introduction	8
3.1. Review Issue List.....	9
3.1.1. Key Efficacy Review Issues.....	9
3.1.1.1. Patient-Reported Outcome Endpoints	9
3.1.1.2. Type III HAE.....	9
3.1.2. Key Safety Review Issues	9
3.1.2.1. Abnormal Coagulation Labs and Risk of Bleeding or Thromboembolism	9
3.1.2.2. Hypersensitivity Reactions	9
3.1.2.3. Injection Site Reactions	9
3.2. Approach to the Clinical Review.....	9
4. Patient Experience Data	11
5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology.....	11
5.1. Nonclinical Assessment of Potential Effectiveness.....	11
5.2. Clinical Pharmacology/Pharmacokinetics	12
6. Efficacy (Evaluation of Benefit)	15
6.1. Assessment of Dose and Potential Effectiveness	15
6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy	18
6.2.1. Design and Conduct, Trial 3001	18
6.2.2. Eligibility Criteria, Trial 3001.....	21
6.2.3. Statistical Analysis Plan, Trial 3001	22
6.2.3.1. Testing Hierarchy and Multiplicity Control, Trial 3001	22
6.2.3.2. Analysis of the Primary Endpoint, Trial 3001.....	23

6.2.3.3. Analysis of the Key Secondary Endpoints, Trial 3001	25
6.2.3.4. Other Secondary/Exploratory Endpoint Analyses, Trial 3001	26
6.2.4. Results of Analyses, Trial 3001	26
6.2.4.1. Subject Disposition, Trial 3001	26
6.2.4.2. Baseline Demographics and Clinical Characteristics, Trial 3001	27
6.2.4.3. Primary Efficacy Results, Trial 3001	29
6.2.4.4. Key Secondary Efficacy Results, Trial 3001	30
6.2.4.5. Additional Efficacy Results, Trial 3001	32
6.2.4.6. Subgroup Analyses, Trial 3001	36
6.3. Key Efficacy Review Issues	41
6.3.1. Patient-Reported Outcome Endpoints.....	41
6.3.2. Type III HAE	44
7. Safety (Risk and Risk Management).....	46
7.1. Potential Risks or Safety Concerns Based on Nonclinical Data.....	46
7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug- Specific Factors	47
7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience	47
7.4. FDA Approach to the Safety Review	48
7.5. Adequacy of the Clinical Safety Database	49
7.6. Safety Results	50
7.6.1. Safety Results, Trial 3001	50
7.6.1.1. Overview of Treatment-Emergent Adverse Events, Trial 3001	50
7.6.1.2. Deaths, Trial 3001	50
7.6.1.3. Serious Adverse Events, Trial 3001	50
7.6.1.4. Treatment-Emergent Adverse Events Leading to Treatment Discontinuation, Trial 3001	51
7.6.1.5. Treatment-Emergent Adverse Events, Trial 3001	51
7.6.1.6. Adverse Events of Special Interest, Trial 3001	53
7.6.1.7. Laboratory Values and Vital Signs, Trial 3001	53
7.6.1.8. Liver Function Tests, Trial 3001	53
7.6.1.9. Safety Subgroup Analyses Trial 3001	53
7.6.2. Safety Results, Study 3002	53

7.6.2.1. Study Design, Study 3002	53
7.6.2.2. Subject Disposition, Study 3002	55
7.6.2.3. Subject Demographics and Baseline Characteristics, Study 3002 ...	55
7.6.2.4. Overview of Treatment-Emergent Adverse Events Summary, Study 3002.....	56
7.6.2.5. Deaths, Study 3002.....	57
7.6.2.6. Serious Adverse Events, Study 3002.....	57
7.6.2.7. Treatment-Emergent Adverse Events Leading to Treatment Discontinuation, Study 3002	59
7.6.2.8. Treatment-Emergent Adverse Events, Study 3002	61
7.6.2.9. Laboratory Findings and Vital Signs, Study 3002	63
7.6.3. Safety Results, Trial 2001	64
7.6.4. 120-Day Safety Update	64
7.7. Key Safety Review Issues	65
7.7.1. Abnormal Coagulation Labs and Risk of Bleeding or Thromboembolism	65
7.7.2. Hypersensitivity Reactions	70
7.7.3. Injection Site Reactions.....	71
8. Therapeutic Individualization	72
8.1. Intrinsic Factors	72
8.1.1. Body Weight	72
8.1.2. Type III (FXII/PLG mutation) HAE	76
8.2. Extrinsic Factors	76
8.3. Plans for Pediatric Drug Development	78
8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential	78
9. Product Quality	80
9.1. Device or Combination Product Considerations	80
10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review	80
11. Advisory Committee Summary.....	81
III. Additional Analyses and Information.....	82
12. Summary of Regulatory History	82
13. Pharmacology Toxicology	84

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application	84
13.1.1. Pharmacology (Primary and Secondary)	84
13.1.2. Safety Pharmacology	87
13.1.3. Absorption, Distribution, Metabolism, Excretion/Pharmacokinetics ...	87
13.1.4. Toxicology	87
13.1.4.1. General Toxicology	87
13.1.4.2. Carcinogenicity.....	102
13.1.4.3. Reproductive Toxicology	103
13.1.4.4. Other Toxicology/Specialized Studies	117
13.1.4.5. Safety Margins.....	118
13.2. Individual Reviews of Studies Submitted With the New Drug Application	118
14. Clinical Pharmacology	119
14.1. In Vitro Studies.....	119
14.2. In Vivo Studies	119
14.2.1. Study 1004 (Relative Bioavailability Study Comparing PFS-NSD and AI)	121
14.2.2. Study 1001 (SAD Study in Healthy Subjects)	127
14.2.3. Study 1003 (SAD Study in Healthy Japanese and Caucasian Subjects).....	134
14.2.4. Trial 2001 (Dose-Ranging Trial in Subjects With HAE)	142
14.2.5. Trial 3001 (Phase 3 Efficacy Trial in Subjects With Type I and II HAE)	154
14.2.6. Study 3002 (Long-Term Open-Label Extension Study in Subjects With HAE)	160
14.3. Bioanalytical Method Validation and Performance	167
14.3.1. PK Bioanalytical Methods	167
14.3.2. PD Bioanalytical Methods	180
14.3.2.1. Activated Factor XII-Mediated Kallikrein Activity	180
14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety...	183
14.5. Pharmacometrics Assessment.....	188
14.5.1. Population PK Analysis	188
14.5.1.1. Executive Summary.....	188

14.5.1.2. PPK Assessment Summary	188
14.5.1.3. PPK Review Issues	208
14.5.1.4. Reviewer’s Independent Analysis	208
14.5.2. Exposure-Response Analysis	209
14.5.2.1. ER (Efficacy) Executive Summary	209
14.5.2.2. ER (Efficacy) Assessment Summary	209
14.5.2.3. ER (Safety) Executive Summary.....	219
14.5.2.4. ER (Safety) Assessment Summary.....	219
14.5.2.5. ER Review Issues	220
14.5.2.6. Reviewer’s Independent Analysis	220
14.6. Pharmacogenetics	220
15. Additional Study/Trial Design Information	220
15.1. Trial 3001: A Multicenter, Double-Blind, Randomized, Placebo- Controlled, Parallel-Arm Study To Investigate the Efficacy and Safety of Subcutaneous Administration of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema.....	220
15.1.1. Definition and Collection of HAE Attacks, Trial 3001	221
15.1.2. Data and Safety Monitoring Committee, Trial 3001	222
15.1.3. Sample Size Considerations, Trial 3001	222
15.1.4. Changes to the Planned Analyses, Trial 3001.....	223
15.1.5. Protocol Amendments, Trial 3001	224
15.1.6. Safety Assessments, Trial 3001	224
15.1.7. Grading of Adverse Events, Trial 3001	228
15.2. Study 3002: An Open-Label Study To Evaluate the Long-Term Safety and Efficacy of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema.....	228
15.2.1. Study Design, Study 3002.....	229
15.2.1.1. Sample Size Assumptions, Study 3002.....	230
15.2.2. Schedule of Assessments, Study 3002.....	230
15.2.3. Primary, Secondary and Exploratory Objectives and Endpoints, Study 3002	233
15.2.4. Analysis Populations, Study 3002.....	234
15.2.5. Time Point Description, Study 3002.....	235
15.2.6. Primary Analysis Description, Study 3002.....	236

15.2.7. Secondary Efficacy Analysis Description, Study 3002	236
15.2.8. Sensitivity and Supportive Statistical Analyses Description, Study 3002	237
15.2.9. Changes to the Planned Analyses, Study 3002	237
15.2.10. Interim Analyses, Study 3002	238
15.2.11. Data and Safety Monitoring Committee, Study 3002	238
15.3. Trial 2001: A Multicenter, Randomized, Placebo-Controlled, Parallel- Arm Study To Investigate the Efficacy, Pharmacokinetics, and Safety of CSL312 in Subjects With Hereditary Angioedema	238
15.3.1. Trial Design, Trial 2001	239
15.3.2. Schedule of Assessments, Trial 2001	241
15.3.3. Eligibility Criteria, Trial 2001	246
15.3.4. Primary and Secondary Objectives and Endpoints, Trial 2001	247
15.3.5. Statistical Analysis Plan, Trial 2001	247
15.3.6. Analysis of the Primary Endpoint, Trial 2001	248
15.3.7. Analysis of the Secondary Endpoint, Trial 2001	248
15.3.8. Data and Safety Monitoring Committee, Trial 2001	249
15.3.9. Sample Size Considerations, Trial 2001	249
15.3.10. Protocol Amendments, Trial 2001	250
15.3.11. Changes to the Planned Analyses, Trial 2001	250
16. Efficacy	250
16.1. Durability of Treatment Effect, Study 3002	250
16.2. Results of Statistical Analyses, Trial 2001	251
16.2.1. Interim Analyses, Trial 2001	258
17. Clinical Safety	258
17.1. Subgroup Analyses, Trial 3001	258
17.1.1. Treatment-Emergent Adverse Events by Sex	258
17.1.2. Treatment-Emergent Adverse Events by Age	260
17.1.3. Treatment-Emergent Adverse Events by Geographic Region, Trial 3001	261
17.1.4. Treatment-Emergent Adverse Events by Race, Trial 3001	263
18. Clinical Virology	268
19. Clinical Microbiology	268
20. Mechanism of Action/Drug Resistance	268

21. Other Drug Development Considerations	268
22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)	268
23. Labeling: Key Changes and Considerations	269
23.1. Approved Labeling Types	271
24. Postmarketing Requirements and Commitments	272
25. Financial Disclosure	272
26. References	273
27. Review Team.....	274
27.1. Reviewer Signatures	275

Table of Tables

Table 1. Application Information	i
Table 2. Benefit-Risk Framework.....	4
Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations ¹ for Garadacimab.....	10
Table 4. Patient Experience Data Submitted or Considered.....	11
Table 5. Summary of Clinical Pharmacology and Pharmacokinetics.....	12
Table 6. Mean (SD) Garadacimab Systemic Exposure Following a Single 200 mg SC Dose in Healthy Subjects	12
Table 7. Loading Dose Justification: Probability of Achieving Exposure Exceeding a 90% Reduction in HAE Attack Rate After the First Dose.....	18
Table 8. Subject Disposition, Trial 3001	27
Table 9. Baseline Demographics and Clinical Characteristics (ITT Analysis Set), Trial 3001	28
Table 10. Primary Efficacy Results (ITT Analysis Set), Trial 3001	29
Table 11. Sensitivity Analysis for the Primary Endpoint: Adjusting for the Baseline Attack Rate (ITT Analysis Set), Trial 3001	30
Table 12. Key Secondary Efficacy Analysis: Number of Attack-Free Subjects in the First 3 Months of the Treatment Period (ITT Analysis Set), Trial 3001	31
Table 13. Key Secondary Efficacy Analysis: SGART Responses at the End of the Treatment Period (ITT Analysis Set), Trial 3001	32
Table 14. Additional Secondary Efficacy Analysis: Percentage Reduction in the Time-Normalized Number of HAE Attacks per Month During the Treatment Period Compared to the Run-in Period (ITT Analysis Set), Trial 3001.....	33
Table 15. Additional Secondary Efficacy Analysis: Time-Normalized Number of HAE Attacks per Month Requiring On-Demand Therapy (ITT Analysis Set), Trial 3001	33
Table 16. Sensitivity Analysis for the Time-Normalized Number of HAE Attacks per Month Requiring On-Demand Therapy: Adjusting for Baseline Attack Rate (ITT Analysis Set), Trial 3001	34
Table 17. Additional Secondary Efficacy Analysis: Time-Normalized Number of Moderate or Severe HAE Attacks per Month (ITT Analysis Set), Trial 3001	34
Table 18. Sensitivity Analysis for the Time-Normalized Number of Moderate or Severe HAE Attacks per Month: Adjusting for the Baseline Attack Rate (ITT Analysis Set), Trial 3001	35
Table 19. Exploratory Efficacy Analysis: Change in AE-QoL Questionnaire Total and Domain Scores From Baseline to Day 182 (ITT Analysis Set), Trial 3001	35

Table 20. HAE Attacks by Location and Severity (ITT Analysis Set), Trial 3001	39
Table 21. Conceptual Framework of the AE-QoL Questionnaire	43
Table 22. Clinical Trials Submitted in Support of Safety Determination for Garadacimab	48
Table 23. Duration of Garadacimab Exposure, Safety Population, Pooled Analyses	49
Table 24. Overview of TEAEs, Safety Population, Trial 3001	50
Table 25. FMQ (Narrow) Group Terms That Occurred in $\geq 5\%$ Subjects and More Frequently Than Placebo, Safety Population, Trial 3001	51
Table 26. TEAEs by PT That Occurred in $\geq 5\%$ Subjects and More Frequently Than Placebo, Safety Population, Trial 3001	52
Table 27. Subject Disposition, Safety Population, Study 3002	55
Table 28. Subject Demographics and Baseline Characteristics, Safety Population, Study 3002	56
Table 29. Overview of TEAEs, Safety Population, Study 3002	56
Table 30. Listing of Subjects With Serious Adverse Events, Safety Population, Study 3002	58
Table 31. Listing of Subjects with TEAEs Leading to Treatment Discontinuation, Safety Population, Study 3002	60
Table 32. Common TEAEs by PT That Occurred in $\geq 5\%$ of Total Subjects, Safety Population, Study 3002	61
Table 33. Subjects with FMQ (Narrow) Group Terms That Occurred in $\geq 5\%$ of the Total Subjects, Safety Population, Study 3002	62
Table 34. Subjects With Viral Infection and Bacterial Infection FMQ (Narrow), Safety Population, Study 3002	63
Table 35. Listing of Subjects With Any Abnormal aPTT Measurement, Safety Population (Garadacimab 200 mg Group), Trial 3001	66
Table 36. Listing of Subjects With Any Abnormal PT Measurement, Safety Population (Garadacimab 200 mg Group), Trial 3001	67
Table 37. Listing of Subjects with Hemorrhage FMQ (Narrow), Safety Population (Garadacimab 200 mg Group), Trial 3001	69
Table 38. Subjects With Injection Site Reaction FMQ (Narrow), Safety Population, Trial 3001	71
Table 39. Subjects With Injection Site Reaction FMQ (Narrow), Safety Population, Study 3002	71
Table 40. Binding Affinities of Anti-FXII Antibodies 3F7 and Garadacimab to Human FXII and Human β FXIIa	84

Table 41. Binding Affinities of Anti-FXII Antibodies 3F7 and Garadacimab to Mouse FXII Proteins.....	85
Table 42. Binding Affinities of Anti-FXII Antibodies 3F7 and Garadacimab to Rabbit FXII Proteins.....	85
Table 43. Binding Affinities of Anti-FXII Antibodies 3F7 and Garadacimab to Cynomolgus Monkey FXII Proteins.....	85
Table 44. Four-Week Mouse Study Information.....	88
Table 45. Design of 4-week toxicology study in mice that included an 8-week recovery period.....	89
Table 46. Four-Week Mouse Study Observations and Results.....	89
Table 47. Toxicokinetics of the 4-Week Mouse Study.....	93
Table 48. Twenty-Six-Week Monkey Study Information.....	94
Table 49. Design of the 26-week toxicology study with monkeys.....	95
Table 50. Twenty-Six-Week Monkey Study Observations and Results.....	95
Table 51. Toxicokinetics of the 26-Week Monkey Study.....	98
Table 52. Methods of Male Rabbit Fertility and Early Embryonic Development Study	105
Table 53. Observations and Results from Male Rabbit Fertility and Early Embryonic Development Study.....	106
Table 54. Methods of Female Rabbit Fertility and Early Embryonic Development Study.....	108
Table 55. Observations and Results from Female Rabbit Fertility and Early Embryonic Development Study.....	109
Table 56. Methods of Rabbit Embryonic and Fetal Development Study.....	111
Table 57. Observations and Results from Rabbit Embryonic and Fetal Development Study.....	112
Table 58. Methods of Prenatal and Postnatal Development Study in Rabbits.....	115
Table 59. Observations and Results from Prenatal and Postnatal Development Study in Rabbits.....	116
Table 60. Summary Human Drug Exposure With Maximum Recommended Human Dose (MRHD) of SC Loading Dose of 400 mg (2×200 mg) Followed by 200 mg Once a Month.....	118
Table 61. Animal to Human Exposure Margins for Garadacimab Based on General and Reproductive Toxicology Studies.....	118
Table 62. Summary of Clinical Pharmacology Studies.....	119
Table 63. Garadacimab Allocation by Device, Injection Site, and Body Weight Group, Study 1004.....	123

Table 64. Garadacimab PK Parameters by Device, Study 1004.....	125
Table 65. Statistical Analysis of C _{max} and AUC for AI Versus NSD, Study 1004	126
Table 66. Mean (SD) Garadacimab PK Parameters by Device and Injection Site, Study 1004	126
Table 67. Baseline Body Weight and Garadacimab Doses in IV Cohorts, Study 1001 ..	129
Table 68. Baseline Body Weight and Garadacimab Doses in SC Cohorts, Study 1001 ..	129
Table 69. Summary of Garadacimab Pharmacokinetic Parameters by Dose in IV and SC Cohorts, Study 1001	131
Table 70. Power Analysis of Dose Proportionality for Garadacimab PK in IV Cohorts, Study 1001.....	132
Table 71. Power Analysis of Dose Proportionality for Garadacimab PK in SC Cohorts, Study 1001.....	132
Table 72. Absolute Bioavailability for SC Versus IV Cohorts, Study 1001	133
Table 73. Baseline Body Weight and Garadacimab Doses in IV Cohorts, Study 1003 ..	136
Table 74. Summary of Garadacimab PK Parameters by Dose in SC Cohorts, Study 1003	138
Table 75. Pharmacokinetics Comparison of Japanese and Caucasian Subjects (All Subjects), Study 1003	139
Table 76. Pharmacokinetics Comparison of Japanese and Caucasian Subjects (Excluding One Subject With Extreme Values), Study 1003.....	139
Table 77. Summary of Garadacimab PK Parameters by Dose in IV Cohorts, Study 1003	140
Table 78. Time-Normalized Number of HAE Attacks per Month by Dose Cohort in C1-INH HAE Subjects (Treatment Period 1), Trial 2001	147
Table 79. Steady-State PK Parameters Following SC Dosing of Garadacimab (Day 63), Trial 2001	151
Table 80. FXIIa-Mediated Kallikrein Activity (Delta A _{405 nm/min}) Over Time at Select Time Points in Treatment Period 1 (C1-INH Blinded and FXII/PLG Open-Label Treatment Arms), Trial 2001	153
Table 81. Summary of Model-Predicted Garadacimab Pharmacokinetics in Subjects With HAE, Trial 3001.....	158
Table 82. Mean (SD) Steady-State Garadacimab Trough Concentrations (ng/mL) From Month 3 Through Month 12 in Adults and Adolescents.....	163
Table 83. PK Method Validation for TP80240.....	168
Table 84. PK Method Validation for TP80003.....	169
Table 85. PK Method Validation for RnD-SOP-000053053.....	170
Table 86. PK Method Validation for RnD-SOP-000053165.....	171

Table 87. PK Method Validation for RnD-VAL-000141302.....	172
Table 88. Bioanalytical Method Performance in Study 1004.....	173
Table 89. Bioanalytical Method Performance in Trial 3001	174
Table 90. Bioanalytical Method Performance in Study 3002.....	174
Table 91. Bioanalytical Method Performance in Study 1001	175
Table 92. Bioanalytical Method Performance in Study 1003.....	177
Table 93. Bioanalytical Method Performance in Trial 2001	178
Table 94. Range of Kallikrein Activity in Spiked Pre-Kallikrein Deficient Plasma (RnD-VAL-000148888)	181
Table 95. Range of Kallikrein Activity in Spiked Pre-Kallikrein Deficient Plasma (REP-019128)	181
Table 96. PD Method Validation for Factor XII-Mediated Kallikrein Activity in 2001, 3001, and 3002.....	182
Table 97. Summary of Immunogenicity Data.....	184
Table 98. Efficacy Data in ADA-Positive Subjects and the Overall Population.....	187
Table 99. PPK Summary.....	188
Table 100. Applicant-Summary of Baseline Characteristics and Laboratory Values in the Dataset, Stratified by Study of The PopPK Dataset.....	193
Table 101. Applicant Summary of Baseline Characteristics and Laboratory Values in the Dataset, Stratified by Study of the PopPK-PD Dataset	196
Table 102. Applicant Parameter Estimates and SE From Final Population PK Model...	199
Table 103. Applicant-Parameter Estimates and SE From Final Population PK-PD Model	200
Table 104. Applicant-Simulated PK and PD Metrics in Adolescent and Adult Subjects Receiving a 400 mg SC Loading Dose Followed by 200 mg SC Q1M Maintenance Doses	207
Table 105. ER (Efficacy) Summary.....	209
Table 106. Applicant-Summary of Baseline Characteristics and Laboratory Values in the Dataset Stratified by Study	211
Table 107. Applicant Parameter Estimates From the Final ER Model.....	213
Table 108. Symptoms and Locations Associated With an HAE Attack.....	221
Table 109. Grading Scale for Adverse Event Severity in Trial 3001	228
Table 110. Definitions of Study Periods (Study 3002).....	235
Table 111. Schedule of Assessments During the Screening and Run-in Periods, Trial 2001	242

Table 112. Schedule of Assessments During Treatment Period 1 for Subjects Receiving Garadacimab Every 4 Weeks, Trial 2001	243
Table 113. Schedule of Assessments During Treatment Period 1 for Subjects Receiving Garadacimab Every 2 Weeks, Trial 2001	244
Table 114. Schedule of Assessments During Treatment Period 2 (Open-Label), Trial 2001	245
Table 115. HAE Attack Rate, Study 3002	251
Table 116. Baseline Demographics and Clinical Characteristics (ITT Analysis Set, Treatment Period 1), Trial 2001	253
Table 117. Primary Efficacy Results (ITT Analysis Set, Treatment Period 1), Trial 2001	254
Table 118. Secondary Efficacy Analysis: Subjects With a $\geq 50\%$ Reduction in the Time-Normalized Number of HAE Attacks per Month Compared to the Run-in Period (ITT Analysis Set, Treatment Period 1), Trial 2001	255
Table 119. Secondary Efficacy Analysis: Number of Attack-Free Subjects (ITT Analysis Set, Treatment Period 1), Trial 2001	255
Table 120. Secondary Efficacy Analysis: Number of Moderate and Severe HAE Attacks (ITT Analysis Set, Treatment Period 1), Trial 2001	256
Table 121. Secondary Efficacy Analysis: Number of Moderate and Severe HAE Attacks Requiring On-Demand Therapy (ITT Analysis Set, Treatment Period 1), Trial 2001	257
Table 122. Subgroup Analysis by Sex of TEAEs by SOC and PT, Safety Population, Trial 3001	258
Table 123. Subgroup Analysis by Age of TEAEs by SOC and PT, Safety Population, Trial 3001	260
Table 124. Subgroup Analysis by Geographic Region of TEAEs by SOC and PT, Safety, Population, Trial 3001	261
Table 125. Subgroup Analysis by Race of TEAEs by SOC and PT, Safety Population, Trial 3001	264
Table 126. Key Labeling Changes and Considerations	269
Table 127. Covered Clinical Studies: 2001, 3001, and 3002	272
Table 128. Reviewers of Integrated Assessment	274
Table 129. Additional Reviewers of Application	275
Table 27-1 Signatures of Reviewers	275

Table of Figures

Figure 1. Relative Risk of an HAE Attack as a Function of Garadacimab Concentration	16
Figure 2. Relative Risk of an HAE Attack as a Function of Garadacimab Steady-State AUC_{τ}	17
Figure 3. Trial Design, Trial 3001	18
Figure 4. Subgroup Analysis for the Primary Endpoint by Sex (ITT Analysis Set), Trial 3001	36
Figure 5. Subgroup Analysis for the Primary Endpoint by Age Group (ITT Analysis Set), Trial 3001	37
Figure 6. Subgroup Analysis for the Primary Endpoint by Race (ITT Analysis Set), Trial 3001	38
Figure 7. Subgroup Analysis for the Primary Endpoint by Geographic Location (ITT Analysis Set), Trial 3001	38
Figure 8. Subgroup Analysis for the Primary Endpoint by HAE Subtype (ITT Analysis Set), Trial 3001	39
Figure 9. Mean Difference in the Time-Normalized Number of HAE Attacks per Month by Location and Severity (ITT Analysis Set), Trial 3001	40
Figure 10. Study Design, Study 3002	54
Figure 11. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study 3002	64
Figure 12. Real-Time Relationship Between aPTT and Garadacimab Plasma Concentrations, Trial 3001	66
Figure 13. Real-Time Relationship Between PT and Garadacimab Plasma Concentrations, Trial 3001	67
Figure 14. Univariate Forest Plot Illustrating Covariate Effects on Garadacimab Steady-State AUC_{τ} Relative to a Reference Subject	73
Figure 15. Monthly HAE Attack Rate Over Time by Baseline Weight Quartile, Trial 3001	74
Figure 16. Mean (SD) Garadacimab Trough Concentration-Time Profiles in Adults and Adolescents, Trial 3001	75
Figure 17. Mean (SD) Garadacimab Trough Concentration-Time Profiles in Adults and Adolescents, Study 3002	75
Figure 18. Simulated Garadacimab Exposure by Concomitant Medication Use in Subjects With HAE Using Empirical Bayes Estimates	77
Figure 19. Simulated Garadacimab Exposure by Rescue Medication Use in Subjects With HAE Using Empirical Bayes Estimates	77

Figure 20. Garadacimab Steady-State Trough Concentrations Following 200 mg SC QM, Stratified by Formulation	121
Figure 21. Study Design, Study 1004	122
Figure 22. Mean (SD) Garadacimab Concentration-Time Profiles by Device, Study 1004	124
Figure 23. Garadacimab C _{max} and AUC Distributions by Device and Injection Site, Study 1004	127
Figure 24. Study Design, Study 1001	128
Figure 25. Mean (SD) Garadacimab Concentration-Time Profiles for IV Cohorts, Study 1001	130
Figure 26. Mean (SD) Garadacimab Concentration-Time Profiles for SC Cohorts, Study 1001	130
Figure 27. Mean (SD) Change From Baseline in FXIIa-Mediated Kallikrein Activity by Dose in IV Cohorts, Study 1001	133
Figure 28. Mean (SD) Change From Baseline in FXIIa-Mediated Kallikrein Activity by Dose in SC Cohorts, Study 1001	134
Figure 29. Study Design, Study 1003	135
Figure 30. Mean (SD) Garadacimab Concentration-Time Profiles for SC Cohorts, Study 1003	137
Figure 31. Mean (SD) Garadacimab Concentration-Time Profiles for IV Cohorts, Study 1003	140
Figure 32. Mean (SD) FXIIa-Mediated Kallikrein Activity by Dose in SC Cohorts, Study 1003	141
Figure 33. Mean (SD) FXIIa-Mediated Kallikrein Activity by Dose in IV Cohorts, Study 1003	142
Figure 34. Mean (SD) Garadacimab PK Profiles in Treatment Period 1 in Blinded Cohorts (C1-INH HAE), Trial 2001	148
Figure 35. Mean (SD) Garadacimab PK Profiles in Treatment Period 1 in the Open-Label Cohort (C1-INH HAE), Trial 2001	149
Figure 36. Mean (SD) Garadacimab PK Profiles in Treatment Period 1 in Subjects with FXII/PLG HAE, Trial 2001	150
Figure 37. Mean (SD) Garadacimab PK Profiles in Treatment Period 2 Among Subjects Receiving the Same Dose in Treatment Period 1, Trial 2001	152
Figure 38. Mean (SD) Garadacimab Concentration-Time Profile in All Subjects, Trial 3001	156
Figure 39. Mean (SD) Garadacimab Concentration-Time Profiles in Adults Versus Adolescents, Trial 3001	157

Figure 40. Mean (SD) FXIIa-Mediated Kallikrein Activity Over Time (Absolute Value), Trial 3001	158
Figure 41. Mean (SD) FXIIa-Mediated Kallikrein Activity Over Time (Percentage of Baseline), Trial 3001	159
Figure 42. Mean (SD) Garadacimab Plasma Concentrations Over Time in All Subjects, Study 3002	162
Figure 43. Mean (SD) Garadacimab Concentration-Time Profiles in Adults Versus Adolescents, Study 3002	163
Figure 44. Mean (SD) FXIIa-Mediated Kallikrein Activity Over Time (Absolute Value), Study 3002	164
Figure 45. Mean (SD) FXIIa-Mediated Kallikrein Activity Over Time (Percentage of Baseline), Study 3002	164
Figure 46. Mean (SD) FXIIa-Mediated Kallikrein Activity Over Time Following the Loading Dose in Garadacimab-Naïve Subjects (Percentage of Baseline), Study 3002	165
Figure 47. Mean (SD) FXIIa-Mediated Kallikrein Activity Over Time in Adults and Adolescents (Percentage of Baseline), Study 3002	166
Figure 48. Dose-Normalized Garadacimab Concentration-Time Profiles by ADA Status	185
Figure 49. Percentage Change From Baseline in FXII-Mediated Kallikrein Activity Over Time by ADA Status	186
Figure 50. Applicant-Goodness-of-Fit Plots for the Final Population PK Model	201
Figure 51. Applicant Goodness-of-Fit Plots for the Final Population PK-PD Model	202
Figure 52. Applicant VPC of the Final Population PK Model, Stratified by Administration Route	203
Figure 53. Applicant-VPC of Final Population PK-PD Model, Stratified by Administration Route and Dose Level	204
Figure 54. Applicant Impact of Significant PK Covariates on Exposure	205
Figure 55. Applicant Impact of Significant PD Covariates on EC ₅₀	206
Figure 56. Applicant-Simulated PK Exposure Metrics Versus Age Group for Subjects With HAE Using Empirical Bayes Estimates (EBE)	208
Figure 57. Applicant-Final Model VPC: Monthly HAE Attack Rate Versus Time Stratified by Study and Quartiles of AUC _{tau,ss} at 3 Months	214
Figure 58. Applicant-Forest Plots: Conditional Simulations of Monthly Attack Rate at Month 1 With Fixed Covariate Levels	218
Figure 59. Applicant Population Simulations: HAE Relative Risk by AUC _{tau,ss} in the Adolescent and Adult Populations	219
Figure 60. Schedule of Assessments (Screening and Run-in Periods), Trial 3001	225

Figure 61. Schedule of Assessments (Treatment Period), Trial 3001	226
Figure 62. Study Schematic, Study 3002.....	229
Figure 63. Schedule of Assessments for Rollover Subjects from Parent Trial 3001 and Garadacimab-Naïve Subjects, Study 3002	231
Figure 64. Schedule of Assessments for Rollover Subjects from Parent Trial 2001, Study 3002	233
Figure 65. Trial Design, Trial 2001	239
Figure 66. Subject Disposition, Trial 2001	252

Glossary

ADA	antidrug antibody
AE	adverse event
AE-QoL	angioedema-quality of life
AESI	adverse event of special interest
AI	autoinjector
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATS	all treated subjects
AUC	area under the concentration-time curve
AUC _{tau,ss}	area under the plasma concentration-time curve over one dosing interval at steady state
BLA	biologics license application
CE	confirmatory evidence
CFR	Code of Federal Regulations
C _{max}	maximum plasma concentration
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
C1-INH	C1-esterase inhibitor
DP	drug product
E-R	exposure-response
FDA	Food and Drug Administration
FMQ	Food and Drug Administration Medical Dictionary for Regulatory Activities query
FXII	Factor XII
FXIIa	activated Factor XII
GLP	good laboratory practice
HAE	hereditary angioedema
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IND	investigational new drug
INR	international normalized ratio
IR	Information Request
ISR	injection site reaction
ITT	intent-to-treat
IV	intravenous
LD	low dose
LS	least squares
MD	mid dose
NDA	new drug application
NOAEL	no observed adverse effect level
OLE	open-label extension

BLA 761367

Andembry / garadacimab

PD	pharmacodynamic
PFS-NSD	prefilled syringe with needle safety device
PI	prescribing information
PK	pharmacokinetic
PLG	plasminogen
	(b) (4)
PRO	patient-reported outcome
PT	preferred term
PT	prothrombin time
QC	quality control
Q2W	every 2 weeks
Q4W	every 4 weeks
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SGART	Subject's Global Assessment of Response to Therapy
SMQ	Standard Medical Dictionary for Regulatory Activities Query
SOC	system organ class
TBM	to-be-marketed
TE-ADA	treatment-emergent antidrug antibody
TEAE	treatment-emergent adverse event
TK	toxicokinetic
T _{max}	time to maximum concentration
ULN	upper limit of normal

I. Executive Summary

1. Summary of Regulatory Action

The Applicant, CSL Behring, submitted a BLA for garadacimab (proposed tradename: ANDEMBRY), a fully human IgG4 monoclonal antibody that targets the catalytic subunit of Factor XIIa, for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and adolescent patients 12 years and older at a dose of 200 mg subcutaneous (SC) monthly following a 400 mg SC loading dose. The BLA was reviewed by a multidisciplinary review team. The clinical, statistical, clinical pharmacology, and pharmacology/toxicology review teams did not identify any issues that preclude approval. However, the Office of Product Quality and Office of Pharmaceutical Manufacturing Assessment review teams have determined that the data submitted in this application are not sufficient to conclude that the manufacture of garadacimab is well-controlled and will lead to a product that is pure and potent, and therefore, recommend a complete response.

The substantial evidence of effectiveness of garadacimab in patients with HAE was established using data from a single adequate and well-controlled trial (CSL312_3001, hereafter referred to as trial 3001) and confirmatory evidence (CE) based on mechanistic data. Trial 3001 demonstrated a statistically significant reduction in the frequency of acute HAE attacks with garadacimab treatment compared to placebo, as measured by the primary endpoint of the time-normalized number of HAE attacks/month over a 6-month Treatment Period. This was supported by the results of secondary endpoints, such as the number of attack-free subjects, moderate-to-severe HAE attacks, and HAE attacks requiring on-demand therapy. The CE providing strong mechanistic support includes the well-established pathophysiology of the disease and the mechanism of action of the therapy. In vitro and in vivo pharmacology data show that garadacimab only antagonizes FXIIa enzymatic activities, prolongs aPTT clotting time in standard human plasma, and inhibits FXIIa-mediated kallikrein activity in a dose-dependent fashion. Extrapolation of efficacy from adults with HAE to adolescent patients 12 to 17 years of age with HAE is supported by the identical disease pathophysiology, mechanism of action, anticipated treatment response, and clinical manifestations across age groups.

The available safety data demonstrated that garadacimab is safe for its intended use. Common adverse reactions include nasopharyngitis and abdominal pain. The safety profile for garadacimab is acceptable for an HAE population and can be adequately managed through labeling and further evaluated during routine pharmacovigilance.

The BLA includes appropriate preapproval nonclinical studies, and there is no anticipated need for additional nonclinical studies or clinical pharmacology studies as postmarketing requirements. The submitted clinical program is adequate to support the efficacy and safety of garadacimab for the prophylaxis to prevent attacks of HAE in patients 12 years of age and older. The clinical review team concludes that the reduction in acute HAE attacks observed with garadacimab treatment compared to placebo outweighs the risks and that garadacimab will provide a novel treatment option in the armamentarium for HAE prophylaxis.

The action for this application will be a Complete Response.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Type I and II hereditary angioedema (HAE) is a rare condition caused by autosomal dominant mutations in the <i>SERPING1</i> gene, resulting in deficiency or dysfunction of C1-esterase inhibitor (C1-INH) protein. • Approximately 85% of patients have Type I HAE, characterized by low production of normal C1-INH protein. The remaining 15% of patients have Type II HAE, characterized by production of dysfunctional C1-INH. Types I and II have the same clinical phenotypes and responses to available treatments. • Insufficient quantities of functional C1-INH lead to dysregulation of the kallikrein-kinin system, a plasma protease cascade initiated by Factor XII and culminating in the generation of bradykinin. Uncontrolled bradykinin production leads to increased vascular permeability and the cutaneous/submucosal swelling seen in acute HAE attacks. • Acute HAE attacks are sporadic, recurrent, unpredictable and typically self-resolve after 48-72 h. Attacks often involve the GI/GU tract, extremities (hands/feet), and face/upper airway. Attacks are associated with significant morbidity due to pain, impact on daily functioning, and disfigurement and can be life-threatening in cases of laryngeal edema resulting in airway compromise.	HAE is a rare, genetic, potentially life-threatening disease characterized by unpredictable, recurrent, self-limited skin and submucosal swelling attacks. The pathophysiology of the disease is well characterized.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	- No cure exists; however, there are several approved therapies for prophylaxis as well as for on-demand treatment of acute attacks. - Therapies for prophylaxis include plasma-derived C1-INH replacement therapies, oral attenuated androgens, and plasma kallikrein inhibitors. Available treatment options include oral and injectable (IV and SC) products. - Many patients continue to have breakthrough acute HAE attacks despite treatment prophylaxis.	Although there are numerous approved prophylactic therapies for patients with HAE, the availability of additional treatment options from a new pharmacologic class and with an infrequent dosing regimen is desirable.
Benefit	- Efficacy is based on the results from a single, adequate and well-controlled trial (3001) in 64 adults and adolescents with Type I or II HAE. Treatment with garadacimab resulted in statistically significant and clinically persuasive reductions in the primary endpoint, number of HAE attacks per month, throughout the 6-month Treatment Period compared to placebo. - Clinically meaningful secondary endpoints, such as number of attack-free subjects, number of moderate to severe HAE attacks, and number of attacks requiring acute treatment, supported the beneficial treatment effect of garadacimab compared to placebo. - Efficacy in adolescents is based on extrapolation from adults.	Garadacimab demonstrated statistically significant and clinically relevant treatment benefits on the reduction of number of acute HAE attacks in adult and adolescent subjects with Types I and II HAE.
Risk and risk management	- TEAEs that were serious, severe, or led to treatment discontinuation were rare. - Common TEAEs were nasopharyngitis and abdominal pain. The majority of TEAEs were mild or moderate in severity.	The safety profile of garadacimab for the proposed HAE population and intended use is favorable. The potential risks can be managed through labeling and routine pharmacovigilance. No REMS is proposed.

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Abbreviations: GI, gastrointestinal; GU, genitourinary; IV, intravenous; REMS, risk evaluation and mitigation strategy; SC, subcutaneous; TEAE, treatment-emergent adverse event

2.2. Conclusions Regarding Benefit-Risk

HAE is a rare, autosomal dominant condition, most often caused by pathogenic variants in the *SERPING-1* gene that encodes C1-esterase inhibitor (C1-INH), a serine protease-inhibitor involved in the kallikrein-kinin pathway as well as the classical and lectin complement, contact system/intrinsic coagulation, and fibrinolytic pathways. Under homeostatic circumstances, activated Factor XII (FXIIa) triggers the kallikrein-kinin system, resulting in the downstream production of bradykinin, a potent vasodilator and enhancer of vascular permeability. C1-INH normally serves as an inhibitory check on the system by inhibiting both kallikrein and FXIIa; in the absence of sufficient quantities of functional C1-INH, bradykinin production is relatively unchecked and leads to recurrent swelling (or angioedema) of the skin and submucosa. Clinically, HAE is characterized by episodic, spontaneous, unpredictable attacks of nonhistaminergic angioedema involving the skin and submucosal surfaces of the face, gastrointestinal tract, genitourinary tract, extremities (hands/feet), and/or throat and upper airway, the last of which can be particularly serious and potentially life-threatening. Several products are approved for the prophylaxis of HAE attacks as well as for the treatment of acute HAE attacks; however, FXIIa represents a novel therapeutic target.

To support the BLA for garadacimab, the Applicant submitted the results of a single, adequate and well-controlled phase 3 trial, 3001. Trial 3001 was a 6-month, randomized, double-blind, placebo-controlled trial evaluating 64 adult and adolescent subjects with HAE Type I or II who received garadacimab 200 mg or placebo SC every month. The primary efficacy endpoint was the time-normalized number of investigator-confirmed HAE attacks per month, an established, clinically meaningful outcome for HAE prophylaxis development programs. Trial 3001 met its primary endpoint, demonstrating a statistically significant and clinically meaningful reduction in the number of HAE attacks per month in the garadacimab group (mean=0.27; 95% CI=0.05, 0.49) compared to the placebo group (mean=2.01; 95% CI=1.44, 2.57). Secondary endpoints—such as the proportion of subjects with a $\geq 50\%$ reduction in attacks and the numbers of attack-free subjects, moderate-to-severe HAE attacks, and HAE attacks requiring acute on-demand treatment—demonstrated results that were supportive of the primary endpoint, all favoring garadacimab treatment.

Given the rarity of HAE, a single adequate and well-controlled trial with support from CE is considered sufficient for demonstration of substantial evidence of effectiveness for the proposed indication. The CE consists of strong mechanistic data from the well-understood pathophysiology of this genetic disease and the mechanism of action of the drug. As described above, the kallikrein-kinin pathway and its components, and the mechanism by which pathologic variants in the *SERPING-1* gene lead to bradykinin overproduction and the clinical manifestations of HAE have been well-characterized. Garadacimab inhibits FXIIa, a key protease in the activation of the contact/kallikrein-kinin system pathway, and thereby reduces the downstream production of bradykinin. As bradykinin is the main mediator of angioedema in HAE, and there are no known alternative pathways for bradykinin production in C1-INH-deficient patients (i.e., with Types I and II HAE), inhibition of FXIIa and its activation of the kallikrein-kinin pathway is expected to result in fewer angioedema episodes.

The safety assessment of garadacimab revealed no concerning safety signals that would preclude approval. No deaths occurred in the clinical development program. Serious adverse events,

severe adverse events, and adverse events leading to treatment discontinuation were rare with no major imbalances between treatment groups. Overall, treatment-emergent adverse events were predominantly mild or moderate in severity, with the most common adverse reactions being nasopharyngitis and abdominal pain. As with other HAE products that target the contact system/kallikrein-kinin pathway, prolongation of the coagulation parameters activated partial thromboplastin time and prothrombin time were asymptomatic and not associated with an increased risk of bleeding or thromboembolism. Potential risks can be addressed through labeling and routine pharmacovigilance.

Although trial 3001 enrolled six adolescent subjects (four garadacimab, two placebo), the efficacy and safety of garadacimab in adolescent patients 12 to <18 years of age is primarily based on extrapolation from adults and matching pharmacokinetic exposure. Extrapolation is supported by the same underlying pathophysiology and clinical manifestations of disease, mechanism of action of garadacimab, and similar expected response to treatment across age groups.

Overall, the review team concludes that the benefit-risk assessment is favorable and supports the approval of garadacimab 200 mg SC monthly for the proposed indication of prophylaxis to prevent HAE attacks in adults and adolescents 12 years of age and above.

II. Interdisciplinary Assessment

3. Introduction

This review serves as the interdisciplinary assessment for BLA 761367. Garadacimab is a new molecular entity, first-in-class, fully human IgG4 monoclonal antibody targeting the catalytic subunit of activated Factor XII (FXIIa). The proposed indication is for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older. The proposed dosage is an initial loading dose of 400 mg administered subcutaneously (SC) on the first day of treatment followed by a maintenance dose of 200 mg SC every month.

HAE is a rare genetic condition with an estimated prevalence of 1 in 10,000 to 50,000 people (~6000 to 30,000 in the United States) ([USHAA 2024](#)). The overwhelming majority of patients with HAE have pathogenic variants in the *SERPING-1* gene that encodes C1-esterase inhibitor (C1-INH), resulting in either low levels of C1-INH (Type I) or normal levels of dysfunctional C1-INH (Type II) ([Busse et al. 2021](#)). A very small fraction of patients has Type III HAE caused by other genetic mutations (e.g., Factor XII (FXII), angiopoietin-1, plasminogen (PLG)) and exhibit normal levels and function of C1-INH. The inheritance of HAE is autosomal dominant; however, approximately 25% of patients have de novo mutations. Patients with HAE experience recurrent episodes of swelling in the hands/feet, genitals, gastrointestinal tract, face and/or throat that typically lasts for 2 to 3 days, but occasionally up to 5 days. Symptom onset is typically in childhood, with 50% of patients experiencing angioedema episodes by age 10 years, and symptoms usually increase after puberty. There is a high degree of inter- and inpatient variability in both the frequency and severity of attacks. Characteristically, HAE symptoms do not respond to mast-cell targeted treatments such as antihistamines, corticosteroids, or epinephrine. Pharmacologic treatment of HAE consists of access to on-demand therapies to treat acute episodes of angioedema and consideration for long-term prophylaxis on an individual basis. Approved therapies for prophylaxis and on-demand treatment of acute attacks generally consist of products that target the kallikrein-kinin pathway (i.e., C1-INH replacements, plasma kallikrein inhibitors, bradykinin B2-receptor antagonists). Danazol, an attenuated androgen, is also approved for prophylaxis, although its mechanism of action in HAE is unclear. Garadacimab represents a novel therapeutic for HAE.

The Applicant submitted an IND application (IND 139936) in 2018 to investigate garadacimab for the prophylaxis of HAE attacks. Garadacimab received Fast Track Designation on December 14, 2021, and orphan drug designation on April 30, 2020. The Agency refused to file the initial BLA submission on August 28, 2023, due to a lack of the required Rabbit Pyrogen Test (21 CFR 610.13). The Applicant resubmitted the BLA on October 13, 2023, after addressing the deficiencies outlined in the Refuse-to-File letter. The application was subsequently filed and is the subject of this review. Refer to Section [13](#) for the complete regulatory history.

During the course of the application review, the review team identified two key efficacy review issues and three key safety review issues, as listed below. In-depth analyses and assessments of the efficacy and safety review issues can be found in Sections [6.3](#) and [7.7](#), respectively.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Patient-Reported Outcome Endpoints

3.1.1.2. Type III HAE

3.1.2. Key Safety Review Issues

3.1.2.1. Abnormal Coagulation Labs and Risk of Bleeding or Thromboembolism

3.1.2.2. Hypersensitivity Reactions

3.1.2.3. Injection Site Reactions

3.2. Approach to the Clinical Review

[Table 3](#) provides an overview of the clinical trials used to support the benefit-risk assessment of garadacimab for the prophylaxis of HAE attacks in adults and adolescents 12 years of age and above. Trial 3001 served as the primary basis for efficacy and safety of garadacimab. Trial 2001 provided data to support dose selection as well as supportive efficacy and safety results. Additionally, the ongoing open-label extension (OLE) study 3002 provided data on the long-term safety of garadacimab.

Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations¹ for Garadacimab

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized²	Number of Centers and Countries
CSL312_3001	Adult and adolescent subjects with Type I or II HAE	6-month R, DB, PC, PG, MC	Garadacimab 200 mg SC monthly	Primary: Time-normalized number of HAE attacks/month Secondary: Percentage reduction in time-normalized HAE attacks compared to placebo	80 Screened 64 Randomized 64 Treated 60 Completed	28 centers US, Canada, Germany, Israel, Netherlands, Japan, Hungary
CSL312_3002	Adult and adolescent subjects with Type I or II HAE	At least 12 months OL, ML	Garadacimab 200 mg SC monthly	Primary: Treatment-emergent adverse events	71 Rollovers 90 Non-rollovers	47 centers US, Canada, Australia, New Zealand, Czech Republic, Germany, Spain, Netherlands, Hong Kong, Japan, Taiwan, Israel, Russia
CSL312_2001	Adult subjects with Type I or II or III HAE	TP1: 13-week R, DB, PC, DR, PG TP2: 44-week OL	Garadacimab • 75 mg q4wks • 200 mg q4wks • 600 mg q4wks • Placebo q4wks • 400 mg q2wks	Primary: Time-normalized number of HAE attacks/month Secondary: Number of subjects who had ≥50% reduction in time-normalized number of HAE attacks, number of subjects who were attack-free during TP1	61 Screened 32 Randomized 44 Treated 44 Completed	19 centers US, Canada, Germany, Israel

Source: Clinical Reviewer from the clinical study reports of trials 3001 and 2001 and study 3002.

¹ Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

² If no randomization, then replace with Actual Enrolled.

Abbreviations: BID, twice daily; d, day; DB, double-blind; h, hour; HAE, hereditary angioedema; LTE, long-term extension; MC, multicenter; mo, month(s); N, number of subjects; NCT, national clinical trial; OL, open-label; PC, placebo-controlled; PG, parallel group; R, randomized; q, every; SC, subcutaneous; TP, Treatment Period; wk, week(s); y, year(s)

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 6.3.1
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	Section 6.3.1
☒	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

5.1. Nonclinical Assessment of Potential Effectiveness

Garadacimab was shown to only antagonize FXIIa enzymatic activities, displaying 100% inhibition of FXIIa catalytic activity for both the α and β fragments, meaning that zymogen FXII functions are negligibly impacted. In an in vitro chromogenic assay, garadacimab inhibited the enzymatic activity of human plasma-derived FXIIa and β FXIIa at equivalent levels (half maximal inhibitory concentration~15nM). Garadacimab prolonged the activated partial thromboplastin time (aPTT) clotting time in standard human plasma.

Garadacimab did not significantly inhibit other serum proteases tested when incubated at an enzyme: antibody ratio of up to 1:500 and exhibited half maximal inhibitory concentration values $>1\mu\text{M}$ for all enzymes tested.

In an in vivo angiotensin-converting enzyme inhibitor (captopril)-induced edema murine model, garadacimab significantly inhibited the angiotensin-converting enzyme inhibitor-induced increase of vascular permeability. Complete ablation of vascular leakage was observed at doses of ≥ 0.5 mg/kg.

The established pharmacologic class for garadacimab has been designated as “FXIIa inhibitor” (monoclonal antibody) based on the in vitro and in vivo pharmacology data.

5.2. Clinical Pharmacology/Pharmacokinetics

Key clinical pharmacology information about garadacimab is summarized in [Table 5](#).

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information						
	Pharmacologic Activity						
Established pharmacologic class (EPC)	Activated Factor XII (FXIIa) inhibitor (monoclonal antibody).						
Mechanism of action	Garadacimab is a fully human IgG4/lambda recombinant monoclonal antibody (molecular weight ~148 kDa) that binds to the catalytic domain of activated Factor XII (FXIIa) and inhibits its catalytic activity. Inhibition of FXIIa prevents the activation of pre-kallikrein to kallikrein and the generation of bradykinin, which is associated with inflammation and swelling in HAE attacks, thus blocking the cascade of events leading to an HAE attack.						
Active moieties	Garadacimab						
QT prolongation	Clinical and nonclinical ECG findings are consistent with the fact that antibodies have a low likelihood of direct ion channel interaction and therefore are not expected to cause concentration-dependent prolongation of the QTc interval. However, ECG data collected by the Applicant cannot serve as a substitute for a thorough QT study. As garadacimab is a monoclonal antibody, a thorough QT/QTc study is not warranted. For additional details, refer to the QT-IRT review in DARRTS dated April 25, 2024.						
	General Information						
Bioanalysis	Plasma concentrations of garadacimab were measured using an enzyme-linked immunosorbent assay (ELISA). Bioanalytical methods were adequately validated.						
Healthy subjects versus patients	Garadacimab PK in patients with HAE is consistent with that in healthy subjects						
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	Table 6. Mean (SD) Garadacimab Systemic Exposure Following a Single 200 mg SC Dose in Healthy Subjects <table border="1"> <thead> <tr> <th>PK Parameter</th> <th>Mean (SD)</th> </tr> </thead> <tbody> <tr> <td>C_{max} ($\mu\text{g/mL}$)</td> <td>18.4 (7.23)</td> </tr> <tr> <td>$\text{AUC}_{0-\text{inf}}$ ($\mu\text{g}\cdot\text{h/mL}$)</td> <td>11470 (4103)</td> </tr> </tbody> </table> Source: Clinical Study Report for study 1004. PK in patients with HAE is consistent with that in healthy subjects. Abbreviations: $\text{AUC}_{0-\text{inf}}$, area under the concentration-time curve from time 0 to infinity; C_{max}, maximum plasma concentration; SC, subcutaneous; SD, standard deviation	PK Parameter	Mean (SD)	C_{max} ($\mu\text{g/mL}$)	18.4 (7.23)	$\text{AUC}_{0-\text{inf}}$ ($\mu\text{g}\cdot\text{h/mL}$)	11470 (4103)
PK Parameter	Mean (SD)						
C_{max} ($\mu\text{g/mL}$)	18.4 (7.23)						
$\text{AUC}_{0-\text{inf}}$ ($\mu\text{g}\cdot\text{h/mL}$)	11470 (4103)						

Characteristic	Drug Information
Range of effective dose(s) or exposure	In HAE subjects, the mean (SD) steady-state trough concentrations of garadacimab ranged from 8.09 (4.28) µg/mL to 8.69 (3.93) µg/mL following 400 mg loading dose with 200 mg once monthly maintenance dosing regimen. In dose-ranging trial 2001, three dosing levels of garadacimab of 75, 200, or 600 mg SC Q4W were evaluated in the 13-week placebo-controlled Treatment Period. A reduction in the mean time-normalized number of HAE attacks per month was observed for all dosing levels relative to placebo without a clear dose-response trend observed between 200 mg and 600 mg. In the pivotal phase 3 trial 3001, subjects randomized to garadacimab 200 mg SC Q1M with 400 mg loading dose had significantly lower mean time-normalized number of HAE attacks per month relative to subjects randomized to placebo. Exposure-response analyses for efficacy based on the relative risk of an HAE attack indicated that dosages ≥200 mg SC once monthly are predicted to yield steady-state plasma trough concentrations associated with a 90% reduction in HAE attack rate compared to placebo. Increasing the dose beyond 200 mg is not predicted to result in significant further reductions in HAE attack rate.
Maximally tolerated dose or exposure	Trial 2001 evaluated SC dosing regimens up to 600 mg Q4W in patients with HAE. In healthy subjects, single IV doses up to 10 mg/kg (median dose of 879 mg) were studied.
Dose proportionality	Garadacimab exposure increased in a dose-proportional manner between IV doses of 0.1 and 10 mg/kg and SC doses of 1 and 10 mg/kg.
Accumulation	No additional accumulation was observed at steady state following the proposed 400 mg loading dose with 200 mg monthly maintenance dosing regimen.
Time to achieve steady-state	Steady state is achieved by the third dose (i.e., after SC administration of the initial loading dose of 400 mg and the first 200 mg dose).
Bridge between to-be-marketed and clinical trial/study formulations	In early clinical trials (i.e., 1001, 1003, and 2001), a 100 mg/mL formulation in a vial presentation was used. The remaining studies used the to-be-marketed 170 mg/mL formulation in a PFS presentation. A comparison of steady state trough concentrations across trials 2001 (100 mg/mL) and 3001 and study 3002 (170 mg/mL) indicated that formulation has no impact on garadacimab PK. The final, to-be-marketed formulation in the PFS-NSD presentation was used in the pivotal clinical trial (3001). The proposed AI presentation was not used in trial 3001. The PFS-NSD and AI presentations were bridged in relative bioavailability study 1004 and bioequivalence was demonstrated.
Bioavailability	Absorption
T _{max}	Estimated absolute bioavailability (95% CI) is 39 (34, 43)%
Food effect (fed/fasted)	Median T _{max} ranged from 5.5 to 7 days
Geometric least square mean and 90% CI	Not applicable
Volume of distribution	Distribution
Plasma protein binding	Following administration of a single 200 mg SC dose in healthy subjects, the mean (SD) apparent volume of distribution is 11.8 (5.17) L
Drug as substrate of transporters	Not applicable
	Not applicable

Characteristic	Drug Information
	<i>Elimination</i>
Mass balance results	Not applicable
Clearance	Following administration of a single 200 mg SC dose in healthy subjects, the mean (SD) apparent clearance is 0.020 (0.008) L/h
Half-life	Mean terminal elimination half-life is about 17 to 20 days
Metabolic pathway(s)	Not applicable
Primary excretion pathways (% dose)	Not applicable
	<i>Intrinsic Factors and Specific Populations</i>
Body weight	Body weight is a significant covariate affecting the PK of garadacimab such that garadacimab exposure is increased in patients with lower body weight. Body weight-based differences in exposures are not clinically relevant and no dose adjustments based on body weight are recommended.
Age	Age (12 to 73 years) did not meaningfully influence the PK of garadacimab
Renal impairment	No dedicated studies have been conducted to evaluate the impact of renal impairment on the PK of garadacimab. Per population PK analysis, renal impairment (eGFR ≥ 90 mL/min/1.73 m ² [normal, N=145]; 60 to < 90 mL/min/1.73 m ² [mild, N=26]; and 30 to < 60 mL/min/1.73 m ² [moderate, N=2]) did not impact the PK of garadacimab.
Hepatic impairment	No dedicated studies have been conducted to evaluate the impact of hepatic impairment on the PK of garadacimab. Per population PK analysis, bilirubin (4 to 13 μ mol/L – 10 th and 90 th percentiles, respectively, in the observed dataset) did not significantly impact garadacimab clearance.
	<i>Drug Interaction Liability (Drug as Perpetrator)</i>
Inhibition/induction of metabolism	Not applicable
Inhibition/induction of transporter systems	Not applicable
	<i>Immunogenicity</i>
Bioanalysis	The immunogenicity assay was a bridging assay that used an acid dissociation treatment step. Acid-treated samples were incubated in the presence of biotinylated and sulfo-tagged garadacimab, which form bridging complexes with ADAs. A tiered approach was used in which samples were screened for ADAs, confirmed positive, and then evaluated for titers.
Incidence	In pivotal trial 3001, the ADA incidence was 2.6% (1/39) in patients who received garadacimab during the 6-month Treatment Period. Among all patients with HAE who received the proposed garadacimab dosing regimen in trial 3001 and study 3002, the incidence of treatment-emergent ADAs was 3.9% (5/129).
Clinical impact	There was no apparent impact of immunogenicity on the PK, efficacy, or safety of garadacimab. Overall, few patients with HAE tested positive for ADAs, precluding a definitive assessment of the impact of ADAs.

Source: Module 2.7.2, Summary of Clinical Pharmacology; Module 2.7.1, Summary of Biopharmaceutic Studies; Integrated Summary of Immunogenicity; Clinical Study Reports for 1001, 1004, 2001, and 3001.

Abbreviations: ADA, antidrug antibody; AI, autoinjector; AUC, area under the plasma concentration-time curve; CI, confidence interval; C_{max}, maximum plasma concentration; C_{trough}, minimum plasma concentration; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ELISA, enzyme-linked immunosorbent assay; FXIIa, activated Factor XII; HAE, hereditary angioedema; PFS-NSD, prefilled syringe with needle safety device; Q1M, every month; Q4W, every 4 weeks; QT-IRT, QT-Interdisciplinary Review Team; SC, subcutaneous; SD, standard deviation

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

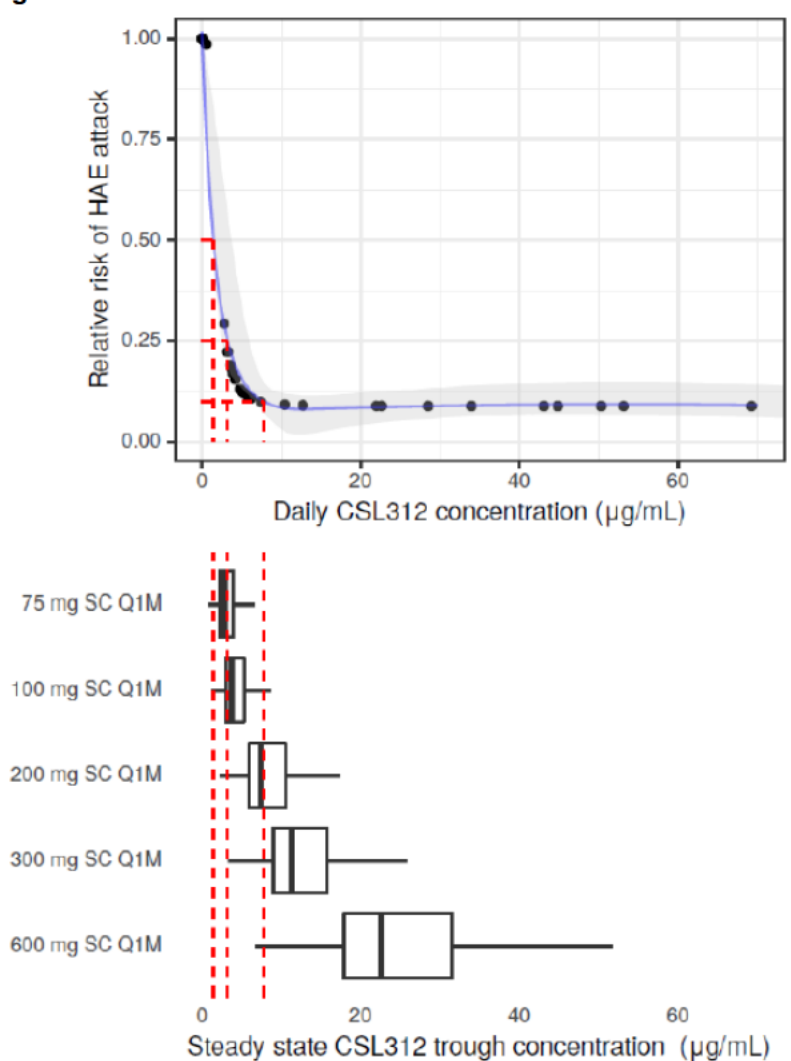
The proposed dose of garadacimab is 200 mg SC every month, with an initial 400 mg loading dose. The dose and dosing regimen were investigated in a phase 2 dose-ranging trial (2001) and a phase 3 pivotal trial (3001), and by pharmacokinetic (PK) modeling.

Trial 2001

Trial 2001, described in detail in Section [16.2](#), evaluated four dosing regimens: 75 mg SC, 200 mg SC, and 600 mg SC every 4 weeks (Q4W) with different intravenous (IV) loading doses (40, 100, and 300 mg, respectively), and 400 mg SC every 2 weeks (open label). The primary endpoint of time-normalized number of HAE attacks per month was compared to placebo for the 200 mg and 600 mg treatment arms (see [Table 117](#)). The primary endpoint was also compared exploratorily between the 200 mg and 600 mg arms. Both the 200 mg and 600 mg arms met the primary objective and showed significant reductions in the time-normalized number of HAE attacks, but injection site reactions (ISRs) were more common in the 600 mg arm compared to the 200 mg arm. In March 2020, a protocol amendment was submitted by the Applicant, and all subjects with C1-INH (Type I or Type II) HAE were switched to the 200 mg arm.

Clinical and PK data from trial 2001 were used to support dose selection for trial 3001. The garadacimab concentration-effect relationships were explored based on the relative risk of an HAE attack using maximal-efficacy model. The model-predicted relative risk of an HAE attack as a function of steady-state garadacimab plasma trough concentration is shown in [Figure 1](#). Model predictions evaluated dosing regimens in which garadacimab was administered SC every month and included administration of an initial loading dose of twofold the monthly dose. Results indicated that dosages ≥ 200 mg administered SC once monthly yielded a steady-state median plasma trough concentration associated with a ~90% reduction, on average, in HAE attack rate compared to placebo. Model predictions also indicated that a plateau phase for reduction of HAE attack rate was reached following the 200-mg dose.

Figure 1. Relative Risk of an HAE Attack as a Function of Garadacimab Concentration



Source: Summary of Clinical Pharmacology, Figure 14.

In the top panel, the blue line is the model prediction, and the gray ribbon is the approximate 95% CI. In the bottom panel, the box plots indicate distribution of steady state garadacimab C_{trough} by dose. The box represents the IQR, the line in the box represents the median, and the whiskers represent 1.5× IQR. Red dashed lines in both panels correspond to relative risk of HAE attacks of 0.50, 0.25, and 0.10 (left to right). Each dosing regimen includes an initial SC loading dose of twofold the Q1M dose.

Abbreviations: CI, confidence interval; CSL312, garadacimab; C_{trough} , plasma trough concentration; HAE, hereditary angioedema; IQR, interquartile range; Q1M, once monthly; SC, subcutaneously

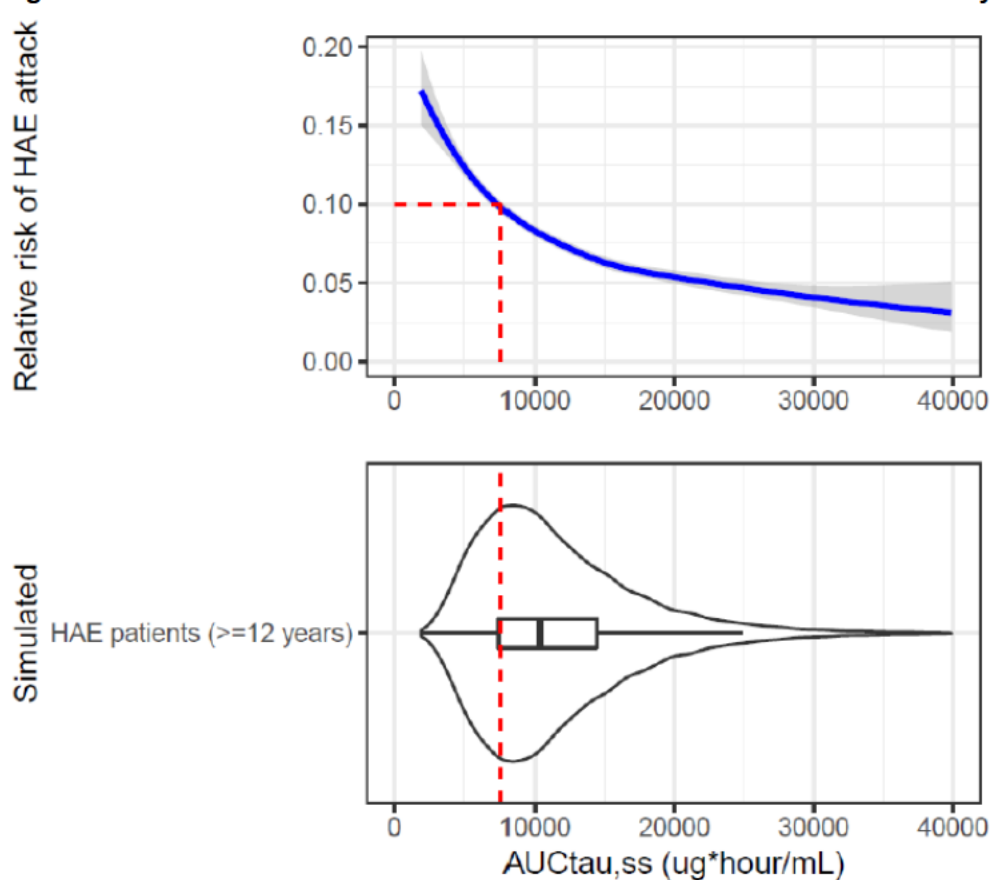
Based on the results of the phase 2 dose-ranging trial (2001) and assessment of exposure-response (E-R) relationships for efficacy, selection of the 200-mg dose for the phase 3 trial (3001) appears to be reasonable.

Trial 3001

The 200 mg monthly maintenance dosing regimen (with a 400 mg loading dose) was further evaluated in the 6-month, randomized, double-blind, placebo-controlled, phase 3 trial (3001). The 200-mg dose met the primary endpoint of time-normalized number of HAE attacks per month and all key secondary efficacy endpoints, demonstrating an improvement over placebo (see Sections [6.2.4.3](#) and [6.2.4.4](#)).

Additionally, the phase 3 PK data were incorporated into the E-R analyses for efficacy based on the relative risk of HAE attacks. The model-predicted relative risk of an HAE attack as a function of simulated steady-state garadacimab exposure (area under the concentration-time curve (AUC) over one dosing interval at steady state) is shown in [Figure 2](#). Simulated steady-state exposure was derived from the proposed dosing regimen consisting of a 400 mg SC loading dose followed by 200 mg SC once monthly. Results indicate that at steady state, the area under the plasma concentration-time curve over one dosing interval at steady state ($AUC_{\tau,ss}$) following the 200 mg once monthly maintenance dose yielded a reduction in the relative risk of HAE attacks near the plateau of the curve. Also, population predictions of exposure indicated that about 75% of subjects will achieve an at least 90% reduction in the HAE attack rate compared to baseline.

Figure 2. Relative Risk of an HAE Attack as a Function of Garadacimab Steady-State AUC_{τ}



Source: Summary of Clinical Pharmacology, Figure 21.

Notes: In the top panel, the simulated mean HAE relative risk is shown as the blue line with an approximate 95% CI for the mean in gray. The bottom panel shows the density of simulated $AUC_{\tau,ss}$ where the boxplot indicates the 25th, 50th, and 75th percentiles with whiskers extending to 1.5× IQR.

Abbreviations: $AUC_{\tau,ss}$, area under the plasma concentration-time curve over one dosing interval at steady state; CI, confidence interval; HAE, hereditary angioedema; IQR, interquartile range

Loading Dose Justification

The proposed dosing regimen includes an initial loading dose of 400 mg SC. This loading dose was incorporated into the regimen administered to subjects randomized to garadacimab in the phase 3 trial (3001). E-R analyses for efficacy (reduction in HAE attack rate) shown above were

used to identify exposure thresholds to reach a 90% relative risk reduction based on area under the concentration-time curve during the dosing interval, maximum plasma concentration (C_{max}), and minimum plasma concentration. Inclusion of the loading dose was justified by demonstrating that the probability of exceeding the 90% responder threshold after the first dose was greater if a loading dose was administered relative to a regimen in which no loading dose was given (see [Table 7](#)).

Table 7. Loading Dose Justification: Probability of Achieving Exposure Exceeding a 90% Reduction in HAE Attack Rate After the First Dose

Regimen	Probability (Exposure $\geq$ 90% Responder Threshold)		
	AUC_{tau}	C_{max}	C_{min}
With loading dose	0.853	0.854	0.889
Without loading dose	0.397	0.472	0.414

Source: Summary of Clinical Pharmacology, Table 11.
 Abbreviations: AUC_{tau} , area under the plasma concentration-time curve over one dosing interval; C_{max} , maximum plasma concentration; C_{min} , minimum plasma concentration; HAE, hereditary angioedema

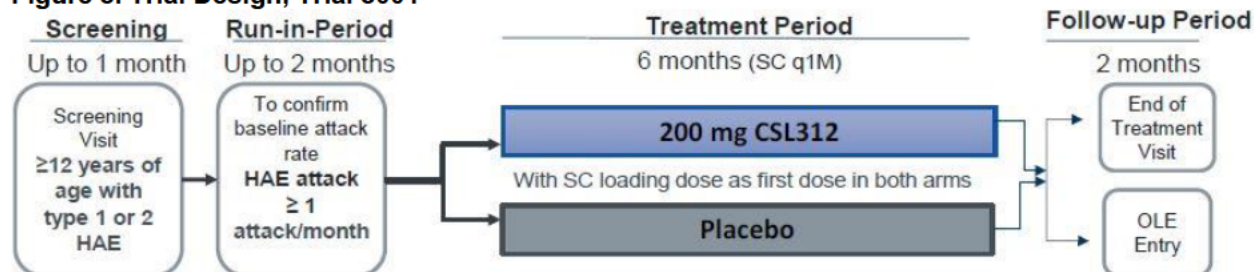
Overall, the data from trials 2001 and 3001 supported the proposed dosing regimen of a 400 mg loading dose administered SC followed by a 200-mg dose administered SC once monthly.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Design and Conduct, Trial 3001

Results of the pivotal trial (3001) served as the basis for efficacy evaluation. This was a 6-month, randomized (3:2 to garadacimab: placebo), double-blind, placebo-controlled, parallel-group, multicenter (9 U.S. sites and 19 ex-U.S. sites), phase 3 trial evaluating 200 mg garadacimab administered SC once monthly in adults (aged 18 to 69 years) and adolescents (aged 12 to 17 years) with C1-INH (Type I or Type II) HAE who had ≥ 2 HAE attacks during the Run-in Period. This trial had a Screening Period of up to 1 month, a Run-in Period of up to 2 months, a 6-month Treatment Period, and a 2-month Follow-up Period ([Figure 3](#)).

Figure 3. Trial Design, Trial 3001



Source: Clinical Study Report (dated October 6, 2022), Figure 9-1, p. 21.
 Abbreviations: CSL312, garadacimab; HAE, hereditary angioedema; OLE, open-label extension; q1m, once monthly; SC, subcutaneous

After obtaining informed consent (or assent for minors), subjects entered the Screening Period to determine eligibility for study enrollment. Individuals with FXII/PLG (Type III) HAE were not enrolled. Screened subjects who met all the inclusion criteria, and none of the exclusion criteria, entered the Run-in Period (see Section [6.2.2](#) for the key inclusion and exclusion criteria). If a subject did not meet all the criteria for entering the Run-in Period within 30 days, the subject could be rescreened once.

Following screening, subjects entered the Run-in Period, which lasted at least 1 month and up to 2 months, to confirm their underlying disease status and assess their eligibility for participation in the Treatment Period. Subjects had to experience ≥ 2 HAE attacks during the Run-in Period to enter the Treatment Period. Subjects who experienced ≥ 2 HAE attacks during the required first month could exit the Run-in Period and enter the Treatment Period. Subjects were not allowed to take prophylaxis during the Run-in Period. Adults on HAE prophylaxis had a minimum 2-week (for C1-INH products, androgens, and antifibrinolytics) or 3-month (for lanadelumab) Washout Period before entering the Run-in Period (subjects not on prophylaxis did not require a Washout Period). Adolescents on routine (long-term) HAE prophylaxis were excluded from the trial.

In the Treatment Period, 64 eligible participants were randomized 3:2 to receive 200 mg garadacimab or matching placebo once monthly for 6 months. Randomization accounted for age (≤ 17 years; > 17 years) and, for adults, baseline attack rate, defined as the time-normalized number of HAE attacks per month during the Run-in Period (1 to < 3 ; ≥ 3).

For details regarding the collection and reporting of HAE data, and the investigator confirmation of HAE attacks, see Section [15.1.1](#).

The overall design of the trial is consistent with previous programs for HAE prophylaxis. The duration of the Treatment Period (6 months) is acceptable for this program.

Participants who completed the Treatment Period were eligible to enroll in a phase 3b, OLE study (3002; see Sections [7.6.2](#) and [16.2](#)).

Primary Objective and Endpoint

The primary objective of this trial was to evaluate the efficacy of garadacimab as prophylaxis to prevent HAE attacks in subjects with C1-INH (Type I or Type II) HAE. The primary efficacy endpoint was the time-normalized number of HAE attacks per month during the Treatment Period compared to matched placebo (only investigator-confirmed HAE attacks, as defined in Section [15.1.1](#), were included). The primary endpoint was calculated per subject as:

$$[\text{number of HAE attacks} \div \text{length of subject treatment in days}] \times 30.4375$$

Length of subject treatment (in days) was calculated as:

$$[\text{date of Study Visit Day 182 or the End-of-Study date (whichever occurred first)} \\ - \text{date of Study Visit Day 1 of Treatment Period} + 1]$$

Secondary and Exploratory Objectives and Endpoints

The secondary trial objectives included characterizing the clinical efficacy of garadacimab in the prophylactic treatment of HAE. Only investigator-confirmed HAE attacks, as defined in

Section [15.1.1](#), were included in the efficacy evaluation. The key secondary efficacy endpoints were:

- Percentage reduction in the mean time-normalized number of HAE attacks per month during the Treatment Period.
- Number of subjects who did not experience an HAE attack (i.e., were attack-free) in the first 3 months of the Treatment Period.
- Percentage of subjects with *good* or *excellent* responses to the Subject's Global Assessment of Response to Therapy (SGART) at the end of the Treatment Period.

The first key secondary endpoint above was calculated as:

$$100 \times [(\text{mean time-normalized number of HAE attacks for garadacimab} - \text{mean time-normalized number of HAE attacks for placebo}) \div \text{mean time-normalized number of HAE attacks for placebo}].$$

The other secondary efficacy endpoints were:

- Percentage reduction ($\geq 50\%$, $\geq 70\%$, $\geq 90\%$, and 100% [attack-free]) in the time-normalized number of HAE attacks per month during the Treatment Period compared to the Run-in Period.
- Time-normalized number of HAE attacks per month requiring on-demand therapy during the Treatment Period.
- Time-normalized number of moderate or severe HAE attacks per month during the Treatment Period.

HAE attack severity was assessed by the investigator based on the subject's description of the attack and reflected the maximum intensity of the attack. The Applicant specified the following qualifiers for investigator determination of HAE attack severity in the clinical study protocol (dated August 4, 2020), though they could have varied between subjects and attacks:

Mild:

- Little to no effect on daily activities.
- Use of HAE on-demand therapy to treat the attack may not be necessary.
- Other concomitant medication (e.g., analgesics) may be used to treat attack symptoms.

Moderate:

- Causes daily activities to be difficult.
- Some assistance may be needed to complete daily activities.
- Use of HAE on-demand therapy to treat the attack is probable.

Severe:

- Causes marked limitation of daily activities.
- Medical assistance and intervention may be required, including at clinic emergency room visit or hospitalization.
- HAE on-demand therapy is used to treat the attack.

An exploratory objective of this trial was to further evaluate the efficacy and quality of life associated with the use of garadacimab in subjects with C1-INH (Type I or Type II) HAE. This included analyzing an exploratory endpoint of change in subject total and domain scores from the angioedema quality of life (AE-QoL) questionnaire from baseline to Day 182 by treatment arm.

6.2.2. Eligibility Criteria, Trial 3001

Key eligibility criteria are summarized below. The trial enrolled subjects ≥ 12 years of age with clinically confirmed HAE and an attack frequency that would likely warrant prophylactic HAE therapy. The inclusion and exclusion criteria are acceptable and consistent with those used in previous studies of approved products for HAE prophylaxis.

Key Inclusion Criteria

- Male or female ≥ 12 years of age at the time of informed consent.
- Diagnosed with clinically confirmed C1-INH (Type I or Type II) HAE:
 - Documented clinical history consistent with HAE (SC or mucosal, nonpruritic swelling episodes without accompanying urticaria), and
 - C1-INH antigen and/or functional activity $\leq 50\%$ of normal, and
 - C4 antigen concentration below the lower limit of the reference range.
- Experienced ≥ 3 HAE attacks during the 3 months before Screening (subjects taking any prophylactic HAE therapy prior to Screening could present documentation of ≥ 3 HAE attacks during the three consecutive months before commencing the prophylactic therapy).

Key Exclusion Criteria

- Concomitant diagnosis of another form of angioedema, such as idiopathic or acquired angioedema, recurrent angioedema associated with urticaria, or FXII/PLG (Type III) HAE.
- For adult subjects: use of C1-INH products, androgens, antifibrinolytics, or other small molecule medications for routine prophylaxis against HAE attacks within 2 weeks prior to the Run-in Period.
- For adolescent subjects (12 to 17 years of age): use of long-term prophylactic therapy for HAE before Screening.
- Use of a monoclonal antibody, such as lanadelumab, within 3 months prior to the Run-in Period.

6.2.3. Statistical Analysis Plan, Trial 3001

The final statistical analysis plan (statistical analysis plan (SAP); version 1.0) is dated April 21, 2021. For details about the sample size calculation for this trial, see Section [15.1.3](#). The following analysis sets were defined by the Applicant:

Screened Analysis Set: All subjects who provided written informed consent (or assent for minors) and who underwent study screening procedures.

Intention-to-Treat Analysis Set: All subjects in the Screened Analysis Set who were randomized. The intent-to-treat (ITT) Analysis Set was analyzed using the treatment to which the subject was randomized, regardless of the treatment actually received. The ITT Analysis Set was the main set used for efficacy evaluation.

Safety Analysis Set: All subjects in the ITT Analysis Set who received at least one dose of investigational product. The Safety Analysis Set was analyzed using the actual treatment received and was the main set used for safety evaluation.

Per Protocol Analysis Set: All subjects in the ITT Analysis Set who received at least one dose of investigational product and complied with the protocol. Decisions regarding exclusion from the Per Protocol Analysis Set were made and documented prior to unblinding.

Use of the phrase “complied with the protocol” in the definition for the Per Protocol Analysis Set is vague, and the Applicant did not provide any further details. However, there was only one major protocol violation in the trial (one subject missed a visit and then withdrew consent).

6.2.3.1. Testing Hierarchy and Multiplicity Control, Trial 3001

Four hypothesis tests (one for the primary endpoint [H01] and three for the key secondary endpoints [H02, H03, and H04]) were performed hierarchically at a two-sided alpha of 5%. Below is a description of the four null hypotheses associated with these four tests, per the Applicant’s final SAP:

1. H01: The time-normalized numbers of HAE attacks in the first 6-month time period of the Active Arm and in the Placebo Arm period are equal.
2. H02: The percentage reductions in the mean time-normalized number of HAE attacks for the 6 months of the Active Arm compared to the 6-month Placebo Arm period are equal to zero.
3. H03: The number of subjects who do not experience a HAE attack in the first 3 months of the Active Arm and the first 3-month Placebo Period are equal.
4. H04: The percentage of subjects with *good* or *excellent* responses to the SGART at the end of the Treatment Period (Day 182) are equal for subjects treated with garadacimab and placebo.

From the final SAP, the general flow of the hypothesis testing was as follows:

The null hypothesis associated with the primary endpoint (H01) was tested first at a two-sided alpha of 5%. If and only if the resulting two-sided p-value was <0.05 , testing of H02 would be performed. If and only if H02 was rejected (with a two-sided p-value <0.05), H03 would be tested. If and only if H03 was rejected (with a two-sided p-value <0.05), H04 would be tested at a two-sided alpha of 5%.

The definition for H02 was unclear in the trial protocol (dated August 4, 2020). Prior to database lock, the Applicant modified H02 in the final SAP, but it included two different specifications for H02. In the Applicant's response (dated June 27, 2024) to an FDA Information Request (IR), it was clarified that H02 was defined as written above. In a separate IR response (dated July 23, 2024), the Applicant also clarified that H02 was evaluating the percentage reduction in the means relative to placebo during the Treatment Period, not the percentage reduction in the means for each treatment arm relative to the Run-in Period (this was an additional secondary endpoint outside of the testing hierarchy). H01 and H02 were essentially evaluating different summary measures of the same endpoint; no rationale was provided for including H02 in the testing hierarchy. The Applicant may have wanted to evaluate the percentage reduction for increased clinical interpretability (since the results of a Wilcoxon rank sum test are not as straightforward) and labeling purposes.

6.2.3.2. Analysis of the Primary Endpoint, Trial 3001

The Applicant's primary objective was to assess the treatment effect of garadacimab during the 6-month Treatment Period (from Day 1 [first study drug administration] through Day 182) while subjects were allowed to treat HAE attacks with on-demand therapy.

Primary Estimand

The Applicant defined the following attributes for the primary estimand:

- Treatment Condition: Monthly treatment of garadacimab or placebo.
- Population: The target subject population defined by the study eligibility criteria and who were randomized (the ITT Analysis Set).
- Variable: Time-normalized number of HAE attacks per month during treatment from Day 1 through Day 182.
- Intercurrent Events: All observed values were used regardless of the occurrence of the following intercurrent events (treatment policy strategy):
 - Administration of on-demand therapy in addition to prophylactic treatment with garadacimab.
 - Prohibited concomitant medications due or not due to coronavirus disease 2019 (COVID-19) or COVID-19 vaccination.
 - Noncompliance to treatment due or not due to COVID-19 or COVID-19 vaccination.
 - Early study discontinuation due or not due to COVID-19.

The intercurrent event of early study discontinuation due or not due to COVID-19 was removed prior to database lock per FDA feedback, as the Agency did not consider this to be an intercurrent event. In the final SAP, the Applicant prespecified that subjects who discontinue treatment or the study but are on study treatment for at least 30 days would be included in the primary analysis. Additionally, no subjects discontinued treatment or the study as a result of COVID-19.

- Population-Level Summary: Median time-normalized number of HAE attacks per month during treatment from Day 1 through Day 182.

Primary Analysis

The analysis method for evaluating the primary endpoint in the ITT Analysis Set was a two-sided Wilcoxon rank sum test at $\alpha=5\%$. The population-level summary specified in the Applicant's primary estimand was the median, but the Wilcoxon rank sum test is not a median test.

If a subject discontinued the study early after being in the Treatment Period for the first 30 days continuously, observation was terminated by the Early Termination Visit. Based on the data from the phase 2 trial (2001), it was assumed that the attack rate for subjects who discontinued the study after Study Day 30 and before the end of Month 6 would be comparable to the attack rate among subjects who completed the entire 6-month Treatment Period. Therefore, the primary endpoint was considered measurable and not missing for these subjects (the time-normalized number of HAE attacks was calculated based on the HAE attacks reported until the subject's Early Termination Visit).

If a subject discontinued treatment due or not due to COVID-19 but continued participation in the study for more than 30 days beyond the last study drug administration, the HAE attacks until the last study drug administration plus 30 days were included in the calculation of the primary endpoint (the study drug was administered monthly). For these subjects, length of treatment (in days) was calculated as:

[date of last study drug administration – date of Study Visit Day 1 of the Treatment Period + 31].

Missing Data

The final SAP prespecified that the primary endpoint (the time-normalized number of HAE attacks per month) would only be considered missing for subjects who discontinued study treatment within 30 days after the first study drug administration.

Sensitivity Analyses

The sensitivity analysis below was specified in the Applicant's final SAP.

To evaluate the robustness of the primary efficacy results, the time-normalized number of HAE attacks per month was compared between the garadacimab and placebo arms using a generalized linear model for count data assuming a Poisson distribution with the log link function and Pearson chi-squared scaling of standard errors to account for potential overdispersion. The model included treatment arm and baseline attack rate (the time-normalized number of HAE attacks per month during the Run-in Period) as covariates. To account for differences in treatment duration among subjects, the logarithm of subject time on treatment was included as an offset term in the model.

From this model, the least squares (LS) mean time-normalized number of HAE attacks per month and associated standard errors were estimated for the garadacimab and placebo arms. To report the mean HAE attack rate per month, the received model estimates were transformed by the exponential function and scaled by time. The corresponding attack ratio for garadacimab relative to placebo and its 95% CI were also reported. The estimated attack ratio was used to calculate the percentage difference in the means as follows: $100\% \times (\text{attack ratio} - 1)$. The 95% CI for the percentage difference in means was calculated using the upper and lower confidence limits obtained for the attack ratio, transformed by subtracting 1 and then multiplying by 100%.

This sensitivity analysis was applied to the ITT Analysis Set.

Subgroup Analyses

In the final SAP, the Applicant prespecified that if five or more Japanese subjects were enrolled in the trial, then a descriptive analysis of the primary endpoint (the time-normalized number of HAE attacks per month) would be conducted for the subset of Japanese subjects (the Applicant did not provide a rationale for this analysis). Since a total of six Japanese subjects were enrolled in the trial, the Applicant completed this subgroup analysis and submitted the results for review. Analyses of the primary endpoint by other clinically relevant subgroups were not prespecified or submitted by the Applicant. Additional analyses of the primary endpoint by other clinically relevant subgroups (by age, sex, geographic location, HAE subtype, HAE attack location and severity, and other races/ethnicities) were completed by the Agency to inform regulatory decision-making. See Section [6.2.4.6](#) for the results of subgroup analyses for the primary endpoint.

6.2.3.3. Analysis of the Key Secondary Endpoints, Trial 3001

The Applicant prespecified the following statistical tests for the three key secondary endpoints:

- Percentage reduction in the means of the time-normalized number of HAE attacks per month was assessed using a two-sided Wilcoxon rank sum test.
- Number of subjects who did not experience an HAE attack (i.e., were attack-free) in the first 3 months of the 6-month Treatment Period was evaluated using a two-sided Fisher exact test.
- Percentage of subjects with *good* or *excellent* responses to the SGART at the end of the Treatment Period was assessed using a two-sided chi-squared test.

The first key secondary endpoint above was defined as:

$$100 \times [(\text{mean time-normalized number of HAE attacks for garadacimab} - \text{mean time-normalized number of HAE attacks for placebo}) \div \text{mean time-normalized number of HAE attacks for placebo}].$$

Its corresponding hypothesis (H02) was “the percentage reduction in means of the time-normalized number of HAE attacks for the 6 months of the Active Arm compared to the 6-month Placebo Arm period are equal to zero” (specified in the protocol, and confirmed by the Applicant’s IR responses dated June 27, 2024, and July 23, 2024). The Wilcoxon rank sum test is a nonparametric approach to test location shift between two distributions. However, H02 was to test whether a summary statistic equaled zero, for which the Wilcoxon rank-sum test would not be applicable. In Section [6.2.4.4](#), only descriptive statistics have been presented for this endpoint.

Key secondary estimands were not defined by the Applicant.

Missing Data

Secondary endpoints based on HAE attack rate (e.g., the first key secondary endpoint) used the same missing data assumptions as the primary endpoint (see *Missing Data* in Section [6.2.3.2](#)).

6.2.3.4. Other Secondary/Exploratory Endpoint Analyses, Trial 3001

Additional secondary and exploratory endpoints in this trial included:

- Percentage reduction ($\geq 50\%$, $\geq 70\%$, $\geq 90\%$ and 100% [attack-free]) in the time-normalized number of HAE attacks per month during the Treatment Period compared to the Run-in Period.
- Time-normalized number of HAE attacks per month requiring on-demand therapy during the Treatment Period.
- Time-normalized number of moderate or severe HAE attacks per month during the Treatment Period.
- Change from baseline to Day 182 in total and domain scores from the AE-QoL questionnaire.

Percentage reductions were assessed descriptively by treatment arm, and an exploratory, two-sided Fisher exact test was prespecified and conducted for subjects with a 100% reduction only. The time-normalized number of HAE attacks per month requiring on-demand therapy and the time-normalized number of moderate or severe HAE attacks per month were evaluated by treatment arm using exploratory, two-sided Wilcoxon rank-sum tests. The Agency was also interested in assessing these two endpoints using exploratory Poisson models structured similarly to the Applicant's sensitivity analysis for the primary endpoint described in Section [6.2.3.2](#).

AE-QoL data were collected only from subjects 18 years of age or older and were summarized descriptively by treatment arm. AE-QoL total and domain scores were calculated as:

$$100 \times [\text{sum of all completed items} \div \text{maximum possible sum of all completed items}].$$

Estimands were not defined for any of the endpoints above.

Missing Data

Additional secondary and exploratory endpoints based on HAE attack rate used the same missing data assumptions as the primary endpoint (see *Missing Data* in Section [6.2.3.2](#)).

For the AE-QoL data, domain scores were not calculated if more than one item was missing for a domain, and total scores were not calculated if more than four items were missing in total. Subjects without an AE-QoL domain and/or total score were excluded from the descriptive summary accordingly.

6.2.4. Results of Analyses, Trial 3001

This section summarizes subject disposition, baseline demographics and clinical characteristics, and the primary, secondary, and exploratory efficacy results for the endpoints listed in Section [6.2.1](#). The results of additional analyses of interest to the Agency are also reported.

6.2.4.1. Subject Disposition, Trial 3001

Disposition information is provided in [Table 8](#). A total of 80 subjects were screened, of which 4 were screen failures due to not obtaining informed consent (N=1), not having a clinically

confirmed diagnosis of C1-INH (Type I or Type II) HAE (N=2), or not experiencing ≥ 3 HAE attacks during the 3 months before screening (N=1). Of the 76 subjects who entered the Run-in- Period, 11 were not eligible to advance to the Treatment Period (most due to < 1 month of participation in the Run-in- Period, an insufficient number of HAE attacks experienced during the Run-in- Period, or clinically significant laboratory abnormalities).

Table 8. Subject Disposition, Trial 3001

Disposition Category	Garadacimab (N=39)	Placebo (N=25)	Total (N=64)
Screened	–	–	80
Screen failure	–	–	4
Entered Run-in Period	–	–	76
Runin Period failure	–	–	11
Randomized and received loading dose	39 (100%)	25 ^a (100%)	64 (100%)
Discontinued treatment	0 (0%)	3 (12%)	3 (5%)
Withdrawal of consent	0 (0%)	3 (12%)	3 (5%)
Discontinued study	1 (3%)	0 (0%)	1 (2%)
Withdrawal of consent	1 (3%)	0 (0%)	1 (2%)
Completed study	38 (97%)	22 (88%)	60 (94%)
Continued to OLE study (3002)	36 (92%)	21 (84%)	57 (89%)
Analysis set			
Intent-to-treat (ITT)	39 (100%)	25 (100%)	64 (100%)
Per-protocol	39 (100%)	24 (96%)	63 (98%)
Safety	39 (100%)	25 (100%)	64 (100%)

Source: Statistical reviewer; Clinical Study Report (dated October 6, 2022), Table 14.1.1.1, p. 164.

^a Twenty-six subjects were randomized to placebo, but one subject was randomized in error and did not receive any study treatment. Abbreviations: N, number of subjects in the ITT Analysis Set; OLE, open-label extension

A total of 65 subjects were randomized 3:2 to garadacimab: placebo, but 1 subject was randomized to placebo in error. This subject had a third HAE attack prior to receiving any study treatment but was ultimately removed from the ITT set (and the per-protocol set) after not attending Visit Day 1 and then withdrawing from the study the next day (no study treatment was received). The ITT and Safety Sets comprised 64 subjects (39 on garadacimab and 25 on placebo), and the per-protocol set comprised 63 subjects (39 on garadacimab and 24 on placebo), as one subject on placebo took lanadelumab within 3 months prior to the Run-in Period and 20 days after first study drug administration. The trial completion rate was 94% for the ITT Set (88% in the placebo arm and 97% in the garadacimab arm). One subject (3%) in the garadacimab arm discontinued the trial (withdrew consent) and three subjects (12%) in the placebo arm discontinued treatment (all withdrew consent). Of the 64 subjects in the ITT Set, 57 (89%) enrolled in an OLE; 36 (92%) from the garadacimab arm and 21 (84%) from the placebo arm. 36 (92%) from the garadacimab arm and 21 (84%) from the placebo arm. 36 (92%) from the garadacimab arm and 21 (84%) from the placebo arm.

Overall, the subject disposition in this trial is reasonable for an HAE program.

6.2.4.2. Baseline Demographics and Clinical Characteristics, Trial 3001

The demographics and clinical characteristics of the ITT Set at baseline are summarized in [Table 9](#) and were appreciably similar between the treatment arms for this small trial (N=64). The

study enrolled more females (59%) than males (41%), which is generally consistent with the enrollment patterns seen in previous HAE programs. A total of six adolescents (9% of the ITT set) were enrolled, of which four were randomized to garadacimab and two to placebo (this is considered adequate, as the pathophysiology of C1-INH [Type I or Type II] HAE is similar across all age groups). Racial and ethnic group representation in this trial is congruent with the overall subject population. Most of the ITT Set had Type I HAE (88%) and a history of laryngeal HAE attacks (59%). Enrollment occurred at sites in the United States (33% of the ITT Set) and outside the United States (67% of the ITT Set). Additionally, 33% of the ITT Set reported use of HAE prophylaxis therapy during the 3 months prior to Screening, 89% had a family history of HAE, and the average HAE duration was 22 years.

Table 9. Baseline Demographics and Clinical Characteristics (ITT Analysis Set), Trial 3001

Demographic/ Clinical Characteristic	Garadacimab (N=39)	Placebo (N=25)	Total (N=64)
Sex, n (%)			
Female	24 (61.5)	14 (56)	38 (59.4)
Male	15 (38.5)	11 (44)	26 (40.6)
Age (years)			
Mean (SD)	43.3 (17.4)	37.8 (12.8)	41.2 (15.9)
Median (min, max)	43 (12, 69)	38 (14, 62)	41 (12, 69)
Age group (years), n (%)			
<18	4 (10.3)	2 (8)	6 (9.4)
18 to 69	35 (89.7)	23 (92)	58 (90.6)
Race, n (%)			
Asian (Japanese)	4 (10.3)	2 (8)	6 (9.4)
Black or African American	0 (0)	1 (4)	1 (1.6)
Native Hawaiian or Pacific Islander	1 (2.6)	0 (0)	1 (1.6)
White	33 (84.6)	22 (88)	55 (85.9)
Other	1 (2.6)	0 (0)	1 (1.6)
Ethnicity, n (%)			
Hispanic	1 (2.6)	2 (8)	3 (4.7)
Non-Hispanic	37 (94.9)	23 (92)	60 (93.8)
Not reported	1 (2.6)	0 (0)	1 (1.6)
BMI (kg/m ²)			
Mean (SD)	27.9 (6.0)	28.4 (7.6)	28.1 (6.6)
Median (min, max)	27.7 (19.3, 52.7)	25.7 (18.7, 42.7)	27.3 (18.7, 52.7)
Location, n (%)			
United States	12 (30.8)	9 (36)	21 (32.8)
Ex-United States	27 (69.2)	16 (64)	43 (67.2)
HAE subtype, n (%)			
Type I	34 (87.2)	22 (88)	56 (87.5)
Type II	5 (12.8)	3 (12)	8 (12.5)
HAE attacks during Run-in Period, n (%)			
1 to <3 attacks	16 (41)	10 (40)	26 (40.6)
≥3 attacks	23 (59)	15 (60)	38 (59.4)
HAE duration ^a (years)			
Mean (SD)	24 (14.7)	18.3 (12.4)	21.7 (14.1)
Median (min, max)	23.5 (0, 57)	24 (0, 40)	24 (0, 57)

Demographic/ Clinical Characteristic	Garadacimab (N=39)	Placebo (N=25)	Total (N=64)
Use of HAE prophylaxis therapy during the 3 months prior to Screening, n (%)	14 (35.9)	7 (28)	21 (32.8)
Family history of HAE, n (%)	34 (87.2)	23 (92)	57 (89.1)
History of laryngeal attacks, n (%)	21 (53.8)	17 (68)	38 (59.4)

Source: Statistical reviewer; Clinical Study Report (dated October 6, 2022), Table 14.1.3.1.1, p. 173.

^a One subject on garadacimab was reported to have an age at first HAE diagnosis larger than their age at baseline and is excluded. Abbreviations: BMI, body mass index; HAE, hereditary angioedema; ITT, intent-to-treat; max, maximum; min, minimum; N, number of subjects in the ITT Analysis Set; n, number of subjects with the respective demographic or clinical characteristic; SD, standard deviation

6.2.4.3. Primary Efficacy Results, Trial 3001

The primary efficacy endpoint was the time-normalized number of HAE attacks per month during the 6-month Treatment Period. This endpoint is clinically meaningful and consistent with previous programs for HAE prophylaxis. Details regarding the reporting, collection, and investigator confirmation of HAE attacks are provided in Section [15.1.1](#).

The primary efficacy results are summarized in [Table 10](#); the total number of HAE attacks in the garadacimab arm was over fourfold lower than in the placebo arm (63 versus 264). The estimated mean time-normalized number of HAE attacks per month was considerably lower in the garadacimab arm (mean=0.27; 95% CI=0.05, 0.49) compared to placebo (mean=2.01; 95% CI=1.44, 2.57), signifying an improvement in the garadacimab arm over placebo. Furthermore, there was a statistically significant difference (Wilcoxon p-value <0.001) in the rank sums of the time-normalized number of HAE attacks per month in the garadacimab and placebo arms (i.e., the rank sum in the garadacimab arm was significantly lower than the placebo arm, assuming that a higher rank indicates a worse outcome).

Table 10. Primary Efficacy Results (ITT Analysis Set), Trial 3001

Variable	Garadacimab (N=39)	Placebo (N=25)
Number of evaluable subjects, n (%)	39 (100)	24 ^a (96)
Number of HAE attacks during the Treatment Period	63	264
Time-normalized number of HAE attacks per month		
Mean (SD)	0.27 (0.68)	2.01 (1.34)
95% CI	0.05, 0.49	1.44, 2.57
Median (min, max)	0 (0, 3.83)	1.35 (0.17, 4.42)
P-value ^b	<0.001	

Source: Statistical reviewer; Clinical Study Report (dated October 6, 2022), Table 11-3, p. 84.

^a One subject in the placebo arm received less than 30 days of study treatment and was excluded.

^b Obtained from a two-sided Wilcoxon rank sum test at alpha=5%.

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; max, maximum; min, minimum; N, number of subjects in the ITT Analysis Set; n, number of evaluable subjects; SD, standard deviation

Missing primary endpoint data only occurred for one subject (4%) on placebo who received less than 30 days of study treatment. Therefore, the impact of the Applicant's missing data approach was minimal, and the primary efficacy results were robust.

Robustness of the primary analysis results is also supported by the Applicant's Poisson model described under *Sensitivity Analyses* in Section [6.2.3.2](#). After adjusting for the baseline attack rate, the estimated mean time-normalized number of HAE attacks per month was considerably

lower in the garadacimab arm (LS mean=0.22, 95% CI=0.1, 0.45) compared to placebo (LS mean=2.01, 95% CI=1.45, 2.79), similar to the primary analysis ([Table 10](#)), with a percentage reduction in the means of 89.2% (95% CI=75.6%, 95.2%) relative to placebo. Additionally, the estimated attack ratio relative to placebo was 0.11 (95% CI=0.05, 0.24). The above results are shown in [Table 11](#) and further signify an improvement in the garadacimab arm over placebo.

Table 11. Sensitivity Analysis for the Primary Endpoint: Adjusting for the Baseline Attack Rate (ITT Analysis Set), Trial 3001

Variable	Garadacimab (N=39)	Placebo (N=25)
Number of evaluable subjects, n (%)	39 (100)	24 ^a (96)
Number of HAE attacks during the Treatment Period	63	264
Time-normalized number of HAE attacks per month		
LS Mean (SE)	0.22 (0.38)	2.01 (0.17)
95% CI	0.1, 0.45	1.45, 2.79
Percentage reduction (95% CI) ^b	89.2% (75.6%, 95.2%)	
Attack ratio (95% CI) ^b	0.11 (0.05, 0.24)	

Source: Statistical reviewer; Clinical Study Report (dated October 6, 2022), Table 11-4, p. 85.

^a One subject in the placebo arm received less than 30 days of study treatment and was excluded.

^b Calculated relative to placebo.

Note: LS means and attack ratio were obtained from a Poisson model accounting for overdispersion with an offset term for time on treatment and fixed effects for treatment arm and baseline HAE attack rate.

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; LS, least squares; N, number of subjects in the ITT Analysis Set; n, number of evaluable subjects; SE, standard error

6.2.4.4. Key Secondary Efficacy Results, Trial 3001

The first key secondary endpoint in the testing hierarchy (see Section [6.2.3.1](#)) was the percentage reduction in the means of the time-normalized number of HAE attacks per month during the Treatment Period. H02 was specified to test “the percentage reduction in means of the time-normalized number of HAE attacks for the 6-months of the Active Arm compared to the 6-month Placebo Arm period are equal to zero.” The mean time-normalized number of HAE attacks per month during the 6-month Treatment Period was 0.27 for the garadacimab arm and 2.01 for the placebo arm ([Table 10](#)). From the Clinical Study Report (dated October 6, 2022), the percentage reduction in the mean relative to placebo was 86.5% (95% CI=57.8%, 95.7%).

As mentioned in Section [6.2.3.3](#), the Wilcoxon rank sum test is a nonparametric approach to test location shift between two distributions and is not applicable to test H02 for “the percentage reduction in means of the time-normalized number of HAE attacks for the 6-months of the Active Arm compared to the 6-month Placebo Arm period are equal to zero.” Furthermore, from the Applicant-submitted software program for analysis of this endpoint, the p-value from the Wilcoxon rank sum test for the primary endpoint was reported as the p-value for this endpoint, which is not appropriate. Therefore, in this review, no p-value is reported for this endpoint.

The first key secondary endpoint and the primary endpoint use different descriptive summary measures (the median for the primary endpoint and the percentage reduction in the means for the first key secondary endpoint) to evaluate the same endpoint (the time-normalized number of HAE attacks per month for the 6-month Treatment Period). The first key secondary endpoint does not provide any new information for evidence of effectiveness of the study drug.

The second key secondary endpoint (H03) was the number of subjects who experienced zero HAE attacks (i.e., were attack-free) in the first 3 months of the 6-month Treatment Period. A total of 30/63 evaluable subjects (48%) did not experience any HAE attacks during the first 3 months of the Treatment Period, of which 28 were on garadacimab (72% of the garadacimab arm; 95% Wilson CI=56%, 83%) and 2 were on placebo (8% of the placebo arm; 95% Wilson CI=2%, 26%), as shown in [Table 12](#). In addition, there was a statistically significant association between treatment arm and the number of attack-free subjects during the first 3 months of the Treatment Period (Fisher p-value <0.001).

Table 12. Key Secondary Efficacy Analysis: Number of Attack-Free Subjects in the First 3 Months of the Treatment Period (ITT Analysis Set), Trial 3001

Variable	Garadacimab (N=39)	Placebo (N=25)
Number of evaluable subjects ^{a,b} , n (%)	39 (100)	24 (96)
Number (%) of subjects who were attack-free ^c	28 (71.8)	2 (8.3)
95% CI ^d	56.2%, 83.5%	2.3%, 25.8%
P-value ^e	<0.001	

Source: Statistical reviewer; Clinical Study Report (dated October 6, 2022), Table 11-6, p. 89.

^a One subject in the placebo arm received less than 30 days of study treatment and was excluded.

^b Percentages based on the ITT Analysis Set.

^c Percentages based on the number of evaluable subjects.

^d Calculated for the percentage of subjects using Wilson's asymptotic confidence limits.

^e Obtained from a two-sided Fisher exact test at alpha=5% (multiplicity-adjusted).

Abbreviations: CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the ITT Analysis Set; n, number of evaluable subjects

The last key secondary endpoint (H04) was the percentage of subjects with SGART responses of *good* or *excellent* at the end of the 6-month Treatment Period. As shown in [Table 13](#), a total of 39/62 evaluable subjects (63%) provided responses of *good* or *excellent*, of which 31 were on garadacimab (82% of the garadacimab arm) and 8 were on placebo (33% of the placebo arm). Furthermore, there was a statistically significant association between treatment arm and the number of subjects with SGART responses of *good* or *excellent* at the end of the Treatment Period (chi-squared p-value <0.001). For more details regarding the SGART and its utility in this HAE setting, see Section [6.3.1](#).

Table 13. Key Secondary Efficacy Analysis: SGART Responses at the End of the Treatment Period (ITT Analysis Set), Trial 3001

Variable	Garadacimab (N=39)	Placebo (N=25)
Number of evaluable subjects ^{a,b} , n (%)	38 (97.4)	24 (96)
SGART Responses ^c , n (%)		
None	1 (2.6)	10 (41.7)
Poor	3 (7.9)	4 (16.7)
Fair	3 (7.9)	2 (8.3)
Good	6 (15.8)	5 (20.8)
Excellent	25 (65.8)	3 (12.5)
Good or excellent	31 (81.6)	8 (33.3)
Fair, poor, or none	7 (18.4)	16 (66.7)
P-value ^d	<0.001	

Source: Statistical reviewer; Clinical Study Report (dated October 6, 2022), Table 11-11, p. 98.

^a One subject on placebo received less than 30 days of study treatment and was excluded; one subject on garadacimab did not complete the SGART at the end of the Treatment Period and was excluded.

^b Percentages based on the ITT Analysis Set.

^c Percentages based on the number of evaluable subjects.

^d Obtained from a two-sided chi-squared test at alpha=5% (multiplicity-adjusted), comparing the “Good or Excellent” category to all other categories [“Fair, Poor, or None”].

Abbreviations: ITT, intent-to-treat; N, number of subjects in the ITT Analysis Set; n, number of subjects in the respective category; SGART, Subject’s Global Assessment of Response to Therapy

All key secondary efficacy results presented above favored garadacimab.

6.2.4.5. Additional Efficacy Results, Trial 3001

Secondary Endpoints

Other clinically meaningful, prespecified secondary endpoints were also analyzed to further examine the effectiveness of garadacimab for the proposed indication of prophylaxis of HAE attacks. These prespecified secondary endpoints included:

- Proportion of subjects with a $\geq 50\%$, $\geq 70\%$, $\geq 90\%$, and 100% reduction in the time-normalized number of HAE attacks per month during the 6-month Treatment Period compared to the Run-in Period.
- Time-normalized number of HAE attacks per month requiring on-demand therapy during the 6-month Treatment Period.
- Time-normalized number of moderate or severe HAE attacks per month during the 6-month Treatment Period.

As shown in [Table 14](#), the proportions of subjects with a $\geq 50\%$, $\geq 70\%$, $\geq 90\%$, and 100% reductions in monthly HAE attacks were 95%, 92%, 74%, and 62% on garadacimab and 33%, 17%, 8%, and 0% on placebo, respectively. These results provide further evidence supporting the efficacy of garadacimab.

Table 14. Additional Secondary Efficacy Analysis: Percentage Reduction in the Time-Normalized Number of HAE Attacks per Month During the Treatment Period Compared to the Run-in Period (ITT Analysis Set), Trial 3001

Variable	Garadacimab (N=39)	Placebo (N=25)
Number of evaluable subjects ^{a,b} , n (%)	39 (100)	24 (96)
Reduction of $\geq 50\%$ ^c , n (%)	37 (94.9)	8 (33.3)
95% CI ^d	83.1%, 98.6%	18.0%, 53.3%
Reduction of $\geq 70\%$ ^c , n (%)	36 (92.3)	4 (16.7)
95% CI ^d	79.7%, 97.3%	6.7%, 35.9%
Reduction of $\geq 90\%$ ^c , n (%)	29 (74.4)	2 (8.3)
95% CI ^d	58.9%, 85.4%	2.3%, 25.8%
Reduction of 100% ^c , n (%)	24 (61.5)	0 (0)
95% CI ^d	45.9%, 75.1%	0%, 13.3%

Source: Statistical reviewer; Clinical Study Report (dated October 6, 2022), Table 11-6, p. 88.

^a One subject on placebo received less than 30 days of study treatment and was excluded.

^b Percentages based on the ITT Analysis Set.

^c Percentages based on the number of evaluable subjects.

^d Calculated for the percentage of subjects using Wilson's asymptotic confidence limits.

Abbreviations: CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the ITT Analysis Set; n, number of subjects in the respective category

The Applicant also assessed the time-normalized number of HAE attacks per month requiring on-demand therapy during the 6-month Treatment Period. A total of 54/63 (86%) of the HAE attacks experienced in the garadacimab arm during the Treatment Period required on-demand therapy, while a slightly higher proportion of 245/264 (93%) of the HAE attacks experienced in the placebo arm required on-demand therapy. As shown in [Table 15](#), the estimated mean time-normalized number of HAE attacks per month requiring on-demand therapy was considerably lower in the garadacimab arm (mean=0.23; 95% CI=0.02, 0.45) compared to placebo (mean=1.86; 95% CI=1.26, 2.46). These exploratory results also favored garadacimab.

Table 15. Additional Secondary Efficacy Analysis: Time-Normalized Number of HAE Attacks per Month Requiring On-Demand Therapy (ITT Analysis Set), Trial 3001

Variable	Garadacimab (N=39)	Placebo (N=25)
Number of evaluable subjects, n (%)	39 (100)	24 ^a (96)
Number of HAE attacks during the Treatment Period	63	264
Number of HAE attacks requiring on-demand therapy ^b , n (%)	54 (85.7)	245 (92.8)
Time-normalized number of HAE attacks per month requiring on-demand therapy		
Mean (SD)	0.23 (0.66)	1.86 (1.41)
95% CI	0.02, 0.45	1.26, 2.46
Median (min, max)	0 (0, 3.83)	1.35 (0, 4.42)

Source: Statistical reviewer; Clinical Study Report (dated October 6, 2022), Table 11-7, p. 91.

^a One subject on placebo received less than 30 days of study treatment and was excluded.

^b Percentages based on the total number of HAE attacks during the Treatment Period.

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; max, maximum; min, minimum; N, number of subjects in the ITT Analysis Set; n, number of evaluable subjects; SD, standard deviation

From a Poisson model structured similarly to the sensitivity analysis for the primary endpoint described in [Section 6.2.3.2](#) (with the baseline attack rate here including only HAE attacks that required on-demand therapy during the Run-in Period), the estimated mean time-normalized number of HAE attacks per month requiring on-demand therapy remained considerably lower in the garadacimab arm (LS mean=0.16; 95% CI=0.07, 0.39) compared to the placebo arm (LS

mean=1.83; 95% CI=1.28, 2.6), with a percentage reduction in the means of 91.2% (95% CI=77.4%, 96.5%) relative to placebo. Additionally, the estimated attack ratio relative to placebo was 0.09 (95% CI=0.03, 0.23). The above results are presented in [Table 16](#) and align with the results of the main analysis in [Table 15](#).

Table 16. Sensitivity Analysis for the Time-Normalized Number of HAE Attacks per Month Requiring On-Demand Therapy: Adjusting for Baseline Attack Rate (ITT Analysis Set), Trial 3001

Variable	Garadacimab (N=39)	Placebo (N=25)
Number of evaluable subjects, n (%)	39 (100)	24 ^a (96)
Number of HAE attacks during the Treatment Period	63	264
Number of HAE attacks requiring on-demand therapy ^b , n (%)	54 (85.7)	245 (92.8)
Time-normalized number of HAE attacks per month requiring on-demand therapy		
LS Mean (SE)	0.16 (0.45)	1.83 (0.18)
95% CI	0.07, 0.39	1.28, 2.6
Percent reduction (95% CI) ^c	91.2% (77.4%, 96.5%)	
Attack ratio (95% CI) ^c	0.09 (0.03, 0.23)	

Source: Statistical reviewer.

^a One subject on placebo received less than 30 days of study treatment and was excluded.

^b Percentages based on the total number of HAE attacks during the Treatment Period.

^c Calculated relative to placebo.

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; N, number of subjects in the ITT Analysis Set; n, number of evaluable subjects; SE, standard error

The time-normalized number of moderate or severe HAE attacks per month during the 6-month Treatment Period was also evaluated by the Applicant. A total of 29/63 (46%) of the HAE attacks experienced in the garadacimab arm were moderate or severe, while a higher proportion of 172/264 (65%) of the HAE attacks experienced in the placebo arm were moderate or severe. As shown in [Table 17](#), the estimated mean time-normalized number of moderate or severe HAE attacks per month was considerably lower in the garadacimab arm (mean=0.13; 95% CI=0.03, 0.22) compared to the placebo arm (mean=1.35; 95% CI=0.86, 1.84). These exploratory results also favored garadacimab.

Table 17. Additional Secondary Efficacy Analysis: Time-Normalized Number of Moderate or Severe HAE Attacks per Month (ITT Analysis Set), Trial 3001

Variable	Garadacimab (N=39)	Placebo (N=25)
Number of evaluable subjects, n (%)	39 (100)	24 ^a (96)
Number of HAE attacks during the Treatment Period	63	264
Number of moderate or severe HAE attacks ^b , n (%)	29 (46)	172 (65.2)
Time-normalized number of moderate or severe HAE attacks per month		
Mean (SD)	0.13 (0.3)	1.35 (1.17)
95% CI	0.03, 0.22	0.86, 1.84
Median (minimum, maximum)	0 (0, 1.17)	0.83 (0, 4.42)

Source: Statistical reviewer; Clinical Study Report (dated October 6, 2022), Table 11-8, p. 93.

^a One subject on placebo received less than 30 days of study treatment and was excluded.

^b Percentages based on the total number of HAE attacks during the Treatment Period.

^c Obtained from a two-sided Wilcoxon rank sum test at alpha=5% (exploratory analysis; not multiplicity-adjusted).

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; N, number of subjects in the ITT Analysis Set; n, number of evaluable subjects; SE, standard error

From a Poisson model structured similarly to the sensitivity analysis for the primary endpoint described in Section 6.2.3.2 (with the baseline attack rate here only including moderate or severe HAE attacks during the Run-in Period), the estimated mean time-normalized number of moderate or severe HAE attacks per month remained considerably lower in the garadacimab arm (LS mean=0.09, 95% CI=0.03, 0.22) compared to placebo (LS mean=1.37, 95% CI=0.99, 1.89), with a percentage reduction in the means of 93.6% (95% CI=82.9%, 97.6%) relative to placebo. Additionally, the estimated attack ratio relative to placebo was 0.06 (95% CI=0.02, 0.17). These results are presented in [Table 18](#) and concur with the results of the main analysis in [Table 17](#).

Table 18. Sensitivity Analysis for the Time-Normalized Number of Moderate or Severe HAE Attacks per Month: Adjusting for the Baseline Attack Rate (ITT Analysis Set), Trial 3001

Variable	Garadacimab (N=39)	Placebo (N=25)
Number of evaluable subjects, n (%)	39 (100)	24 ^a (96)
Number of HAE attacks during the Treatment Period	63	264
Number of moderate or severe HAE attacks ^b , n (%)	29 (46)	172 (65.2)
Time-normalized number of moderate or severe HAE attacks per month		
LS mean (SE)	0.09 (0.47)	1.37 (0.16)
95% CI	0.03, 0.22	0.99, 1.89
Percentage reduction (95% CI) ^c	93.6% (82.9%, 97.6%)	
Attack ratio (95% CI) ^c	0.06 (0.02, 0.17)	

Source: Statistical reviewer.

^a One subject on placebo received less than 30 days of study treatment and was excluded.

^b Percentages based on the total number of HAE attacks during the Treatment Period.

^c Calculated relative to placebo.

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; N, number of subjects in the ITT Analysis Set; n, number of evaluable subjects; SE, standard error

While the prespecified secondary endpoints above were analyzed exploratorily and were not multiplicity-adjusted, they are clinically meaningful outcomes for patients with HAE and informative for providers. Each of these endpoints also favored garadacimab.

Exploratory Endpoints

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

As shown in [Table 19](#), the mean changes in total score and all domain scores from baseline to Day 182 were better in the garadacimab arm compared to the placebo arm (note that more negative values indicate greater improvement).

Table 19. Exploratory Efficacy Analysis: Change in AE-QoL Questionnaire Total and Domain Scores From Baseline to Day 182 (ITT Analysis Set), Trial 3001

Variable	Garadacimab (N=39)	Placebo (N=25)
Number observed ^a , n (%)	33 (84.6)	20 (80)
Total score		
Mean change from baseline (SD)	-26.5 (17.9)	-2.2 (19.1)
95% CI	-32.8, -20.1	-11.2, 6.7

Variable	Garadacimab (N=39)	Placebo (N=25)
Functioning domain		
Mean change from baseline (SD)	-35.8 (23.2)	1.9 (29.6)
95% CI	-44, -27.6	-12, 15.7
Fatigue/mood domain		
Mean change from baseline (SD)	-21.1 (22.9)	-5.8 (27.1)
95% CI	-29.2, -13	-18.4, 6.9
Fears/shame domain		
Mean change from baseline (SD)	-28 (24.1)	-2.5 (18.6)
95% CI	-36.6, -19.5	-11.2, 6.2
Nutrition domain		
Mean change from baseline (SD)	-16.7 (23.3)	-0.6 (16.5)
95% CI	-24.9, -8.4	-8.3, 7.1

Source: Clinical Study Report (dated October 6, 2022), Table 11-12, pp. 101-102.

* The AE-QoL questionnaire was only completed by subjects aged ≥18 years.

Abbreviations: AE-QoL, Angioedema Quality of Life; CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the ITT Analysis Set; n, number of evaluable subjects; SD, standard deviation

The exploratory efficacy results presented above also favored garadacimab.

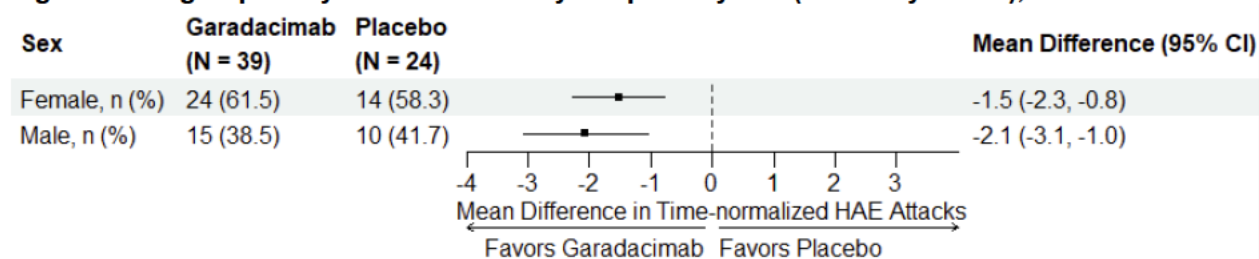
6.2.4.6. Subgroup Analyses, Trial 3001

Garadacimab met its prespecified primary efficacy endpoint of time-normalized number of HAE attacks per month (see Section 6.2.4.3) in adults and adolescents with C1-INH (Type I or Type II) HAE in trial 3001. However, when evaluating the efficacy of garadacimab, we also considered whether the primary endpoint was consistent across clinically relevant subgroups that were not considered by the Applicant, including by sex, age, race, ethnicity, geographic location, HAE subtype, and HAE attack location and severity.

Efficacy by Sex

For both males and females, there was a clinically meaningful and statistically persuasive reduction in the mean time-normalized number of HAE attacks per month relative to placebo (Figure 4). These results are similar to the overall primary analysis results (Table 10).

Figure 4. Subgroup Analysis for the Primary Endpoint by Sex (ITT Analysis Set), Trial 3001



Source: Statistical reviewer.

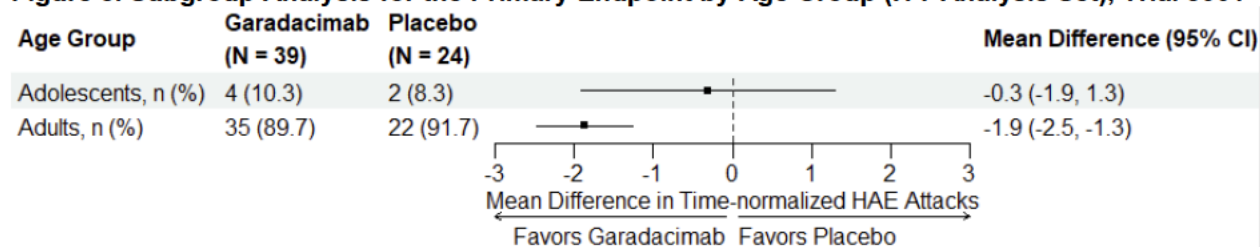
One subject in the ITT Analysis Set on placebo received less than 30 days of study treatment and was excluded; percentages are based on the number of evaluable subjects in the ITT Analysis Set.

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; N, number of evaluable subjects in the ITT Analysis Set; n, number of subjects in the respective category

Efficacy by Age

The primary efficacy endpoint was further analyzed by age subgroups (adolescents 12 to <18 years of age, adults 18 to <65 years of age, and geriatrics ≥ 65 years of age). For adults, there was a clinically meaningful and statistically persuasive reduction in the mean time-normalized number of HAE attacks per month relative to placebo ([Figure 5](#)), which aligns with the overall primary analysis results ([Table 10](#)). Although the point estimate favored garadacimab in the adolescent subpopulation, the CI is very wide given the small number of adolescent subjects enrolled (N=6). The observed treatment effect in adolescents may have also been less robust because subjects had less disease severity, as the trial eligibility criteria did not allow prior use of prophylactic therapies for adolescent subjects.

Figure 5. Subgroup Analysis for the Primary Endpoint by Age Group (ITT Analysis Set), Trial 3001



Source: Statistical reviewer.

One subject in the ITT Analysis Set on placebo received less than 30 days of study treatment and was excluded; percentages are based on the number of evaluable subjects in the ITT Analysis Set.

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; N, number of evaluable subjects in the ITT Analysis Set; n, number of subjects in the respective category

Conclusions regarding the effectiveness of garadacimab in adolescents primarily relied on matching PK exposure to adults and extrapolating efficacy from the adult population, as the pathophysiology of HAE is the same across all age groups. Extrapolation of the efficacy of garadacimab in the adolescent population was based on matching of the PK profile and the mean garadacimab concentration-time profile to the adult population (see Section [15.2.5](#) for further details). While the pivotal trial (3001) was not statistically powered to draw efficacy conclusions in the adolescent subpopulation, it is reassuring that the primary efficacy endpoint in adolescents trended in the same direction as adults ([Figure 5](#)).

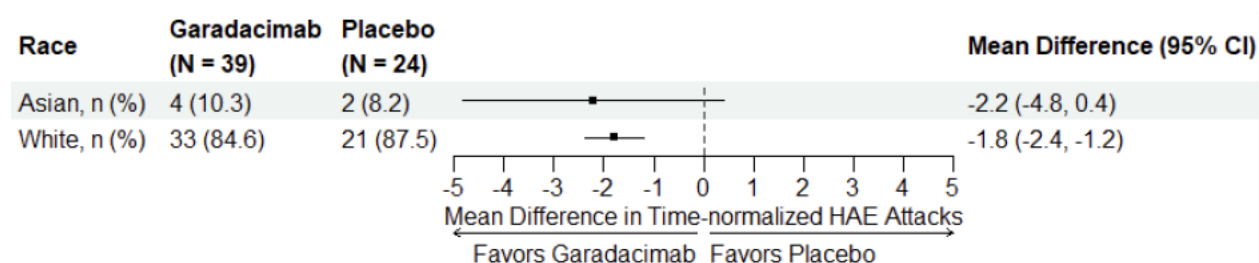
Additionally, there were six geriatric subjects in trial 3001, all of whom were randomized to garadacimab. For the geriatric subjects, the mean time-normalized number of HAE attacks per month was 0.03 (95% CI=0, 0.1), which is a meaningful reduction compared to the overall placebo group ([Table 10](#)).

Altogether, garadacimab appeared effective at reducing HAE attacks during the 6-month Treatment Period irrespective of age.

Efficacy by Race and Ethnicity

The point estimates for the primary analysis by race subgroups that comprised more than one subject per arm ([Figure 6](#)) were generally consistent with the overall study population ([Table 10](#)). However, due to the small number of Asian (Japanese) subjects enrolled in the trial (N=6), substantive conclusions for this subgroup cannot be drawn.

Figure 6. Subgroup Analysis for the Primary Endpoint by Race (ITT Analysis Set), Trial 3001



Source: Statistical reviewer.

One subject in the ITT Analysis Set on placebo received less than 30 days of study treatment and was excluded; percentages are based on the number of evaluable subjects in the ITT Analysis Set.

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; N, number of evaluable subjects in the ITT Analysis Set; n, number of subjects in the respective category

Additionally, there was one Black/African American subject on placebo who had a monthly HAE attack rate of 0.18, one Native Hawaiian/Other Pacific Islander subject on garadacimab who had a monthly HAE attack rate of 0.17, and one subject on garadacimab with race Other who did not experience any HAE attacks during the Treatment Period.

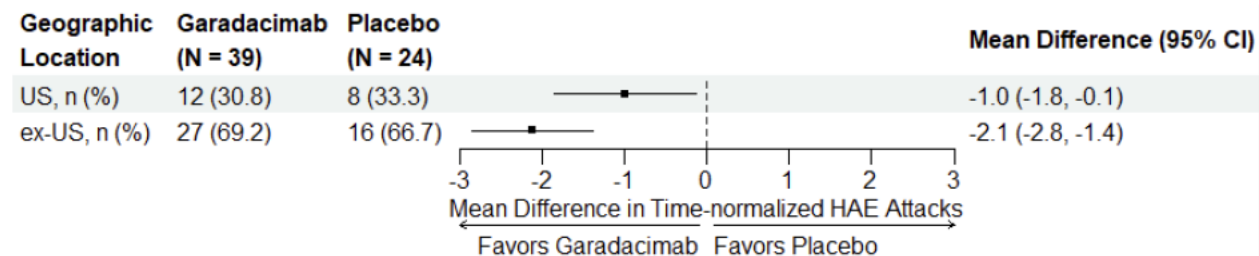
With regard to ethnicity, there were three subjects who were Hispanic or Latino, one on garadacimab with a monthly HAE attack rate of 0.17 and two on placebo with monthly HAE attack rates of 0.17 and 1.27.

Given the small number of subjects who self-identified as non-white in the trial, it is difficult to draw definitive conclusions regarding efficacy by race/ethnicity; however, the data do not raise substantial concerns regarding a differential treatment effect.

Efficacy by Geographic Location

The primary efficacy endpoint was also evaluated by geographic location ([Figure 7](#)). For subjects at U.S. and ex-U.S. sites, there was a clinically meaningful and statistically persuasive reduction in the mean time-normalized number of HAE attacks per month relative to placebo. While the results for the ex-U.S. subgroup aligned more with the overall primary analysis results ([Table 10](#)) than those for the U.S. subgroup, both trended in the same direction favoring garadacimab.

Figure 7. Subgroup Analysis for the Primary Endpoint by Geographic Location (ITT Analysis Set), Trial 3001



Source: Statistical reviewer.

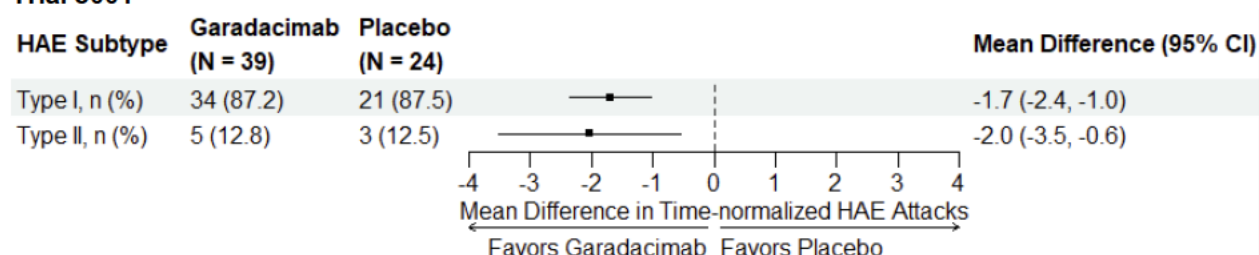
Notes: One subject in the ITT Analysis Set on placebo received less than 30 days of study treatment and was excluded; percentages are based on the number of evaluable subjects in the ITT Analysis Set.

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; N, number of evaluable subjects in the ITT Analysis Set; n, number of subjects in the respective category

Efficacy by HAE Subtype

For both subjects with Type I and Type II HAE, there was a clinically meaningful and statistically persuasive reduction in the mean time-normalized number of HAE attacks per month relative to placebo ([Figure 8](#)). These results are similar to the overall primary analysis ([Table 10](#)).

Figure 8. Subgroup Analysis for the Primary Endpoint by HAE Subtype (ITT Analysis Set), Trial 3001



Source: Statistical reviewer.

Notes: One subject in the ITT Analysis Set on placebo received less than 30 days of study treatment and was excluded; percentages are based on the number of evaluable subjects in the ITT Analysis Set.

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; N, number of evaluable subjects in the ITT Analysis Set; n, number of subjects in the respective category

Trial 3001 enrolled only subjects with Type I or Type II HAE (subjects with Type III HAE were excluded). However, the phase 2 trial (2001) included a nonrandomized, open-label treatment arm for subjects with Type III HAE, which enrolled three subjects with FXII mutation and three subjects with PLG mutation. Type III HAE, and the six aforementioned subjects in trial 2001, are discussed further in [Section 6.3.2](#).

Efficacy by Attack Location and Severity

A summary of the HAE attacks experienced during the 6-month Treatment Period by location and severity is provided in [Table 20](#). Fewer subjects experienced abdominal, cutaneous, and laryngeal attacks in the garadacimab arm (28%, 26%, and 5%, respectively) compared to the placebo arm (88%, 88%, and 20%, respectively). While similar conclusions can be drawn for attack severity, a higher number of mild abdominal attacks were experienced in the garadacimab arm compared to placebo (20 versus 14), and two subjects in each treatment arm experienced a severe laryngeal attack.

Table 20. HAE Attacks by Location and Severity (ITT Analysis Set), Trial 3001

Analysis Statistic	Garadacimab (N=39)	Placebo (N=25)	Total (N=64)
HAE attack location ^b , n (%) [number of attacks]			
Abdominal	11 (28.2) [36]	22 (88) [101]	33 (51.6) [137]
Cutaneous	10 (25.6) [47]	22 (88) [191]	32 (50) [238]
Laryngeal	2 (5.1) [2]	5 (20) [7]	7 (10.9) [9]

Analysis Statistic	Garadacimab (N=39)	Placebo (N=25)	Total (N=64)
HAE attack severity ^b , n (%) [number of attacks]			
Abdominal			
Mild	5 (12.8) [20]	7 (28) [14]	12 (18.8) [34]
Moderate	7 (17.9) [13]	19 (76) [75]	26 (40.6) [88]
Severe	2 (5.1) [3]	7 (28) [12]	9 (14.1) [15]
Cutaneous			
Mild	6 (15.4) [28]	15 (60) [83]	21 (32.8) [111]
Moderate	6 (15.4) [14]	19 (76) [94]	25 (39.1) [108]
Severe	4 (10.3) [5]	10 (40) [14]	14 (21.9) [19]
Laryngeal			
Mild	0 (0) [0]	1 (4) [1]	1 (1.6) [1]
Moderate	0 (0) [0]	4 (16) [4]	4 (6.3) [4]
Severe	2 (5.1) [2]	2 (8) [2]	4 (6.3) [4]
Subjects with a history of laryngeal HAE attacks ^b , n (%)	21 (54)	17 (68)	38 (59)

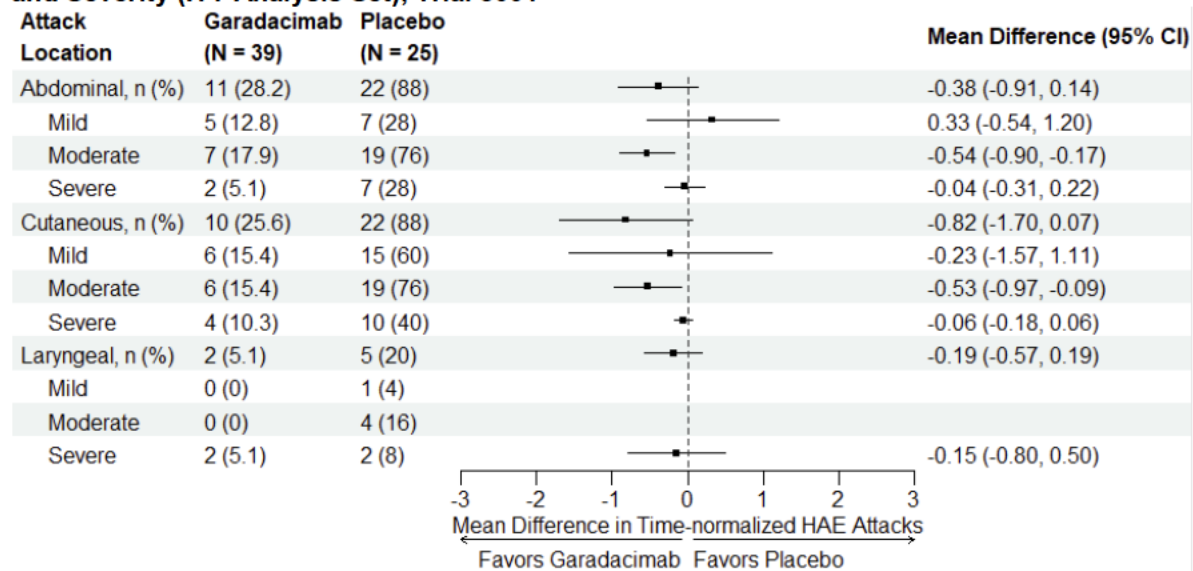
Source: Statistical reviewer.

^a Percentages are based on the number of subjects in the ITT Analysis Set.

Abbreviations: HAE, hereditary angioedema; ITT, intent-to-treat; n, number of subjects with at least one occurrence

Subgroup analyses of the primary efficacy endpoint by HAE attack location and severity are shown in [Figure 9](#). While statistically persuasive results were not achieved for every category, likely due to small sample sizes, the mean difference in the time-normalized number of HAE attacks per month relative to placebo trended in the same direction (favoring garadacimab) for all locations and severities, except for mild abdominal attacks.

Figure 9. Mean Difference in the Time-Normalized Number of HAE Attacks per Month by Location and Severity (ITT Analysis Set), Trial 3001



Source: Statistical reviewer.

Percentages are based on the number of subjects in the ITT Analysis Set.

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; N, number of subjects in the ITT Analysis Set; n, number of subjects in the respective category

During the clinical site inspection, the Office of Regulatory Affairs inspector noted some discrepancies in the HAE attack location recorded on the case report form (CRF) and the line

listing provided in the clinical study report (CSR). In some instances, the CSR did not reflect all locations involved in an HAE attack that were recorded in the CRF. For example, the CRF might have documented the attack location as “eyelids bilaterally, buttock (right), left arm, right arm, abdomen,” but the CSR line listing only contained the terms “cutaneous, extremities,” omitting “abdomen.” This discrepancy may affect the accuracy of the subgroup analyses by location but did not affect the primary efficacy endpoint, as the overall number of HAE attacks reported in the source documents matched the number reported by the Applicant in the CSR. See Section [23](#) for additional details.

Overall, the results reported above align with the primary analysis results and support the effectiveness of garadacimab in reducing HAE attacks, irrespective of attack location and severity.

Conclusion

While the interpretation of the subgroup analyses above is limited by small sample sizes, the treatment benefit of garadacimab based on the primary endpoint appears to be similar regardless of sex, age, race, ethnicity, geographic location, HAE subtype, and HAE attack location and severity. Furthermore, due to the pathophysiology of HAE being the same across all age groups, extrapolation of the adult efficacy data to adolescents is clinically reasonable and supported by PK matching (see Section [15.2.5](#)).

6.3. Key Efficacy Review Issues

6.3.1. Patient-Reported Outcome Endpoints

Issue

Determine whether the SGART and the AE-QoL questionnaires are fit-for-purpose for this context of use to support regulatory decision-making (b) (4)

Background

HAE is characterized by unpredictable, recurrent episodes of angioedema, which greatly impact quality of life and daily functioning. At the HAE Patient-Focused Drug Development meeting held at the Agency on September 25, 2017¹, patients with HAE shared the aspects of the disease that had the most impact on their lives, including the unpredictability of attack occurrence, the painful abdominal attacks, the dramatic change swelling had on their physical appearance, and the emotional toll the disease had on their lives.

The SGART and AE-QoL were used to derive secondary and exploratory endpoints, respectively, in trial 3001, (b) (4)
(b) (4). There are currently no fit-for-purpose patient-reported outcomes (PROs) for use in HAE prophylaxis clinical trials.

¹ <https://www.fda.gov/files/about%20fda/published/The-Voice-of-the-Patient---Hereditary-Angioedema.pdf>.

Assessment

The Applicant did not request Agency feedback on the SGART or AE-QoL endpoints during development, nor did they provide exact copies of the SGART and AE-QoL that they administered during the study (e.g., electronic screen shots) or any associated training materials or user manuals for review. The Applicant did not provide a PRO evidence dossier to support the measurement properties of the SGART and AE-QoL and to establish their fitness-for-purpose for the context of use. While existing literature demonstrate acceptable psychometric properties of the AE-QoL ([Weller et al. 2012](#); [Weller et al. 2016](#)), this will not replace or rectify problems with its content validity. In general, the content validity of a clinical outcome assessment needs to be established prior to establishing its quantitative psychometric properties.

SGART

The SGART is a self-reported instrument completed electronically via a provisioned electronic device (e.g., a tablet) at the study site to measure a subject's overall treatment response to the investigational product based on the question: "Considering all of the ways HAE affects you, please rate your response to the study medication you were given to prevent HAE attacks during this Treatment Period." Specifically, subjects of all ages responded to the single-item question using a 5-point verbal rating scale on Days 91 and 182, respectively. The five response options were:

- (0) None – worse or no response at all, not acceptable.
- (1) Poor – very little response, not acceptable.
- (2) Fair – some response, acceptable but could be better.
- (3) Good – good response, acceptable.
- (4) Excellent – excellent response, as good as can be imagined.

To construct the key secondary endpoint, the SGART asks subjects to respond based on their experience in the past 6 months, making it susceptible to recall error. A global impression score may be influenced by factors outside of the disease process, is unable to characterize the drug's effect on individual signs/symptoms, and may mask the fact that an overall improvement in score can be achieved by improvement in some signs/symptoms with concurrent worsening in other signs/symptoms. In addition, the SGART appears to assess some aspect of treatment satisfaction based on the phrasing of its item and response options. From a regulatory perspective, it is more appropriate to assess whether subjects experienced a meaningful improvement in symptoms rather than satisfaction with treatment. Although the percentage of subjects with good/excellent SGART responses at the end of the 6-month Treatment Period was a prespecified secondary endpoint in the testing hierarchy and achieved statistically significant results compared to placebo, the SGART does not appear to be content-valid for the context of use [REDACTED] (b) (4).

AE-QoL

The AE-QoL questionnaire was developed to assess quality of life impairment in recurrent angioedema patients, including patients with HAE ([Weller et al. 2012](#)). It is a 17-item instrument that uses a 5-point Likert scale with response options of never, rarely, sometimes, often, and very

often as well as a recall period of the last four weeks. The 17 items within the AE-QoL are organized into four distinct domains labeled as follows: functioning, fatigue/mood, fears/shame, and food/nutrition ([Table 21](#)).

Table 21. Conceptual Framework of the AE-QoL Questionnaire

Item	Domain	General Concept
Item 1: Restrictions in work because of swelling episodes	Functioning	Functioning limitations associated with swelling episodes
Item 2: Restrictions in physical activity because of swelling episodes		
Item 3: Restrictions in leisure time because of swelling episodes		
Item 4: Restrictions in social relations because of swelling episodes		
Item 6: Difficulty falling asleep	Fatigue/mood	Fatigue or mood difficulties associated with swelling episodes
Item 7: Waking up during the night		
Item 8: Being tired during the day		
Item 9: Difficulty concentrating		
Item 10: Feeling depressed		
Item 12: Burden associated with swelling episodes	Fears/shame	Fears or shame associated with swelling episodes
Item 13: Afraid of swelling episodes that occur suddenly		
Item 14: Afraid of increased frequency of swelling episodes		
Item 15: Ashamed to go out in public because of swelling episodes		
Item 16: Feeling embarrassed or self-conscious because of swelling episodes		
Item 17: Afraid of negative long-term treatment effects		
Item 5: Restrictions in eating and drinking because of swelling episodes	Food	Food limitations associated with swelling episodes
Item 11: Limited food or beverage choices because of swelling episodes		

Source: Division of Clinical Outcome Assessment Reviewer.
Abbreviations, AE-QoL, Angioedema-Quality of Life Questionnaire

Each domain has its own score, and a total score can also be calculated. The items are scored from 0 to 4, and they are summed to provide raw domain scores, which are then transformed into linear scores ranging from 0 to 100. The total score is the sum of all 17 items. Higher scores in the AE-QoL domain and total scores indicate greater levels of impairment of quality of life. In trial 3001, subjects ≥ 18 years were asked to complete the AE-QoL via a provisioned electronic device at the trial site on Days 1, 31, 61, 91, 121, 151, and 182, respectively.

There is inadequate qualitative evidence in [Weller et al. \(2012\)](#) to support the content validity of the AE-QoL for use in the Applicant's drug development program. In addition, the domains of the AE-QoL are not well-defined and reliable to inform regulatory decision-making. Specifically, for the AE-QoL functioning domain, we note that asking patients about restrictions

swelling episodes have on their daily lives regardless of whether or not they have actually experienced swelling episodes during a 4-week period will not provide useful information for assessing treatment benefit in the context of trial 3001. While the core concepts of disease-related symptoms and physical function are reasonable PRO measurement strategies for demonstrating treatment benefit, emotional impacts (such as anxiety and embarrassment) as assessed by the AE-QoL fears/shame domain are distal concepts that may be affected by factors external to HAE disease or effect of the investigational product. In addition, we do not agree that the 4-week recall period of the AE-QoL is appropriate as patients may not reliably recall the occurrence of their HAE attacks during this timeframe. As such, we do not believe that the AE-QoL is content valid for the context of use.

The Applicant proposed a 6-point change as a minimal clinically important difference in the AE-QoL total and domain scores, positioned as exploratory endpoints in trial 3001. In general, endpoints positioned as exploratory endpoints and not multiplicity-controlled are (b) (4). The Applicant did not conduct anchor-based analyses to interpret meaningful within-patient score changes in PRO endpoints scores in trial 3001 as no external anchor scales (e.g., a Patient Global Impression of Severity or Patient Global Impression of Change) were included in trial 3001. Instead, the Applicant referenced the 6-point minimal clinically important difference threshold reported in [Weller et al. \(2016\)](#). Given the issues with the content validity of the AE-QoL, it is premature to evaluate meaningful score changes for the AE-QoL. While an anchor-based method is the primary method for deriving a range of thresholds that would constitute a meaningful within-patient change in target PRO scores, it should be supplemented with empirical cumulative distribution function and probability density function curves. In addition, estimation of clinically meaningful within-patient change thresholds should be confirmed in the specific context of the drug development trial. Detailed recommendations on the conduct of anchor-based analyses, including properties of appropriate anchor scales, can be found in FDA's Patient-Focused Drug Development Discussion Document: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making.²

Conclusion

Based on the evidence available to date and the construction of the instruments, the SGART and AE-QoL are not well-defined and reliable to inform regulatory decision making and thus, not fit-for-purpose (b) (4).

6.3.2. Type III HAE

Issue

Determine if there is sufficient evidence to conclude that garadacimab is effective in FXII/PLG (Type III) HAE patients (or a subset of Type III HAE patients) for the purposes of labeling.

Background

HAE is a rare autosomal disease classified into three subtypes: I, II, and III. HAE is most commonly caused by variants in the *SERPING1* gene, resulting in low or absent levels of C1-INH (Type I, most common) or normal to elevated levels of dysfunctional C1-INH (Type II).

² <https://www.fda.gov/media/166830/download>

However, HAE can also present with normal C1-INH (Type III) resulting from variants in other genes (e.g., *F12*, *PLG*, *ANGPT1*, *KNG1*, *MYOF*, *HS3ST6*); Type III HAE is a very rare, heterogeneous subtype ([Santacroce et al. 2021](#)). Genetic variants in *PLG* and factor XII (*F12*) are the most commonly reported variants in patients with Type III HAE ([Bork et al. 2018](#)). In addition to genetic differences, the *F12* and *PLG* variants also translate to differences in clinical presentation. For example, estrogen has a markedly aggravating effect on angioedema in *F12* HAE, and there is a higher frequency of tongue swelling in *PLG* HAE³. Erythema marginatum is occasionally observed in Type I and Type II HAE, but has not been reported for Type III HAE. Although the three types of HAE share the clinical presentation of episodic angioedema, Type III HAE exhibits some clinical phenotypic differences, such as predominant face/tongue swelling and less frequent abdominal attacks, when compared to Type I and Type II HAE.

Garadacimab is a monoclonal antibody targeting the catalytic domain of factor XIIa, blocking its activation of the kallikrein-kinin system and in turn preventing the proteolytic conversion of high-molecular-weight kininogen to bradykinin. In Type I and Type II HAE, excess bradykinin generation has been shown to be the primary mechanism leading to angioedema. In Type III HAE, the mutations seem to affect the fibrinolytic and kallikrein-kinin system pathways at different levels which ultimately lead to bradykinin-mediated angioedema; however, the different gene mutations lead to different biochemical disturbances, resulting in different clinical features, which has led some authors to suggest that each Type III subtype be considered a distinct disease entity ([Bork et al. 2020](#)).

Currently available HAE products are approved for patients with HAE, but historically clinical trials have only evaluated subjects with Type I and Type II HAE (due to both the rarity of and challenges in diagnosing Type III HAE), a fact which is reflected in the descriptions of the study populations in the product labeling. Although trial 3001 enrolled only subjects with Type I and Type II HAE, available response data from the subgroup of subjects with Type III HAE enrolled in the phase 2 trial (2001) are available for evaluation.

Assessment

The Applicant enrolled six subjects with Type III HAE in the phase 2 trial (2001). All six Type III HAE subjects received open-label garadacimab 600 mg SC Q4W (with a 300 mg IV loading dose). The Type III HAE subjects did not have a comparator arm for efficacy or safety assessments in trial 2001. Of the six Type III HAE subjects, three subjects had variants in *PLG*, and three had variants in *F12*. According to an IR response dated April 9, 2024, the three subjects with *PLG* variants each had the gain-of-function variant Lys330Glu, and the three subjects with variants in *F12* included Thr328Lys, deletion of 72 base pairs (c.971_1018 + 24del72), or duplication of 18 base pairs (c.892-909dup). Unlike Type I and Type II HAE subjects enrolled in trial 2001 who received multiple dosing regimens, subjects with Type III HAE were dosed at the highest garadacimab dose level studied (600 mg Q4W SC) throughout Treatment Periods 1 and 2 ([Figure 65](#)). The three subjects with variants in *PLG* exhibited less than a 50% reduction from baseline in HAE attacks; however, one subject experienced a decrease from three HAE attacks per month during the Run-in Period to 1.67 attacks per month while on garadacimab treatment. Two of the three subjects with *F12* variants responded to garadacimab ($\geq 50\%$ reduction in HAE attacks) and enrolled in the phase 3b OLE study (3002).

³ <https://ojrd.biomedcentral.com/counter/pdf/10.1186/s13023-020-01570-x.pdf>.

One subject with a *F12* variant experienced two HAE attacks per month during the Run-in Period and 2.33 attacks per month while on garadacimab treatment. In comparison, the Type I and Type II subjects in the 75 mg, 200 mg, and 400 mg garadacimab arms had reductions of $\geq 50\%$. Most Type I and Type II subjects (86%) in the 600 mg garadacimab arm also met this endpoint. No Type I or Type II subject on placebo achieved a $\geq 50\%$ reduction. Refer to Sections [15.3](#) and [16.2](#) for more details.

Although the number of subjects with *PLG* variants studied was small, the lack of response to garadacimab in some subjects with *PLG* variants suggests that the development of HAE attacks in these subjects may occur by a mechanism that bypasses factor XIIa, the target of garadacimab. This is supported by a report that *PLG* gain-of-function variants may result in the formation of bradykinin via downstream mechanisms ([Hintze et al. 2022](#)). Additionally, in vivo studies have shown that the incubation of *PLG* gain-of-function protein enhanced the breakdown of high-molecular-weight kininogen as compared to wild-type *PLG* protein, thereby increasing the formation of bradykinin ([Maas 2019](#)).

Conclusion

The garadacimab development program studied a small number of subjects with FXII-HAE (N=3) and PLG-HAE (N=3) in a phase 2 trial (2001) at a dosage higher than that included in the approved labeling. Of the subjects studied, 2/3 subjects with FXII-HAE and 0/3 with PLG-HAE responded to garadacimab (defined as a $\geq 50\%$ reduction from baseline in HAE attacks). Subjects with *F12* and *PLG* mutations had variable responses to garadacimab treatment that could potentially be explained by emerging mechanistic data from in vivo studies. Given the extremely small sample size, lack of a control arm, and heterogeneity in disease genotype and phenotype, it is difficult to draw conclusions regarding the response to garadacimab treatment in the subset of subjects with Type III HAE. Therefore, no statement regarding patients with Type III HAE will be included in the PI. A broad HAE indication is reasonable for garadacimab, provided that language in the labeling describes that approval is supported only by results in subjects with Type I and Type II HAE. This approach is consistent with prior approvals and labeling for HAE prophylactic therapies. Further studies of whether subsets of subjects with Type III HAE respond to FXIIa inhibition with garadacimab, particularly PLG-HAE, are needed. Given that HAE patients typically receive healthcare from subspecialists with expertise in angioedema, academic research in the published literature may be the most efficient method for acquiring and disseminating information about differential treatment effects of garadacimab and other approved HAE products in patients with Type III HAE with specific mutations.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Prolongation of aPTT was observed in nonclinical studies conducted with multiple nonclinical test species (e.g., monkeys, rabbits). There was no evidence of bleeding events in these nonclinical studies.

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

Garadacimab is a first-in-class inhibitor of activated FXIIa. FXIIa initiates the contact system and the intrinsic blood coagulation system. Based on its mechanism of action, potential risks include bleeding, thromboembolism, and abnormal coagulation laboratory values; however, patients with genetic FXII deficiency do not typically exhibit a bleeding tendency (see Section [7.7.1](#) for a discussion). These risks were monitored during the clinical trial and will be discussed in this review.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Not applicable. This drug is not yet commercially available in any country.

7.4. FDA Approach to the Safety Review

The sources of the clinical trial safety database are shown in [Table 22](#).

Table 22. Clinical Trials Submitted in Support of Safety Determination for Garadacimab

Trial Identifier/ Dates/ ClinicalTrials.gov ID#	Treatment Duration/ Trial		Trial Population	Primary and Key Secondary Endpoints	No. of Subjects Treated	No. of Centers and Countries
	Design	Regimen				
CSL312_3001 01/27/21 – 06/07/22 NCT046556418	6-month R, DB, PC, PG, MC	• 200 mg QMonth • Placebo QMonth	Adult and adolescent subjects with Type I or II HAE	• Time-normalized # of HAE attacks/month • % reduction in time-normalized HAE attacks compared to placebo	64 Treated	28 centers US, Canada, Germany, Israel, Netherlands, Japan, Hungary
CSL312_3002 03/29/21 – ongoing NCT04739059	30 months OL, MC	• 200 mg QMonth	Adult and adolescent subjects with Type I or II HAE	• Treatment-emergent adverse events (TEAEs)	161 Treated	47 centers US, Canada, Australia, New Zealand, Czech Republic, Germany, Spain, Netherland, Hong Kong, Japan, Taiwan, Israel, Russia
CSL312_2001 10/29/2018 – 10/15/2021 NCT03712228	TP1: 13-week R, DB, PC, DR, PG TP2: 44-week OL	• 75 mg Q4W • 200 mg Q4W • 600 mg Q4W • 400 mg Q2W (OL) • Placebo Q4W	Adult subjects with Type I or II or III HAE	• Time-normalized number of HAE attacks/month • Number of subjects who had ≥50% reduction in time-normalized number of HAE attacks • No. of subjects who were attack free during TP1	44 Treated • Placebo, n=8 • 75 mg, n=9 • 200 mg, n=8 • 600 mg, n=13 • 400 mg, n=6	19 centers US, Canada, Germany, Israel

Source: Reviewer generated and adapted from Applicant-provided clinical study reports of individual studies.

Abbreviations: DB, double-blind; DR, dose-ranging; HAE, hereditary angioedema; MC, multicenter; no., number; OL, open-label; PC, placebo-controlled; PG, parallel group; Q, every; R, randomized; TP, Treatment Period; W, weeks

The clinical data scientists and clinical reviewer performed independent safety analyses using R Studio 4.1.3, JMP, MAED, and Office of Computational Science Analysis Studio software programs. The safety assessment is primarily based on data from trial 3001 with support from the OLE study 3002 and phase 2 dose-ranging trial 2001. Given the differences in design and duration across trials, safety data were not pooled, but reviewed from each trial independently. All safety analyses were conducted in the safety population, which consisted of any subject who received at least one dose of garadacimab. For both trial 3001 and study 3002, the safety population and the ITT population were the same. The safety results are presented in Sections [7.6.1](#) and [7.6.2](#) for trial 3001 and OLE study 3002, respectively. A summary of safety data from trial 2001 is provided; however, results are not presented in detail within this review given the short treatment duration and small number of subjects who received the proposed dose of garadacimab in the trial.

7.5. Adequacy of the Clinical Safety Database

No data quality or integrity issues were identified in the submitted datasets or CRFs. Definitions of adverse events (AEs) and serious adverse events (SAEs) were consistent with Code of Federal Regulations 312.32. The Applicant coded AEs using the Medical Dictionary for Regulatory Activities version 25.1 and determined AE severity using the mild, moderate, and severe grading scale (see Section [15.1.7](#) for definitions). The Applicant's translation of verbatim terms to the Medical Dictionary for Regulatory Activities preferred terms (PTs) for the events reported in the trial was reviewed and found to be acceptable. Safety monitoring in the clinical program was adequate to inform the risks of garadacimab. See Sections [15.1.6](#), [15.2.2](#), and [15.3.2](#) for the schedules and review of safety assessments.

Overall Exposure

[Table 23](#) represents exposure to the proposed 200 mg dose of garadacimab in the HAE development program. Across the three trials, 172 subjects with HAE received at least one 200 mg dose of garadacimab, and there was >1 year of exposure to garadacimab in the majority of subjects. Overall, the safety database is of sufficient size and duration for a rare disease such as HAE to assess the safety of garadacimab for the proposed indication.

Table 23. Duration of Garadacimab Exposure, Safety Population, Pooled Analyses

Parameter	Garadacimab 200 mg N=172
Duration of treatment, weeks	
Mean (SD)	88.8 (55.4)
Median (minimum, maximum)	66.4 (10, 219)
Interquartile range	55.9-94.4
Subjects treated, by duration, n (%)	
Any duration (at least 1 dose)	172 (100%)
<48 weeks	26 (15%)
48 to <96 weeks	105 (61%)
96 to <144 weeks	5 (3%)
144 to <192 weeks	21 (12%)
192 to <220 weeks	15 (9%)

Source: Clinical reviewer generated in JMP using ISS adsl.xpt, where SAFFL=Y, DSG200FL=Y.

7.6. Safety Results

7.6.1. Safety Results, Trial 3001

As the safety and ITT populations were the same, subject disposition and demographics/baseline disease characteristics are presented in Sections [6.2.4.1](#) and [6.2.4.2](#).

7.6.1.1. Overview of Treatment-Emergent Adverse Events, Trial 3001

The general overview of all treatment-emergent adverse events (TEAEs), defined as any untoward medical occurrence in a subject who develops it after administration of the investigational product, regardless of whether it is considered related to the investigational product, is shown in [Table 24](#). The overall occurrence of TEAEs was roughly similar between treatment groups with numerically more moderate TEAEs in the garadacimab group. TEAEs that were severe, serious, or led to treatment discontinuation were rare.

Table 24. Overview of TEAEs, Safety Population, Trial 3001

Event Category	Garadacimab		Risk Difference % (95% CI)
	200 mg N=39 n (%)	Placebo N=25 n (%)	
Any TEAE	25 (64.1)	15 (60.0)	4.1 (-19.5, 28.3)
Severe and life-threatening	1 (2.6)	0	2.6 (-11.1, 13.3)
Moderate	15 (38.5)	7 (28.0)	10.5 (-13.9, 32.3)
Mild	9 (23.1)	8 (32.0)	-8.9 (-32.0, 12.9)
TEAE leading to dose modification of study drug	0	0	0.0 (-13.5, 9.1)
TEAE leading to permanent discontinuation of study drug	0	0	0.0 (-13.5, 9.1)
SAE	1 (2.6)	0	2.6 (-11.1, 13.3)
Fatality	0	0	0.0 (-13.5, 9.1)
Life-threatening	0	0	0.0 (-13.5, 9.1)
Requiring hospitalization	1 (2.6)	0	2.6 (-11.1, 13.3)

Source: adae.xpt; software: R.

Treatment-emergent adverse events with a start date and time occurring after the first administration of the study treatment. Duration is 6 months.

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

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; CI, confidence interval; CSL312, garadacimab injection; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

7.6.1.2. Deaths, Trial 3001

There were no deaths in trial 3001.

7.6.1.3. Serious Adverse Events, Trial 3001

In trial 3001, there was one SAE. A 31-year-old female with Type I HAE in the garadacimab treatment group experienced a severe HAE laryngeal attack on Study Day 99, resulting in hospitalization. The subject reported sudden onset of globus sensation and difficulty swallowing. She self-treated with 3,000 IU of C1-INH and received 30 mg of ictatibant in the emergency

department. No further on-demand treatment was administered during the hospitalization and her vitals remained stable. She was discharged from the hospital the following day and continued to receive study drug without interruption. She completed trial 3001 and continued treatment in OLE study 3002. As many HAE patients continue to experience breakthrough attacks despite prophylaxis therapy, this event is likely due to the underlying condition rather than an adverse reaction related to garadacimab treatment.

7.6.1.4. Treatment-Emergent Adverse Events Leading to Treatment Discontinuation, Trial 3001

There were no TEAEs that led to treatment discontinuation in trial 3001.

7.6.1.5. Treatment-Emergent Adverse Events, Trial 3001

Given the small size of the trial, additional analyses to identify adverse drug reactions focused on TEAEs occurring at a frequency $\geq 5\%$ (i.e., two or more subjects). To explore potential safety signals, broad and narrow FDA Medical Dictionary for Regulatory Activities queries (FMQs) were performed on the AE datasets. [Table 25](#) displays the narrow FMQs observed with $\geq 5\%$ frequency and more common in the garadacimab group along with the individual PTs that contributed to the FMQ group terms.

Table 25. FMQ (Narrow) Group Terms That Occurred in $\geq 5\%$ Subjects and More Frequently Than Placebo, Safety Population, Trial 3001

FMQ Group Term Preferred Term	Garadacimab	Placebo	Risk Difference % (95% CI)
	200 mg N=39 n (%)	N=25 n (%)	
Abdominal pain	3 (7.7)	0	7.7 (-6.2, 20.5)
Abdominal pain	2 (5.1)	0	5.1 (-8.7, 17.0)
Abdominal pain lower	1 (2.6)	0	2.6 (-11.1, 13.3)
Nasopharyngitis	8 (20.5)	3 (12.0)	8.5 (-12.2, 26.3)
Nasopharyngitis	3 (7.7)	1 (4.0)	3.7 (-12.9, 17.2)
Rhinitis	1 (2.6)	0	2.6 (-11.1, 13.3)
Upper respiratory tract infection	4 (10.3)	2 (8.0)	2.3 (-16.2, 17.4)
Bacterial infection	4 (10.3)	1 (4.0)	6.3 (-10.6, 20.5)
Urinary tract infection (UTI)	2 (5.1)	0	5.1 (-8.7, 17.0)
<i>Helicobacter</i> infection	1 (2.6)	0	2.6 (-11.1, 13.3)
Pyelonephritis ¹	1 (2.6)	0	2.6 (-11.1, 13.3)
Tooth infection	1 (2.6)	0	2.6 (-11.1, 13.3)
Bacterial test positive	0	1 (4.0)	-4.0 (-19.7, 5.3)
White blood cells urine positive	0	1 (4.0)	-4.0 (-19.7, 5.3)
Back pain	2 (5.1)	1 (4.0)	1.1 (-15.2, 13.7)
Hemorrhage	2 (5.1)	1 (4.0)	1.1 (-15.2, 13.7)
Injection site bruising	1 (2.6)	0	2.6 (-11.1, 13.3)
Traumatic hematoma	1 (2.6)	0	2.6 (-11.1, 13.3)
Contusion	0	1 (4.0)	-4.0 (-19.7, 5.3)

Source: Trial 3001 adae.xpt; software: R.

¹One subject reported UTI and pyelonephritis for the same event.

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

Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term

Adverse reactions of abdominal pain, nasopharyngitis, and back pain were consistent with the signal identified in the common TEAE analysis by PT (see [Table 26](#)). Regarding bacterial infections, a total of four garadacimab-treated subjects reported five events, all of which were nonserious and mild or moderate in severity. None of the infections appear to have been complicated as all resolved following treatment with oral antibiotics. None of the events led to garadacimab treatment discontinuation. Although there is an imbalance in the number of bacterial infections, the lack of consistent pattern to the type/anatomical location of infection or presumptive causative microorganism makes it difficult to draw conclusions regarding drug causality. Overall, considering the lack of a consistent microorganism or pattern of infection, that none of the infections were serious or severe in nature, and the lack of a plausible mechanism of action, this imbalance does not significantly alter the benefit/risk assessment, and this FMQ term does not warrant inclusion in labeling.

The PTs contributing to the Hemorrhage FMQ are reflective of bruising and discussed under the review issue Bleeding and Abnormal Coagulation Laboratory Values, Section [7.7.1](#).

An analysis of common TEAEs (by PT with pooling of synonymous terms) occurring in $\geq 5\%$ (i.e., ≥ 2 subjects) and more frequently in the garadacimab treatment group than in the placebo group is shown in [Table 26](#). Additional TEAEs not captured by the narrow FMQ group terms showed small numerical differences in frequency between treatment groups. All of the events were mild or moderate in severity. There were no concerning safety signals that significantly altered the risk of garadacimab in the HAE population.

Due to the small sample size, a cutoff of 7% (or 3) subjects in the garadacimab arm reporting the same or similar TEAE was used as the threshold for inclusion in the draft labeling.

Table 26. TEAEs by PT That Occurred in $\geq 5\%$ Subjects and More Frequently Than Placebo, Safety Population, Trial 3001

Preferred Term	Garadacimab 200 mg, N=39 n (%)	Placebo N=25 n (%)	Risk Difference (95% CI)
Nasopharyngitis ¹	8 (20.5)	3 (12.0)	8.5 (-12.2, 26.3)
Abdominal pain ²	3 (7.7)	0 (0.0)	7.7 (-6.2, 20.5)
Back pain	2 (5.1)	1 (4.0)	1.13 (-9.21, 11.47)
Conjunctivitis	2 (5.1)	0 (0.0)	5.13 (-1.79, 12.05)
Diarrhea	2 (5.1)	1 (4.0)	1.13 (-9.21, 11.47)
Gastrointestinal infection	2 (5.1)	1 (4.0)	1.13 (-9.21, 11.47)
Oropharyngeal pain	2 (5.1)	1 (4.0)	1.13 (-9.21, 11.47)
Sinusitis	2 (5.1)	0 (0.0)	5.13 (-1.79, 12.05)
Urinary tract infection	2 (5.1)	0 (0.0)	5.13 (-1.79, 12.05)
Visual impairment	2 (5.1)	0 (0.0)	5.13 (-1.79, 12.05)
Contusion ³	2 (5.1)	1 (4.0)	1.1 (-15.2, 13.7)

Source: Clinical reviewer generated from common TEAEs and FMQ (Narrow) that are $\geq 5\%$ frequency and more frequent with garadacimab treatment, using OCS Analysis Studio, trial 3001 adae.xpt, SAFFL=Y.

¹ Includes PTs of nasopharyngitis, rhinitis, and upper respiratory infection.

² Includes PTs of abdominal pain, abdominal pain lower.

³ Includes PTs of injection site bruising, traumatic hematoma, and contusion.

Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; PT, preferred term; TEAE, treatment-emergent adverse event

7.6.1.6. Adverse Events of Special Interest, Trial 3001

Prespecified AEs of special interest (AESIs) included thromboembolic events, bleeding events, severe hypersensitivity reactions and anaphylaxis. Analyses of AEs by PT, Standard Medical Dictionary for Regulatory Activities Query (SMQ), and FMQ revealed no severe or life-threatening/serious AESIs or AESIs that led to treatment discontinuation. The individual AESIs are discussed in more detail under key safety review issues (Section [7.7](#)).

7.6.1.7. Laboratory Values and Vital Signs, Trial 3001

Routine clinical testing (hematology, serum chemistry with liver function tests, and coagulation) were collected at baseline, Month 3, and Month 6 during the Treatment Period. The results of the coagulation studies are discussed in *Review Issues* in Section [7.7.1](#). Otherwise, there was no significant clinical difference between the garadacimab and placebo groups in laboratory parameters during the Treatment Period. Additionally, no clinically meaningful changes in mean or median vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, temperature) were observed with garadacimab treatment compared to placebo across trial visits.

7.6.1.8. Liver Function Tests, Trial 3001

Liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin were collected from subjects at baseline, Month 3 and Month 6 during the 6-month Treatment Period. Subjects had an additional lab collection on Day 1 if baseline labs were collected more than 90 days prior to the first dose of garadacimab administration. There were no potential Hy's law cases in the program. One subject in the garadacimab treatment group was noted to have isolated elevations of ALP; the values were $<3\times$ upper limit of normal (ULN). None of the AST/ALT or ALP or total bilirubin values exceeded $3\times$ ULN. No significant difference in ALT, AST, ALP, and total bilirubin were found between the garadacimab and placebo groups.

7.6.1.9. Safety Subgroup Analyses Trial 3001

Subgroup analyses by age, sex, race, and geographic region revealed no major differences in safety; however, the number of subjects within certain subgroups was small. Detailed analyses of TEAEs by subgroup are located in Section [18](#).

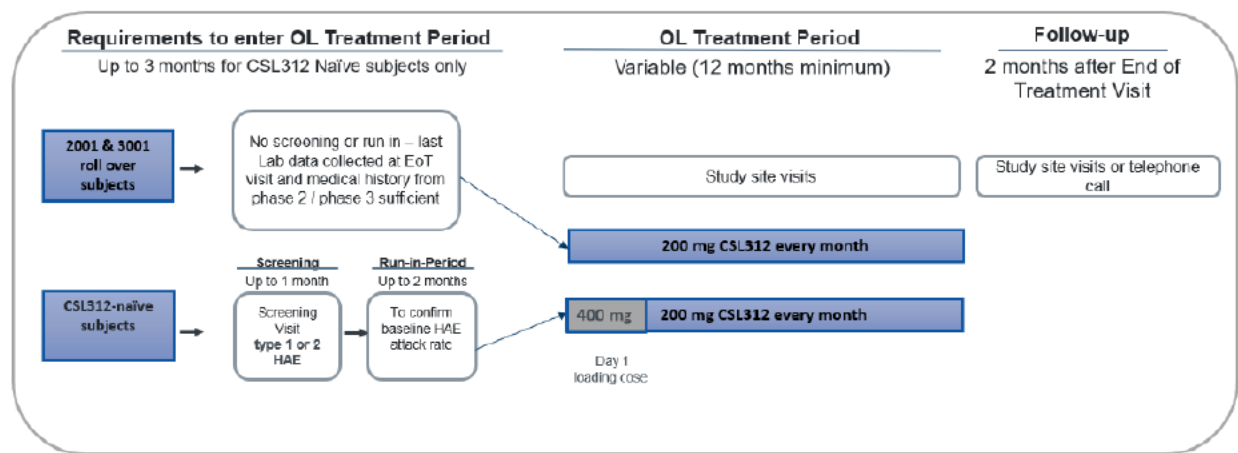
7.6.2. Safety Results, Study 3002

7.6.2.1. Study Design, Study 3002

Study 3002 is an ongoing phase 3b, single arm, OLE study evaluating the long-term safety of garadacimab 200 mg SC every month in subjects with Types I, II, and III HAE. The trial enrolled rollover subjects who completed trial 2001 or 3001 as well as garadacimab-naïve subjects. For additional details regarding screening and the Run-in Period of study 3002, see

Section 16.2.1. The planned trial duration is 30 months. The study schematic is shown in Figure 10. Refer to Section 16.2 for more details on the study protocol.

Figure 10. Study Design, Study 3002



Source: Study 3002 Protocol, p. 38.

Abbreviations: CSL312, garadacimab; EOT, end of treatment; HAE, hereditary angioedema; OL, open-label

Key Inclusion Criteria

1. Successful completion of trial 2001 or 3001.
OR
2. For garadacimab-naïve subjects to enter the Run-in Period of the trial, they must meet the following criteria:
 - a. Age ≥ 12 years.
 - b. Diagnosed with C1-INH as defined by documented clinical history consistent with HAE, C1-INH antigen concentration and/or functional activity $\leq 50\%$ of normal, and C4 antigen concentration below the lower limit of the reference range as documented in the subject's medical record.
 - c. Documentation of ≥ 3 HAE attacks during the 3 months before screening. For subjects taking HAE prophylaxis, the ≥ 3 HAE attacks could be documented over 3 consecutive months before commencing the prophylactic therapy.
3. For garadacimab-naïve subjects to exit the Run-in Period and enter the Treatment Period, they must meet the following criteria:
 - a. Participated in the Run-in Period for at least 1 month.
 - b. Experienced at least an average of one HAE attack per month during the Run-in Period.
 - c. No laboratory clinical abnormalities in the hematology, chemistry, or urinalysis assessments performed during screening.
 - d. Verified C1-INH functional activity and antigen and C4 antigen concentration at screening.

Key Exclusion Criteria (for Garadacimab-Naïve Subjects)

1. Concomitant diagnosis of another form of angioedema, such as idiopathic or acquired or recurrent angioedema associated with urticaria.
2. Use of C1-INH products, androgens, antifibrinolytics or other small-molecule medications for routine prophylaxis against HAE attacks ≥ 2 weeks before the first day of the Run-in Period.
3. Use of monoclonal antibodies (including lanadelumab) 3 months before the first day of the Run-in Period.
4. Female subject's use of estrogen-containing medications with systemic absorption (e.g., oral contraceptive or hormonal replacement therapy) within 4 weeks prior to the Run-in Period.

7.6.2.2. Subject Disposition, Study 3002

Subject disposition as of the cutoff date of February 13, 2023, is summarized in [Table 27](#). As the study is ongoing, the majority of subjects, 146 (90%), are continuing to receive garadacimab treatment. A total of 79 garadacimab-naïve subjects consented to participate in study 3002, two subjects discontinued the study prior to the Run-in Period and eight subjects discontinued during the Run-in Period. The most common reason for discontinuation during the Run-in Period was an insufficient number of HAE attacks (five subjects).

Table 27. Subject Disposition, Safety Population, Study 3002

Disposition	n (%)
Entered Treatment Period (safety population)	161 (100)
Rollover	92 (57)
Parent Trial 2001	35 (22)
Parent Trial 3001	57 (35)
Garadacimab-naïve	69 (44)
Discontinued treatment	12 (8)
Site terminated by the Applicant	3 (25)
TEAE leading to discontinuation	3 (25)
Pregnancy	1 (8)
Mood swings	1 (8)
Injection site reaction	1 (8)
Lost to follow-up	1 (8)
Withdrawal by subject	3 (25)
Physician decision	2 (17)
Completed study	3 (2)

Source: Clinical reviewer generated from the study 3002 CSR, p. 143.

Abbreviations: CSR, clinical study report; OLE, open-label extension; TEAE, treatment-emergent adverse event

7.6.2.3. Subject Demographics and Baseline Characteristics, Study 3002

[Table 28](#) provides the demographics and baseline characteristics of the subjects enrolled in study 3002. The subject demographics and baseline characteristics are similar to those of trial 3001 and generally representative of the broader HAE population.

Table 28. Subject Demographics and Baseline Characteristics, Safety Population, Study 3002

Characteristic	Garadacimab-Naïve N=90	Rollover N=71	Total N=161
Sex, n (%)			
Female	60 (66.7)	41 (57.7)	101 (62.7)
Male	30 (33.3)	30 (42.3)	60 (37.3)
Age, years			
Mean (SD)	40.8 (15.2)	44.1 (15.4)	42.3 (15.3)
Median (min, max)	42 (13, 73)	43 (13, 70)	42 (13, 73)
Age group, years, n (%)			
≤17	7 (7.8)	3 (4.2)	10 (6.2)
>17	83 (92.2)	68 (95.8)	151 (93.8)
Age group ≥65, years, n (%)			
≥65	6 (6.7)	9 (12.7)	15 (9.3)
Race, n (%)			
Asian	17 (18.9)	5 (7.0)	22 (13.7)
Black or African American	2 (2.2)	0	2 (1.2)
Multiple	0	1 (1.4)	1 (0.6)
Other	0	1 (1.4)	1 (0.6)
White	71 (78.9)	64 (90.1)	135 (83.9)
Ethnicity, n (%)			
Hispanic or Latino	7 (7.8)	2 (2.8)	9 (5.6)
Not Hispanic or Latino	81 (90.0)	69 (97.2)	150 (93.2)
Country of participation, n (%)			
Canada	9 (10.0)	10 (14.1)	19 (11.8)
Germany	15 (16.7)	19 (26.8)	34 (21.1)
Israel	6 (6.7)	15 (21.1)	21 (13.0)
United States	17 (18.9)	19 (26.8)	36 (22.4)
Others	43 (47.8)	8 (11.3)	51 (31.7)
Is in United States, n (%)			
United States	17 (18.9)	19 (26.8)	36 (22.4)
Non-United States	73 (81.1)	52 (73.2)	125 (77.6)

Source: adsl.xpt; Software: R, SAFFL=Y.

Abbreviations: N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation

7.6.2.4. Overview of Treatment-Emergent Adverse Events Summary, Study 3002

An overview of the TEAEs that occurred through the cutoff date of February 13, 2023 is provided in [Table 29](#). A higher proportion of subjects experienced TEAEs within each category compared to trial 3001; however, this is likely due to the longer duration of exposure in study 3002. Occurrence of TEAEs categorized as severe, serious, or leading to treatment discontinuation remained rare.

Table 29. Overview of TEAEs, Safety Population, Study 3002

Event Category	Garadacimab Naïve N=90 n (%)	Rollover N=71 n (%)	Total N=161 n (%)
Any TEAE	73 (81)	62 (87)	135 (84)
Severe and worse	5 (6)	4 (6)	9 (6)
Moderate	43 (48)	34 (48)	77 (48)
Mild	25 (28)	24 (34)	49 (30)

Event Category	Garadacimab Naïve N=90 n (%)	Rollover N=71 n (%)	Total N=161 n (%)
TEAE leading to dose modification of study drug	1 (1)	0	1 (1)
AE leading to interruption of study drug	1 (1)	0	1 (1)
AE leading to reduction of study drug	0	0	0
AE leading to dose delay of study drug	0	0	0
TEAE leading to permanent discontinuation of study drug	1 (1)	2 (3)	3 (2)
SAE	2 (2)	1 (1)	3 (2)
Life-threatening or fatal SAEs	0	0	0
SAEs requiring hospitalization	2 (2)	1 (1)	3 (2)

Source: adae.xpt; software: R.

Treatment-emergent adverse events defined as AEs with a start date and time occurring after the first administration of the study treatment. AEs with missing or partial start date or time were also considered TEAEs following the worst-case principle, unless the partial data clearly indicates that the AE started before first administration date and time.

Duration is minimum, 5.1 months; mean, 13 months; maximum, 21.1 months.

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

7.6.2.5. Deaths, Study 3002

There were no deaths in study 3002.

7.6.2.6. Serious Adverse Events, Study 3002

Three subjects reported three SAEs shown in [Table 30](#). Based on review of the case narratives, none of the events appear to be related to garadacimab treatment.

Table 30. Listing of Subjects With Serious Adverse Events, Safety Population, Study 3002

Subject ID	Age/Sex HAE Subtype	SAE	AE Onset Date	AE Resolution Date	Garadacimab Treatment D/C	Investigator Assessment of Relatedness
(b) (6)	19/F Type I	Hospitalization for COVID-19 infection		(b) (6)	No	Unlikely related
(b) (6)	20/F Type I	Hospitalization for hereditary angioedema abdominal attack			No	Unlikely related
(b) (6)	63/F Type I	Hospitalization for COVID-19 infection			No	Unlikely related

Source: Clinical reviewer generated from the study 3002 Clinical Study Report.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; D/C, discontinuation; F, female; HAE, hereditary angioedema; ID, identity; SAE, serious adverse event

7.6.2.7. Treatment-Emergent Adverse Events Leading to Treatment Discontinuation, Study 3002

Three subjects experienced a total of three AEs leading to treatment discontinuation shown in [Table 31](#). Based on a review of the case narratives, only the TEAE of ISR appeared to be related to study drug treatment. ISRs are further discussed under Review Issues in Section [7.7.3](#). The TEAE of mood swings leading to discontinuation had an onset >1 year after initiation of garadacimab treatment, and the subject had pre-existing psychiatric comorbidities. Because of the confounding factors and late onset, it is difficult to determine if mood swings are an adverse reaction related to garadacimab.

Table 31. Listing of Subjects with TEAEs Leading to Treatment Discontinuation, Safety Population, Study 3002

Subject ID	Age/Sex HAE Type	MedDRA Preferred Term	Verbatim Term	Severity	Duration of Treatment Exposure ¹	Resolution of TEAE after Treatment D/C	Applicant Assessment of Relatedness	Reviewer's Assessment
(b) (6)	30F Type I	Mood swings	Extreme irritability and difficulty managing emotions	Severe	18 months	Yes	Yes	The subject had a past medical history of migraines and anxiety. Of note, the TEAE occurred 16 months after starting garadacimab treatment. It is unclear whether garadacimab contributed to the mood swings.
	18F Type I	Pregnancy	Pregnancy	Not applicable	10 months	Not applicable	No	Agree with the Applicant's assessment that the TEAE of pregnancy is not related to garadacimab treatment.
	37F Type I	Injection site reaction	Injection site reaction	Moderate	4 months	Yes	Yes	Agree with the Applicant's assessment that the injection site reaction is related to garadacimab treatment.

Source: Clinical reviewer generated from the study 3002 Clinical Study Report.

¹ Where applicable, the duration of treatment exposure includes exposure from the parent trial (2001 or 3001).

Abbreviations: D/C, discontinuation; F, female; HAE, hereditary angioedema; ID, identity; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event

7.6.2.8. Treatment-Emergent Adverse Events, Study 3002

The review analyzed the AE dataset for TEAEs occurring in $\geq 5\%$ of the total subjects by PT, as shown in [Table 32](#). Similar to the results from trial 3001, nasopharyngitis/upper respiratory infection was one of the most common TEAEs. COVID-19 infection, however, was the most common TEAE. The high frequency of COVID-19 events is not unexpected given the timing of study initiation on March 29, 2021, during the midst of the COVID-19 pandemic, and these events are unlikely to be related to garadacimab. The majority of TEAEs were mild or moderate in severity for both rollover and garadacimab-naïve subjects ([Table 29](#)), which is reflective of trial 3001. The most common mild or moderate TEAEs were nasopharyngitis and COVID-19. The reported severe TEAEs were diarrhea, tendonitis, nasopharyngitis, toothache, headache, pulpitis, gastroenteritis, mood swings, and COVID-19. The number of subjects who reported each TEAE was small, one or two subjects each. All the severe TEAEs resolved without changing the dose or stopping garadacimab treatment (except for mood swing, as described in [Table 31](#)).

Table 32. Common TEAEs by PT That Occurred in $\geq 5\%$ of Total Subjects, Safety Population, Study 3002

	Garadacimab Naive N=90 n (%)	Rollover N=71 n (%)	Total N=161 n (%)
Preferred Term			
COVID-19	33 (37)	25 (35)	58 (36)
Nasopharyngitis	15 (17)	12 (17)	27 (17)
Headache	10 (11)	0	10 (6)
Injection site erythema	10 (11)	1 (1)	11 (7)
Influenza	7 (8)	4 (6)	11 (7)
Upper respiratory tract infection	3 (3.3)	6 (8.5)	9 (6)

Source: adae.xpt; software: R.

Treatment-emergent adverse events defined as AEs with a start date and time occurring after the first administration of the study treatment. AEs with missing or partial start date or time were also considered TEAEs following the worst-case principle, unless the partial data clearly indicates that the AE started before first administration date and time.

Duration is minimum, 5.1 months, mean, 13 months; maximum, 21.1 months.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; TEAE, treatment-emergent adverse event

To search for additional safety signals, the AE dataset was further analyzed by narrow FMQ terms. [Table 33](#) shows the narrow FMQ terms that occurred in $\geq 5\%$ of the total subjects. Nasopharyngitis and hemorrhage FMQ terms are consistent with those seen in trial 3001; the hemorrhage FMQ primarily consisted of PTs related to bruising and is discussed further in [Section 7.7.1](#). Local administration reactions are discussed in [Section 7.7.3](#). Although ISRs occurred in trial 3001, there was no imbalance between treatment groups in the pivotal controlled

trial. The viral infection and bacterial infection FMQs are reviewed in more detail below. No new safety signal was detected in the open-label, long-term safety data.

Table 33. Subjects with FMQ (Narrow) Group Terms That Occurred in $\geq 5\%$ of the Total Subjects, Safety Population, Study 3002

	Garadacimab Naïve N=90 n (%)	Rollover N=71 n (%)	Total N=161 n (%)
FMQ (Narrow)			
Viral infection	39 (43)	28 (40)	67 (42)
Nasopharyngitis	20 (22)	20 (28)	40 (25)
Local administration reaction	15 (17)	2 (3)	17 (11)
Bacterial infection	6 (7)	6 (9)	12 (8)
Hemorrhage	7 (7)	4 (6)	10 (6)
Headache	10 (11)	1 (1)	11 (7)

Source: Clinical reviewer generated using study 3002 adae.xpt dataset in MAED, SAFFL=Y.

Abbreviation: FMQ, FDA Medical Query

Given that ‘bacterial infection’ was a frequently occurring FMQ group term in trial 3001, the clinical reviewer assessed the individual TEAEs contributing to the viral and bacterial infection FMQs. A breakdown of the viral infection and bacterial infection FMQs by PT is shown in [Table 34](#). ‘Viral infection’ was primarily driven by COVID-19 and influenza infections, as evident in the analysis of common TEAEs by PT. No new or concerning signals for viral infection were identified.

Similar to trial 3001, the TEAEs contributing to ‘bacterial infection’ were primarily single events representing a broad range of infection types, locations and presumptive causal microorganisms. Except for pulpitis, all infections were mild or moderate in severity. Most of the bacterial infection TEAEs were recorded as resolved. None of the bacterial infections were serious or resulted in stopping or changing the dose of garadacimab. Overall, considering the lack of consistent microorganism or pattern of infection, severity, and plausible mechanism of action, this potential signal does not appear to be a clear safety issue that alters the benefit/risk assessment.

Table 34. Subjects With Viral Infection and Bacterial Infection FMQ (Narrow), Safety Population, Study 3002

FMQ (Narrow) Preferred Term	Garadacimab Naïve N=90 n (%)	Rollover N=71 n (%)	Total N=161 n (%)
Viral infection (FMQ)	39 (43)	28 (40)	67 (42)
COVID-19	33 (37)	25 (35)	58 (36)
Influenza	7 (8)	4 (6)	11 (7)
Gastroenteritis viral	3 (3)	0	3 (2)
Oral herpes	2 (2)	1 (1)	3 (2)
Bacterial infection (FMQ)	6 (7)	6 (9)	12 (8)
Pulpitis dental	2 (2)	1 (1)	3 (2)
Cellulitis	0	2 (3)	2 (1)
Tooth abscess	0	1 (1)	1 (1)
Tooth infection	0	1 (1)	1 (1)
Wound infection	0	1 (1)	1 (1)
Dermatitis infected	1 (1)	0	1 (1)
Pharyngitis streptococcal	1 (1)	0	1 (1)
Urinary tract infection	1 (1)	0	1 (1)
Hordeolum	1 (1)	0	1 (1)

Source: adae.xpt; software: R.

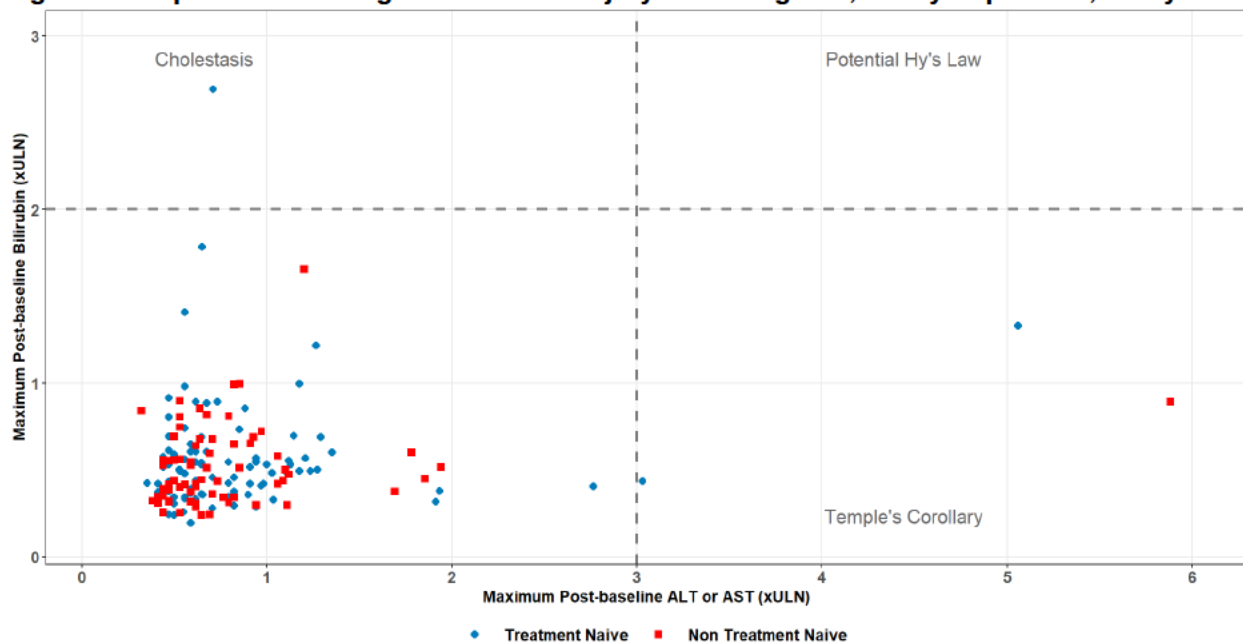
Abbreviations: COVID-19, coronavirus disease 2019; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term

7.6.2.9. Laboratory Findings and Vital Signs, Study 3002

Routine clinical testing, including hematology, serum chemistry with liver function tests, and coagulation studies, was performed every 3 months. Although study 3002 lacked a comparator group, lab and vital sign findings while on treatment did not detect any new safety signals. A discussion of the abnormal coagulation laboratory values can be found under Review Issues in Section [7.7.1](#).

[Figure 11](#) shows a screening assessment for potential cases of drug-induced liver injury. There were no potential Hy's law cases. Two subjects reported a maximum AST or ALT >5× ULN; however, both subjects had elevated AST and/or ALT at screening and confounding factors such as prior danazol use and past medical history of alcohol use and hepatic steatosis. The AST and ALT levels for these two subjects fluctuated over time with no apparent correlation to garadacimab administration.

Figure 11. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study 3002



Source: adlb.xpt; software: R.

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

A potential Hy's Law case (red circle) was defined as having any postbaseline total bilirubin equal to or exceeding 2× ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3× ULN, and ALP less than 2× ULN (note ALP values are not circled). All patients with at least one postbaseline ALT or AST and bilirubin are plotted. The within-30-days analysis window rule does not apply to cholestatic DILI and temple's corollary cases.

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

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ULN, upper limit of normal

7.6.3. Safety Results, Trial 2001

Treatment Period 1 of trial 2001 was a phase 2, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging trial in 44 adults with HAE. The trial randomized 32 subjects to one of three dosage regimens (75 mg Q4 weeks, 200 mg Q4 weeks, 600 mg Q4 weeks) and assigned an additional six subjects to open-label garadacimab 400 mg Q2 weeks and an additional six subjects with Type III HAE to open-label garadacimab 600 mg Q4 weeks. A total of eight subjects received the proposed dose of garadacimab 200 mg Q4 weeks. See Section [15.3.1](#) for details of the study design. Overall, the safety results from Treatment Period 1 of trial 2001 were consistent with those of trial 3001; no new risks were identified.

7.6.4. 120-Day Safety Update

The Applicant submitted a 120-day safety update for this BLA with a data cutoff of June 13, 2023, that consisted solely of data from study 3002, the only ongoing clinical investigation. Updated safety data from study 3002 included no deaths, one drug rash SAE due to dipyrone, and one treatment discontinuation due to an ISR. The ISR consisted of a large itchy wheal, starting within 24 h of garadacimab administration, that was mild in severity and resolved after 5 days. Commonly reported TEAEs were generally consistent with the safety profile observed to date. The safety update did not identify any new or concerning safety signals for garadacimab.

7.7. Key Safety Review Issues

7.7.1. Abnormal Coagulation Labs and Risk of Bleeding or Thromboembolism

Issue

Because of its mechanism of action, garadacimab has the potential to cause prolongation of coagulation parameters and result in bleeding or thromboembolic AEs.

Background

Garadacimab is a monoclonal antibody that inhibits the catalytic subunit of FXIIa. FXII is the first component of the intrinsic coagulation pathway and is typically activated on contact with substances that reflect tissue injury or damage, such as nucleic acids, heparin, collagen, and polyphosphates, to promote coagulation. Although inhibition of FXIIa might theoretically cause abnormal coagulation and a predisposition to bleeding, patients with genetic FXII deficiency demonstrate prolonged aPTT, but rarely exhibit a bleeding tendency. On the contrary, some literature suggests that FXII deficiency is associated with an increased risk of thrombosis; however, the data are inconclusive.

Assessment

Prolongations of aPTT were observed in nonclinical studies conducted in monkeys and rabbits, as well as in human subjects in the phase 1 and 2 clinical trials. In trial 3001 and OLE study 3002, the Applicant prospectively monitored coagulation parameters and bleeding or thromboembolic events as AESIs. Subjects with clinically significant bleeding due to coagulopathy or thrombotic disorders were excluded from enrollment, but subjects were allowed to receive anticoagulants (*i.e.*, Factor X inhibitor), antiplatelet medications, or tranexamic acid as concomitant medications during the trials.

Activated Partial Thromboplastin Time

The aPTT was obtained every 3 months during trial 3001 and study 3002. In trial 3001, 3 of 39 subjects in the garadacimab treatment group had aPTT prolongation (normal range 24.3 to 43.4), as shown in [Table 35](#). Two of the three subjects had a solitary occurrence of aPTT elevation that self-resolved without garadacimab dose modification or treatment discontinuation. None of the subjects experienced clinical manifestations of coagulation pathway abnormalities. Subject (b) (6) reported taking apixaban (Factor X inhibitor) for a history of bilateral pulmonary embolism. Otherwise, aPTT prolongations did not correspond to concomitant medication use.

Table 35. Listing of Subjects With Any Abnormal aPTT Measurement, Safety Population (Garadacimab 200 mg Group), Trial 3001

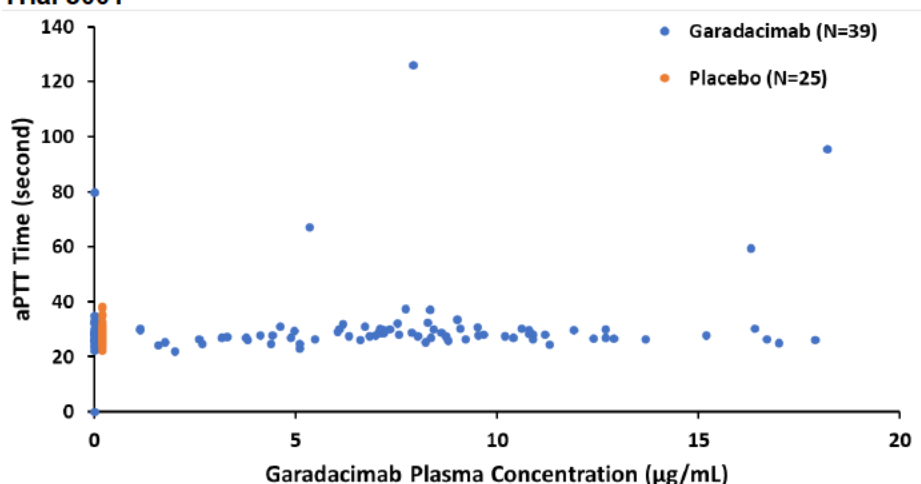
Subject ID	Study Day					
	Screening	Day 91	Day 182	Day 272	Day 362	Day 452
(b) (6)	37.5	59.4 H	95.5 H	88.7 H	114 H	
	28	29	67 H	30.6	27.9	29.9
	30.6	33.6	126 H	36.4	38.7	

Source: Clinical reviewer using ADLB.xpt files from trial 3001 and study 3002.
 Abbreviations: aPTT, activated partial thromboplastin time; H, high; ID, identity

Pooled PK Analysis by aPTT

Further analyses were conducted exploring the real-time relationship between garadacimab plasma concentrations and aPTT prolongation using data from subjects with HAE in trial 3001, which evaluated the proposed maintenance dose of 200 mg SC once monthly. The relationship between garadacimab plasma concentration and aPTT was generally flat in trial 3001 when subjects received the proposed maintenance dose of 200 mg SC once monthly (see [Figure 12](#)). Some data points fell above the general trend, and these represent subjects with prolonged aPTT. These subjects have been described above.

Figure 12. Real-Time Relationship Between aPTT and Garadacimab Plasma Concentrations, Trial 3001



Source: Reviewer's analysis using adpc.xpt and adlb.xpt datasets.
 Note that in trial 3001, only garadacimab trough concentrations were measured.
 Abbreviations: aPTT, activated partial thromboplastin time; HAE, hereditary angioedema

Prothrombin Time

As presented in [Table 36](#), there were a total of six subjects with prolonged prothrombin time (PT) $>1.3 \times$ ULN (normal range 9.8 to 12.1) in the garadacimab group (two of whom are mentioned above) and one subject in the placebo group (not shown). Most prolongations were singular events that resolved without garadacimab dose modification or treatment discontinuation. There was no clear correlation with other concomitant medications or other underlying conditions or risk factors. None of the subjects experienced clinical manifestations of bleeding diatheses or thromboemboli. Again, of note, subject (b) (6) reported taking apixaban (Factor X inhibitor), which may prolong PT.

Table 36. Listing of Subjects With Any Abnormal PT Measurement, Safety Population (Garadacimab 200 mg Group), Trial 3001

Subject ID	Study Day					
	Screening	Day 1	Day 91	Day 182	Day 272	Day 362
(b) (6)	12.1		11.1	19.4 H	11.8	11.8
	12.6 H	29.2 H	12.6 H	23.6 H	12.9 H	12.9 H
	9.8	11.4	10	17.2 H	9.8	11.5
	11.6	11.8	12	24 H	11.4	12.3 H
	20.2 H	11.4	11.6	22 H	11.7	12
	11	11.6	23.3 H	14.5 H	11.9	11.6

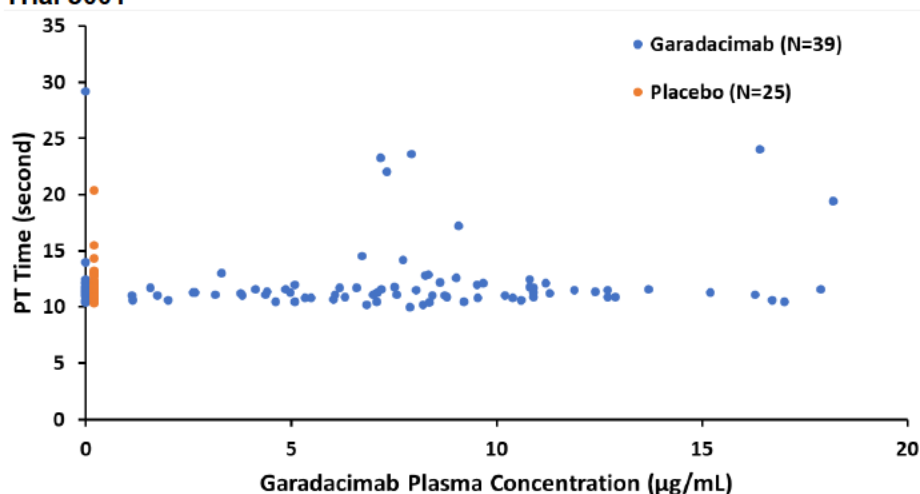
Source: Clinical reviewer using ADLB.xpt files from trial 3001 and study 3002.
 Abbreviations: H, high; ID, identity; PT, prothrombin time

The international normalized ratio (INR) is a calculation of the subject’s PT divided by the control PT. $INR = \frac{\text{Subject Prothrombin Time}}{\text{Control Prothrombin Time}}$. The review team also independently reviewed the INR values of the garadacimab and placebo groups in trial 3001. The same six subjects in [Table 36](#) also had $INR > 1.3 \times ULN$ with none exceeding an $INR > 2.2 \times ULN$.

Pooled PK Analysis by PT

The real-time relationship between garadacimab plasma concentrations and PT was explored. No apparent E-R relationship between plasma trough concentrations and PT was found (see [Figure 13](#)). Some data points fell above the general trend, and these represent subjects with prolonged PT. These subjects have been described above.

Figure 13. Real-Time Relationship Between PT and Garadacimab Plasma Concentrations, Trial 3001



Source: Reviewer’s analysis using adpc.xpt and adlb.xpt datasets.
 Note that in trial 3001, only garadacimab trough concentrations were measured.
 Abbreviations: HAE, hereditary angioedema; PT, prothrombin time

Bleeding and Thromboembolism Adverse Events

The review team analyzed AE datasets for TEAEs related to bleeding or thromboembolism by PTs, SMQs (hemorrhage, embolic and thrombotic events), and FMQs (hemorrhage, thrombosis). Across the garadacimab clinical development program, there were no deaths, serious or severe bleeding/thromboembolic AEs, or events leading to treatment discontinuation. In trial 3001, no

thromboembolic events occurred. The broad and narrow FMQs for hemorrhage identified two TEAEs in two subjects in the garadacimab treatment group ([Table 37](#)). Both cases self-resolved and are more accurately characterized as injury-induced bruising rather than representative of an increased risk for spontaneous hemorrhage or bleeding.

Similarly, in study 3002, there were no thromboembolic events reported. The most commonly reported bleeding related TEAE in study 3002 was contusion (bruising), reported in four subjects. The other bleeding related TEAEs, each reported by one subject, consisted of epistaxis, injection site bruising, injection site hematoma, intermenstrual bleeding, and vaginal bleeding. The female subjects who reported intermenstrual bleeding and vaginal bleeding were both <50 years of age. All bleeding related TEAEs were rated as mild in severity, associated with normal coagulation laboratory values, and did not result in treatment discontinuation.

In trial 2001, one subject who received garadacimab 600 mg Q4 weeks (with a 300 mg IV loading dose) experienced mild spontaneous epistaxis that self-resolved the same day. Treatment with garadacimab continued at the same dose with no further bleeding. There was a single TEAE of vessel puncture site thrombosis in the 200 mg Q4 week group that is unlikely related to study drug.

Lastly, the review team also examined concomitant use of anticoagulants, antiplatelet or blood-thinning medications and identified four subjects with concomitant medication use. One subject (ID (b) (6)), described above, was taking apixaban. Two subjects were on tranexamic acid (antiplasmin) and one subject was on ticagrelor (antiplatelet). None of the four subjects reported a bleeding event, and only the subject taking apixaban had abnormal coagulation laboratory markers.

Table 37. Listing of Subjects with Hemorrhage FMQ (Narrow), Safety Population (Garadacimab 200 mg Group), Trial 3001

Subject ID	Age/Sex HAE Type	MedDRA Preferred Term	Verbatim Term	Severity	Duration of Event	Coagulation Markers ¹ Normal	Treatment D/C	Related- ness	Reviewer's Assessment
(b) (6)	31/F Type I	Traumatic hematoma	Traumatic hematoma of left buttock	Mild	11 days	Yes	No	N	The subject had a mechanical fall while roller skating and developed a traumatic hematoma of the left buttock. The hematoma resolved after 11 days without medical intervention. Agree with the assessment that the event is unrelated to garadacimab treatment.
(b) (6)	50/F Type I	Injection site bruising	Bruising at injection site	Mild	3 days	Yes	No	Y	Agree with the assessment that the event is related to garadacimab treatment.

Source: Clinical reviewer generated using the trial 3001 Clinical Study Report, adsl.xpt dataset, and the Applicant's response to a Clinical Information Request.

¹ aPTT, PT/INR

Abbreviations: AESI, adverse event of special interest; aPTT, activated prothrombin time; F, female; HAE, hereditary angioedema; ID, identity; INR, international normalized ratio; MedDRA, Medical Dictionary for Regulatory Activities; N, no; PT, preferred term; Y, yes

Conclusion

The prolongations in aPTT and PT coagulation parameters associated with garadacimab treatment do not exhibit an E-R relationship and appear to be asymptomatic without an increased risk for bleeding or thromboembolic adverse reactions. No safety signal emerged for bleeding or thromboemboli irrespective of coagulation markers. Prolongation of coagulation markers without an increased bleeding risk has also been observed with other approved HAE therapies that target the intrinsic coagulation pathway. Therefore, this finding might be related to the mechanism of action of garadacimab and/or interaction between the drug and laboratory test. Information regarding asymptomatic aPTT/PT prolongation may be useful for healthcare providers and will be added to the draft PI.

7.7.2. Hypersensitivity Reactions

Issue

[REDACTED] (b) (4)
[REDACTED]. Does the garadacimab safety data warrant a Warnings and Precautions statement for hypersensitivity reactions?

Background

Hypersensitivity reactions are frequently associated with injectable products and the therapeutic class of monoclonal antibodies, regardless of the therapeutic target. As such, hypersensitivity reactions were prespecified as an AESI in trial 3001 and study 3002.

The Warnings and Precautions section is intended to include serious or clinically significant adverse reactions in which there is reasonable evidence of causal relationship between the drug and the AE. Considerations for evidence of causal relationship include frequency of reporting and whether the rate of the event was greater in drug compared to placebo.

Assessment

The review team analyzed the TEAEs in trial 3001 and study 3002 by PT, narrow and broad FMQ for hypersensitivity, and SMQ for hypersensitivity. No hypersensitivity TEAEs were reported with garadacimab treatment in trial 3001. In study 3002, only the FMQ (Broad) and the SMQ searches yielded TEAEs related to hypersensitivity; however, none of the PTs were specific or clinically relevant to an immediate hypersensitivity reaction (i.e., allergic rhinitis, eczema, pruritus).

Conclusion

Immediate hypersensitivity reactions would not be an unexpected safety signal; however, no events occurred in trial 3001 or study 3002. Per labeling policy, Warnings and Precautions are reserved for observed, rather than theoretical, risks except in the case of drug class labeling. Hypersensitivity is not considered class labeling for monoclonal antibodies. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]

7.7.3. Injection Site Reactions

Issue

ISRs are a common adverse reaction from SC injectable drug products and were observed during the garadacimab development program. The Applicant proposes to include ISRs (b) (4) in Section 6 of the PI.

Background

In the phase 2, dose-ranging trial 2001 (see Section 15.3), there was a dose-dependent increase in ISRs. ISRs occurred in one (11.1%), one (12.5%), and four (57.1%) subjects in the 75 mg, 200 mg, and 600 mg dose groups, respectively. Because of the relatively high proportion of ISRs in the 600 mg dose group, the Applicant carried forward the 200 mg dose for evaluation in phase 3.

Assessment

Analyses of AE datasets for trial 3001 and study 3002 by Local Administration Reaction FMQ (Narrow and Broad) are shown in Table 38 and Table 39. The narrow and broad search queries produced the same results. In trial 3001, there was no significant difference in ISRs between the garadacimab and placebo treatment groups during the placebo-controlled 6-month Treatment Period.

ISRs were reported by both treatment-naïve and rollover subjects in study 3002, with a higher frequency in the rollover subjects. Most of the ISRs for the garadacimab-naïve subjects were reported within the first 6 months of starting garadacimab. One subject in the garadacimab-naïve treatment group discontinued treatment due to ISR (Section 7.6.2.7).

Table 38. Subjects With Injection Site Reaction FMQ (Narrow), Safety Population, Trial 3001

FMQ (Narrow) Preferred Term	Garadacimab		Risk Difference % (95% CI)
	200 mg	Placebo	
	N=39 n (%)	N=25 n (%)	
Local administration reaction	2 (5.1)	2 (8.0)	-2.9 (-20.7, 10.5)
Injection site bruising	1 (2.6)	0	2.56 (-2.4, 7.5)
Injection site erythema	1 (2.6)	2 (8.0)	-5.44 (-17.2, 6.3)

Source: adae.xpt; software: R.

Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA Medical Query; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term

Table 39. Subjects With Injection Site Reaction FMQ (Narrow), Safety Population, Study 3002

FMQ (Narrow) Preferred Term	Garadacimab Naïve	Rollover	Total
	N=90 n (%)	N=71 n (%)	N=161 n (%)
Local administration reaction (FMQ)	14 (16)	2 (3)	16 (10)
Injection site bruising	1 (1)	0	1 (1)
Injection site erythema	10 (11)	1 (1)	11 (6)
Injection site hematoma	0 (0)	1	1 (1)
Injection site pruritus	4 (4)	0	4 (2)
Injection site urticaria	2(2)	0	2 (1)

Source: Clinical Reviewer generated using the study 3002 adae.xpt dataset in Analysis Studio, Safety Explorer.

Abbreviation: FMQ, FDA Medical Query

Conclusion

Local ISRs occurred more frequently with placebo in trial 3001, and therefore will not be listed as an adverse drug reaction from this trial. However, given the higher frequency of ISRs reported in study 3002 and the high likelihood that these events are treatment-related adverse drug reactions, information regarding the ISRs observed in study 3002 will be included in the draft PI.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Based on population PK analyses, intrinsic factors including age (12 to 73 years), [REDACTED], and race were not found to meaningfully influence the PK of garadacimab after body weight was introduced as a covariate. No dedicated studies have been conducted to evaluate the impact of renal impairment or hepatic impairment on the PK of garadacimab. Per the population PK analysis, renal impairment categories (estimated glomerular filtration rate ≥ 90 mL/min/1.73 m² [normal, N=145]; 60 to <90 mL/min/1.73 m² [mild, N=26]; and 30 to <60 mL/min/1.73 m² [moderate, N=2]) did not impact the PK of garadacimab. In addition, bilirubin (4 to 13 μ mol/L; 10th and 90th percentiles, respectively, in the observed dataset) did not have a large impact on garadacimab clearance.

For additional details on population PK analyses, refer to Section [14.5](#).

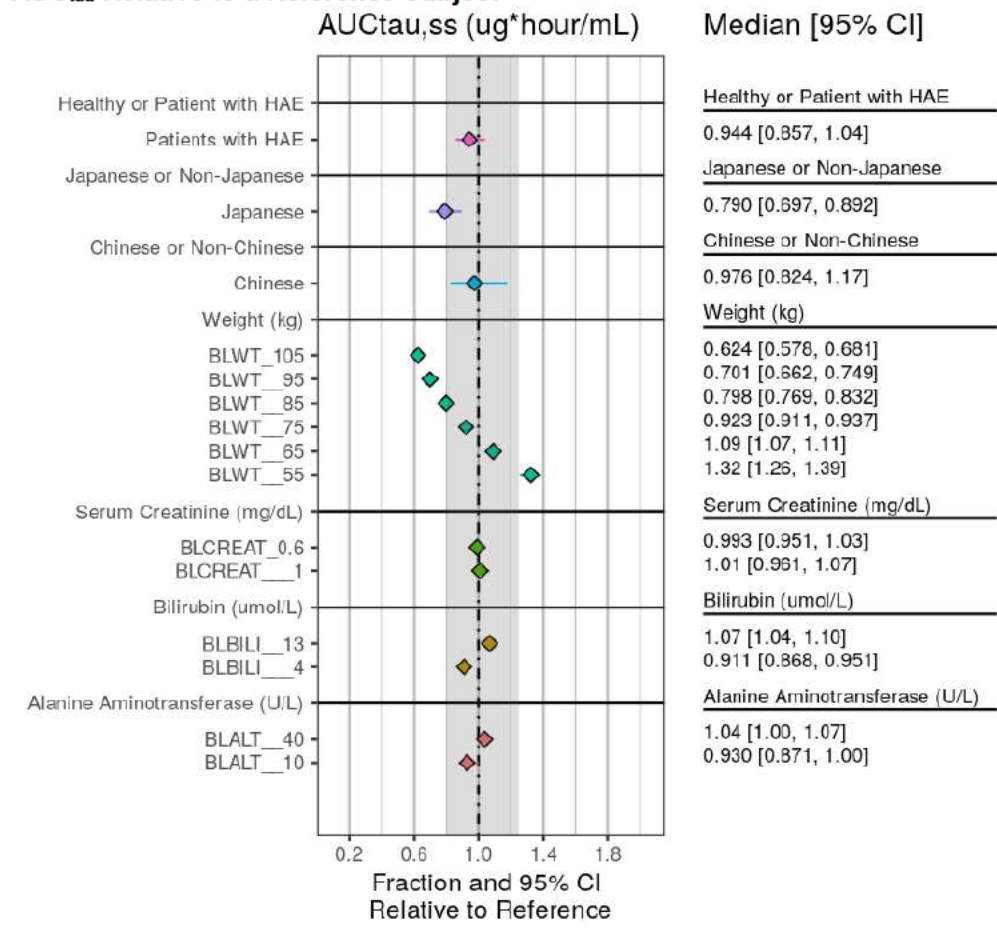
8.1.1. Body Weight

Overall, no dosage adjustments are recommended based on body weight.

In population PK analysis, body weight was identified as a significant covariate impacting the clearance and volume of distribution of garadacimab. In general, garadacimab exposure is higher in subjects with lower body weight. The impact of various covariates, including body weight, on garadacimab AUC_{tau,ss} is shown in [Figure 14](#). The median AUC_{tau,ss} in a subject weighing 105 kg or weighing 55 kg is predicted to be about 38% lower or 32% higher, respectively, relative to the reference AUC_{tau,ss} of a typical patient weighing 70 kg. Although differences in exposure are predicted based on body weight, no clear trend in monthly HAE attack rate by baseline weight quartile was observed in trial 3001 ([Figure 15](#)).

These observations are supported by results from trial 2001, which evaluated various garadacimab dosing regimens ranging from 75 mg every Q4W to 600 mg SC Q4W over a 13-week double-blind Treatment Period. A reduction relative to placebo in the mean time-normalized number of HAE attacks per month was observed for all dosages evaluated with no apparent dose-response relationship observed from 75 mg to 600 mg. As the observed monthly HAE attack rate in the 200 mg group was numerically the lowest across all treatment groups, the 200-mg dose was carried over to the phase 3 trial 3001. For additional details, refer to Section [14.2.4](#).

Figure 14. Univariate Forest Plot Illustrating Covariate Effects on Garadacimab Steady-State AUC_{τ} Relative to a Reference Subject

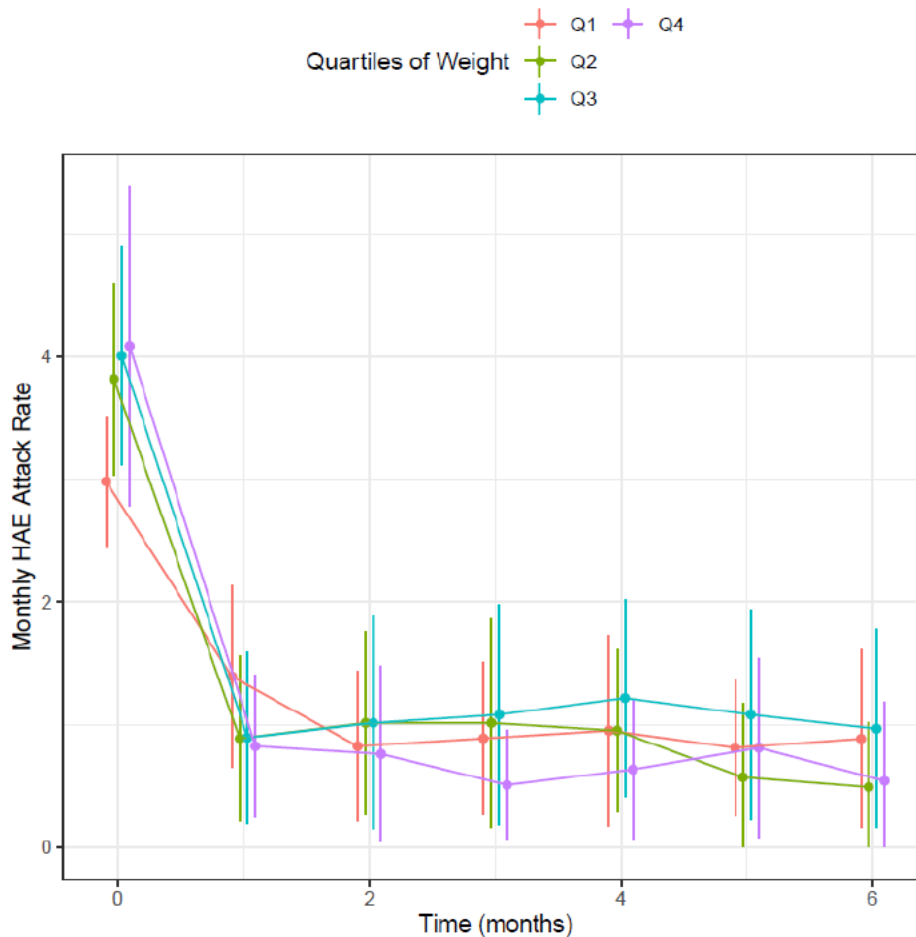


Source: Figure S82, Population PK/PD Report.

Covariates in the model were visualized by varying single covariates individually while keeping all other conditions constant. Results are presented relative to a reference subject, i.e., a non-Japanese, non-Chinese, healthy volunteer with baseline body weight of 70 kg, baseline serum creatinine of 0.75 mg/dL, baseline ALT of 25 U/L, and baseline bilirubin of 8 μmol/L. Colored diamonds represent the median and the solid horizontal lines represent the 95% confidence interval. The gray shaded reference range of 80 to 125% was analogous to the region of practical equivalence. For continuous covariates, the upper and lower values used in the simulations were determined based on the 10th and 90th percentiles in the observed dataset.

Abbreviations: $AUC_{\tau,ss}$, area under the plasma concentration-time curve over one dosing interval at steady state; BLALT, baseline alanine aminotransferase; BLBILI, baseline bilirubin; BLCREAT, baseline serum creatinine; BLWT, baseline body weight; CI, confidence interval; HAE, hereditary angioedema; PD, pharmacodynamics; PK, pharmacokinetics

Figure 15. Monthly HAE Attack Rate Over Time by Baseline Weight Quartile, Trial 3001

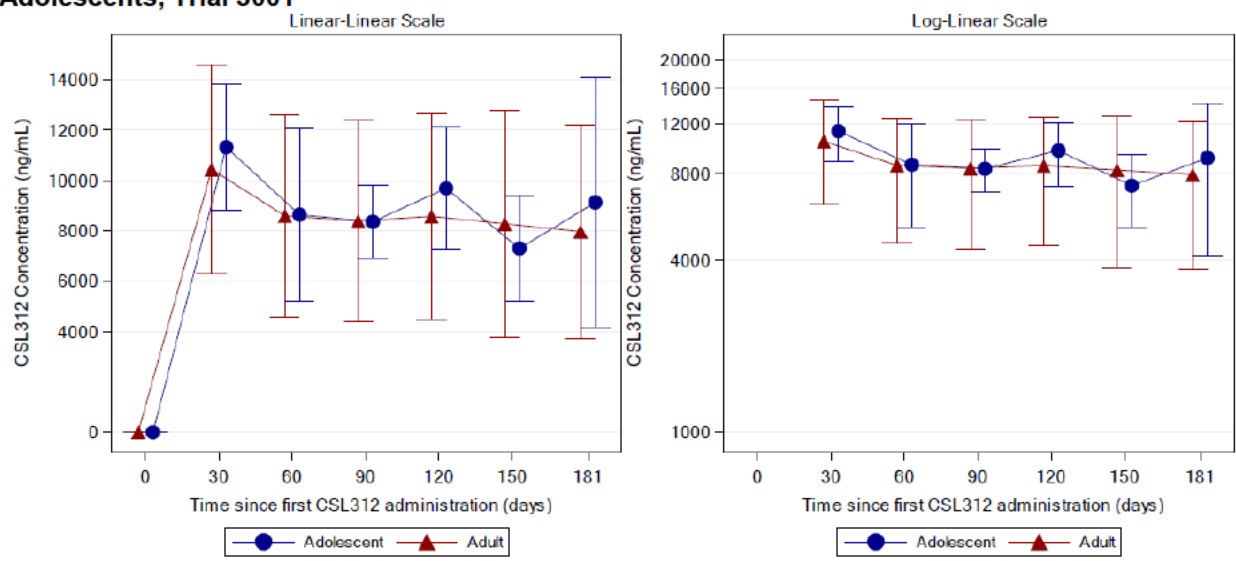


Source: Figure S31, Exposure-Response Report.
Solid circles represent the mean monthly HAE attack rate. Vertical bars represent the 95% confidence interval of the mean monthly HAE attack rate. Colors represent different covariate levels.
Abbreviation: HAE, hereditary angioedema; Q, quartile

The proposed population for garadacimab includes adolescent subjects with HAE aged 12 years and older. Adolescent subjects with HAE were enrolled in trial 3001 (N=6) and study 3002 (N=10, including 5 rollover subjects from trial 3001). In both studies, the median body weight among adolescents receiving garadacimab was lower than the overall median body weight among all subjects receiving garadacimab (trial 3001: 60.3 kg and 78.0 kg for adolescents and overall, respectively; study 3002: 55.7 kg and 78.3 kg for adolescents and overall, respectively).

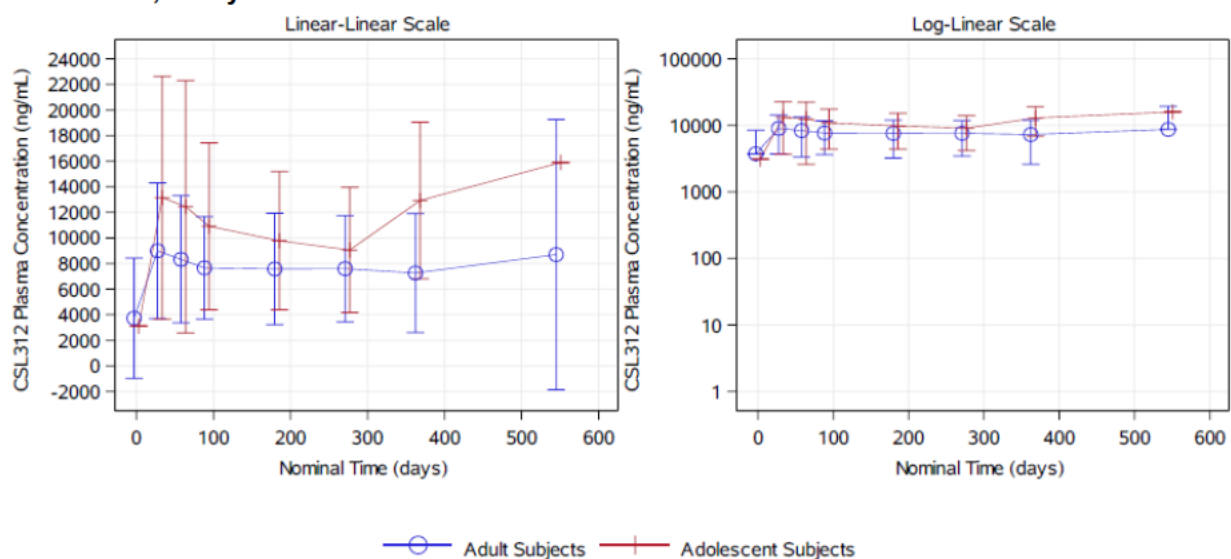
Despite the lower body weight in adolescents relative to the overall population enrolled in trial 3001, there was no apparent difference in the observed garadacimab trough concentrations throughout the Treatment Period (Figure 16). In study 3002, garadacimab trough concentrations were 1.2 to 1.8-fold greater in adolescents relative to adults from Month 3 through Month 12 (Figure 17). Note that only three adolescent subjects provided data at Month 12, the time point that showed 1.8-fold greater exposure among adolescents. Data at Month 12 should be interpreted with caution.

Figure 16. Mean (SD) Garadacimab Trough Concentration-Time Profiles in Adults and Adolescents, Trial 3001



Source: Figure 14.2.5.2.3, Clinical Study Report for trial 3001.
 Abbreviations: CSL312, garadacimab; SD, standard deviation

Figure 17. Mean (SD) Garadacimab Trough Concentration-Time Profiles in Adults and Adolescents, Study 3002



Source: Figure 14.2.5.2.3, Clinical Study Report for study 3002.
 Abbreviations: CSL312, garadacimab; SD, standard deviation

In study 3002, peak plasma concentrations at steady state in adolescents were achieved at 3 to 7 days postdose, with mean (SD) concentrations of 21.9 (15.4) $\mu\text{g/mL}$ on Day 3 and 21.7 (11.5) $\mu\text{g/mL}$ on Day 7. These values are approximately 1.4-fold greater than the observed steady state C_{max} following 200 mg SC Q4W from adults in trial 2001 (mean [SD] C_{max} =15.9 [5.2] $\mu\text{g/mL}$), and 2.6-fold lower than the observed steady state C_{max} following 600 mg SC Q4W from adults in trial 2001 (mean [SD] C_{max} =56.4 [15.9] $\mu\text{g/mL}$).

Population PK simulations following the proposed dosage (i.e., 400 mg SC loading dose, then 200 mg SC Q4W) in adults and adolescents predict 1.33-fold greater C_{max} at steady state and 1.36-fold greater $AUC_{tau,ss}$ in adolescents relative to adults (mean [SD] adolescent [N=10,000] C_{max} at steady state and $AUC_{tau,ss}=27.3$ [14.4] $\mu\text{g/mL}$ and 13,700 [6670] $\mu\text{g}\cdot\text{h/mL}$, respectively; mean [SD] adult [N=10,000] C_{max} at steady state and $AUC_{tau,ss}=20.5$ [10.0] $\mu\text{g/mL}$ and 10100 [4400] $\mu\text{g}\cdot\text{h/mL}$, respectively) (data derived from Table SYN6, Population PK/Pharmacodynamic Report).

For additional details on garadacimab PK in adolescents in trial 3001 and study 3002, refer to Sections [14.2.5](#) and [14.2.6](#). For additional details on population PK, refer to Section [14.5](#).

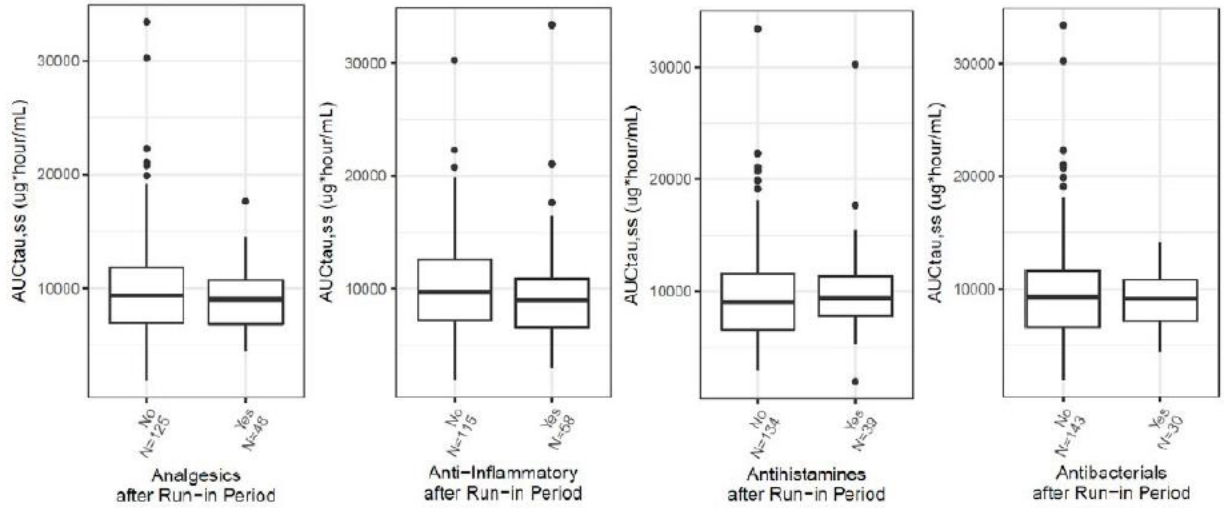
8.1.2. Type III (FXII/PLG mutation) HAE

Refer to Section [6.3.2](#).

8.2. Extrinsic Factors

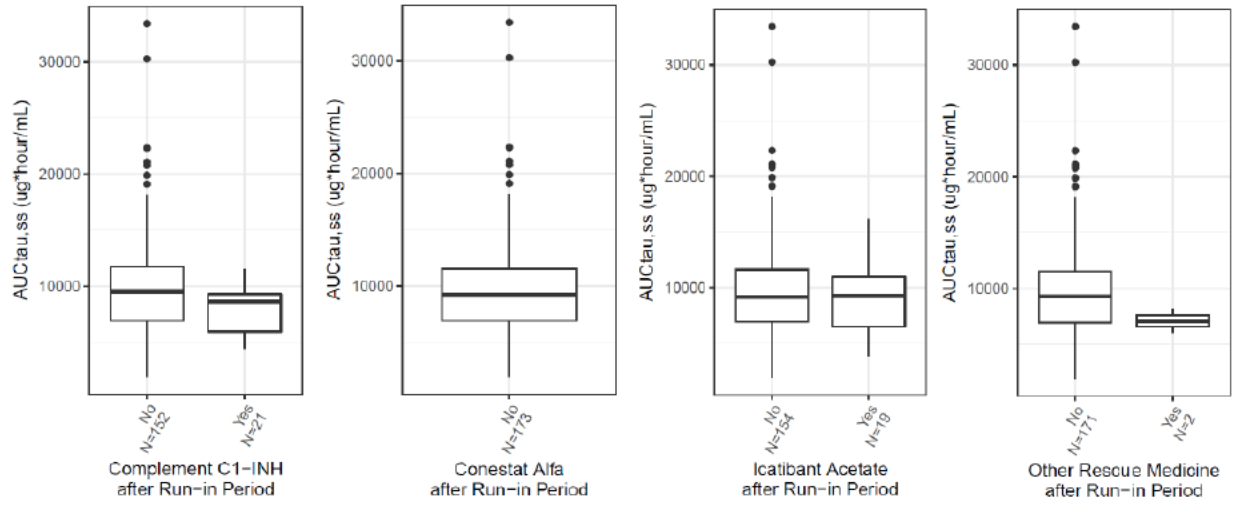
Dedicated drug-drug interaction studies with garadacimab have not been conducted. As garadacimab is a monoclonal antibody, direct drug-drug interactions via inhibition or induction of cytochrome P450 enzymes or transporters are not expected. The Applicant conducted a population PK analysis to evaluate whether use of concomitant medications had an impact on garadacimab steady-state exposure. The $AUC_{tau,ss}$ of garadacimab was similar regardless of whether subjects used analgesics, anti-inflammatory medications, antihistamines, or antibacterials ([Figure 18](#)). Simulated garadacimab exposure was also evaluated depending on whether subjects used rescue medications for treatment of HAE attacks. Similar garadacimab $AUC_{tau,ss}$ was observed regardless of whether complement C1-INH or icatibant acetate was used ([Figure 19](#)). Note that [Figure 19](#) also includes box plots for conestat alfa and a category of “Other Rescue Medicine.” No subjects used conestat alfa while two subjects were categorized as using other rescue medications. Thus, their impact on steady state garadacimab exposure could not be evaluated.

Figure 18. Simulated Garadacimab Exposure by Concomitant Medication Use in Subjects With HAE Using Empirical Bayes Estimates



Source: Figure 22, Summary of Clinical Pharmacology.
 The box represents the IQR, the horizontal line within the box represents the median, the whiskers represent 1.5x IQR, and the circles represent individual data outside of 1.5x IQR.
 Abbreviations: AUC_{tau,ss}, area under the concentration-time curve over one dosing interval at steady state; HAE, hereditary angioedema; IQR, interquartile range

Figure 19. Simulated Garadacimab Exposure by Rescue Medication Use in Subjects With HAE Using Empirical Bayes Estimates



Source: Figure 23, Summary of Clinical Pharmacology.
 Box represents the IQR, the horizontal line within the box represents the median, the whiskers represent 1.5x IQR, and the circles represent individual data outside of 1.5x IQR.
 Abbreviations: AUC_{tau,ss}, area under the concentration-time curve over one dosing interval at steady state; C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema; IQR, interquartile range

For additional details on the population PK analysis, refer to Section [14.5](#).

8.3. Plans for Pediatric Drug Development

Garadacimab was granted Orphan Drug Designation in April 2020 for bradykinin-mediated angioedema (which includes hereditary angioedema) and is therefore exempt from Pediatric Research Equity Act study requirements.

(b) (4)

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

The potential reproductive toxicity of garadacimab was evaluated in fertility and early embryonic development studies with male and female rabbits, an embryofetal development study with female rabbits, and a pre- and postnatal development study with female rabbits. Rabbits were determined to be a pharmacologically relevant species.

Fertility and Developmental Toxicology

In the male fertility and early embryonic development study, male rabbits were treated with garadacimab (IV doses of 10, 30, or 100 mg/kg q3 days) for 4 weeks prior to mating, during the mating period, and continuing to Postpairing Day 8. Females were not dosed and assigned to each group for mating purposes only. There were no treatment-related effects on mating and

fertility parameters, reproductive indices, or sperm assessments. The no observed adverse effect level (NOAEL) for this study was the HD of 100 mg/kg/dose based on a lack of findings.

In the female fertility and early embryonic development study, female rabbits were treated with garadacimab (IV doses of 10, 30, or 100 mg/kg q3 days) for 2 weeks prior to mating, during the mating period, and continuing to Gestation Day 8. Males were not dosed and were assigned to each group for mating purposes only. No garadacimab-related effects on maternal reproductive parameters or embryo survival were observed. The NOAEL for female fertility and embryo survival was the HD, 100 mg/kg/dose.

Embryo-Fetal Development

In the embryo-fetal development study, pregnant rabbits were administered IV doses of 10, 30, and 100 mg/kg q3 days on Gestation Days 6, 9, 12, 15 and 18. Necropsies were conducted on Gestation Day 29. There was no effect on treated females observed related to garadacimab treatment. There were no treatment-related external, visceral, or skeletal major or minor abnormalities. The NOAEL for maternal and fetal toxicity was concluded to be 100 mg/kg/occasion (HD).

Prenatal and Postnatal Development

In the rabbit pre-and postnatal development study, pregnant rabbits (F0) were treated with garadacimab from Gestation Day 7 through Lactation Day 38. SC doses of 0, 10 (low dose), 30 (mid dose), and 100 (HD) mg/kg/dose and an IV dose of 100 (HD) mg/kg were administered once every 5 days on Gestation Day 7, 12, 17, 22, and 27 and Lactation Days 3, 8, 13, 18, 23, 28, 33, and 38. The F1 generation was not directly administered the test article. Prolongation of aPTT values and toxicokinetic indicated that drug exposure was continuous during the gestation and lactation periods in F0 maternal animals.

On Gestation Day 29, fetal parturition plasma garadacimab concentrations were 76.6%, 136.6%, and 40.8% of the maternal concentrations, at SC low dose, SC mid dose, and SC HD, respectively. At IV HD, maternal and fetal concentrations were approximately equivalent. Garadacimab was able to cross the placenta.

For F0 dams, no garadacimab-related effects were observed on mortality, clinical signs, body weight, natural delivery, litter data, or maternal macroscopic observations. The maternal NOAEL was 100 mg/kg/dose (HD) SC/IV.

For the F1 generation, no garadacimab-related effects were observed on mortality, clinical signs, body weight, developmental signs, functional observation battery, eye-blink response, presence of motile sperm, reproductive performance, cesarean section parameters, or preweaning or postweaning macroscopic observations. In the F1 generation, the NOAEL for fetal development was 100 mg/kg/dose (HD) SC/IV. The NOAEL for developmental, neurobehavioral, and reproductive performance in the F1 generation was 100 mg/kg/dose (HD) SC/IV.

Prolongation of aPTT was observed in all four studies with F₀ male and female rabbits, but not associated with any bleeding events. aPTT was not measured in F₁ rabbits in the pre-and postnatal development study.

9. Product Quality

Complete Response With Quality Issues

Although the Office of Pharmaceutical Quality review team has assessed BLA 761367 with respect to drug substance and immunogenicity assay and has determined that it meets all of those applicable standards to support the identity, strength, quality, and purity that it purports, the facility, microbiology and DP disciplines have unresolved quality issues. The DP facility (CSL Behring GmbH, Marburg, Germany, FEI 3003098680) recommendation is Withhold. The DP process design is inadequate to minimize potential contamination of the sterile DP, and the DP process control and process validation data are insufficient to ensure product quality consistency and process performance consistency. Therefore, from an Office of Pharmaceutical Quality perspective, this BLA is not deemed ready for approval in its present form until the above-mentioned issues are satisfactorily resolved. As such, Office of Pharmaceutical Quality recommends a complete response action from facility, microbiology, and product quality perspectives.

9.1. Device or Combination Product Considerations

The Applicant proposed two to-be-marketed DP presentations for SC administration: 1) a 200 mg/1.2 mL prefilled syringe with needle safety device (PFS-NSD) and a 200 mg/1.2 mL autoinjector (AI). The Division of Drug Delivery, General Hospital & Human Factors in the Center for Devices and Radiological Health reviewed the device descriptions, labeling, design controls, risk analysis, and design verification of the AI and PFS-NSD devices, and determined that both the PFS-NSD and the AI devices are approvable. The essential performance requirements including design specifications, verification method, validation, biocompatibility and stability were found to be acceptable for both the PFS-NSD and the AI (for full details see the Center for Devices and Radiological Health review submitted on May 28, 2024 and August 21, 2024).

In the pivotal trial 3001, only the PFS-NSD presentation was used; however, the AI presentation was administered in the OLE study 3002. The Applicant conducted a phase 1, relative bioavailability bridging study 1004, to compare the PK of garadacimab following a single SC injection as the PFS-NSD or the AI; the results are presented in Section [14.2](#).

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

Human Subjects Protections

As stated by the Applicant, the clinical trials were conducted in compliance with Good Clinical Practice, as required by the ICH guidance for industry *E6 Good Clinical Practice* ([November 2016](#)). The clinical studies also met the requirements of the Declaration of Helsinki and, where

applicable, national laws and regulations regarding ethical committee review, informed consent, and protection of human subjects participating in biomedical research. All studies submitted in this application were conducted in accordance with FDA requirements under IND 139936.

Clinical Site Inspections

FDA clinical site inspections were performed at two sites in the United States for trial 3001 and study 3002. Refer to Section [22](#) for details.

Financial Disclosure

The Applicant adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry, Financial Disclosure by Clinical Investigators ([February 2013](#)) and by 21 Code of Federal Regulations 54.4. None of the investigators in the clinical studies were employed by the Applicant. Three clinical investigators disclosed financial interests and arrangements with the Applicant (see Section [25](#)). To minimize bias, an independent data monitoring committee was established to monitor the safety and efficacy data generated from the clinical trials. Additionally, the small number of subjects who participated at each site also minimized the potential for bias.

In conclusion, the likelihood that trial results were biased on financial interests is minimal and should not affect the approvability of the application.

11. Advisory Committee Summary

An advisory committee was not held for this application. The application did not raise challenging efficacy or safety issues that required external input.

III. Additional Analyses and Information

12. Summary of Regulatory History

2018, July 14	IND 139936 considered safe to proceed
2020, April 30	Orphan Drug designation granted for the treatment of bradykinin-mediated angioedema
2020, July 7	End of phase 2 meeting, key discussion points: - The FDA recommended increasing the sample size and extending the placebo controlled treatment period (b) (4) to 6 months to ensure adequate safety assessment - Agreement with primary efficacy endpoint
2021, February 10	Type C meeting, key points: - Recommendations provided on the design of the PK study to bridge PFS and AI presentations - Feedback on establishing the commercial shelf life for the final drug product and device content requirements to support the BLA
2021, December 14	Fast Track Designation granted
2023, March 10	(b) (4)
2023, January 10	Type C meeting, key points: - Feedback on the Essential Performance Requirements (EPRs), the control strategy implemented, and the release processes for the combination products used in the clinical development program. - Agreement with the Sponsor's proposal to conduct functionality performance test based on the device EPRs during the final combination product lot release and the functionality performance testing plan for the combination product. - Disagreement with the Sponsor's proposal to (b) (4) of all excipients

	(polysorbate 80, L-histidine, L-proline, and (b) (4) arginine) from (b) (4) drug quality release and recommended the Sponsor to control (b) (4) at release and stability to ensure the product quality
2023, March 17	Pre-BLA meeting preliminary responses issued (meeting canceled): • Agreement with Sponsor’s proposal to submit the 36-month stability data during the BLA review cycle. • Agreement with proposal for the 4-month safety update and safety database to support filing of the BLA. • The content of the nonclinical package appeared acceptable. • Regarding the proposed indication, the Division noted that Type III HAE is rare and has unmet need with no approved therapies; however, the pivotal trial only evaluated patients with Types I and II HAE. • Feedback provided regarding the submission of the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS), and the immunogenicity data.
2023, June 29	Initial BLA submitted
2023, August 28	Refuse-to-File letter issued because of unavailability of the results of the Rabbit Pyrogen Test conducted on three batches of garadacimab drug at the time of the BLA submission or at the time of filing
2023, September 27	Type A meeting preliminary responses issued (meeting canceled): • Agreement that submission of the results of the Rabbit Pyrogen Test conducted on three batches of garadacimab drug product would address the issue identified in the Refuse-to-File letter. • The FDA advised the Sponsor to include an updated manufacturing schedule in the BLA resubmission to facilitate the planning of pre-license inspections and that manufacturing facilities should be in operation and manufacturing the product under review during the inspections.

13. Pharmacology Toxicology

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

13.1.1. Pharmacology (Primary and Secondary)

The nonclinical pharmacology studies were originally reviewed under the IND. Summaries are provided here.

Primary Pharmacology

In vitro

Garadacimab is a fully humanized, affinity matured monoclonal antibody that was developed to bind specifically to activated FXII (FXIIa) and render it inactivated, thereby arresting kallikrein-kinin system activation and contact-mediated thrombosis without affecting hemostasis. Using an amino acid mutagenesis approach, it was shown that garadacimab binds to the catalytic site of FXIIa.

Effects of garadacimab on Factor XII (FXII) activity were evaluated in human, cynomolgus monkey, mouse and rabbit plasma blood samples ([Table 40](#), [Table 41](#), [Table 42](#), and [Table 43](#)). Inhibition of FXII activity was similar in human and monkey. In contrast, inhibition of FXII activity was lower in mouse and rabbit. Inhibition of FXII with garadacimab was observed in all nonhuman species tested. The affinity matured aFXII antagonist, garadacimab, has high affinity to human β FXIIa (140pM) and is cross-reactive with mouse, rabbit, and cynomolgus β FXIIa (700pM, 400pM and 19nM, respectively).

Table 40. Binding Affinities of Anti-FXII Antibodies 3F7 and Garadacimab to Human FXII and Human β FXIIa

Antibody	Antigen	k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (nM)	Report	Lab book
CSL312	Human FXII	1.0×10^6	5.7×10^{-2}	55	6-410	5532
CSL312	Human β FXIIa	6.0×10^5	8.5×10^{-5}	0.14	5-410	5532
3F7	Human FXII	8.2×10^3	4.6×10^{-5}	56	36-270	4505
3F7	Human β FXIIa	3.2×10^5	1.0×10^{-3}	3	26-270	4351

Source: Excerpted from the Applicant's submission.

Abbreviations: k_a , absorption rate constant; k_d , dissociation constant; K_D , equilibrium dissociation constant

Table 41. Binding Affinities of Anti-FXII Antibodies 3F7 and Garadacimab to Mouse FXII Proteins

Antibody	Antigen	k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (nM)	Report	Lab book
CSL312	Mouse FXII	-	-	800 [†]	19-410	5669
CSL312	Mouse FXIIa	5.8×10^5	2.0×10^{-4}	0.3	18-410	5669
CSL312	Mouse β FXIIa	4.5×10^5	3.2×10^{-4}	0.7	18-410 19-410	5669
3F7	Mouse FXII	-	-	6132 [†]	19-410	5669
3F7	Mouse FXIIa	6.1×10^5	2.1×10^{-3}	3.5	18-410 19-410	5669
3F7	Mouse β FXIIa	5.8×10^5	3.6×10^{-3}	6	18-410 19-410	5669

[†] Value obtained from steady-state analysis included for reference.

Source: Excerpted from the Applicant's submission.

Abbreviations: k_a , absorption rate constant; k_d , dissociation constant; K_D , equilibrium dissociation constant

Table 42. Binding Affinities of Anti-FXII Antibodies 3F7 and Garadacimab to Rabbit FXII Proteins

Antibody	Antigen	k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (nM)	Report	Lab book
CSL312	Rabbit FXII	2.1×10^5	6.9×10^{-5}	0.3	14-410	5483
CSL312	Rabbit FXIIa	6.0×10^5	4.4×10^{-5}	0.1	14-410	5483
CSL312	Rabbit β FXIIa	1.8×10^5	8.1×10^{-5}	0.4	22-410	6393
3F7	Rabbit FXII	3.6×10^5	2.0×10^{-3}	5.6	14-410	5483
3F7	Rabbit FXIIa	6.9×10^5	2.3×10^{-3}	3.4	14-410	5483
3F7	Rabbit β FXIIa	6.5×10^5	4.2×10^{-3}	6.6	22-410	6393

Source: Excerpted from the Applicant's submission.

Abbreviations: k_a , absorption rate constant; k_d , dissociation constant; K_D , equilibrium dissociation constant

Table 43. Binding Affinities of Anti-FXII Antibodies 3F7 and Garadacimab to Cynomolgus Monkey FXII Proteins

Antibody	Antigen	k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (nM)	Report	Lab book
CSL312	Cyno FXII	3.4×10^4	4.7×10^{-3}	143	7-410	5483
CSL312	Cyno β FXIIa	8.2×10^5	1.5×10^{-2}	19	7-410	5483

Source: Excerpted from the Applicant's submission.

Abbreviations: k_a , absorption rate constant; k_d , dissociation constant; K_D , equilibrium dissociation constant

Using dextran sulfate activated plasma, garadacimab inhibited FXII activity, resulting in lowered production of bradykinin.

Garadacimab was shown to only antagonize FXIIa enzymatic activities, displaying 100% inhibition of FXIIa catalytic activity for both the α and β fragments; this means that zymogen FXII functions were negligibly impacted. In an in vitro chromogenic assay, garadacimab inhibited the enzymatic activity of human plasma-derived FXIIa and β FXIIa at equivalent levels (half-maximal inhibitory concentration $\sim$ 15nM). Garadacimab produced a prolongation of activated partial thromboplastin time (aPTT) clotting times in standard human plasma.

Garadacimab was evaluated for its ability to inhibit FXII activity in blood samples collected from subjects with hereditary angioedema (HAE). Plasma FXII concentrations and activities were analyzed in HAE Type I, II, III, and acquired angioedema samples. Elevated FXII activities were observed in HAE Type I and III samples compared to control samples. No differences in FXII activities were observed with HAE Type II or acquired angioedema samples. Garadacimab inhibited FXIIa activity following activation of plasma samples from normal, HAE Types I, II, III, and C1-esterase inhibitor (C1-INH)-AAE donors with dextran sulfate. Dextran sulfate activates plasma via initial contact activation of FXII and models initiation of an HAE attack, leading to bradykinin-mediated swelling. Garadacimab dose-dependently inhibited FXIIa chromogenic activity, with maximal FXIIa inhibition observed at 10 μ g/mL for all normal and patient plasma samples examined.

In Vivo

In an angiotensin converting enzyme inhibitor (captopril)-induced edema murine model (heterozygous C1-INH-deficient (C1INH+/-) mice treated with 2.5 mg/kg captopril), garadacimab significantly inhibited the angiotensin-converting enzyme inhibitor-induced increase of vascular permeability. Complete ablation of vascular leakage was observed at garadacimab doses of $\geq$ 0.5 mg/kg.

In a murine passive cutaneous anaphylaxis model, FXII-dependent IgE-mediated activation of mast cells has been shown to increase vascular permeability by heparin-initiated bradykinin formation. In this model, garadacimab significantly inhibited FXIIa-mediated bradykinin formation.

Recommendation for Designation of the Established Pharmacological Classification

The recommended established pharmacologic class for garadacimab is “FXIIa inhibitor” (monoclonal antibody). Garadacimab is a fully humanized, affinity matured monoclonal antibody that was developed to bind specifically to FXIIa and renders it inactivated, thereby arresting kallikrein-kinin system activation and contact-mediated thrombosis without affecting hemostasis. Using an amino acid mutagenesis approach, it was shown that garadacimab binds to the catalytic site of FXIIa. It acts at a different point in coagulation cascade than the other drugs approved for the treatment of HAE.

Ecallantide, lanadelumab, and Berotralstat are listed in the FDA established pharmacologic class Text Phrasing as plasma kallikrein inhibitors. These drugs bind to plasma kallikrein and inhibit its proteolytic activity. Plasma kallikrein is a protease that cleaves high-molecular-weight kininogen to generate cleaved high-molecular-weight kininogen and bradykinin.

13.1.2. Safety Pharmacology

Safety pharmacology parameters were incorporated into the pivotal repeat-dose 26-week monkey toxicology study. With intravenous (IV) doses up to 100 mg/kg/week and subcutaneous (SC) doses up to 200 mg/kg/week, no treatment-related effects on electrocardiogram, blood pressure, respiration rate, or pulse rate were observed during the 26-week Treatment Period.

In a mouse study evaluating respiratory parameters, garadacimab at IV doses of 3, 10, 30 and 100 mg/kg or SC doses of 60 and 200 mg/kg produced no statistically significant or biologically relevant effects on respiratory rate, tidal volume, or minute volume at any postdose time point. The no observed adverse effect levels (NOAELs) were identified as 100 mg/kg (IV) and 200 mg/kg (SC).

13.1.3. Absorption, Distribution, Metabolism, Excretion/Pharmacokinetics

A single-dose pharmacokinetic (PK) study using the IV and SC routes was conducted in cynomolgus monkeys. The SC bioavailability of garadacimab (6 mg/kg) was ~66% in monkeys. Mean estimated $t_{1/2}$ values for garadacimab in the single-dose PK study with monkeys ranged from 147 to 581 h (IV) and 206 to 424 h (SC).

13.1.4. Toxicology

13.1.4.1. General Toxicology

Repeat-Dose Toxicity

The Applicant characterized the toxicity profile of garadacimab by conducting 4-week mouse and 26-week monkey toxicology studies with garadacimab using the IV and SC routes. Immunogenicity in mice precluded conducting longer toxicology studies in this species.

CSL312: Repeat-Dose Toxicity Study by Intravenous and Subcutaneous Administration to CD-1 Mice for 4 Weeks Followed by an 8-Week Recovery Period (Study # (b) (4))

Key Study Findings

- In a 4-week toxicity and toxicokinetic (TK) study, CD-1 mice (12/sex/group) received garadacimab at IV doses of 0, 3, 10, 30, and 100 mg/kg and SC doses of 0, 60, and 200 mg/kg (SC).
- There were 23 unscheduled deaths during the study (16 males and 7 females). The deaths of one HD IV male, one low dose (LD) SC male, and two LD SC females were considered to be due to the blood sampling procedure. The deaths and/or premature euthanasia of the remaining animals, primarily in the LD IV group, were attributed to immunogenicity based upon observed adverse clinical signs, although there were no histopathological findings.

- Significant prolongations of the aPTT were observed for males (up to 127%) and females (up to 123%) in all garadacimab treatment groups (IV and SC) relative to control animals at the end of the 4-week Treatment Period.
- The target organs of toxicity were identified as the lymph nodes (axillary and inguinal) and SC injection sites. An increase in incidence and severity of minimal to slight inflammatory cell infiltrates at the SC injection sites (dorsal 1 and 2) were observed for females in the 60 and 200 mg/kg SC treatment groups at the end of the Treatment Period.
- An increased incidence and/or severity of minimal to slight lymphocyte cellularity in the axillary and/or inguinal lymph nodes was observed for males and/or females in the 60 and 200 mg/kg SC treatment groups at the end of the 4-week Treatment Period.
- Systemic exposure (maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) from 0 to 96 h) to garadacimab increased in a dose-proportional manner for males and females from 3 to 100 mg/kg (Day 1) and 10 to 100 mg/kg (Day 29) following IV administration. Moderate accumulation of garadacimab was observed in the IV dosing groups (1.56 to 3.08) and SC groups (1.38 to 2.33) during the study period. No clear differences in systemic exposure between males and females were observed.
- The determined NOAEL was the high SC dose of 200 mg/kg.

Table 44. Four-Week Mouse Study Information

Study Features and Methods	Details
GLP Compliance:	Yes
Dose and frequency of dosing:	0, 3, 10, 30, and 100 mg/kg (IV) 0, 60 and 200 mg/kg (SC) Twice weekly with dose administration on Days 1, 4, 8, 11, 15, 18, 22, 25, and 29 (Groups 1, 3-7) Days 1, 4, 8, and 12 (Group 2 females) Days 1, 4, 8, 11, 15, and 18 (Group 2 males)
Route of administration:	Intravenous bolus and subcutaneous
Formulation/vehicle:	Isotonic saline (0.9%)
Species/strain:	Mouse/CD1(ICR)
Number/sex/group:	12/sex/group (main study) 6/sex/group (recovery period, control and HD IV and SC groups only)
Age:	Males were 60-68 days old and females were 62-70 days old at the start of treatment
Satellite groups/unique design:	Yes (TK and ADA analysis)/No
Deviation from study protocol affecting interpretation of results:	None that affected the integrity of the study

Table prepared by Dr. Yu-Chen Tsai:

Abbreviations: ADA, antidrug antibodies; GLP, good laboratory practices; HD, high dose; IV, intravenous; SC, subcutaneous; TK, toxicokinetic

Table 45. Design of 4-week toxicology study in mice that included an 8-week recovery period

Group	Treatment	Dose (mg/kg/occasion)	Route	Number of animals					
				Main study		Recovery phase		Satellite study†	
				Male	Female	Male	Female	Male	Female
1	Control	0	i.v./s.c.#	12	12	6	6	6	6
2	CSL312	3	i.v.	12	12	-	-	18	18
3	CSL312	10	i.v.	12	12	-	-	18	18
4	CSL312	30	i.v.	12	12	-	-	18	18
5	CSL312	100	i.v.	12	12	6	6	18	18
6	CSL312	60	s.c.	12	12	-	-	18	18
7	CSL312	200	s.c.	12	12	6	6	18	18

Control animals were used for both intravenous and subcutaneous dosing.

† Satellite animals were used for toxicokinetic, anti-drug antibody and contingency sampling only.

Source: Excerpted from Applicant's submission.

Abbreviations: CSL312, garadacimab; IV, intravenous

Table 46. Four-Week Mouse Study Observations and Results

Parameter	Major Findings
Mortality	There were 23 unscheduled deaths during the study (16 males and 7 females). The Applicant's report stated that four of the deaths (i.e., 100 mg/kg IV male, 60 mg/kg SC male, and two 60 mg/kg SC females) were due to the blood sampling procedure and not test article related. Five males in the 3 mg/kg/day IV group and one female in the 30 mg/kg/day IV group were found dead during or immediately following the dose administration. An additional four animals were found dead on dosing days (3 mg/kg IV female, three 10 mg/kg IV females). A further nine animals were prematurely euthanized for welfare reasons, because of clinical signs observed (i.e., eight 3 mg/kg IV males and one 10 mg/kg IV male). Clinical signs prior to termination consisted of mainly swollen limbs and muzzle and/or reddening of the limbs or muzzle sometimes associated with signs of decreased activity, shallow or slow breathing and flattened posture. These deaths were most likely due to immunogenicity based on adverse clinical signs that occurred shortly after dosing. The remaining 14 low dose males and 29 low dose females were terminated on Day 18 following the sixth dose and Days 12-13 after the fourth dose, respectively. Terminal procedures were conducted on low dose males and females after sacrifice.

Parameter	Major Findings
Clinical signs	Clinical observations of swollen muzzle, piloerection, hunched posture, decreased activity, partially closed eyelids, and rapid breathing were observed for individual animals during the Treatment Period: • Female #329 (10 mg/kg, IV, Day 22) • Male #38 (30 mg/kg, IV, Day 18) • Female #342 (30 mg/kg, IV, Day 22) Bruising at the intravenous injection site on the tail was also observed in several animals (including controls). Clear dose-dependent effects were not observed. This finding was not considered toxicologically significant.
Body weights	No treatment-related effects.
Ophthalmoscopy	No treatment-related effects.
Hematology	Significant prolongations of the activated partial thromboplastin time (aPTT) were observed for males (up to 127%) and females (up to 123%) in all treatment groups (IV and SC) relative to control animals at the end of the 4-week Treatment Period. These findings were reversible. These findings were due to the pharmacological effect of the drug. These findings were considered clinically monitorable.

Other findings: Decrease in hematocrit; increases in white blood cell, monocyte, lymphocyte, eosinophil, neutrophil counts.

Hematology parameters in mice (IV administration) at the end of the 4-week Treatment Period

Parameter	Males					Females				
	0	3	10	30	100	0	3	10	30	100
IV										
APTT sec	31.0	-	59.1 (191%)	69.4 (224%)	65.8 (212%)	35.9	-	79.9 (223%)	56.4 (157%)	56.0 (156%)
Hct L/L	0.452	-	0.462	0.457	0.465	0.482	-	0.446 (93%)	0.439 (91%)	0.447 (93%)
M 10 ⁹ /L	0.09	-	0.10	0.09	0.12	0.09	-	0.10	0.06	0.19 (211%)
N 10 ⁹ /L	0.82	-	0.56	0.57	0.62	0.57	-	0.45	0.40	0.79 (139%)
MCV fL	50.2	-	51.1	50.0	51.1	53.6	-	52.3	49.0 (91%)	51.3 (96%)
MCHC g/dL	29.5	-	27.1	30.1	29.7	29.6	-	30.1	31.0 (105%)	30.4 (103%)

Table prepared by primary pharmacology/toxicology reviewer under the IND.

Parameter	Major Findings					
	Hematology parameters in mice (SC administration) at the end of the 4-week Treatment Period					
Parameter	Males			Females		
	0	60	200	0	60	200
APTT Sec	31.0	67.2 (217%)	70.5 (227%)	35.9	62.3 (174%)	56.3 (157%)
PT sec	11.6	11.6	11.6	12.1	11.4 (94%)	11.5 (95%)
Hct L/L	0.452	0.475	0.469	0.482	0.481	0.451 (94%)
WBC 10 ⁹ /L	2.41	4.92 (204%)	5.92 (246%)	2.86	4.59 (160%)	4.03 (141%)
M 10 ⁹ /L	0.09	0.16	0.26 (289%)	0.09	0.09	0.09
L 10 ⁹ /L	1.67	3.81 (228%)	5.16 (309%)	2.09	3.63 (174%)	3.06 (146%)
E 10 ⁹ /L	0.11	0.15	0.18	0.08	0.30 (375%)	0.22 (275%)
LUC 10 ⁹ /L	0.01	0.03	0.05 (500%)	0.02	0.04	0.04
MCV fL	50.2	50.9	49.9	53.6	52.0	51.4 (96%)
MCHC g/dL	29.5	30.0	30.4	29.6	30.6 (103%)	30.9 (104%)

Table prepared by primary pharmacology/toxicology reviewer for the IND review.

Clinical chemistry	Significant increases in potassium levels were observed for males (up to 18%) and females (up to 17%) at ≥ 30 mg/kg/day garadacimab (IV) relative to control animals. A significant increase in potassium levels were also observed for males (up to 13%) in both SC treatment groups. Clear dose-dependent effects were not observed. These findings are clinically monitorable. Slight increases in total protein levels were observed for males (up to 4%) in all IV treatment groups relative to control animals. Clear dose-dependent effects were not observed. These findings were considered clinically monitorable. Significant increases in A1 and gamma globulin protein fractions were observed for males (up to 100%) in all treatment groups (A1) and at ≥ 30 mg/kg/day garadacimab IV (gamma) relative to control animals. Significant increases in gamma globulin protein fractions were also observed for males (up to 100%) and females (up to 100%) in SC treatment groups relative to control animals. Clear dose-dependent effects were not observed. These findings are clinically monitorable. Significant decreases in phosphorous levels were observed for females (up to 20%) in the SC treatment groups relative to control animals. These findings are clinically monitorable.
Gross pathology	An increased incidence of enlarged axillary and/or inguinal lymph nodes were observed in males and females at ≥ 60 mg/kg/day garadacimab (SC) relative to control animals. These findings correlated with histopathological findings of minimal to slight increased generalized cellularity in the inguinal and axillary lymph nodes in the SC treatment groups.

Parameter	Major Findings
Organ weights	Liver weights were slightly decreased for males in the 3-10 mg/kg IV treatment groups and for males in the 200 mg/kg SC treatment group. Liver weights were also slightly decreased for females at ≥ 30 mg/kg IV and 200 mg/kg SC treatment groups. These findings were reversible. There were no correlating histopathological findings at the end of the Treatment Period.
Histopathology Adequate battery: Yes	The potential target organs of toxicity were identified as the lymph nodes (axillary and inguinal) and subcutaneous injection sites. An increase in incidence and severity of minimal to slight inflammatory cell infiltrates at the subcutaneous injection sites (dorsal 1 and 2) were observed for females in the 60 and 200 mg/kg SC treatment groups at the end of the Treatment Period. The Applicant's report stated that this finding was characterized mainly by a diffuse neutrophilic infiltrate in the subcutaneous connective tissue. Minimal inflammatory cell infiltrates at the subcutaneous injection sites (dorsal 1 and 2) were also observed for males (2/12) in the 200 mg/kg SC treatment group. These findings were reversible. These findings were not considered dose-limiting and are clinically monitorable. An increase in incidence and/or severity of minimal to slight lymphocyte cellularity in the axillary and/or inguinal lymph nodes was observed for males and/or females in the 60 and 200 mg/kg SC treatment groups at the end of the 4-week Treatment Period. These findings were reversible and were not considered adverse. These findings correlated with macroscopic findings of enlarged lymph nodes (axillary and inguinal) for selected males and females in these treatment groups. The Applicant's report stated that these findings were considered a localized, secondary response to the inflammatory infiltrate observed at the subcutaneous injection sites primarily in females treated with 200 mg/kg garadacimab (SC).
Toxicokinetics	Systemic exposure (C_{max} and AUC_{0-96}) to garadacimab increased in a dose-proportional manner for males and females from 3 to 100 mg/kg (Day 1) and 10 to 100 mg/kg (Day 29) following IV administration. Moderate accumulation of garadacimab was observed in the IV dosing groups (1.56-3.08) and SC groups (1.38-2.33) during the study period. No clear differences in systemic exposure between males and females were observed; however, systemic exposure (C_{max} and AUC_{0-96}) was slightly higher in females than males following SC administration of garadacimab. Toxicokinetic data are summarized in Table 47 .
Immunogenicity:	According to the Applicant's report, four samples (i.e., three 10 mg/kg IV females and a 60 mg/kg SC female) were confirmed positive for ADAs against garadacimab.

Table prepared by Dr. Yu-Chen Tsai:

Abbreviations: ADA, antidrug antibodies; AUC, area under the concentration-time curve; C_{max} , maximum plasma concentration; GLP, good laboratory practices; HD, high dose; IV, intravenous; SC, subcutaneous; TK, toxicokinetic

Table 47. Toxicokinetics of the 4-Week Mouse Study

Admin route	Group	Dose (mg/kg)	Day	Gender	C _{max} (µg/mL)	T _{max} (h)	AUC ₀₋₂₄ (h*µg/mL)	AUC ₀₋₇₂ (h*µg/mL)	AUC ₀₋₉₆ (h*µg/mL)
i.v.	2	3	1	Female	171.38	1.00	1088.73	2056.62	2539.20
				Male	54.52	1.00	843.14	2142.61	2682.90
				Mean	112.95	1.00	965.94	2099.61	2611.05
	3	10	1	Female	184.21	0.08	2332.16	6283.27	8013.56
				Male	142.58	1.00	2688.60	6699.68	8531.23
				Mean	163.39	0.54	2510.38	6491.47	8272.39
			29	Female	303.65	0.08	4779.35	12483.57	15776.58
				Male	503.13	1.00	7641.71	20998.84	26274.15
				Mean	403.39	0.54	6210.53	16741.21	21025.37
	4	30	1	Female	796.21	0.08	8973.70	29637.28	34472.16
				Male	648.63	0.08	9011.38	20890.40	26338.31
				Mean	722.42	0.08	8992.54	25263.84	30405.23
			29	Female	1045.50	6.00	21067.54	51202.30	63100.56
				Male	1006.41	6.00	21172.22	52798.95	67359.57
				Mean	1025.95	6.00	21119.88	52000.62	65230.06
	5	100	1	Female	2038.70	0.08	23122.56	43829.76	57159.67
				Male	1632.46	1.00	23459.52	50901.63	62041.95
				Mean	1835.58	0.54	23291.04	47365.70	59600.81
29			Female	2123.31	1.00	32569.99	78613.30	94870.62	
			Male	1695.71	1.00	33893.67	78574.21	96814.15	
			Mean	1909.51	1.00	33231.83	78593.75	95842.38	
s.c.	6	60	1	Female	712.71	96.00	5384.34	20834.91	32839.30
				Male	324.94	24.00	4753.50	18987.37	25111.02
				Mean	518.82	60.00	5068.92	19911.14	28975.16
			29	Female	877.41	16.00	16604.84	46182.20	59797.83
				Male	810.96	32.00	14195.57	43055.60	58456.25
				Mean	844.18	24.00	15400.21	44618.90	59127.04
	7	200	1	Female	987.71	16.00	16886.52	59802.31	72494.55
				Male	727.58	72.00	11040.58	44849.60	60605.92
				Mean	857.65	44.00	13963.55	52325.95	66550.23
			29	Female	1637.87	24.00	29591.73	83555.41	106918.02
				Male	1051.87	24.00	19404.24	65822.89	83360.74
				Mean	1344.87	24.00	24497.99	74689.15	95139.38

Note: The treatment of Group 2 was terminated earlier. Therefore, no data for day 29 were obtained.

Source: Excerpted from the Applicant's submission.

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; IV, intravenous; SC, subcutaneous; T_{max}, time to maximum plasma concentration

CSL312: Toxicity Study by Intravenous (Bolus) and Subcutaneous Administration to Cynomolgus Monkeys for 26 Weeks Followed by an 8-Week Recovery Period (Study # (b) (4))

Key Study Findings

- In a 26-week toxicity and TK study, cynomolgus monkeys (4 sex/group), received garadacimab at IV doses of 0, 10, 30, and 100 mg/kg/week and SC doses of 0, 60, and 200 mg/kg/week.
- There were two unscheduled deaths in the study. One HD SC female was euthanized on Day 66 due to an immunogenic reaction (i.e., adverse clinical signs and detection of antidrug

antibodies (ADAs)). One HD IV male was euthanized on Day 119 due to rapid onset of adverse clinical signs consistent with an immunological reaction to the test article.

- The target organs of toxicity were identified as the SC and IV injection sites. The injection site findings were not considered adverse and are clinically monitorable.
- Significant dose-dependent prolongations of aPTT were observed for males and females in all IV and SC treatment groups relative to control animals.
- Increased incidences and/or severity of minimal to slight SC hemorrhage and minimal to slight inflammatory cell infiltration at the SC injection sites (sites 1 and 2) were observed for males and females in the 200 mg/kg SC treatment groups relative to control animals.
- Minimal to slight lymphoid aggregates at the SC injection sites (sites 1 and 2) were observed for males and females in the 200 mg/kg SC treatment group.
- Increased incidences and/or severity of minimal to slight SC hemorrhage, minimal to slight inflammatory cell infiltration, and minimal dermal inflammatory cell infiltration at the venous injection site (left) was observed for females in the 100 mg/kg IV treatment group.
- Systemic exposure to garadacimab (C_{max} and AUC_{0-168}) generally increased in a dose proportional manner for males and females from 10 to 100 mg/kg IV and 60 to 200 mg/kg SC during the 26-week Treatment Period. Moderate accumulation of garadacimab was observed in the dosing groups during the study period (i.e., one-to-four-fold). No clear differences in systemic exposure between males and females were observed.
- NOAELs were identified as the mid doses (MDs) of 30 mg/kg/week (IV) and 60 mg/kg/week (SC) based upon deaths observed at 100 mg/kg/week (IV) and 200 mg/kg/week (SC).

Table 48. Twenty-Six-Week Monkey Study Information

Study Features and Methods	Details
GLP Compliance:	Yes
Dose and frequency of dosing:	0, 10, 30, and 100 mg/kg (IV) 0, 60 and 200 mg/kg (SC) Weekly
Route of administration:	Intravenous bolus and subcutaneous
Formulation/vehicle:	Isotonic saline (0.9%)
Species/strain:	Monkey/Cynomolgus
Number/sex/group:	4/sex/group (main study) 2/sex/group (recovery period, control and HD IV and SC groups only)
Age:	Monkeys were 28 to 30 months old at start of treatment
Satellite groups/unique design:	No/no
Deviation from study protocol affecting interpretation of results:	None that affected the integrity of the study

Table prepared by Dr. Yu-Chen Tsai:

Abbreviations: GLP, good laboratory practices; HD, high dose; IV, intravenous; SC, subcutaneous

Table 49. Design of the 26-week toxicology study with monkeys

Group	Treatment	Dose (mg/kg/occasion)	Number of animals					
			Main study		Interim phase		Recovery phase	
			Male	Female	Male	Female	Male	Female
1	Control	0 (IV and SC)*	4	4	2	2	2	2
2	CSL312	10 (IV)	4	4	0	0	0	0
3	CSL312	30 (IV)	4	4	0	0	0	0
4	CSL312	100 (IV)	4	4	2	2	2	2
5	CSL312	60 (SC)	4	4	0	0	0	0
6	CSL312	200 (SC)	4	4	2	2	2	2

* Control animals used for both intravenous and subcutaneous dosing

IV Intravenous (bolus)

SC Subcutaneous injection

Excerpted from Applicant's submission:

Abbreviations: CSL312, garadacimab; IV, intravenous; SC, subcutaneous

Table 50. Twenty-Six-Week Monkey Study Observations and Results

Parameter	Major Findings
Mortality	There were two unscheduled deaths during the Treatment Period. One female animal (Animal #537) in the 200 mg/kg/week SC group was euthanized for welfare reasons on Day 66 (Week 10). The Applicant's report stated that Animal #537 exhibited rapid development of a large swelling starting on the right-hand mandible, extending across the right-hand side of the throat and down the right shoulder immediately prior to termination. The animal also had clinical signs of a distinct raspiness on vocalization, an elevated body temperature (i.e., 39.3°C), and its breathing was reportedly slightly pyrexia. The animal exhibited macroscopic abnormalities of dark colored lungs, discolored (pale and dark areas) and enlarged kidneys, abnormal shape of the gallbladder, enlarged mandibular lymph node, raised areas of the skeletal muscle, thyroids cysts, edematous mandibular salivary gland, and dark areas at the subcutaneous injection sites. This animal exhibited histopathological findings of marked myofiber necrosis and slight regeneration of the skeletal muscle, minimal plasmacytosis of the mandibular lymph node, minimal inflammatory cell infiltration of the mandibular and sublingual salivary glands and slight hemorrhage and inflammatory cell infiltration of the subcutaneous injection sites which correlated with observed macroscopic findings. This animal was confirmed as ADA-positive. One male animal (Animal #238) in the 100 mg/kg/week IV group was euthanized on Day 119 (Week 17) due to a sudden onset of abdominal swelling, swollen muzzle (which was considered severe enough to necessitate euthanasia), and subcutaneous fluid accumulation. The Applicant's report stated that a postmortem examination revealed edematous adipose tissue, pancreas, salivary glands, and skin/subcutis, and gastrointestinal findings of thickened jejunum and duodenum with red mucosa of the jejunum. This animal exhibited histopathological findings of edema in the pancreas and inflammatory cell infiltration of the heart, kidneys, esophagus,

Parameter	Major Findings
	mandibular and sublingual salivary glands. This animal was ADA-negative following a confirmatory analysis. The Applicant's report stated that the major factor leading to the decision to euthanize this animal was the marked clinical observations.
Clinical signs	No treatment-related effects.
Body weights	No treatment-related effects.
Ophthalmoscopy	No treatment-related effects.
ECG	No treatment-related effects on ECG, blood pressure, respiration rate, or pulse rate.
Hematology	An increase in neutrophil counts was observed for males (up to 92%) in the 60 and 200 mg/kg SC treatment groups relative to control animals at the end of the 26-week Treatment Period. Clear dose-dependent effects were not observed. These findings were not considered adverse and were considered monitorable in a clinical setting. A slight decrease in red blood cell (up to 7%) and hematocrit (up to 6%) levels were observed for females in the 200 mg/kg SC treatment group relative to control animals. The findings were not considered adverse and are judged to be monitorable in a clinical setting.
Coagulation	A significant dose-dependent prolongation of activated partial thromboplastin times (aPTT) were observed for males and females in all intravenous and subcutaneous treatment groups relative to control animals during the 26-week Treatment Period. On Day 1, aPTT prolongation times for the IV treatment groups peaked at either 0.25 or 5 h postdose (i.e., males up to 3.5-fold and females up to 3.2-fold the control) and remained elevated up to 168 h postdose. In addition, aPTT was also prolonged in the subcutaneous treatment groups and peaked at 96 and 48 h postdose in males (up to 2.5-fold the control) and females (up to 3.1-fold the control), respectively, and remained extended up to 168 h postdose. The findings were an expected pharmacological effect of the drug. The findings were not completely reversible by the end of the 8-week recovery period. No treatment-related effects on prothrombin times were observed during the study period.
Clinical chemistry	A slight increase in potassium concentration was observed for females (up to 27%) in the 60 and 200 mg/kg SC treatment groups relative to control animals. Clear dose-dependent effects were not observed. The toxicological significance, if any, of these findings is unclear. These findings were considered monitorable in a clinical setting.
Urinalysis	A significant decrease in potassium (up to 48%) and chloride (up to 70%) levels were observed for females in the 200 mg/kg/week SC treatment group relative to control animals at the end of the 26-week Treatment Period. The toxicological significance, if any, of these findings is unclear. These findings were considered clinically monitorable.
Gross pathology	Dark areas and thickening observed at the subcutaneous or intravenous injection sites were observed for several animals at the end of the Treatment Period. These findings were not considered toxicologically significant.
Organ weights	No treatment-related effects.

Parameter	Major Findings
Histopathology Adequate battery: Yes	The potential target organs of toxicity were identified as the subcutaneous and intravenous injection sites. An increased incidence and/or severity of minimal to slight subcutaneous hemorrhage and minimal to slight inflammatory cell infiltration at the subcutaneous injection sites (sites 1 and 2) were observed for males and females in the 200 mg/kg SC treatment groups relative to control animals. These findings were considered test article related. These findings were reversible. Minimal to slight lymphoid aggregates at the subcutaneous injection sites (sites 1 and 2) was observed for males and females in the 200 mg/kg SC treatment groups. These findings were considered test article related. The findings were not completely reversible at the end of the 8-week recovery period. An increased incidence and/or severity of minimal to slight subcutaneous hemorrhage, minimal to slight inflammatory cell infiltration, and minimal dermal inflammatory cell infiltration at the venous injection site (left) was observed for females in the 100 mg/kg IV treatment group relative to control animals. These findings were reversible. The injection site findings were not considered adverse and are clinically monitorable.
Other evaluations	No treatment-related effects on complement C3a, D-dimer concentrations, thrombin-antithrombin complex, C-reactive protein, cytokine release, and immunophenotyping of lymphocytes.
Toxicokinetics	Systemic exposure (C_{max} and AUC_{0-168}) to garadacimab generally increased in a dose proportional manner for males and females from 10 to 100 mg/kg IV and 60 to 200 mg/kg SC during the 26-week Treatment Period. Moderate accumulation of garadacimab was observed in the dosing groups during the study period (i.e., 1-4-fold). No clear differences in systemic exposure between males and females were observed. $T_{1/2}$ ranged from 167 to 211 h (Week 14) for IV administration and 165 to 208 h (Week 14) for SC administration. Toxicokinetic data are summarized in Table 51 .

Table prepared by Dr. Yu-Chen Tsai:

Abbreviations: ADA, antidrug antibodies; AUC, area under the concentration-time curve; C_{max} , maximum plasma concentration; ECG, electrocardiogram; IV, intravenous; SC, subcutaneous; $T_{1/2}$, half-life

Table 51. Toxicokinetics of the 26-Week Monkey Study

		Group 2 (10 mg/kg, i.v.)						
		C ₀	C _{max}	T _{max}	AUC ₀₋₂₄	AUC ₀₋₁₆₈	T _{1/2}	
		(µg/mL)	(µg/mL)	(h)	(h ² µg/mL)	(h ² µg/mL)	(h)	
Week 1	Males & Females	N	6	6	6	6	6	6
		Mean	214	211	0.25	3690	14149	143
		Min	148	145	0.25	2401	10182	121
		Median	190	196	0.25	3601	13678	135
	Max	293	288	0.25	5354	18727	217	
	Males	N	4	4	4	4	4	4
		Mean	266	264	0.25	4840	17521	153
		Min	220	219	0.25	4440	16346	126
		Median	275	274	0.25	4793	17506	135
	Max	293	288	0.25	5354	18727	217	
	Females	N	4	4	4	4	4	4
		Mean	161	158	0.25	2540	10776	133
Min		148	145	0.25	2401	10182	121	
Median		160	156	0.25	2500	10957	132	
Max	177	173	0.25	2752	11010	147		
Week 14	Males & Females	N	6	6	6	6	6	6
		Mean	310	306	0.25	5791	27224	203
		Min	236	234	0.25	4393	18956	137
		Median	297	293	0.25	5573	27312	201
	Max	433	429	0.25	8339	40857	263	
	Males	N	4	4	4	4	4	4
		Mean	293	290	0.25	5363	24939	225
		Min	248	246	0.25	4855	22121	137
		Median	293	289	0.25	5229	24857	240
	Max	330	334	0.25	6130	27923	283	
	Females	N	4	4	4	4	4	4
		Mean	326	323	0.25	6219	29509	180
Min		236	234	0.25	4393	18956	151	
Median		317	314	0.25	6072	29112	175	
Max	433	429	0.25	8339	40857	220		
Week 27	Males & Females	N	6	6	6	6	0	0
		Mean	360	358	0.84	7114	-	-
		Min	293	294	0.25	6316	-	-
		Median	355	352	0.25	6696	-	-
	Max	430	426	5.00	8308	-	-	
	Males	N	4	4	4	4	0	0
		Mean	349	347	1.44	6870	-	-
		Min	293	294	0.25	6316	-	-
		Median	336	333	0.25	6428	-	-
	Max	430	426	5.00	8308	-	-	
	Females	N	4	4	4	4	0	0
		Mean	372	370	0.25	7358	-	-
Min		342	340	0.25	6884	-	-	
Median		361	360	0.25	7324	-	-	
Max	424	421	0.25	8098	-	-		

Source: Excerpted from the Applicant's submission.
 Abbreviations: AUC, area under the concentration-time curve; C₀, plasma concentration at time 0; C_{max}, maximum plasma concentration; IV, intravenous; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration

Table continued

		Group 3 (30 mg/kg, i.v.)						
		C ₀	C _{max}	t _{max}	AUC ₀₋₂₄	AUC ₀₋₁₆₈	t _{1/2}	
		(µg/mL)	(µg/mL)	(h)	(h*µg/mL)	(h*µg/mL)	(h)	
Week 1	Males & Females	N	8	8	8	8	8	8
		Mean	582	579	0.84	10358	30115	145
		Min	491	495	0.25	8395	34370	131
		Median	565	578	0.25	10189	30214	141
		Max	705	699	5.00	12624	45146	181
	Males	N	4	4	4	4	4	4
		Mean	615	618	1.44	11644	41223	140
		Min	526	548	0.25	10625	37762	131
		Median	614	611	0.25	11664	40992	142
		Max	705	699	5.00	12624	45146	147
	Females	N	4	4	4	4	4	4
		Mean	548	540	0.25	9072	37007	150
Min		491	495	0.25	8395	34370	138	
Median		549	543	0.25	9074	30253	140	
Max		604	590	0.25	9753	41151	181	
Week 14	Males & Females	N	8	8	8	8	8	8
		Mean	690	699	0.25	16692	75666	167
		Min	595	599	0.25	10517	34949	98.0
		Median	610	602	0.25	17247	78473	165
		Max	1045	1037	0.25	20587	97620	208
	Males	N	4	4	4	4	4	4
		Mean	833	827	0.25	16058	70191	156
		Min	595	590	0.25	10517	34949	98.0
		Median	647	642	0.25	16565	74098	156
		Max	1045	1037	0.25	20587	97620	208
	Females	N	4	4	4	4	4	4
		Mean	962	951	0.25	17325	81141	176
Min		894	889	0.25	16156	74622	157	
Median		964	953	0.25	17247	78473	178	
Max		1026	1006	0.25	16650	92995	201	
Week 27	Males & Females	N	8	8	8	8	0	0
		Mean	1021	1012	0.25	18565	-	-
		Min	776	784	0.25	12514	-	-
		Median	1062	1044	0.25	16544	-	-
		Max	1166	1156	0.25	22631	-	-
	Males	N	4	4	4	4	0	0
		Mean	1016	1002	0.25	17275	-	-
		Min	776	784	0.25	12514	-	-
		Median	1062	1044	0.25	16977	-	-
		Max	1166	1156	0.25	22631	-	-
	Females	N	4	4	4	4	0	0
		Mean	1026	1021	0.25	19854	-	-
Min		640	632	0.25	16886	-	-	
Median		1032	1026	0.25	20306	-	-	
Max		1099	1092	0.25	21914	-	-	

Source: Excerpted from the Applicant's submission.

Abbreviations: AUC, area under the concentration-time curve; C₀, plasma concentration at time 0; C_{max}, maximum plasma concentration; IV, intravenous; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration

Table continued

		Group 4 (100 mg/kg, i.v.)						
		C ₀	C _{max}	t _{max}	AUC ₀₋₂₄	AUC ₀₋₁₆₈	t _{1/2}	
		(µg/mL)	(µg/mL)	(h)	(h ² µg/mL)	(h ² µg/mL)	(h)	
Week 1	Males & Females	N	10	10	10	10	10	10
		Mean	2155	2145	0.55	36132	134795	116
		Min	1733	1714	0.25	27974	112936	65.0
		Median	2106	2155	0.25	39517	133547	113
	Max	2624	2571	5.00	47811	165532	198	
	Males	N	8	8	8	8	8	8
		Mean	2312	2287	0.25	30742	142337	106
		Min	1997	1975	0.25	33700	116818	89.6
		Median	2338	2318	0.25	40014	144913	111
	Max	2624	2571	0.25	44087	165532	139	
	Females	N	8	8	8	8	8	8
		Mean	1999	2003	0.84	36523	127252	125
Min		1733	1714	0.25	27974	112936	65.0	
Median		1995	1985	0.25	35068	128470	129	
Max	2455	2455	5.00	47811	148115	198		
Week 14	Males & Females	N	16	16	16	15	12	11
		Mean	2871	2844	0.25	51522	202810	211
		Min	2309	2262	0.25	38618	128895	109
		Median	2809	2804	0.25	50455	202229	140
	Max	3227	3199	0.25	60282	262574	548	
	Males	N	8	8	8	8	6	5
		Mean	2888	2862	0.25	52546	205735	255
		Min	2309	2262	0.25	38618	128895	109
		Median	2934	2903	0.25	52999	204711	161
	Max	3227	3199	0.25	60282	262574	548	
	Females	N	8	8	8	8	6	6
		Mean	2853	2825	0.25	50497	199884	174
Min		2654	2647	0.25	47881	176738	128	
Median		2847	2821	0.25	49701	202220	148	
Max	2990	2936	0.25	54946	210022	304		
Week 27	Males & Females	N	11	11	11	11	4	4
		Mean	3079	3057	0.25	57246	200280	170
		Min	2717	2707	0.25	52736	193311	131
		Median	2957	2931	0.25	56882	196966	191
	Max	3402	3361	0.25	64256	209837	203	
	Males	N	5	5	5	5	2	2
		Mean	3029	3011	0.25	58349	-	-
		Min	2717	2707	0.25	52736	-	-
		Median	2955	2931	0.25	57887	-	-
	Max	3328	3306	0.25	64256	-	-	
	Females	N	6	6	6	6	2	2
		Mean	3121	3094	0.25	56328	-	-
Min		2929	2921	0.25	53530	-	-	
Median		3040	3011	0.25	56585	-	-	
Max	3402	3361	0.25	58774	-	-		

Source: Excerpted from the Applicant's submission.

Abbreviations: AUC, area under the concentration-time curve; C₀, plasma concentration at time 0; C_{max}, maximum plasma concentration; IV, intravenous; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration

Table continued

Group 5 (60 mg/kg, s.c.)							
			C _{max}	t _{max}	AUC ₀₋₂₄	AUC ₀₋₉₆	
			(µg/mL)	(h)	(h ² µg/mL)	(h ² µg/mL)	
Week 1	Males & Females	N	8	8	8	8	3
		Mean	335	41.00	4057	43046	154
		Min	271	24.00	3002	36345	135
		Median	339	48.00	3955	43075	138
	Max	397	48.00	5202	48575	169	
	Males	N	4	4	4	4	2
		Mean	322	38.00	4221	41726	-
		Min	271	24.00	3002	36345	-
		Median	318	40.00	4341	41327	-
	Max	380	48.00	5202	47905	-	
	Females	N	4	4	4	4	1
		Mean	349	44.00	3893	44366	-
Min		315	32.00	3210	40517	-	
Median		341	48.00	3955	44186	-	
Max	397	48.00	4453	48575	-		
Week 14	Males & Females	N	8	8	8	8	6
		Mean	686	27.00	13559	89395	208
		Min	595	24.00	11311	75491	153
		Median	690	24.00	13724	91121	208
	Max	771	32.00	15343	102258	293	
	Males	N	4	4	4	4	4
		Mean	639	28.00	12426	82159	184
		Min	595	24.00	11311	75491	153
		Median	635	28.00	12025	79541	185
	Max	691	32.00	14345	94061	215	
	Females	N	4	4	4	4	4
		Mean	732	26.00	14682	96630	231
Min		690	24.00	13104	89884	175	
Median		734	24.00	15161	97100	228	
Max	771	32.00	15343	102259	293		
Week 27	Males & Females	N	8	8	8	0	0
		Mean	596	24.00	12418	-	-
		Min	347	24.00	7538	-	-
		Median	625	24.00	13175	-	-
	Max	790	24.00	16096	-	-	
	Males	N	4	4	4	0	0
		Mean	463	24.00	9602	-	-
		Min	347	24.00	7538	-	-
		Median	465	24.00	9618	-	-
	Max	575	24.00	11634	-	-	
	Females	N	4	4	4	0	0
		Mean	728	24.00	15234	-	-
Min		675	24.00	14717	-	-	
Median		723	24.00	15062	-	-	
Max	790	24.00	16096	-	-		

Source: Excerpted from the Applicant's submission.

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; SC, subcutaneous; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration

Table continued

Group 6 (200 mg/kg, s.c.)							
		C_{max}	t_{max}	AUC ₀₋₂₄	AUC ₀₋₄₈	$t_{1/2}$	
		(µg/mL)	(h)	(h*µg/mL)	(h*µg/mL)	(h)	
Week 1	Males & Females	N	16	16	16	16	5
		Mean	1093	42.00	12949	138150	152
		Min	927	24.00	9264	113186	91.30
		Median	1080	43.00	12788	141429	148
	Max	1276	49.00	17605	160730	201	
	Males	N	8	8	8	8	2
		Mean	1118	44.00	13365	140684	-
		Min	1003	32.00	9944	124300	-
		Median	1102	49.00	12653	145903	-
	Max	1264	48.00	17605	155511	-	
	Females	N	8	8	8	8	3
		Mean	1067	40.00	12534	135310	137
Min		927	24.00	9264	113186	91.30	
Median		1050	48.00	12153	134800	126	
Max	1276	49.00	15432	168738	195		
Week 14	Males & Females	N	15	15	15	11	10
		Mean	2023	31.47	37423	247627	165
		Min	1408	24.00	27650	104861	130
		Median	2030	32.00	37396	245814	169
	Max	2586	72.00	46560	304489	211	
	Males	N	8	8	8	6	6
		Mean	2016	30.00	37212	255710	167
		Min	1737	24.00	33427	215372	130
		Median	2014	32.00	36478	249910	164
	Max	2407	32.00	42758	304489	211	
	Females	N	7	7	7	5	4
		Mean	2030	33.14	37665	237917	163
Min		1408	24.00	27650	104861	136	
Median		2066	24.00	40214	245814	169	
Max	2586	72.00	46560	276357	178		
Week 27	Males & Females	N	11	11	11	4	4
		Mean	1711	29.36	32069	249403	221
		Min	1176	24.00	22759	232162	135
		Median	1683	24.00	32279	248518	229
	Max	2281	48.00	42929	268654	290	
	Males	N	6	6	6	2	2
		Mean	1640	29.33	30959	-	-
		Min	1369	24.00	24888	-	-
		Median	1666	24.00	31557	-	-
	Max	1983	49.00	35764	-	-	
	Females	N	5	5	5	2	2
		Mean	1797	27.20	33401	-	-
Min		1176	24.00	22759	-	-	
Median		2010	24.00	33030	-	-	
Max	2281	32.00	42929	-	-		

Source: Excerpted from the Applicant's submission.

Abbreviations: AUC, area under the concentration-time curve; C_{max} , maximum plasma concentration; SC, subcutaneous; $T_{1/2}$, half-life; T_{max} , time to maximum plasma concentration

13.1.4.2. Carcinogenicity

An assessment of the carcinogenic potential associated with chronic inhibition of FXIIa by garadacimab was conducted by the Applicant and the Nonclinical Reviewers.

- The mouse was demonstrated to be a pharmacologically relevant species with garadacimab. A 4week study with garadacimab was conducted in the mouse; however, this study showed that mice developed an immunogenic response to treatment with this heterologous humanized monoclonal antibody. Therefore, a 2-year mouse carcinogenicity study was not considered technically feasible.
- A 2-year carcinogenicity study in rats would not provide meaningful information for the safety assessment of garadacimab as the rat was not a pharmacologically relevant species (i.e., no binding of garadacimab to rat FXIIa).

- The 26-week toxicity study in monkeys did not show any evidence of preneoplastic or neoplastic findings.
- The evidence from the published scientific literature regarding inhibition of activated FXII or zymogen FXII deficiency does not suggest any carcinogenic risk. Evidence suggests that inflammatory responses and possible maintenance and progression of cancer could be reduced by inhibition of FXIIa.
- There is general agreement that hereditary FXII deficiency does not usually result in a hemorrhagic diathesis. FXII knock-out mice are not impacted negatively, although zymogen FXII has biologic activity in various cells in vivo.
- FXII plasma levels are low in patients with lung, gastrointestinal, and colorectal cancer, suggesting that FXIIa-driven pathways are active in patients with malignancy. Experimental venous thromboembolism models in mice and studies with cancer patients revealed that prostate cancer cells and associated exosomes display inorganic polymer polyphosphates on their plasma membranes. Polyphosphates activate FXII and initiate thrombus formation. Pharmacologic inhibition of FXIIa protects mice from venous thromboembolism and reduces thrombin coagulant activity in plasma of patients with prostate cancer.
- Garadacimab was shown to only antagonize FXIIa enzymatic activities, displaying 100% inhibition of FXIIa catalytic activity for both the α and β fragments, meaning that zymogen FXII functions are negligibly impacted. In contrast, garadacimab did not significantly inhibit the other serum proteases evaluated. Due to its specific binding to FXIIa without impacting other coagulation factors or serum proteases, it was considered unlikely that garadacimab will induce preneoplastic or neoplastic lesions.

Based on the weight of evidence, the Division agreed with the Applicant that a rodent carcinogenicity study was not technically feasible. Further, there appears to be a low or negligible carcinogenic potential based on the results of the 26-week monkey study and review of the published literature regarding chronic inhibition of FXIIa.

Genotoxicity studies with biologics such as garadacimab are not required. As per International Council for Harmonisation (ICH) guideline, S6(R1) *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* ([June 2011](#)), standard in vitro and in vivo genotoxicity studies are not applicable to biologics because these molecules are unlikely to interact directly with DNA or chromosomal material.

13.1.4.3. Reproductive Toxicology

The potential reproductive toxicity of garadacimab was evaluated in fertility and early embryonic development studies with male and female rabbits, an embryofetal development study with female rabbits, and a pre- and postnatal development study with female rabbits.

Rabbits were determined to be a pharmacologically relevant species.

- Garadacimab binds with high affinity to rabbit FXIIa and β FXIIa as well as FXII zymogen. Data demonstrated that rabbits are a pharmacologically relevant species for toxicological investigation (REP-21280).

- Garadacimab inhibited dextran sulfate-mediated FXIIa activity in diluted plasma from rabbit, human, and other animal species confirming rabbits as a pharmacologically relevant species and supporting their use in toxicological investigations (REP-21282).

In correspondence dated March 29, 2019, the Division agreed with the Applicant's reproductive toxicity program. Rats were not a pharmacologically relevant species.

Rabbits are not commonly used in male and female fertility studies.

- The duration of the spermatogenic cycle is 48 days in the rabbit as compared to 52 days in rats, which are more commonly used in fertility studies. Treatment of rabbits with garadacimab once every 3 days for a total of 15 doses should cover the majority of the duration of the spermatogenic cycle in rabbits. Rabbits were not used in general toxicology studies with garadacimab, so there were no microscopic evaluations of the testes in longer studies. The assessment of fertility using male rabbits appears to be generally acceptable as the fertility study covered the majority of the spermatogenic cycle.
- Female rabbits differ from female humans in that they do not have an estrus cycle. Females ovulate once they are mounted by a male (induced ovulation). The female rabbit can become impregnated any time, although it is not recommended that females be bred before 4 weeks of age. The assessment of fertility using female rabbits appears to be generally acceptable, although potential effects of estrus cycle could not be determined.

Rabbits are commonly used in embryofetal development studies.

Pre- and postnatal development studies are not commonly conducted with female rabbits. The Applicant appropriately adjusted dosing to cover the duration of the gestation and lactation periods in rabbits. Monitoring of the growth and development of the F1 generation was also appropriately adjusted for the use of rabbits.

Fertility and Early Embryonic Development Studies Conducted With Male and Female Rabbits

The 26-week repeat-dose monkey study was conducted in sexually immature male and female animals, and estrous cycling was not monitored in females. Therefore, an assessment of the effects of garadacimab on male and female fertility was not possible from this study. The Applicant conducted fertility and early embryonic development studies with male and female rabbits.

Intravenous Injection Male Fertility and Early Embryonic Development to Implantation and Toxicokinetics Study With CSL312 in Rabbits (Study # (b) (4))

Good laboratory practice (GLP) compliance: Yes

Key Study Findings

- In this study, male rabbits were administered IV doses of 10, 30, or 100 mg/kg/dose every 3 days from 4 weeks prior to mating, during the mating period, and up to 8 days after the mating period (dosing on Preparing Days 0, 3, 6, 9, 12, 15, 18, 21, 24, and 27; Pairing Days 2 and 5; and on Postpairing Days 2, 5, and 8 for a total of 15 doses). Females were not dosed and assigned to each group for mating purposes only.

- Six males (four LD and two MD males) died or were sacrificed prior to the scheduled sacrifice. However, there were questionable relationships of these early mortalities to treatment with garadacimab based on observed lack of dose-response with no deaths in the HD group. The role of ADAs in these deaths was unclear.
- Expected garadacimab pharmacologically related prolonged aPTT was observed in all drug-treated groups.
- There were no treatment-related effects on mating and fertility parameters, reproductive indices, or sperm assessment.
- Prolonged aPTT and TK indicated that drug-treated males were continuously exposed to drug from 4 weeks prior to dosing through Postpairing Day 8.
- The NOAEL for this study was the HD of 100 mg/kg/dose based on a lack of findings.

Table 52. Methods of Male Rabbit Fertility and Early Embryonic Development Study

Parameter	Method Details
Dose and frequency of dosing:	10 (LD), 30 (MD), and 100 (HD) mg/kg/dose Male rabbits were administered IV doses of 10, 30, or 100 mg/kg/dose every 3 days from 4 weeks prior to mating, during the mating period, and up to 8 days after the mating period (dosing on Preparing Days 0, 3, 6, 9, 12, 15, 18, 21, 24, and 27; Pairing Days 2 and 5; and on Postpairing Days 2, 5, and 8 for a total of 15 doses) by IV prior to mating and until termination. Females were not dosed and assigned to each group for mating purposes only.
Route of administration:	Intravenous
Formulation/vehicle:	Drug formulation: 20mM L-histidine, 150mM (b) (4) arginine monohydrochloride, 140mM L-proline, 0.02% w/v polysorbate 80; pH 6.1 Control: 0.9% sodium chloride for injection
Species/strain:	Rabbit Hra:(NZW)SPF Males were received from (b) (4). At initiation of dosing, males were 7 to 8 months old, and body weights ranged from 2908 to 4102 g. Females were received from (b) (4). Naïve teaser females were 7 months old at arrival. At initiation of pairing, females were 7 to 8 months old and body weights ranged from 2726 to 3807 g.
Number/sex/group:	• Control: 25 Males, 30 naïve females • LD: 25 Males, 24 naïve females • MD and HD: 25 Males, 28 naïve females
Study design:	Basis of dose selection and dosing interval: An intravenous tolerability study in rabbits (dosing on Days 1, 4, and 8) conducted by the Applicant employed dose levels of 10 and 100 mg/kg garadacimab IV. No effect on mortality, body weight, or clinical observations were noted, accordingly. A subsequent preliminary embryofetal development study ((b) (4)) was conducted in pregnant rabbits with garadacimab. Animals were administered 1, 10, or 100 mg/kg garadacimab once every 3 days on GD 6, 9, 12, 15, and 18 and exhibited no adverse findings; only the pharmacologically expected test article-related prolongation of APTT was observed. The applied dosing regimen of once in 3 days resulted in continuous exposure of animals throughout the gestation period.

Parameter	Method Details
Deviation from study protocol affecting interpretation of results:	None that affected the integrity of the study.

Table generated by pharmacology/toxicology primary reviewer.

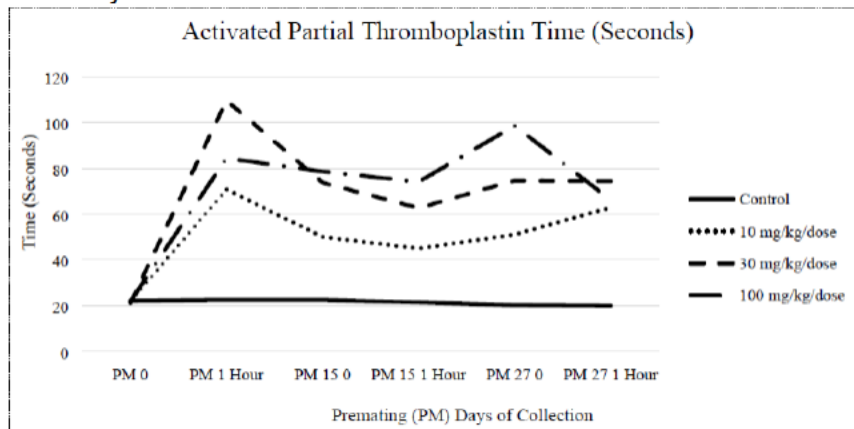
Abbreviations: APTT, activated partial thromboplastin time; GD, gestation day; HD, high dose; IV, intravenous; LD, low dose; MD, mid dose; NZW, New Zealand white

Table 53. Observations and Results from Male Rabbit Fertility and Early Embryonic Development Study

Parameter	Major Findings																																								
Mortality	No garadacimab -related mortality was observed among males. Six males (four LD and two MD males) died or were sacrificed in a moribund condition prior to the scheduled sacrifice, with an uncertain association to antidrug antibodies formed because of exposure to the heterologous human protein. There were no deaths in the HD group receiving 100 mg/kg/dose.																																								
Clinical signs	No treatment-related effects.																																								
Body weights	No treatment-related effects.																																								
Necropsy findings	No treatment-related effects.																																								
Fertility and pregnancy parameters	No treatment-related effects on mating, fertility, or fecundity indices. No treatment-related effects were observed on sperm motility or concentration or caudal epididymal weight.																																								
	Drug-treated male mating and fertility parameters following mating with untreated females																																								
	<table border="1"> <thead> <tr> <th>Variable</th> <th>Control</th> <th>LD</th> <th>MD</th> <th>HD</th> </tr> </thead> <tbody> <tr> <td>Males cohabitated</td> <td>25</td> <td>21</td> <td>24</td> <td>25</td> </tr> <tr> <td>Unscheduled deaths during cohabitation</td> <td>0</td> <td>0</td> <td>1</td> <td>0</td> </tr> <tr> <td>Males mating with at least 1 female</td> <td>23</td> <td>20</td> <td>22</td> <td>23</td> </tr> <tr> <td>Males impregnating at least 1 female</td> <td>22</td> <td>16</td> <td>21</td> <td>22</td> </tr> <tr> <td>Mating index (%)</td> <td>92</td> <td>95</td> <td>92</td> <td>92</td> </tr> <tr> <td>Fecundity index (%)</td> <td>96</td> <td>80</td> <td>95</td> <td>96</td> </tr> <tr> <td>Fertility index (%)</td> <td>88</td> <td>76</td> <td>88</td> <td>88</td> </tr> </tbody> </table>	Variable	Control	LD	MD	HD	Males cohabitated	25	21	24	25	Unscheduled deaths during cohabitation	0	0	1	0	Males mating with at least 1 female	23	20	22	23	Males impregnating at least 1 female	22	16	21	22	Mating index (%)	92	95	92	92	Fecundity index (%)	96	80	95	96	Fertility index (%)	88	76	88	88
Variable	Control	LD	MD	HD																																					
Males cohabitated	25	21	24	25																																					
Unscheduled deaths during cohabitation	0	0	1	0																																					
Males mating with at least 1 female	23	20	22	23																																					
Males impregnating at least 1 female	22	16	21	22																																					
Mating index (%)	92	95	92	92																																					
Fecundity index (%)	96	80	95	96																																					
Fertility index (%)	88	76	88	88																																					
	Table generated by pharmacology/toxicology primary reviewer.																																								
	Mating index %=(number of males mating with at least 1 female÷number of males cohabitated with at least 1 female)×100																																								
	Fecundity index %=(number of males impregnating at least 1 female÷number of males mating with at least 1 female)×100																																								
	Fertility index %=(number of males impregnating at least 1 female÷number of males cohabitated with at least 1 female)×100																																								

Parameter	Major Findings
aPTT	Garadacimab-related prolonged aPTT was observed for drug-treated males at all doses. The prolonged aPTT was nonprogressive, and generally dose dependent. Prolongation of aPTT was not associated with any bleeding events in drug-treated males.

Summary of aPTT values in male rabbits



Source: Excerpted from the Applicant's submission.

Toxicokinetics	The increases in C_{max} and AUC_{0-72} values were generally dose proportional except C_{max} on Premating Day 15, where values were greater than dose proportional from the LD to MD and less than dose proportional from MD to the HD. Slight accumulation of garadacimab was observed after multiple doses in rabbits on premating Days 15 and 27.
ADA	Animals administered 0, 10, 30 or 100 mg/kg/dose had ADA incidences, at least one time after dosing, of approximately 28, 32, 16, or 72%, respectively, tested positive for ADA. The Applicant considered the ADA incidence of 28% from the control group to be false positives for unknown reasons. There was no evidence that control animals had received garadacimab (all concentration values of garadacimab in the vehicle-control group were below the lower limit of quantitation, <500 ng/mL). The positive ADA results from the treated animals were therefore hard to interpret.

Table generated by pharmacology/toxicology primary reviewer.

Abbreviations: ADA, antidrug antibodies; APTT, activated partial thromboplastin time; AUC, area under the concentration-time curve; C_{max} , maximum plasma concentration; HD, high dose; IV, intravenous; LD, low dose; MD, mid dose

Intravenous Injection Female Fertility and Early Embryonic Development to Implantation and Toxicokinetics Study With CSL312 in Rabbits (Study # (b) (4))

GLP Compliance: Yes

Key Study Findings

- In this study, female rabbits were administered IV doses of 10, 30, or 100 mg/kg/dose every 3 days over 2 weeks prior to mating, during the mating period, and up to Gestation Day 7 (dosed on Premating Days 0, 3, 6, 9, and 12; Pairing Days 1 and 4 (unless mating was confirmed beforehand); and on Gestation Days 1, 4, and 7 for a total of eight to ten administrations, depending on mating status). For females without evidence of mating, dosing continued after completion of the 7-day pairing phase, on Postpairing Days 1, 4, and 7. Males were not dosed and were assigned to each group for mating purposes only.

- No garadacimab-related clinical observations, or changes in female body weight or body weight gain were noted.
- No garadacimab-related effects were noted on mating index, fecundity index, or fertility index. The fertility rates for drug-treated females in the control, LD, MD, and HD groups were 96, 92, 96, and 92%, respectively.
- No garadacimab-related effects on maternal reproductive parameters or embryo survival were observed.
- Prolonged aPTT and TK indicated that drug-treated females were continuously exposed to drug from 2 weeks prior to mating through Gestation Day 7. Prolongation of aPTT was not associated with any bleeding events.
- The NOAEL for maternal and developmental toxicity and female fertility was the HD, 100 mg/kg/dose.

Table 54. Methods of Female Rabbit Fertility and Early Embryonic Development Study

Parameter	Method Details
Dose and frequency of dosing:	10 (LD), 30 (MD), and 100 (HD) mg/kg/dose Once every 3 days
Route of administration:	INTRAVENOUS
Formulation/vehicle:	Drug formulation: 20mM L-histidine, 150mM (b) (4) arginine monohydrochloride, 140mM L-proline, 0.02% w/v polysorbate 80; pH 6.1 Control: 0.9% sodium chloride for injection
Species/strain:	Rabbit/Hra:(NZW)SPF
Number/sex/group:	25 Females/group
Study design:	Basis of dose selection and dosing interval: An intravenous tolerability study in rabbits (dosed on Days 1, 4, and 8), conducted by the Applicant, employed IV dose levels of 10 and 100 mg/kg garadacimab. No effects on mortality, body weights, or clinical observations were noted, accordingly. A subsequent preliminary embryo-fetal development study ((b) (4)) was conducted with garadacimab in pregnant rabbits. Animals were administered 1, 10, or 100 mg/kg garadacimab once every 3 days on Gestation Days (GD) 6, 9, 12, 15, and 18; results indicated no adverse findings, and only the pharmacologically expected test article-related aPTT prolongation was observed. The dosing regimen applied resulted in continuous exposure of animals throughout the gestation phase and was, therefore, considered appropriate for the purpose of that study. A GLP embryo-fetal development study ((b) (4)) using the same study design was also conducted with garadacimab in pregnant rabbits.
Deviation from study protocol affecting interpretation of results:	None that affected the integrity of the study.

Table generated by pharmacology/toxicology primary reviewer.

Abbreviations: aPTT, activated partial thromboplastin time; GLP, good laboratory practices; HD, high dose; LD, low dose; MD, mid dose; NZW, New Zealand white

Table 55. Observations and Results from Female Rabbit Fertility and Early Embryonic Development Study

Parameter	Major Findings																																																																																					
Mortality	No treatment-related effects.																																																																																					
Clinical signs	No treatment-related effects.																																																																																					
Body weights	No treatment-related effects.																																																																																					
Necropsy findings	No treatment-related effects. No treatment-related effects on maternal reproductive parameters or embryo survival.																																																																																					
Cesarean section data																																																																																						
Fertility and pregnancy parameters	No treatment-related effects on mating, fecundity, or fertility indexes																																																																																					
	Mating and fertility parameters of drug-treated females paired with untreated males																																																																																					
	<table border="1"> <thead> <tr> <th>Variable</th> <th>Control</th> <th>LD</th> <th>MD</th> <th>HD</th> </tr> </thead> <tbody> <tr> <td>Females cohabited</td> <td>24</td> <td>25</td> <td>25</td> <td>25</td> </tr> <tr> <td>Unscheduled deaths during cohabitation</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>Females mated</td> <td>24</td> <td>24</td> <td>25</td> <td>25</td> </tr> <tr> <td>Pregnant females</td> <td>23</td> <td>23</td> <td>24</td> <td>23</td> </tr> <tr> <td>Nonpregnant females</td> <td>1</td> <td>2</td> <td>1</td> <td>2</td> </tr> <tr> <td>Pregnant with total litter loss</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>Females with live fetuses</td> <td>23</td> <td>23</td> <td>24</td> <td>23</td> </tr> <tr> <td>Days of matings during the period of cohabitation</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td> Day 0</td> <td>23</td> <td>22</td> <td>25</td> <td>21</td> </tr> <tr> <td> Day 1</td> <td>0</td> <td>1</td> <td>0</td> <td>2</td> </tr> <tr> <td> Day 2</td> <td>1</td> <td>1</td> <td>0</td> <td>1</td> </tr> <tr> <td> Day 4</td> <td>0</td> <td>0</td> <td>1</td> <td>0</td> </tr> <tr> <td> Day 6</td> <td>0</td> <td>0</td> <td>0</td> <td>1</td> </tr> <tr> <td>Mating index (%)</td> <td>100</td> <td>96</td> <td>100</td> <td>100</td> </tr> <tr> <td>Fecundity index (%)</td> <td>96</td> <td>96</td> <td>96</td> <td>92</td> </tr> <tr> <td>Fertility index (%)</td> <td>96</td> <td>92</td> <td>96</td> <td>92</td> </tr> </tbody> </table>	Variable	Control	LD	MD	HD	Females cohabited	24	25	25	25	Unscheduled deaths during cohabitation	0	0	0	0	Females mated	24	24	25	25	Pregnant females	23	23	24	23	Nonpregnant females	1	2	1	2	Pregnant with total litter loss	0	0	0	0	Females with live fetuses	23	23	24	23	Days of matings during the period of cohabitation					Day 0	23	22	25	21	Day 1	0	1	0	2	Day 2	1	1	0	1	Day 4	0	0	1	0	Day 6	0	0	0	1	Mating index (%)	100	96	100	100	Fecundity index (%)	96	96	96	92	Fertility index (%)	96	92	96	92
Variable	Control	LD	MD	HD																																																																																		
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	Table generated by pharmacology/toxicology primary reviewer. Mating index %=mated females/females cohabited (excluding females sacrificed during cohabitation)×100 Fecundity index %=pregnant females/mated females (excluding females with an undetermined pregnancy status)×100 Fertility index %=pregnant females/females cohabited (excluding females sacrificed during cohabitation or with an undetermined pregnancy status)×100																																																																																					
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Parameter	Major Findings																																																																																								
Toxicokinetics	The increases in C_{max} and AUC_{0-72} values were generally dose proportional. The mean concentrations of garadacimab were generally slightly higher after multiple doses indicating potential accumulation of garadacimab. Summary of the garadacimab TK parameters in female rabbit plasma <table border="1"> <thead> <tr> <th>Interval</th> <th>Dose Group</th> <th>Dose Level (mg/kg/dose)</th> <th>C_0 ($\mu\text{g/mL}$)</th> <th>C_{max} ($\mu\text{g/mL}$)</th> <th>T_{max} (h)</th> <th>AUC_{0-72} ($\text{h} \cdot \mu\text{g/mL}$)</th> </tr> </thead> <tbody> <tr> <td rowspan="3">Day 1 of Dosing</td> <td>2</td> <td>10</td> <td>177^a</td> <td>186</td> <td>1.00</td> <td>7290</td> </tr> <tr> <td>3</td> <td>30</td> <td>522</td> <td>515</td> <td>0.0833</td> <td>15900</td> </tr> <tr> <td>4</td> <td>100</td> <td>1910</td> <td>1880</td> <td>0.0833</td> <td>49100</td> </tr> <tr> <td rowspan="3">Pre-mating Day 6</td> <td>2</td> <td>10</td> <td>295</td> <td>287</td> <td>0.0833</td> <td>11600</td> </tr> <tr> <td>3</td> <td>30</td> <td>666</td> <td>662</td> <td>0.0833</td> <td>26900</td> </tr> <tr> <td>4</td> <td>100</td> <td>2170</td> <td>2150</td> <td>0.0833</td> <td>75500</td> </tr> <tr> <td rowspan="3">Pre-mating Day 12</td> <td>2</td> <td>10</td> <td>282</td> <td>280</td> <td>0.0833</td> <td>12100</td> </tr> <tr> <td>3</td> <td>30</td> <td>718^a</td> <td>1430</td> <td>1.00</td> <td>31200</td> </tr> <tr> <td>4</td> <td>100</td> <td>2600</td> <td>2530</td> <td>0.0833</td> <td>85200</td> </tr> <tr> <td rowspan="3">GD 7</td> <td>2</td> <td>10</td> <td>315</td> <td>309</td> <td>0.0833</td> <td>13500</td> </tr> <tr> <td>3</td> <td>30</td> <td>812</td> <td>798</td> <td>0.0833</td> <td>30500</td> </tr> <tr> <td>4</td> <td>100</td> <td>2450</td> <td>2430</td> <td>0.0833</td> <td>85200</td> </tr> </tbody> </table> GD = Gestation day. Notes: Due to an inability to characterize the elimination phase per SOP criteria AUC_{0-inf} and CL (Day 1 of dosing only), $t_{1/2}$, V_{ss}, and MRT were not able to be calculated from any profile. Non-pregnant animals were excluded from GD 7. ^a C_0 was determined by negative back-extrapolation and should be interpreted with caution. Source: Excerpted from the Applicant's submission.						Interval	Dose Group	Dose Level (mg/kg/dose)	C_0 ($\mu\text{g/mL}$)	C_{max} ($\mu\text{g/mL}$)	T_{max} (h)	AUC_{0-72} ($\text{h} \cdot \mu\text{g/mL}$)	Day 1 of Dosing	2	10	177 ^a	186	1.00	7290	3	30	522	515	0.0833	15900	4	100	1910	1880	0.0833	49100	Pre-mating Day 6	2	10	295	287	0.0833	11600	3	30	666	662	0.0833	26900	4	100	2170	2150	0.0833	75500	Pre-mating Day 12	2	10	282	280	0.0833	12100	3	30	718 ^a	1430	1.00	31200	4	100	2600	2530	0.0833	85200	GD 7	2	10	315	309	0.0833	13500	3	30	812	798	0.0833	30500	4	100	2450	2430	0.0833	85200
Interval	Dose Group	Dose Level (mg/kg/dose)	C_0 ($\mu\text{g/mL}$)	C_{max} ($\mu\text{g/mL}$)	T_{max} (h)	AUC_{0-72} ($\text{h} \cdot \mu\text{g/mL}$)																																																																																			
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ADA	Positive ADA results were noted for the control and HD groups. The reason for ADA-positive response in control group samples was unclear. There was no evidence that control animals received garadacimab (all concentration values of garadacimab in the vehicle-control group were below the lower limit of quantitation, <500 ng/mL). The presence of ADA did not appear to have a neutralizing effect or consistently cause a reduction in observed exposure (concentration results from ADA-positive and ADA-negative animals were generally similar at comparable doses and timepoints) to garadacimab. Results from ADA-positive animals were not excluded from descriptive statistics or toxicokinetic analysis.

Table generated by pharmacology/toxicology primary reviewer.

Abbreviations: ADA, antidrug antibodies; AUC, area under the concentration-time curve; C_0 , concentration at time 0; C_{max} , maximum plasma concentration; HD, high dose; LD, low dose; MD, mid dose; MRT, mean residence time; SOP, standard operating procedure; $T_{1/2}$, half-life; T_{max} , time to maximum plasma concentration; V_{ss} , apparent volume of distribution at steady-state

CSL312: Study for Effects on Embryo-Fetal Development in the New Zealand White Rabbit by Intravenous (Bolus) Administration (Study # (b) (4))

GLP Compliance: Yes

Key Study Findings

- In this study, pregnant rabbits were administered IV doses of 10, 30, and 100 mg/kg/occasion on Gestation Days 6, 9, 12, 15 and 18. Necropsies were conducted on Day 29 after mating.
- Two HD animals were euthanized prematurely due to welfare reasons. A relationship of the two early deaths to garadacimab treatment could not be completely excluded; however, it seems unlikely given no mortality in the fertility and early embryonic development and pre- and postnatal development studies with an identical IV dose of 100 mg/kg.

- As expected for the pharmacological mechanism of action of garadacimab, an increase in aPTT was observed during treatment. The increase persisted until the end of the observation period (11 days after cessation of treatment). The aPTT prolongation suggested FXIIa inhibition at all dose levels tested. Prolongation of aPTT was not associated with any bleeding events.
- Systemic drug exposures were continuous during the period of organogenesis from Gestation Days 6 to 18 based on TK and aPTT data.
- There was no evidence of maternal toxicity related to garadacimab treatment. There were no effects of garadacimab treatment of does on F₁ offspring at all dose levels tested (e.g., no evidence of fetal harm). There were no treatment-related effects on fetal body weights and placental weights.
- There were no treatment-related external, visceral, or skeletal major abnormalities.
- Increased numbers of thoracolumbar vertebrae (20), a minor abnormality, were observed for fetuses in all garadacimab-treated groups. This finding was not reported in the laboratory historical control data.
- The NOAEL for maternal and fetal toxicity was concluded to be 100 mg/kg/occasion (HD).

Table 56. Methods of Rabbit Embryonic and Fetal Development Study

Parameter	Method Details
Dose and frequency of dosing:	10 (LD), 30 (MD), and 100 (HD) mg/kg/occasion On Gestation Days 6, 9, 12, 15 and 18 (period of organogenesis)
Route of administration:	INTRAVENOUS BOLUS
Formulation/vehicle:	0.9% isotonic saline (NaCl)
Species/strain:	New Zealand White rabbit Age of the animals at the start of the study (Day 0 after mating): 18 to 24 weeks old. Weight range of the animals at the start of the study (Day 0 after mating): 2.45 to 4.28 kg
Number/sex/group:	22/group
Study design:	Basis of dose selection and dosing frequency: A preliminary embryofetal development study (# (b) (4)) was conducted in pregnant rabbits with garadacimab. Animals were dosed with garadacimab once every 3 days on Gestation Days 6, 9, 12, 15 and 18 at doses of 1, 10 and 100 mg/kg and showed no adverse findings. The dose of 100 mg/kg was selected for the preliminary study as it was the dose for toxicity studies in mice, rabbits, and monkeys with no adverse findings. In a prior FDA review for IND 139936 dated March 25, 2019 by Dr. Brett Jones, the summary of the preliminary study was reviewed. The HD represents a 10-fold margin of the maximum intended clinical IV dose (10 mg/kg). Per ICH S5(R3), the dose should provide an approximately 10-fold exposure multiple over the maximum exposure to be achieved in the clinic.
Deviation from study protocol affecting interpretation of results:	None that affected the integrity of the study

Table generated by pharmacology/toxicology primary reviewer.

Abbreviations: HD, high dose; ICH, International Council for Harmonisation; IND, investigational new drug; LD, low dose; MD, mid dose

Table 57. Observations and Results from Rabbit Embryonic and Fetal Development Study

Parameter	Major Findings																				
Mortality	Two HD animals were euthanized prematurely due to welfare reasons. • Animal #78 was killed on Gestation Day 16. Clinical signs comprised thin build, loose feces, fecal fur staining and little or no diet eaten. Necropsy examination revealed ten live embryos. • Animal #69 was killed on Gestation Day 22. Clinical signs comprised little hay and food eaten, little water drunk, thin build, reduced fecal output, and red/pink staining on the tray paper. Necropsy examination revealed eight late resorptions and no live embryos; the red/pink staining on the undertray was considered to be due to the commencement of the expulsion of the fetal material. Decreased food consumption and disturbances of fecal output were evident in both HD females. It is noted that pregnant rabbits are sensitive to experimental manipulations that can result in gut disturbances, inappetence and subsequent abortions (Cappon et al. 2005). There was no evidence of toxicity for the F0 females in the FEED and PPND studies with an identical IV dose of 100 mg/kg administered once every 3 or 5 days. It is difficult to completely exclude a treatment relationship for the deaths of the 2 HD does; however, a relationship seems unlikely.																				
Clinical signs	No treatment-related effects.																				
Body weights	No treatment-related effects.																				
Necropsy findings	No treatment-related macroscopic abnormality.																				
Cesarean section data	The numbers of corpora lutea, implantations, implantation loss, resorptions, live fetuses and fetal sex ratio were unaffected by treatment. Fetal body weights and placental weights were unaffected by treatment.																				
Necropsy findings	No effect with treatment on litter sizes, and mean placental, litter or fetal weights.																				
Offspring	The incidence of external, visceral, and skeletal abnormalities showed no dose-relationship to garadacimab treatment at all dose levels tested. Increased observations of sternebrae fused/partially fused, a minor abnormality, were observed for fetuses in the high dose group. The incidence does not appear to exceed the laboratory historical control incidence. Increased numbers of thoracolumbar vertebrae (20), a minor abnormality, were observed for fetuses in all garadacimab-treated groups. This finding was not reported in the laboratory historical control data. Minor skeletal abnormalities <table border="1"> <thead> <tr> <th></th> <th>0</th> <th>10 mg/kg</th> <th>30 mg/kg</th> <th>100 mg/kg</th> </tr> </thead> <tbody> <tr> <td>Fetuses/Litters examined</td> <td>167(105)/21</td> <td>165(104)/21</td> <td>136(85)/19</td> <td>143(91)/17</td> </tr> <tr> <td>Sternebrae fused/partially fused</td> <td>1/1</td> <td>2/2</td> <td>1/1</td> <td>4/4</td> </tr> <tr> <td>Thoracolumbar vertebrae - 20</td> <td>5/3</td> <td>15/7</td> <td>12/6</td> <td>14/6</td> </tr> </tbody> </table> Parentheses list intact skeletons examined Table generated by pharmacology/toxicology primary reviewer.		0	10 mg/kg	30 mg/kg	100 mg/kg	Fetuses/Litters examined	167(105)/21	165(104)/21	136(85)/19	143(91)/17	Sternebrae fused/partially fused	1/1	2/2	1/1	4/4	Thoracolumbar vertebrae - 20	5/3	15/7	12/6	14/6
	0	10 mg/kg	30 mg/kg	100 mg/kg																	
Fetuses/Litters examined	167(105)/21	165(104)/21	136(85)/19	143(91)/17																	
Sternebrae fused/partially fused	1/1	2/2	1/1	4/4																	
Thoracolumbar vertebrae - 20	5/3	15/7	12/6	14/6																	

Parameter	Major Findings
Toxicokinetics	Increases of systemic exposures were dose proportional. Plasma C _{max} and AUC ₀₋₄₈ values increased in a dose-proportional manner with dose following multiple dosing. The mean half-life (t _{1/2}) values were in the range of 29-49 h. The mean accumulation ratios for C _{max} (RAC _{max}) were in the range 1.24-1.65. The mean accumulation ratios for AUC ₀₋₄₈ (RAAUC ₀₋₄₈) were in the range of 1.33-1.63. An accumulation of up to 1.81-fold was observed.

Toxicokinetic parameters from the rabbit EFD study

Group & Dose	Day		C ₀ (µg/mL)	C _{max} (µg/mL)	t _{max} (h)	AUC ₀₋₄₈ (h*µg/mL)	AUC ₀₋₇₂ (h*µg/mL)	t _{1/2} (h)	RA _{Cmax}	RA _{AUC0-48}
1 0 mg/kg	6	N	5	5	-	-	-	-	-	-
		Mean	blq	blq	-	-	-	-	-	-
		Min	blq	blq	-	-	-	-	-	-
		Median	blq	blq	-	-	-	-	-	-
		Max	blq	blq	-	-	-	-	-	-
	18	N	5	5	-	-	-	-	-	-
		Mean	blq	blq	-	-	-	-	-	-
		Min	blq	blq	-	-	-	-	-	-
		Median	blq	blq	-	-	-	-	-	-
		Max	blq	blq	-	-	-	-	-	-
2 10 mg/kg	6	N	5	5	5	5	5	5	5	5
		Mean	231	267	0.45	6878	8509	32.7	-	-
		Min	116	250	0.08	6210	7738	29.8	-	-
		Median	251	255	0.08	6544	7884	30.6	-	-
		Max	295	292	1.00	8473	10968	42.6	-	-
	18	N	5	5	5	5	5	5	5	5
		Mean	444	439	0.26	11131	13911	36.9	1.65	1.63
		Min	403	405	0.08	9949	12254	33.2	1.39	1.52
		Median	446	443	0.08	10939	13781	35.1	1.70	1.56
		Max	475	463	1.00	12955	16129	47.3	1.81	1.76
3 30 mg/kg	6	N	5	5	5	5	5	5	5	5
		Mean	889	883	0.26	21008	25411	29.3	-	-
		Min	786	814	0.08	19184	22337	23.7	-	-
		Median	834	822	0.08	20813	25785	31.1	-	-
		Max	1055	1033	1.00	23081	27545	33.9	-	-
	18	N	5	5	5	5	5	5	5	5
		Mean	1144	1133	0.26	31461	39602	49.1	1.28	1.49
		Min	625	614	0.08	20018	27526	29.8	0.75	1.04
		Median	1233	1219	0.08	32728	40887	36.8	1.36	1.57
		Max	1411	1384	1.00	37568	45701	94.8	1.63	1.71
4 100 mg/kg	6	N	5	5	5	5	5	5	-	-
		Mean	3053	3058	0.26	65362	77696	28.7	-	-
		Min	2673	2635	0.08	54247	67428	21.7	-	-
		Median	2710	2888	0.08	62549	74218	26.7	-	-
		Max	4260	4197	1.00	84347	98440	37.1	-	-
	18	N	5	5	5	5	5	5	5	5
		Mean	3633	3677	0.26	85332	106828	42.8	1.24	1.33
		Min	3072	3469	0.08	75320	99845	26.6	0.83	1.01
		Median	3668	3593	0.08	83105	105101	38.2	1.32	1.34
		Max	4162	4146	1.00	102432	123029	68.0	1.41	1.61

blq below limit of quantification (<100.726 ng/mL)

Excerpted from Applicant's submission

ADA	The ADA results were inconclusive as the control animals were tested positive. In the control, 4/22 (approx. 18.2%) animals tested positive on Day 19, and 3 of these 4 animals remained positive on Day 29. These results are considered false positive due to unknown reasons, as no garadacimab was detected in plasma (toxicokinetic) samples taken from the control. garadacimab plasma concentration at the time of ADA sampling remained above the drug tolerance level in the assay system. Since exposure to garadacimab and pharmacodynamic activity (i.e., aPTT prolongation) was confirmed throughout the study, potential ADA formation was not considered to have impacted the outcome of the study.
APTT	Mean aPTT values determined approximately 5 min after the first injection were more than three-fold higher in garadacimab-treated animals than in the control. The mean aPTT on Day 18 (approximately 5 min after the fifth and final administration) showed mean values approximately 4- to 5-fold higher than the control. On Day 29 after mating (11 days after the last dose), mean aPTT values of treated animals remained approximately 4- to 6-fold higher than the control. There was no clear dose-relationship shown.

Parameter	Major Findings			
	Based on an in vitro spike study (# (b) (4)) performed in the same laboratory (garadacimab spiked in rabbit plasma followed by aPTT determination) and the doses/dosing regimen used in the present study, the lack of dose-dependency in aPTT was expected since maximum FXIIa inhibition and respective aPTT prolongation would be expected at all doses. Prolongation of APTT was not associated with any bleeding events.			
	Mean aPTT values in seconds (x, -fold over the control)			
Group	Day 6 (post dose – approximately 5 minutes after first dosing)	Day 12 (pre-dose - after two doses, one on each of Days 6 and 9)	Day 18 (post dose – approximately 5 min after fifth doses)	Day 29 (eleven days after last dose)
1	28.7 sec	30.6 sec	30.1 sec	22.8 sec
2	x3.31**	x3.74**	x4.81**	x3.80**
3	x3.82**	x3.77**	x5.20**	x6.36**
4	x3.33**	x3.23**	x3.96**	x5.79**

** statistically significant (p<0.01)

Source: Excerpted from the Applicant's submission.

Abbreviations: ADA, antidrug antibodies; APTT, activated partial thromboplastin time; AUC, area under the concentration-time curve; C₀, concentration at time 0; C_{max}, maximum plasma concentration; FEED, fertility and early embryonic development; HD, high dose; IV, intravenous; PPND, pre- and postnatal development; RAAUC₀₋₄₈, accumulation ratio for the area under the concentration-time curve from 0-48 h; RAC_{max}, accumulation ratio of the maximum plasma concentration; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration

CSL312: A Pre- and Postnatal Development Study Including Toxicokinetics Following a Subcutaneous or Intravenous Injection in Rabbits (Study #8410864)

GLP Compliance: Yes

Key Study Findings

- In this study, pregnant rabbits (F0) were administered garadacimab doses of 0, 10 (LD), 30 (MD), and 100 (HD) mg/kg/dose by SC, and 100 (HD) mg/kg/dose by IV, once every 5 days from implantation (Gestation Day 7) through weaning (Lactation Day 38). F0 toxicity animals were dosed on Gestation Day 7, 12, 17, 22, and 27 and Lactation Days 3, 8, 13, 18, 23, 28, 33, and 38. F0 placental transfer animals were dosed on Gestation Day 7, 12, 17, 22, and 27. The F1 generation were not directly administered the test article.
- For F0 dams, no garadacimab-related effects were observed on mortality, clinical signs, body weight, natural delivery, litter data, or maternal macroscopic observations.
- For the F1 generation, no garadacimab-related effects were observed on mortality, clinical signs, body weight, developmental signs, functional observation battery, eye blink response, presence of motile sperm, reproductive performance, cesarean section parameters, or preweaning or postweaning macroscopic observations.
- Garadacimab-related prolongation in aPTT was observed in all treated F0 females. It was an expected pharmacological effect of garadacimab.
 - For TK, the increases in exposures (mean C_{max} and AUC₀₋₁₂₀ values) were generally less than dose proportional in dose levels from 10 to 100 mg/kg SC. Accumulation was observed after multiple SC and IV doses. Fetal to maternal concentration ratios ranged from 2% to 6.5% following SC doses and 2.8% following IV doses. On Gestation

- Day 29, fetal parturition plasma garadacimab concentrations were 76.6%, 136.6%, and 40.8% of the maternal concentrations, at SC LD, SC MD, and SC HD, respectively. At IV HD, maternal and fetal garadacimab concentrations were approximately equivalent.
- Prolongation of aPTT values and TK indicated that drug exposure was continuous during the gestation and lactation periods in F0 maternal animals.
 - Maternal ADA incidence was 43.6% (17 of 39), 16.7% (7 of 42), and 11.1% (5 of 45) for SC LD, SC MD, and SC HD, respectively, and 6.8% (3 of 44) for IV HD. ADA was all negative for control maternal animals. The SC LD appeared to have a higher incidence of maternal positive ADA induction.
 - The maternal NOAEL is 100 mg/kg/dose (HD) SC/IV. In the F1 generation, the NOAEL for fetal development is 100 mg/kg/dose (HD) SC/IV. The NOAEL for developmental, neurobehavioral, and reproductive performance in the F1 generation is 100 mg/kg/dose (HD) SC/IV.

Table 58. Methods of Prenatal and Postnatal Development Study in Rabbits

Parameter	Method Details
Dose and frequency of dosing:	SC: 10 (LD), 30 (MD), and 100 (HD) mg/kg/dose IV: 100 (HD) mg/kg/dose The test article, garadacimab, on pregnant and lactating females when administered once every 5 days by subcutaneous or intravenous injection to female rabbits from implantation (GD 7) through weaning (Lactation Day 38) and to assess the maturation, reproductive function, and neurobehavioral development of F1 offspring. F0 toxicity animals were dosed on GD 7, 12, 17, 22, and 27 and Lactation Days 3, 8, 13, 18, 23, 28, 33, and 38. F0 placental transfer, animals were dosed on GD 7, 12, 17, 22, and 27.
Route of administration:	SC and IV (bolus) injection
Formulation/vehicle:	Drug formulation: 20mM L-histidine, 150mM ^(b) arginine monohydrochloride, 140mM L-proline, 0.02% w/v polysorbate 80; pH 6.1 Control: 0.9% sodium chloride for injection
Species/strain:	Rabbit/HsdHra:(NZW)SPF Time-mated female HsdHra:(NZW) SPF rabbits were received from ^{(b) (4)} At initiation of dosing, animals were 8 months old, and body weights ranged from 3099 to 4088 g.
Number/sex/group:	Toxicity animals: 25 Females/group Placental transfer animals: 3 Females/group

Parameter	Method Details
Study design:	Basis of dose selection: The dose levels for this pre- and postnatal developmental toxicity study were determined based upon the previously conducted male and female fertility studies with garadacimab ((b) (4) Study (b) (4) and (b) (4) Study (b) (4)). The male and female fertility studies were conducted in NZW rabbits at dose levels of 10, 30, and 100 mg/kg administered once every 3 days via IV injection. No garadacimab-related paternal or maternal mortality occurred. No garadacimab-related clinical observations or effects on mean body weight or mean food consumption were observed. Mating and fertility indices in both sexes were not affected by garadacimab. Dose levels for this prenatal and postnatal developmental toxicity study were 10, 30, or 100 mg/kg once every 5 days. The dosing frequency was changed from once every 3 days to once every 5 days.
Deviation from study protocol affecting interpretation of results:	None that affected the integrity of the study

Table generated by pharmacology/toxicology primary reviewer.

Abbreviations: GD, gestational day; HD, high dose, IV, intravenous; LD, low dose; MD, mid dose; NZW, New Zealand white

Table 59. Observations and Results from Prenatal and Postnatal Development Study in Rabbits

Parameter	Major Findings
F0 Dams mortality	No treatment-related effects.
F0 Dams clinical signs	No treatment-related effects.
F0 Dams body weights	No treatment-related effects.
F0 Dams litter observations	No treatment-related effects on natural delivery or litter data were observed. The number of kits found dead (stillborn) was elevated for the SC HD group (0.56 versus 0.17 per litter for the control group); however, no difference evident for the IV HD group in which higher systemic drug exposures were achieved.
F0 Dams necropsy findings	No treatment-related F0 maternal macroscopic observations.
F1 Mortality	No treatment-related mortality occurred following weaning.
F1 Clinical signs	No treatment-related effects.
F1 Body weights	No treatment-related effects.
F1 Development	No treatment-related effects.
F1 Neurobehavioral assessments - functional observation battery and eye blink response	No treatment-related effects.
F1 Prewaning necropsy	During the lactation phase, no treatment-related macroscopic observations
F1 Sperm presence	No treatment-related effects.
F1 Reproductive indices	No treatment-related effects on mating, fecundity, or fertility indices.
F1 Necropsy for assessments of mating and reproductive performance	No treatment-related macroscopic observations.
Cesarean section data for F1 does	No treatment-related effects.

Table generated by pharmacology/toxicology primary reviewer.

Abbreviations: HD, high dose, LD, low dose; MD, mid dose; SC, subcutaneous

13.1.4.4. Other Toxicology/Specialized Studies

Cross-Reactivity Study in Human Tissues and Selective Cynomolgus Monkey Tissues (Study # (b) (4))

The aim of this GLP study was to assess the potential cross-reactivity of garadacimab with specified tissues from human and cynomolgus monkey origin. Garadacimab (5, 2.5, and 1.25 µg/mL) and an isotype control antibody (5 and 2.5 µg/mL) were applied to a full panel of normal human and cynomolgus monkey tissues. Specific staining was observed with garadacimab in many human tissues; with strongest staining intensities observed in liver, bone marrow, lung, spinal cord, cerebral cortex, and eye (optic nerve). No staining was observed with garadacimab on human ovary, cervix, striated muscle, colon, ileum, thyroid, and endothelium. Specific staining in cynomolgus monkeys was predictive of staining in human tissues, with the exception of parathyroid, where only specific staining was observed in human tissues.

Local Tolerance and Bioequivalence Study of Two CSL312 Formulations Following Subcutaneous Administration in Rabbits (Study # (b) (4))

Key Study Findings

- In the GLP-compliant local tolerance study, two groups (3 sex/group, around 5 weeks old) of New Zealand white rabbits were treated with two formulations of garadacimab (batch no. 834101076 or batch no. 8120000014) SC on the right side (dorsal skin) of the animals on test days 1 and 8. All animals were treated with 0.9% NaCl solution as negative control on the left side. Following an observation period of 11 days after administration, all animals were sacrificed and the injection sites were examined macro- and microscopically.
- There were no signs of toxicity evident from clinical signs, body weights, macroscopic changes, and microscopic changes.
- In group 1, lymphohistiocytic infiltration (3/3 males), neutrophilic granulocytes in the subcutis (2/3 males), and hemorrhage (3/3 females) were noted on the right side (garadacimab-treated). In group 2, lymphohistiocytic infiltration (1/3 males, 1/3 females), neutrophilic granulocytes in the subcutis (1/3 males, 1/3 females), and hemorrhage (1/3 females) were noted on the right side (garadacimab treated).
- The two formulations showed similar PK profiles.
- Repeated SC administration of two formulations of garadacimab on 2 days was well tolerated and did not reveal any test item-related changes at the injection sites.

Extractables and Leachables Studies With the Container Closure System

Garadacimab was developed as a combination product incorporating a prefilled syringe which contains 200 mg of the formulated garadacimab active substance, defined as the garadacimab semifinished product 200 mg. Extractables and leachables studies were conducted with the container closure system which were evaluated (see review dated June 5, 2024). (b) (4)

(b) (4). The levels of leachables from the primary container closure system of garadacimab

semifinished product 200 mg were judged to pose no safety concerns. The assessment was not ideal as only one batch was evaluated.

13.1.4.5. Safety Margins

NOAELs in nonclinical toxicology and reproductive toxicity studies provide adequate safety margins for the clinical dose, consisting of a loading dose at 400 mg (2×200 mg) followed by 200 mg once a month.

Table 60. Summary Human Drug Exposure With Maximum Recommended Human Dose (MRHD) of SC Loading Dose of 400 mg (2×200 mg) Followed by 200 mg Once a Month

Variable	AUC _{0-30 days} (h·ng/mL)	C _{max} (ng/mL)
MRHD ¹ : 400 mg SC loading dose followed by 200 mg once a month	10300000	21200

Table generated by pharmacology/toxicology primary reviewer.

¹ Based on trial 3001.

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; SC, subcutaneous

Table 61. Animal to Human Exposure Margins for Garadacimab Based on General and Reproductive Toxicology Studies

Study	NOAEL (mg/kg/dose)	Nonclinical		Nonclinical C _{max} (ng/mL)	AUC Margins	C _{max} Margins
		Nonclinical AUC (ng·h/mL)	AUC Adjusted to AUC _{0-30 days} (ng·h/mL)			
Monkey 26-Week	60 mg/kg/week (SC)	89395000 (AUC _{0-168h})	383121429	596000	37.2	28
Monkey 26-Week	30 mg/kg/week (IV)	75666000 (AUC _{0-168h})	324282857	1012000	31.5	47.7
Male rabbit FEED study	100	106000000 (AUC _{0-72h})	1060000000	2930000	103	138
Female rabbit FEED study	100	85200000 (AUC _{0-72h})	852000000	2430000	82.7	114.5
Rabbit EFD study	100	106828000 (AUC _{0-72h})	1068280000	3677000	103.7	173.3
Rabbit PPND study	100 (SC, for both F0 and F1)	91800000 (AUC _{0-120h})	550800000	927000	53.5	43.7

Table generated by pharmacology/toxicology primary reviewer.

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; EFD, embryofetal development; FEED, fertility and early embryonic development; IV, intravenous; NOAEL, no observed adverse effect level; PPND, pre-and postnatal development; SC, subcutaneous

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

None. All studies were submitted to the IND.

14. Clinical Pharmacology

14.1. In Vitro Studies

Not applicable.

14.2. In Vivo Studies

Clinical studies providing clinical pharmacology information for garadacimab are summarized in [Table 62](#).

Table 62. Summary of Clinical Pharmacology Studies

Study/ Trial	Design	Drug Product and Formulation ^a	Dose and Regimen ^b
1001	Phase 1 SAD in healthy subjects	Vialed product 100 mg/mL solution	IV: 0.1, 0.3, 1, 3, or 10 mg/kg; single dose infused over 60 min SC: 1, 3, or 10 mg/kg; single dose
1003	Phase 1 SAD in healthy Japanese and Caucasian subjects	Vialed product (IV) 100 mg/mL solution 200 mg PFS (SC) 170 mg/mL solution	IV: 3 or 10 mg/kg; single dose infused over 60 min SC: 200 or 600 mg; single dose
1004	Phase 1 relative BA study between PFS and AI in healthy subjects	200 mg PFS 200 mg AI 170 mg/mL solution	200 mg SC; single-dose administered via PFS or AI
2001	Phase 2 dose-ranging trial in subjects with HAE	Vialed product 100 mg/mL solution	Blinded Treatment Period (13 weeks) ^c : 40 mg IV loading dose then 75 mg SC Q4W 100 mg IV loading dose then 200 mg SC Q4W 300 mg IV loading dose then 600 mg SC Q4W 400 mg SC Q2W Open-Label Treatment (44 weeks): 200 or 600 mg SC Q4W
3001	Phase 3 efficacy trial in subjects with HAE	200 mg PFS 170 mg/mL solution	400 mg SC loading dose then 200 mg SC Q4W ^d
3002	Phase 3 open-label long-term extension study in subjects with HAE	200 mg PFS 200 mg AI 170 mg/mL solution	Rollover from 2001 or 3001: 200 mg SC Q4W Garadacimab-naïve: 400 mg SC loading dose then 200 mg SC Q4W ^d

Source: Table 1, Summary of Clinical Pharmacology; Table 1, Tabular Listing of Clinical Studies; Clinical Study Reports for 1001, 1003, 1004, 2001, 3001, and 3002.

^a The to-be-marketed formulation and presentation is the 170 mg/mL solution available as PFS or AI. These formulations/presentations were used in studies 1003, 1004, and 3002 and trial 3001.

^b Only garadacimab dosage regimens are shown. Study 1001 and trials 2001 and 3001 also included placebo arms.

^c In the blinded Treatment Period in 2001, IV loading doses were administered on Day 1 and administration of SC doses began approximately 1 week later.

^d In 3001 and 3002, the 400 mg SC loading dose was administered on Day 1 and administration of the 200 mg SC doses began approximately 1 month later.

Abbreviations: AI, autoinjector; BA, bioavailability; HAE, hereditary angioedema; IV, intravenous; PFS, prefilled syringe; Q4W, every 4 weeks; SAD, single ascending dose; SC, subcutaneous

The proposed to-be-marketed (TBM) drug products for SC administration include a 200 mg/1.2 mL prefilled syringe with needle safety device (PFS-NSD) and a 200 mg/1.2 mL autoinjector (AI). The TBM formulation is a solution with a garadacimab concentration of 170 mg/mL. The TBM formulation in the PFS-NSD presentation was used in studies 1003, 1004, and 3002 and trial 3001. The AI presentation was used in studies 1004 and 3002.

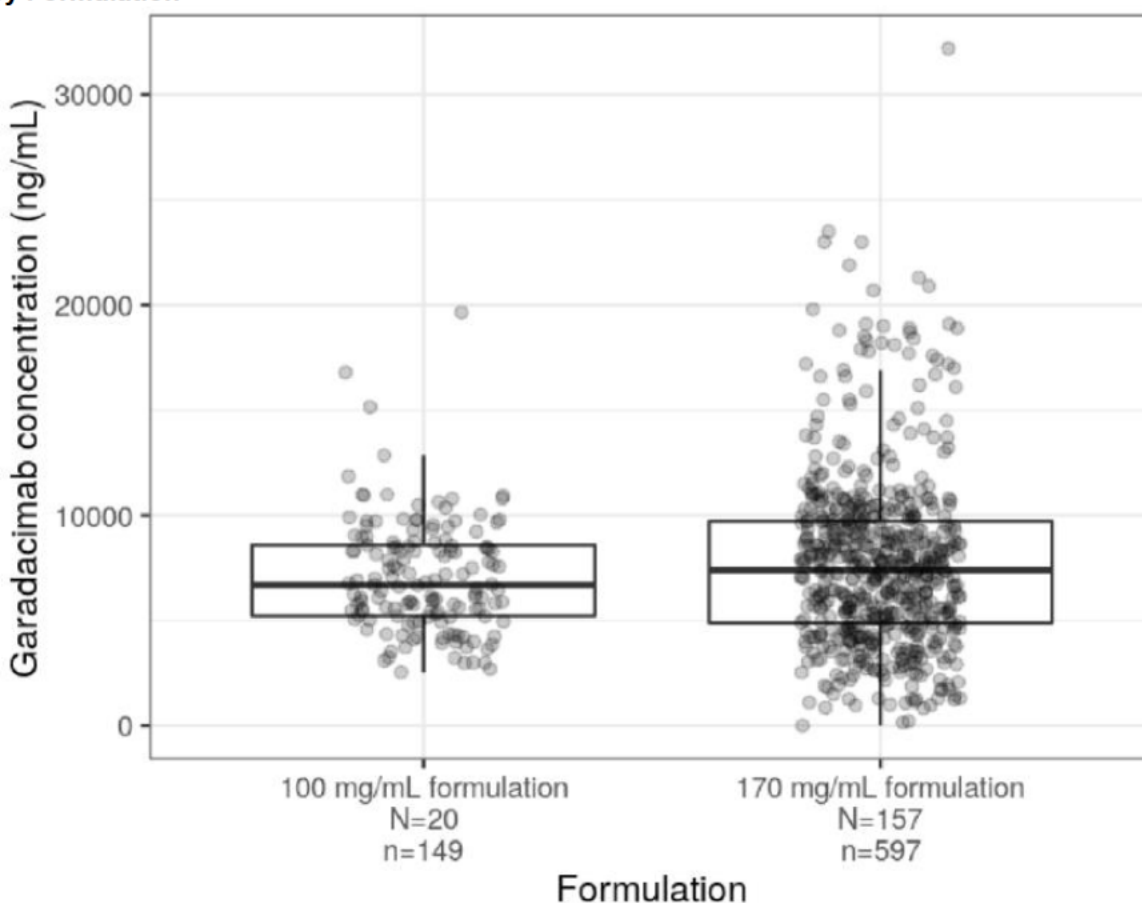
Across all clinical studies, two drug product formulations have been evaluated, including a 100 mg/mL solution formulation (vial presentation), and the TBM 170 mg/mL solution formulation. The two formulations contain the same excipients at the same concentration and only differ in garadacimab concentration. The 100 mg/mL formulation was used in studies 1001, and 1003 (IV arms only) and trial 2001. Direct clinical data comparing garadacimab exposure following administration of the two formulations are not available. The Applicant's rationale to support equivalence of the formulations is based on the following:

- A single dose nonclinical PK study in rabbits comparing the two formulations at a dose of 20 mg/kg showing a similar PK profile.
- A comparison of the steady state trough concentration across trials 2001 (100 mg/mL) and 3001 and study 3002 (170 mg/mL) using population PK indicated that formulation has no impact on garadacimab PK.

Garadacimab steady state trough concentrations following a 200-mg dose, stratified by formulation, are shown in [Figure 20](#). The data show that the median steady state trough concentrations are slightly higher using the 170 mg/mL formulation (visually estimated at about 7500 ng/mL) relative to the 100 mg/mL formulation (visually estimated at about 7000 ng/mL). However, there is large overlap in the distributions based on the observed data.

The mean (SD) steady-state trough concentrations in trial 2001 among subjects who were randomized to receive 200 mg SC every 4 weeks (Q4W) ranged from 6414 (2728) to 7001 (1715) ng/mL in Treatment Period 1; and 5718 (2271) to 7656 (2728) ng/mL in Treatment Period 2 (data derived from Table 14.2.2.6.4, Clinical Study Report [CSR] for trial 2001). Mean (SD) steady state trough concentrations in trial 3001 ranged from 8087 (4277) to 8692 (3934) ng/mL. Mean (SD) steady-state trough concentrations in study 3002 ranged from 7429 (4759) to 7882 (4276) ng/mL. Overall, garadacimab trough concentrations at steady state overlap between the 100 mg/mL formulation and the 170 mg/mL formulation.

Figure 20. Garadacimab Steady-State Trough Concentrations Following 200 mg SC QM, Stratified by Formulation



Source: Figure 11, Summary of Clinical Pharmacology.
The 100 mg/mL formulation was used in trial 2001 and the 170 mg/mL formulation was used in trial 3001 and study 3002. All observations were taken at steady state (following 3 months of dosing) and between 24 and 34 days after the previous dose (200 mg SC QM or Q4W only). Boxes represent the IQR; horizontal line within the boxes represent medians, and whiskers represent 1.5× IQR. Circles represent individual observed data.
Abbreviations: IQR, interquartile range; Q4W, once every 4 weeks; QM, once monthly; SC, subcutaneous

14.2.1. Study 1004 (Relative Bioavailability Study Comparing PFS-NSD and AI)

Title

A phase 1, randomized, open-label, parallel-group study to compare the PK properties of garadacimab administered by SC prefilled syringe assembled to AI to prefilled syringe assembled to needle safety device in healthy adult subjects.

Objectives

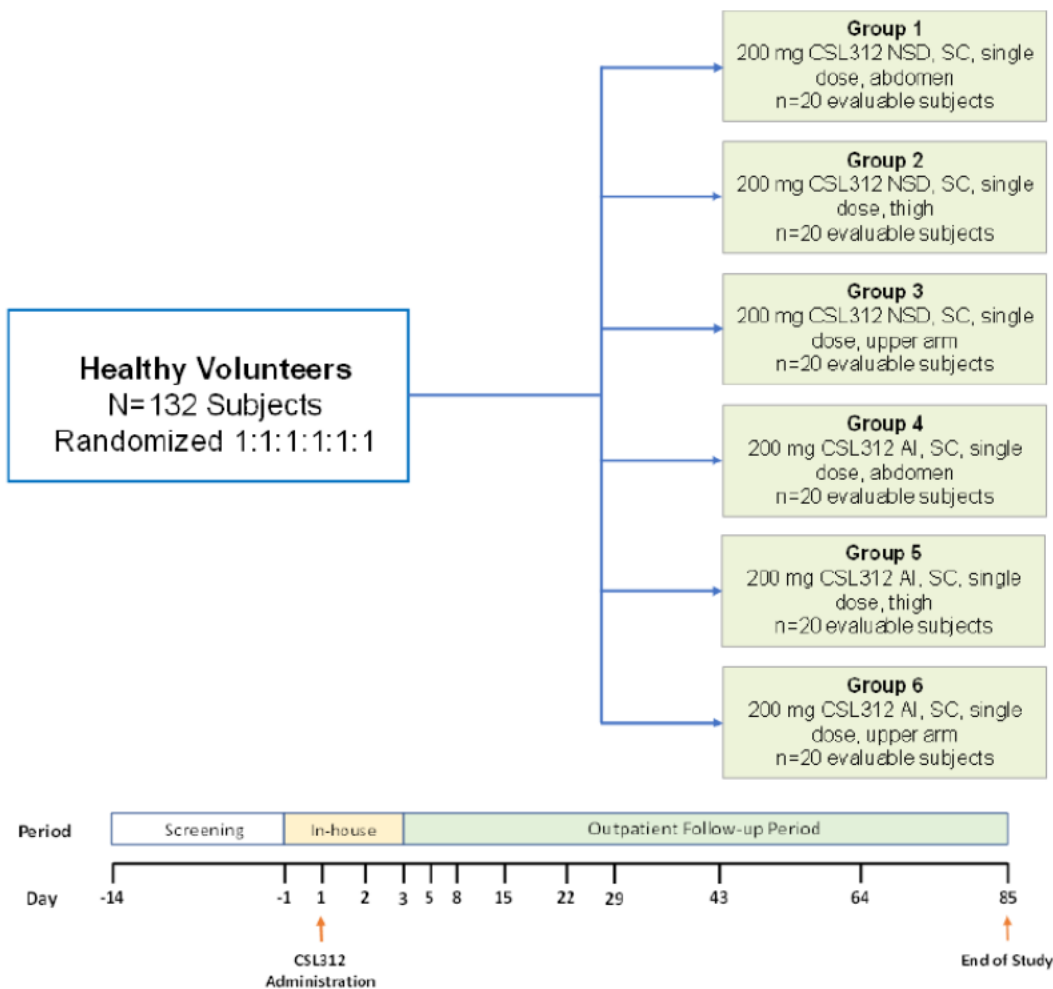
Primary objectives of the study were to characterize and compare the PK of a single SC injection of garadacimab administered via garadacimab AI or garadacimab PFS-NSD. Safety and tolerability were also assessed as secondary objectives.

Study Design

Study 1004 was designed as an open-label, parallel-group study in healthy adult subjects (Figure 21). Subjects were stratified by body weight (i.e., <80 kg or ≥80 kg) and then randomized 1:1:1:1:1:1 to one of six groups defined based on device (i.e., PFS-NSD or AI) and injection site (i.e., abdomen, thigh, or upper arm). All subjects received a single 200 mg SC dose of garadacimab.

The study enrolled male or female subjects aged 18 to 55 years, with body weight between 50 and 100 kg, inclusive, and body mass index between 18 and 30 kg/m², inclusive. The only permitted therapies included hormonal contraceptives, as required; therapies to treat adverse events (AEs); and all non-live vaccines, including vaccines against COVID-19. Administration of any other investigational agent within five half-lives of 30 days, whichever was longer, before administration of garadacimab was prohibited during the study.

Figure 21. Study Design, Study 1004



CSL312 AI = prefilled CSL312 syringe assembled with an autoinjector; CSL312 NSD = prefilled CSL312 syringe assembled with a needle safety device; N = total number of subjects; SC = subcutaneous.

Source: Figure 9-1, Clinical Study Report for study 1004.
Abbreviations: CSL312, garadacimab

PK and Immunogenicity Sampling

Blood PK samples were collected at predose on Day 1, and postdose at Hours 8, 24, 32, and 48 and Days 5, 8, 15, 22, 29, 43, 64, and 85.

Immunogenicity samples were collected at predose on Day 1, and on Days 29 and 85.

Subject Disposition and Demographics

A total of 132 subjects were randomized to treatment and received garadacimab, including 66 subjects each who received the AI and PFS-NSD (AI: N=22 per injection site; PFS-NSD: N=21 to 23 per injection site). Overall, 131 subjects completed the study. One subject in the AI group was lost to follow-up and discontinued the study ([Table 63](#)).

The mean (SD) body weight at baseline was 73.0 (9.8) kg in the PFS-NSD group and 75.2 (11.5) kg in the AI group. In each device group, most subjects had body weight <80 kg: 46/66 (70%) subjects in the AI group, and 47/66 (71%) subjects in the PFS-NSD group.

Table 63. Garadacimab Allocation by Device, Injection Site, and Body Weight Group, Study 1004

	CSL312 DP 200 mg NSD (N = 66)			CSL312 DP 200 mg AI (N = 66)		
	< 80 kg n (%)	≥ 80 kg n (%)	Total n (%)	< 80 kg n (%)	≥ 80 kg n (%)	Total n (%)
Anatomical Location						
Abdomen	15 (31.9)	6 (31.6)	21 (31.8)	15 (32.6)	7 (35.0)	22 (33.3)
Thigh	16 (34.0)	6 (31.6)	22 (33.3)	15 (32.6)	7 (35.0)	22 (33.3)
Upper Arm	16 (34.0)	7 (36.8)	23 (34.8)	16 (34.8)	6 (30.0)	22 (33.3)
Total	47 (100.0)	19 (100.0)	66 (100.0)	46 (100.0)	20 (100.0)	66 (100.0)

AI = autoinjector; CSR = clinical study report; DP = drug product; NSD = needle safety device.

Note 1: Percentages are calculated with the number of subjects in each treatment group as the denominator (N).

Note 2: The AI (garadacimab 200 mg AI) is a device that contains the same prefilled syringe as in garadacimab 200 mg NSD. For the purposes of the CSR, the nomenclature in the data outputs of 200 mg CSL312 AI and 200 mg CSL312 NSD has been revised to CSL312 DP 200 mg AI and CSL312 DP 200 mg NSD, respectively, to remain consistent with the updated nomenclature implemented in the clinical development program.

Source: Table 12-1, Clinical Study Report for study 1004.

Abbreviation: CSL312, garadacimab

PK Analysis

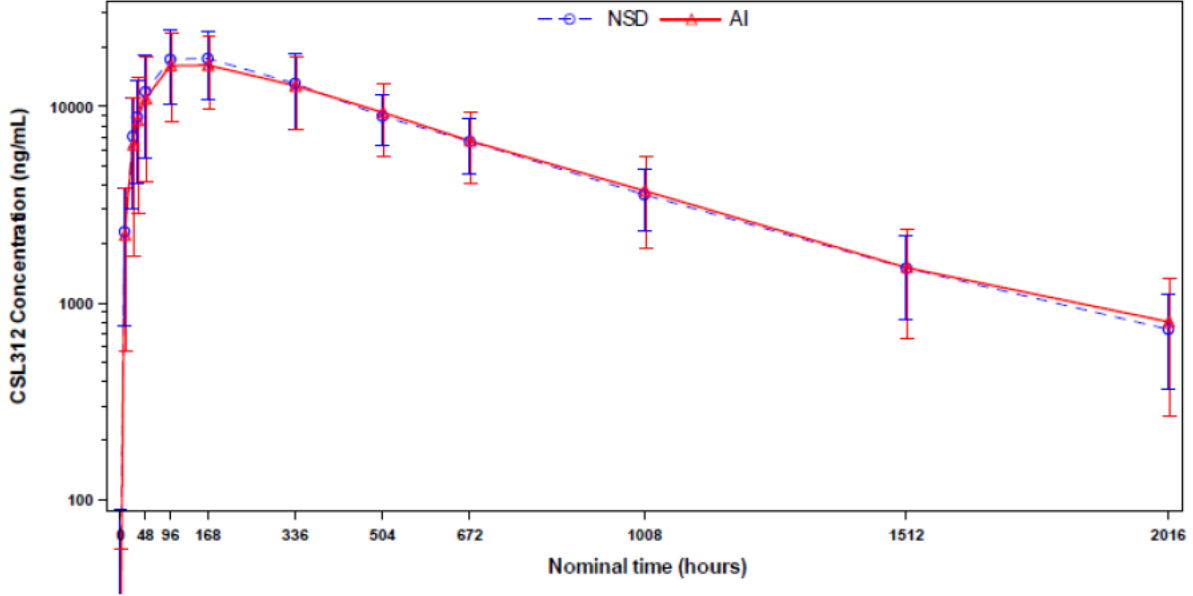
The 132 subjects in the PK Analysis Set comprised those who received garadacimab and had at least one quantifiable concentration measurement. PK parameters were estimated using noncompartmental analyses. Point estimates and 90% CIs for geometric mean ratios were derived from log-transformed PK parameters.

PK Results

Mean (SD) garadacimab concentration-time profiles by device are shown in [Figure 22](#). PK parameters by device are shown in [Table 64](#). Statistical analyses of C_{max} and AUC_{0-inf} are shown in [Table 65](#). Across both treatment groups, the median time to maximum concentration (T_{max}) was approximately 6 days and the mean (SD) half-life was 17.4 (3.1) days. Bioequivalence

criteria were met between the PFS-NSD and the AI. The geometric mean ratios and 90% CIs for C_{max} and AUC_{0-inf} comparing the AI to the needle safety device were 0.923 (0.813, 1.05) and 0.963 (0.866, 1.07), respectively.

Figure 22. Mean (SD) Garadacimab Concentration-Time Profiles by Device, Study 1004



AI = autoinjector; NSD = needle safety device; SD = standard deviation.
Source: Figure 11-1, Clinical Study Report for study 1004.
Data shown on a log-linear scale.
Abbreviation: CSL312, garadacimab

Table 64. Garadacimab PK Parameters by Device, Study 1004

Variable	CSL312 DP 200 mg NSD (N = 66)	CSL312 DP 200 mg AI (N = 66)	Total (N = 132)
C_{max} (µg/mL)			
n	66	66	132
Mean (SD)	18.900 (7.0549)	17.944 (7.4230)	18.422 (7.2296)
Median	18.550	17.100	17.800
Min, Max	6.20, 42.10	3.57, 36.30	3.57, 42.10
T_{max} (h)			
n	66	66	132
Median	144.88	145.08	144.93
Min, Max	48.0, 313.8	48.0, 360.8	48.0, 360.8
AUC_{0-inf} (h•µg/mL)			
n	66	65	131
Mean (SD)	11,542.051 (3723.2243)	11,393.525 (4484.7026)	11,468.355 (4103.4526)
Median	11,446.916	10,380.492	11,254.509
Min, Max	4149.21, 22,797.44	3872.18, 26,861.40	3872.18, 26,861.40
AUC_{0-last} (h•µg/mL)			
n	66	66	132
Mean (SD)	11,066.617 (3513.9507)	10,732.825 (4329.3133)	10,899.721 (3931.2595)
Median	10,906.074	9968.163	10,669.207
Min, Max	4016.93, 22,047.94	1103.54, 24,644.23	1103.54, 24,644.23
t_{1/2} (h)			
n	66	65	131
Mean (SD)	422.497 (69.5073)	414.284 (81.0526)	418.422 (75.2785)
Median	426.001	394.484	414.974
Min, Max	293.67, 605.89	206.32, 596.63	206.32, 605.89
CL/F (L/h)			
n	66	65	131
Mean (SD)	0.01934 (0.007308)	0.02059 (0.009192)	0.01996 (0.008288)
Median	0.01747	0.01927	0.01777
Min, Max	0.0088, 0.0482	0.0074, 0.0517	0.0074, 0.0517
V_d/F (L)			
n	66	65	131
Mean (SD)	11.585 (4.1792)	12.096 (6.0427)	11.839 (5.1745)
Median	10.585	11.445	10.975
Min, Max	5.02, 29.66	5.58, 41.65	5.02, 41.65

AI = autoinjector; AUC_{0-inf} = AUC from time 0 extrapolated to infinite time; AUC_{0-last} = area under the concentration-time curve from time 0 to the last measurable concentration; CL/F = apparent clearance; C_{max} = maximum concentration; CSR = clinical study report; DP = drug product; Max = maximum; Min = minimum; n = number of subjects with non-missing value; N = number of subjects; NSD = needle safety device; SD = standard deviation; t_{1/2} = half-life; T_{max} = time to maximum plasma concentration; V_d/F = apparent volume of distribution

Source: Table 11-2, Clinical Study Report for study 1004.

Abbreviation: CSL312, garadacimab

Table 65. Statistical Analysis of C_{max} and AUC for AI Versus NSD, Study 1004

Parameter	Geometric Mean				Geometric Mean Ratio	90% CI (%)
	AI	n	NSD	n		
C _{max} (µg/mL)	16.2	66	17.6	66	0.923	0.813, 1.05
AUC _{0-inf} (µg•h/mL)	10,556	65	10,957	66	0.963	0.866, 1.07

AI = autoinjector; AUC_{0-inf} = area under the plasma concentration-time curve extrapolated to infinity;
CI = confidence interval; C_{max} = maximum plasma concentration; CSR = clinical study report; NSD = needle safety device.

Source: Table 5, Summary of Clinical Pharmacology.

The reviewer’s statistical analysis was conducted by performing nonlinear mixed effects modeling to determine the geometric mean ratios and associated 90% CIs of C_{max}, AUC_{0-last}, and AUC_{0-inf}. The reviewer’s analysis corroborates the Applicant’s conclusions that bioequivalence criteria were met between the PFS-NSD and AI.

PK by Injection Site

PK parameters by device and injection site are shown in [Table 66](#). The distributions of C_{max} and AUC_{0-inf} by injection site and device are shown in [Figure 23](#). In general, PK parameters, including C_{max}, AUC, T_{max}, and T_{1/2}, were similar across injection sites and devices.

Table 66. Mean (SD) Garadacimab PK Parameters by Device and Injection Site, Study 1004

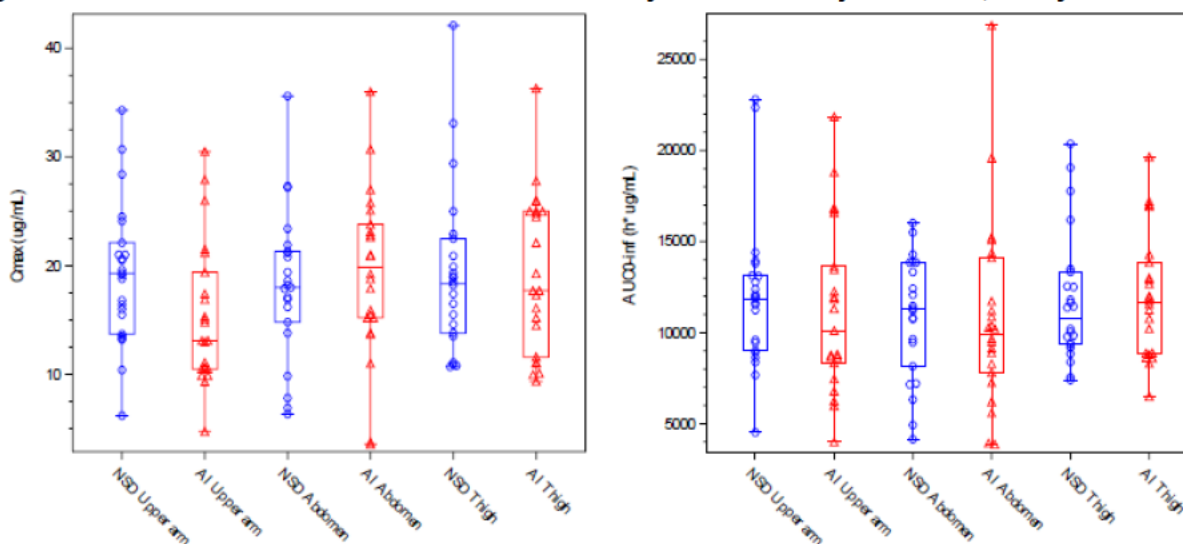
PK Parameter	200 mg PFS-NSD			200 mg AI		
	Abdomen (N=21)	Thigh (N=22)	Upper Arm (N=23)	Abdomen (N=22)	Thigh (N=22)	Upper Arm (N=22)
C _{max} (µg/mL)	18.2 (7.1)	19.3 (7.8)	19.1 (6.5)	19.2 (7.8)	19.2 (7.4)	15.3 (6.7)
AUC _{0-inf} (µg•h/mL)	10808 (3437)	11802 (3635)	11964 (4104)	10873 (5249)	11982 (3439)	11322 (4725)
AUC _{last} (µg•h/mL)	10352 (3242)	11308 (3462)	11488 (3841)	10480 (4902)	11430 (3265)	10288 (4748)
T _{max} ^a (days)	6.0 (3.9, 7.2)	6.1 (2.0, 13)	6.0 (2.0, 7.2)	5.2 (2.0, 14)	6.1 (3.8, 15)	6.2 (4.0, 14)
T _{1/2} (days)	18 (2.7)	18 (3.2)	17 (2.9)	16 (3.7)	18 (3.4)	18 (2.9)

Source: Reviewer-generated table adapted from Table 14.2.2.2, Clinical Study Report for study 1004.

^a Reported as median (min, max)

Abbreviations: AI, autoinjector; AUC_{0-inf}, area under the concentration-time curve from time 0 extrapolated to infinite time; AUC_{last}, area under the concentration-time curve from time 0 to the last measurable concentration; C_{max}, maximum concentration; PK, pharmacokinetics; PFS-NSD, prefilled syringe with needle safety device; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration

Figure 23. Garadacimab C_{max} and AUC Distributions by Device and Injection Site, Study 1004



AI = autoinjector; AUC_{0-inf} = area under the curve from time 0 to infinity; C_{max} = maximum plasma concentration; NSD = needle safety device.

Note: Horizontal lines, bottom to top, denote minimum, 1st quartile, median, 3rd quartile, and maximum.

Source: Figure 11-3, Clinical Study Report for study 1004.

Immunogenicity Results

No subjects in the study developed garadacimab ADAs.

14.2.2. Study 1001 (SAD Study in Healthy Subjects)

Title

A phase 1, single-center, randomized, double-blind, placebo-controlled, single ascending dose study to investigate the safety, tolerability, and PKs of IV and SC garadacimab in healthy subjects.

Objectives

Primary objective of this study was to assess the safety and tolerability of escalating doses of garadacimab after a single IV infusion or SC injection in healthy subjects. Characterization of PK and immunogenicity were also included as secondary objectives.

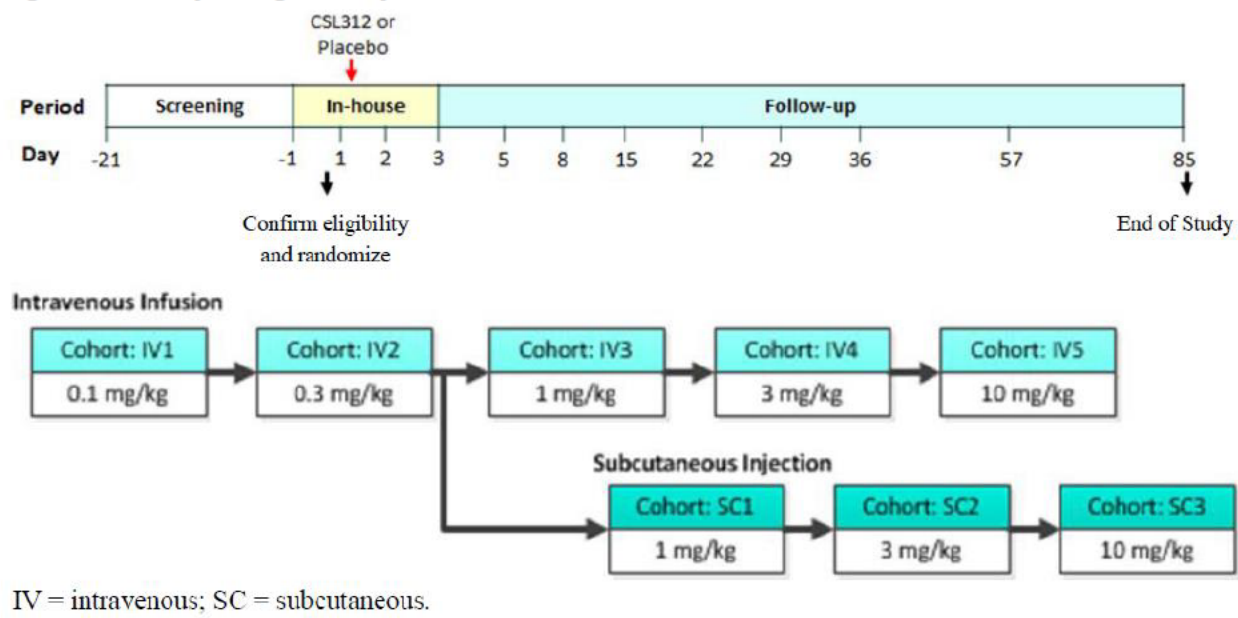
Study Design

Study 1001 was designed as a single-center, randomized, double-blind, placebo-controlled, single ascending dose study in healthy adult subjects (Figure 24). All subjects received a single IV or SC dose of garadacimab and were followed until 85 days postdose. A total of eight cohorts ($n=6$ /cohort; 4 active, 2 placebo) were enrolled, including five IV cohorts in which subjects received placebo or garadacimab at doses of 0.1, 0.3, 1, 3, or 10 mg/kg, and three SC cohorts in which subjects received placebo or garadacimab at doses of 1, 3, or 10 mg/kg. Both IV and SC

doses were administered using a 100 mg/mL solution formulation in a vial presentation. IV doses were given as an infusion at a volume of 60 mL over 60 min.

The study enrolled male subjects aged 18 to 45 years, with body mass index between 18 and <30 kg/m². Use of prescription or over-the-counter medications, including herbal products and dietary supplements, anticoagulant therapy or drugs with antiplatelet action were prohibited within 23 days before administration of the investigational product. All medications were prohibited during the study except for acetaminophen.

Figure 24. Study Design, Study 1001



IV = intravenous; SC = subcutaneous.

Source: Figures 9-1 and 9-2, Clinical Study Report for study 1001.
Abbreviation: CSL312, garadacimab

PK, PD, and Immunogenicity Sampling

Blood PK samples were collected at predose on Day 1, and postdose at Hours 0.5 (IV only), 1, 6, 12, 24, 32 (SC only), and 48 and Days 5, 8, 15, 22, 29, 36, 57, and 85. Samples to assess FXIIa-mediated kallikrein activity were collected at the same time points as PK samples.

Immunogenicity samples were collected at predose on Day 1, and on Days 29 and 85.

Subject Disposition and Demographics

A total of 48 subjects were randomized, including 32 subjects who received garadacimab and 16 subjects who received placebo. Among subjects receiving garadacimab, 20 received an IV infusion (n=4 per IV cohort) and 12 received a SC injection (n=4 per SC cohort). All the subjects completed the study.

Body weight at baseline and garadacimab doses received in the IV and SC cohorts are shown in [Table 67](#) and [Table 68](#), respectively.

Table 67. Baseline Body Weight and Garadacimab Doses in IV Cohorts, Study 1001

Parameter	IV Cohort 1 0.1 mg/kg (N=4)	IV Cohort 2 0.3 mg/kg (N=4)	IV Cohort 3 1 mg/kg (N=4)	IV Cohort 4 3 mg/kg (N=4)	IV Cohort 5 10 mg/kg (N=4)
Weight (kg)					
Median	87.75	78.65	65.80	70.35	87.85
Min, max	77.5, 97.3	67.1, 90.2	59.7, 73.9	69.8, 78.0	65.1, 101.5
Dose ^a (mg)					
Median	8.8	24	66	211	879
Min, max	7.8, 9.7	20, 27	60, 74	209, 234	651, 1015

Source: Reviewer-generated table adapted from Table 11-1, Clinical Study Report for study 1001.

^a Refers to garadacimab dose. Value calculated as body weight multiplied by the mg/kg dose (i.e., 0.1, 0.3, 1, 3, or 10).

Abbreviation: IV, intravenous; min, minimum; max, maximum

Table 68. Baseline Body Weight and Garadacimab Doses in SC Cohorts, Study 1001

Parameter	SC Cohort 1 1 mg/kg (N=4)	SC Cohort 2 3 mg/kg (N=4)	SC Cohort 3 10 mg/kg (N=4)
Weight (kg)			
Median	73.70	78.05	75.75
Min, max	72.2, 94.5	73.9, 86.6	72.0, 84.1
Dose ^a (mg)			
Median	74	234	758
Min, max	72, 95	222, 260	720, 841

Source: Reviewer-generated table adapted from Table 11-2, Clinical Study Report for study 1001.

^a Refers to garadacimab dose. Value calculated as body weight multiplied by the mg/kg dose (i.e., 1, 3, or 10).

Abbreviation: min, minimum; max, maximum; SC, subcutaneous

PK Analysis

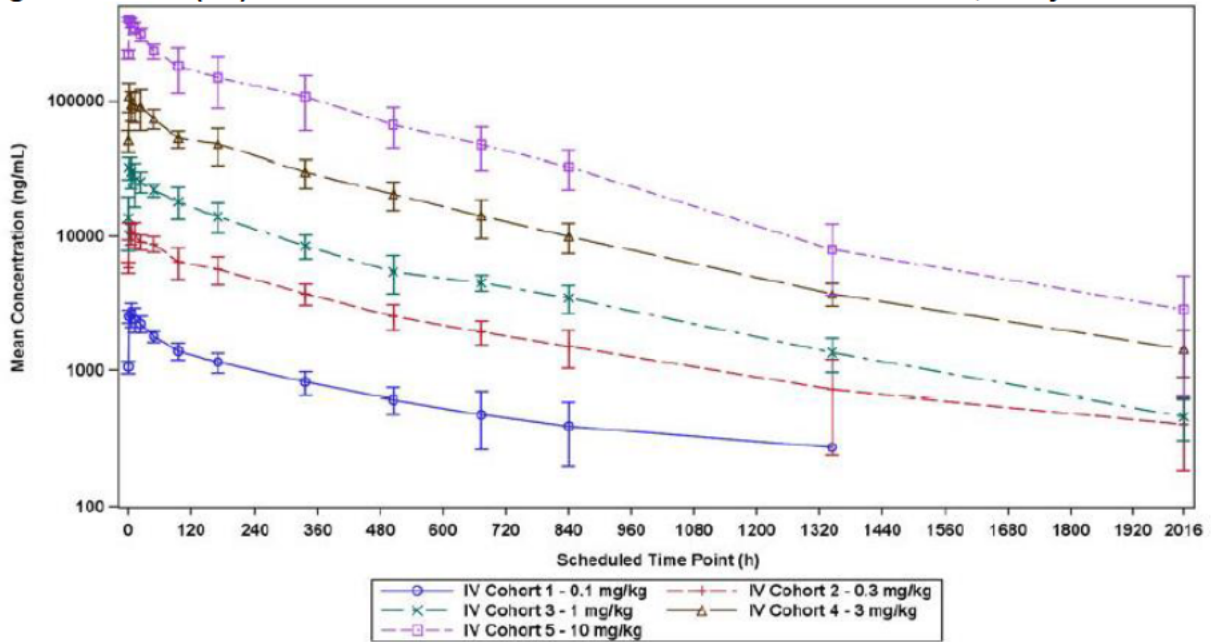
The 48 subjects in the PK analysis set comprised those who received one dose of garadacimab and for whom at least one concentration value was reported. PK parameters were estimated using noncompartmental analyses.

PK Results

Note that the following PK results from study 1001 should be interpreted with caution due to limitations of in-study analysis. In each of 14 runs (~10% of passing runs), the mean concentration for one of the quality control (QC) levels fell outside the acceptance criteria. Replicate QC data were not provided. Therefore, the reviewer is unable to verify whether the acceptance criteria were met based on at least 50% of QCs per QC level falling within $\pm 20\%$ of nominal values ([Table 91](#)). The impact to the reported PK results is unclear. Therefore, results should be interpreted with caution.

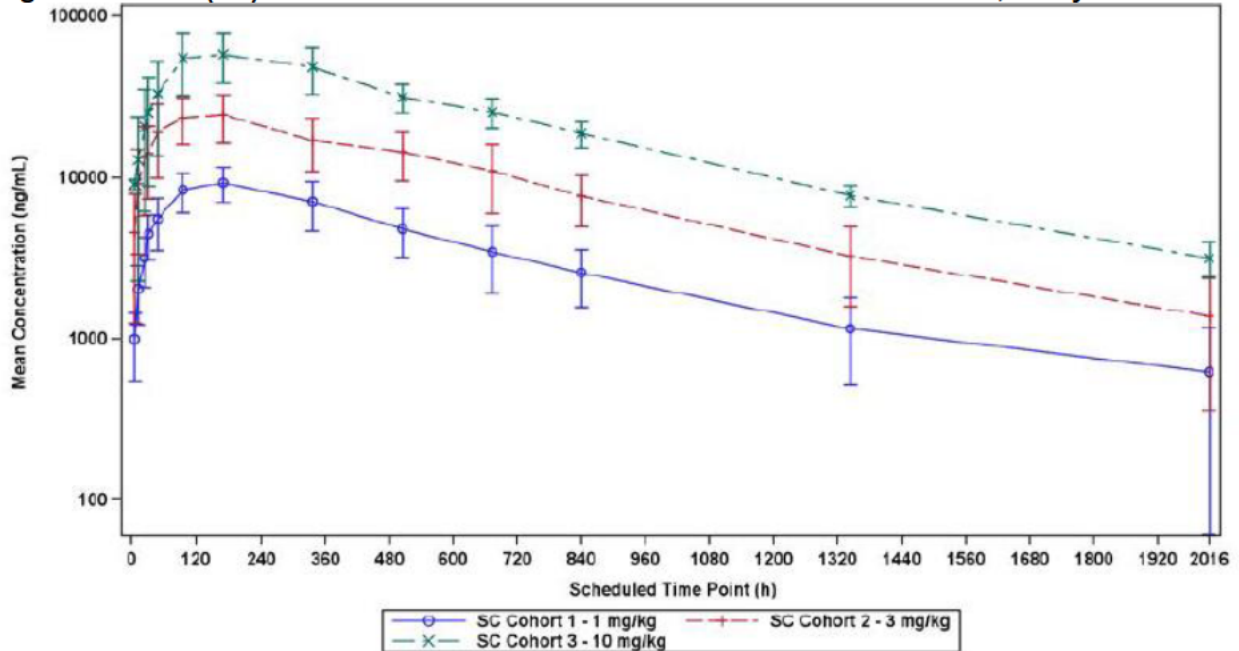
Mean (SD) garadacimab concentration-time profiles by dose group for the IV and SC cohorts are shown in [Figure 25](#) and [Figure 26](#), respectively. PK parameters by dose and route of administration are shown in [Table 69](#). Following single IV infusions of garadacimab, plasma concentrations generally peaked at the end of infusion, approximately 1 h. However, the median T_{max} in the 0.1 mg/kg IV cohort was approximately 3.5 h. In SC cohorts, the median T_{max} ranged from 5.5 to 7 days. Across all IV and SC cohorts, the mean half-life ranged from 14 to 20 days.

Figure 25. Mean (SD) Garadacimab Concentration-Time Profiles for IV Cohorts, Study 1001



Source: Figure 11-1, Clinical Study Report for study 1001.
Abbreviation: IV, intravenous

Figure 26. Mean (SD) Garadacimab Concentration-Time Profiles for SC Cohorts, Study 1001



Source: Figure 11-1, Clinical Study Report for study 1001.
Abbreviation: IV, intravenous

Table 69. Summary of Garadacimab Pharmacokinetic Parameters by Dose in IV and SC Cohorts, Study 1001

Pharmacokinetic Parameter	IV Cohort 1 0.1 mg/kg (N = 4) ^a	IV Cohort 2 0.3 mg/kg (N = 4)	IV Cohort 3 1 mg/kg (N = 4)	IV Cohort 4 3 mg/kg (N = 4)	IV Cohort 5 10 mg/kg (N = 4)	SC Cohort 1 1 mg/kg (N = 4)	SC Cohort 2 3 mg/kg (N = 4)	SC Cohort 3 10 mg/kg (N = 4)
C_{max} (µg/mL)								
Mean (SD)	2.73 (0.447)	11.0 (1.69)	32.5 (6.30)	110 (27.1)	410 (17.5)	9.40 (2.17)	24.7 (8.02)	59.0 (20.6)
Min, Max	2.35, 3.36	9.62, 13.5	26.6, 40.3	88.3, 149	386, 425	6.77, 11.4	16.0, 32.4	33.7, 77.1
Median	2.60	10.5	31.6	101	414	9.73	25.3	62.6
AUC_{0-t} (µg^h/mL)								
Mean (SD)	762 (217)	4063 (1028)	9484 (1862)	31279 (7167)	100101 (24598)	6007 (2246)	17133 (6302)	40701 (8776)
Min, Max	571, 1041	3033, 4976	7252, 11808	24175, 39264	78910, 135462	3799, 8924	10872, 24572	28747, 49234
Median	717	4122	9438	30838	93015	5652	16544	42412
AUC_{0-inf} (µg^h/mL)								
Mean (SD)	967 (252)	4348 (1263)	9765 (1936)	32095 (7436)	101777 (24164)	6468 (2610)	18110 (7150)	42936 (7906)
Min, Max	712, 1215	3147, 5574	7390, 12119	24676, 40476	79801, 135804	3885, 9942	11147, 26936	31959, 50462
Median	974	4336	9775	31614	95751	6023	17179	44661
t_{max} (h)								
Median	3.50	1.00	1.03	1.00	1.00	168.13	133.23	168.76
Min, Max	1.00, 12.00	1.00, 12.00	1.00, 6.00	1.00, 1.00	1.00, 6.02	94.45, 170.42	48.00, 169.52	122.33, 169.38
t_{1/2} (h)								
Mean (SD)	352.98 (64.18)	489.68 (205.91)	408.22 (47.48)	393.45 (12.23)	343.97 (116.36)	439.74 (101.60)	437.21 (94.68)	470.15 (104.43)
Min, Max	296.97, 439.37	209.01, 696.21	352.57, 466.11	383.24, 410.49	214.86, 497.11	347.20, 566.61	350.95, 572.13	353.04, 589.71
Median	337.78	526.75	407.09	390.03	331.95	422.58	412.87	468.93
CL, CL/F (mL/h)								
Mean (SD)	9.83 (3.19)	5.64 (0.978)	6.98 (1.45)	7.05 (1.82)	8.65 (2.02)	13.3 (3.41)	14.6 (5.00)	18.5 (4.30)
Min, Max	7.96, 13.5	4.52, 6.51	6.00, 9.11	5.17, 8.62	6.50, 10.9	10.1, 18.0	8.9, 20.6	14.3, 24.4
Median	8.01	5.76	6.40	7.21	8.57	12.6	14.3	17.6
V_z, V_z/F (L)								
Mean (SD)	4.82 (1.12)	3.79 (1.23)	4.04 (0.418)	4.02 (1.10)	4.22 (1.33)	8.15 (1.17)	8.73 (1.60)	12.9 (5.69)
Min, Max	3.59, 5.79	1.96, 4.54	3.69, 4.63	2.86, 5.11	2.32, 5.40	6.73, 9.58	7.36, 10.4	7.27, 20.8
Median	5.07	4.34	3.93	4.05	4.58	8.14	8.56	11.8

AUC_{0-inf} = area under the plasma concentration-time curve extrapolated to infinity; AUC_{0-t} = area under the plasma concentration-curve from time of dosing up to collection time t; CL = total systemic clearance for the IV cohorts; CL/F = total systemic clearance for the SC cohorts; C_{max} = maximum plasma concentration; IV = intravenous; N = number of evaluable subjects; SC = subcutaneous; t_{1/2} = terminal elimination half-life; t_{max} = time to reach maximum concentration in plasma; V_z = volume of distribution during the elimination phase for the IV cohorts; V_z/F = volume of distribution during the elimination phase for the SC cohorts.

^a N = 3 for AUC_{0-inf} and CL.

Source: Table 11-3, Clinical Study Report for study 1001.

Among the IV cohorts, C_{max} increased approximately 4-, 12-, 40-, and 150-fold with a 3-, 10-, 30-, and 100-fold increase in dose from 0.1 to 0.3, 1, 3, and 10 mg/kg, respectively. Mean AUC_{0-t} increased 5-, 12-, 41-, and 131-fold with 3-, 10-, 30-, and 100-fold increases in dose. In SC cohorts, C_{max} increased approximately 3- and 6-fold with 3- and 10-fold increases in dose from 1 to 3 and 10 mg/kg, respectively. Mean AUC_{0-t} increased 3- and 7-fold with 3- and 10-fold increases in dose. The Applicant assessed dose proportionality of garadacimab C_{max}, AUC_{0-inf}, and AUC_{0-t} using a Power Law model. Slopes and 90% CIs were estimated using body weight adjusted doses and total doses. Data for IV and SC cohorts are shown in [Table 70](#) and [Table 71](#), respectively. Based on total dose, garadacimab C_{max} and AUC were concluded to increase in a dose-proportional manner between IV doses of 0.1 and 10 mg/kg. Among SC cohorts, garadacimab AUC was noted to increase dose-proportionally between doses of 1 and 10 mg/kg as the 90% CI for the estimated slopes were contained within the predefined critical interval of 0.7 to 1.3. Note that per [Table 71](#), this is applicable to analyses conducted based on total dose, but not based on body weight-adjusted dose, indicating that garadacimab exposure increases in a

slightly less than dose-proportional manner. Following an SC dose, C_{max} was found to increase in a slightly less than dose-proportional manner between doses of 1 and 10 mg/kg.

Table 70. Power Analysis of Dose Proportionality for Garadacimab PK in IV Cohorts, Study 1001

Type of dose	Parameter	Power Model			90% Confidence Interval	
		Coefficient	Estimate	p-value	Lower Limit	Upper Limit
Body weight adjusted dose (mg/kg)	AUC _{0-inf}	Intercept	9.276	<.001	9.169	9.384
		Estimated Slope	0.975	<.001	0.908	1.043
	AUC _{0-t}	Intercept	9.193	<.001	9.080	9.306
		Estimated Slope	1.025	<.001	0.956	1.095
	C _{max}	Intercept	3.532	<.001	3.464	3.599
		Estimated Slope	1.071	<.001	1.029	1.112
Total dose (mg)	AUC _{0-inf}	Intercept	5.013	<.001	4.672	5.353
		Estimated Slope	0.981	<.001	0.909	1.053
	AUC _{0-t}	Intercept	4.712	<.001	4.362	5.061
		Estimated Slope	1.031	<.001	0.955	1.107
	C _{max}	Intercept	-1.145	<.001	-1.394	-0.895
		Estimated Slope	1.076	<.001	1.022	1.130

Note: Critical interval for estimated slope = 0.85 to 1.15
 Note: The model includes logarithm e dose as fixed effect and logarithm e transformed PK parameters as outcome variable.
 Note: Subjects with AUC_{max} >20% have been excluded from summary of AUC_{0-inf}, as this is considered as unreliable for AUC_{0-inf}.

Source: Table 14.3.18.3.1, Clinical Study Report for study 1001.

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; IV, intravenous; PK, pharmacokinetic

Table 71. Power Analysis of Dose Proportionality for Garadacimab PK in SC Cohorts, Study 1001

Type of dose	Parameter	Power Model			90% Confidence Interval	
		Coefficient	Estimate	p-value	Lower Limit	Upper Limit
Body weight adjusted dose (mg/kg)	AUC _{0-inf}	Intercept	8.735	<.001	8.474	8.996
		Estimated Slope	0.852	<.001	0.675	1.029
	AUC _{0-t}	Intercept	8.675	<.001	8.422	8.928
		Estimated Slope	0.854	<.001	0.683	1.026
	C _{max}	Intercept	2.236	<.001	1.984	2.488
		Estimated Slope	0.792	<.001	0.620	0.963
Total dose (mg)	AUC _{0-inf}	Intercept	4.946	<.001	4.074	5.818
		Estimated slope	0.866	<.001	0.710	1.023
	AUC _{0-t}	Intercept	4.880	<.001	4.033	5.727
		Estimated Slope	0.868	<.001	0.716	1.020
	C _{max}	Intercept	-1.259	0.029	-2.155	-0.364
		Estimated Slope	0.800	<.001	0.639	0.961

Note: Critical interval for estimated slope = 0.7 to 1.3
 Note: The model includes logarithm e dose as fixed effect and logarithm e transformed PK parameters as outcome variable.
 Note: Subjects with AUC_{max} >20% have been excluded from summary of AUC_{0-inf}, as this is considered as unreliable for AUC_{0-inf}.

Source: Table 14.3.18.3.2, Clinical Study Report for study 1001.

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; PK, pharmacokinetic; SC, subcutaneous

Absolute bioavailability was determined via an intersubject comparison of the same dose levels for IV and SC administration (i.e., 1, 3, and 10 mg/kg). Geometric mean ratios and 90% CIs at each dose level and overall are shown in [Table 72](#). Garadacimab SC bioavailability decreased with increasing dose. Across all doses, the overall estimated bioavailability (90% CI) was about 50 (41, 60)%.

Table 72. Absolute Bioavailability for SC Versus IV Cohorts, Study 1001

Parameter (Unit)	SC versus IV Dose	N	Geometric Mean Ratio ^a	90% CI (%) ^a
AUC _{0-inf} (µg*h/mL)	1 mg/kg	8	63.3	40.96, 97.91
AUC _{0-inf} (µg*h/mL)	3 mg/kg	8	54.3	34.63, 85.04
AUC _{0-inf} (µg*h/mL)	10 mg/kg	8	42.4	31.69, 56.80
AUC _{0-inf} (µg*h/mL)	Overall (1-10 mg/kg)	24	49.7	41.18, 59.91

AUC_{0-inf} = area under the plasma concentration-time curve extrapolated to infinity; CI = confidence interval; IV = intravenous; PK = pharmacokinetic; SC = subcutaneous.

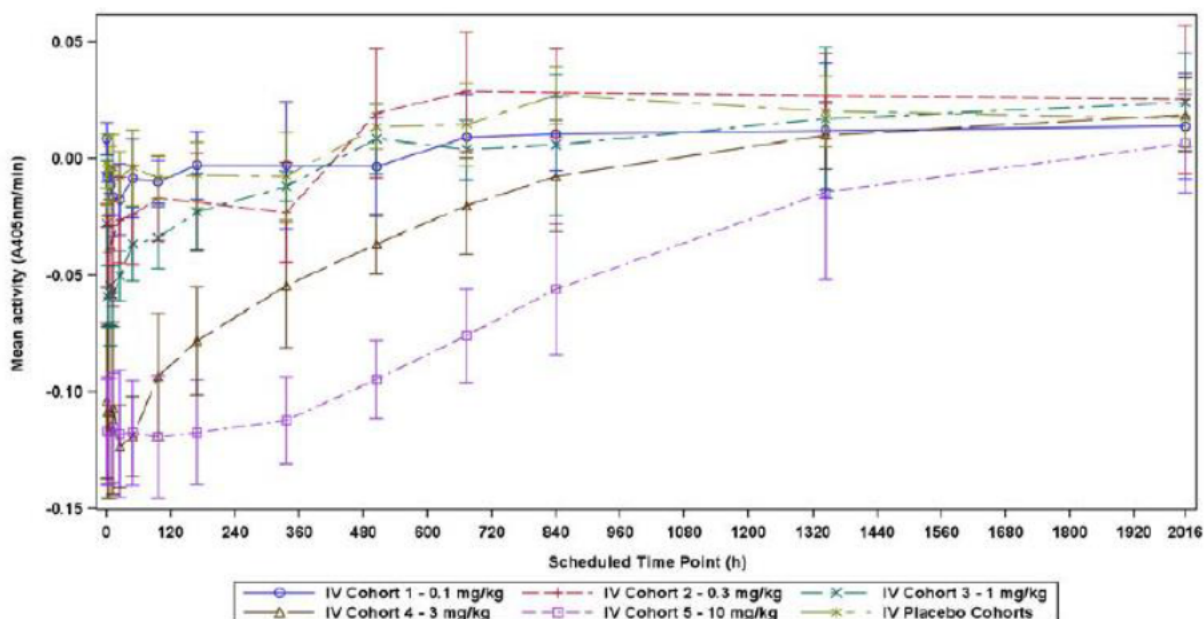
^a Estimates of the mean and CI limits for the ln values were exponentiated and multiplied by 100.

Source: Table 11-4, Clinical Study Report for study 1001.

PD Results

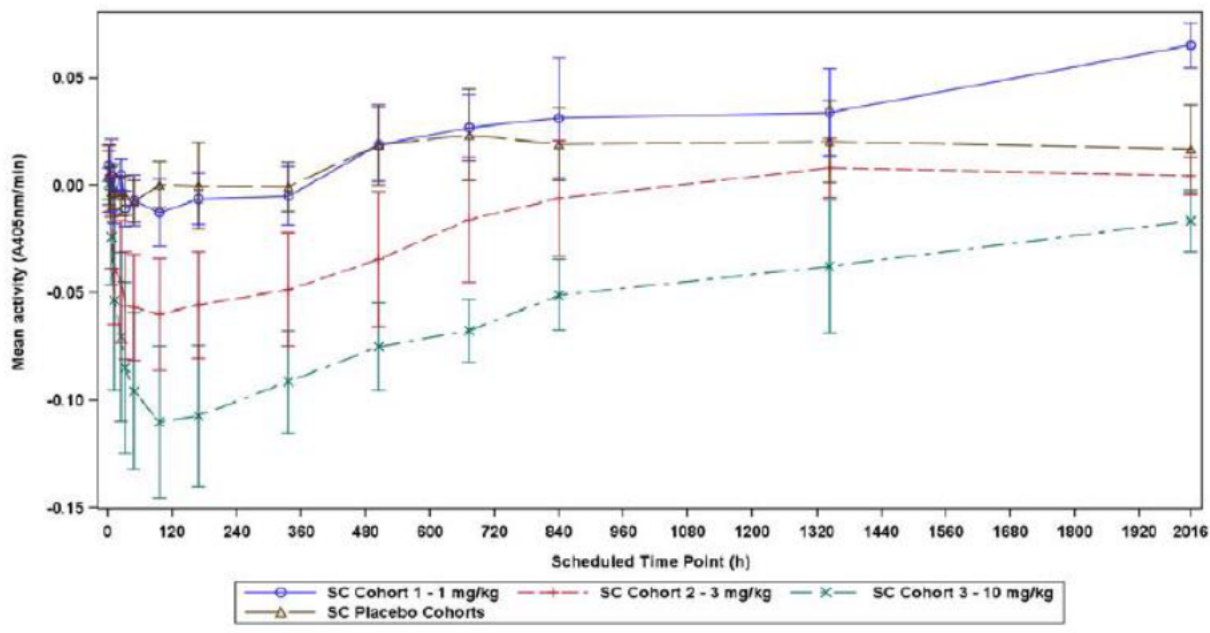
FXIIa-mediated kallikrein activity was assessed as a pharmacodynamic (PD) marker. Garadacimab showed dose-dependent inhibition of FXIIa-mediated kallikrein activity ([Figure 27](#) and [Figure 28](#)). A clear inhibition trend was observed at the highest doses of 3 or 10 mg/kg in both IV and SC cohorts when compared to placebo group. The duration of inhibition was also longer for the higher doses with a return to baseline range at about Day 56 for 3 mg/kg IV or SC, and at about Day 85 for 10 mg/kg IV. The FXIIa-mediated kallikrein activity following 10 mg/kg SC was kept slightly lower than baseline at Day 85. In SC cohorts, the time of peak response appears to correlate with the garadacimab T_{max}, suggesting a real-time PK/PD relationship.

Figure 27. Mean (SD) Change From Baseline in FXIIa-Mediated Kallikrein Activity by Dose in IV Cohorts, Study 1001



Source: Figure 11-2, Clinical Study Report for study 1001.
Abbreviation: IV, intravenous

Figure 28. Mean (SD) Change From Baseline in FXIIa-Mediated Kallikrein Activity by Dose in SC Cohorts, Study 1001



Source: Figure 11-3, Clinical Study Report for study 1001.
Abbreviation: SC, subcutaneous

Immunogenicity Results

No subject in the study developed garadacimab ADAs.

14.2.3. Study 1003 (SAD Study in Healthy Japanese and Caucasian Subjects)

Title

A two-part, phase 1, single-center, open-label, single ascending dose study to investigate the PKs, PDs, safety, and tolerability of SC and IV garadacimab in healthy adult Japanese and Caucasian subjects.

Objectives

The primary objectives of this study were to characterize the PK of garadacimab in Japanese subjects after SC dosing and to compare the PK of garadacimab in Japanese and Caucasian subjects at the 200 mg SC dose. Further characterization of PK (including in IV cohorts), PD (FXIIa-mediated kallikrein activity), and immunogenicity were the secondary objectives.

Study Design

Study 1003 was designed as a two-part, single-center, open-label, single ascending dose study in healthy adult Japanese and Caucasian subjects (Figure 29). All subjects received a single IV or SC dose of garadacimab and were followed until 85 days postdose. A total of five cohorts were

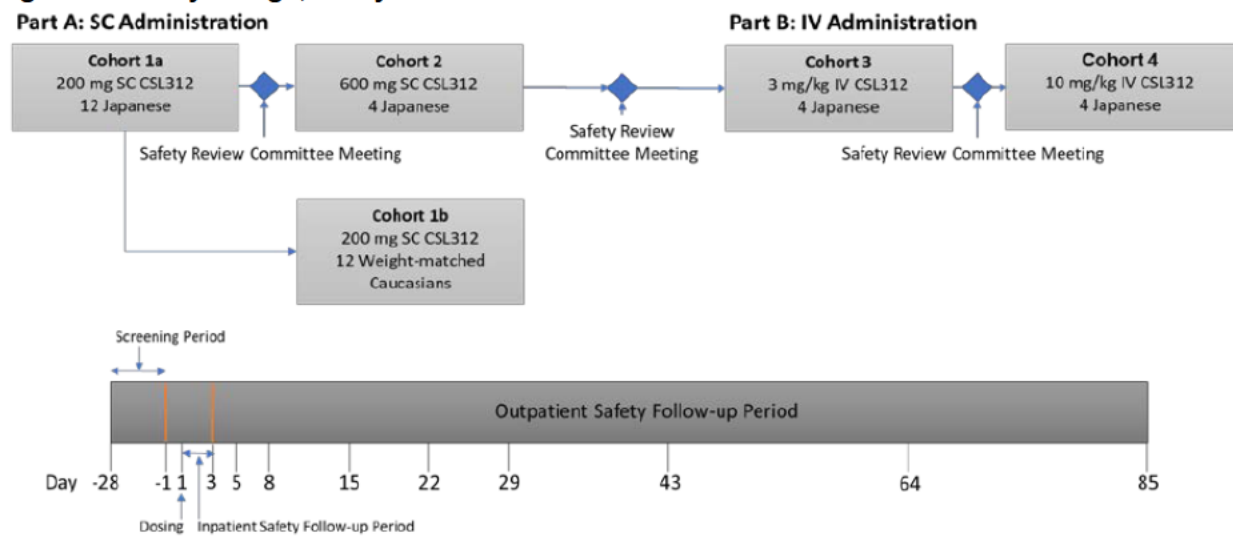
enrolled (N=36; n=12/cohort for Cohorts 1a and 1b; n=4 for Cohorts 2 to 4). Parts A and B evaluated SC and IV administration, respectively. Cohort enrollment and dosing was as follows:

- Cohort 1a: 12 Japanese subjects – 200 mg SC
- Cohort 1b: 12 Caucasian subjects, weight-matched $\pm$ 15% to Cohort 1a – 200 mg SC
- Cohort 2: 4 Japanese subjects – 600 mg SC
- Cohort 3: 4 Japanese subjects – 3 mg/kg IV
- Cohort 4: 4 Japanese subjects – 10 mg/kg IV

SC doses were administered using a 170 mg/mL solution in 1.2 mL PFS-NSD devices. SC injections were administered as 1 $\times$ 1.2 mL (200 mg) or 3 $\times$ 1.2 mL (600 mg), with preferred site of injection in the abdomen. IV doses were administered using a 100 mg/mL formulation in a vial presentation. IV doses were given as an infusion at a volume of 60 mL over 60 min.

The study enrolled healthy male or female subjects aged 18 to 55 years, with body weight between 50 and 100 kg, and body mass index between 18 and <30 kg/m², all inclusive. Caucasian subjects were weight-matched $\pm$ 15% 1:1 with Japanese subjects. Use of prescription or over-the-counter medications, including herbal products and dietary supplements, anticoagulant therapy or drugs with antiplatelet action were prohibited within 21 days before administration of the investigational product. All medications were prohibited during the study except for acetaminophen, and oral or intranasal medications to treat seasonal allergies. Hormonal contraceptives were also permitted.

Figure 29. Study Design, Study 1003



Source: Figure 9-1, Clinical Study Report for study 1003.
Abbreviations: CSL312, garadacimab; IV, intravenous; SC, subcutaneous

PK, PD, and Immunogenicity Sampling

Blood PK samples were collected at predose on Day 1, and postdose at Hours 0.5 (IV only), 1, 8, 24, 32 (SC only), and 48 and Days 5, 8, 15, 22, 29, 43, 64, and 85.

Samples to assess FXIIa-mediated kallikrein activity were collected at the same time points as PK samples. Immunogenicity samples were collected predose on Day 1, and on Days 29 and 85.

Subject Disposition and Demographics

A total of 37 subjects received treatment, including 12 Japanese subjects in Cohort 1a, 13 Caucasian subjects in Cohort 1b, and 4 subjects each in Cohorts 2 to 4. One Caucasian subject in Cohort 1b was lost to follow-up and discontinued from the study. Overall, 36 subjects completed the study.

Among the SC cohorts, the mean (SD) body weight in Cohort 1a (Japanese, 200 mg), Cohort 1b (Caucasian, 200 mg), and Cohort 2 (Japanese, 600 mg) were 64.6 (9.6) kg, 63.6 (9.6) kg, and 64.1 (11.4) kg, respectively. Body weight at baseline and garadacimab doses received in IV cohorts are shown in [Table 73](#).

Table 73. Baseline Body Weight and Garadacimab Doses in IV Cohorts, Study 1003

Parameter	IV Cohort 3 3 mg/kg (N=4)	IV Cohort 4 10 mg/kg (N=4)
Weight (kg)		
Median	67.90	67.90
Minimum, maximum	53.4, 90.5	51.4, 75.3
Dose ^a (mg)		
Median	204	679
Minimum, maximum	160, 272	514, 753

Source: Reviewer-generated table adapted from Table 11-2, Clinical Study Report for study 1003.

^a Refers to garadacimab dose. Value calculated as body weight multiplied by the mg/kg dose (i.e., 3 or 10).

Abbreviation: IV, intravenous

PK Analysis

All 37 subjects were included in the PK analysis set comprised of subjects who received garadacimab and had at least one quantifiable concentration measurement. PK parameters were estimated using noncompartmental analyses.

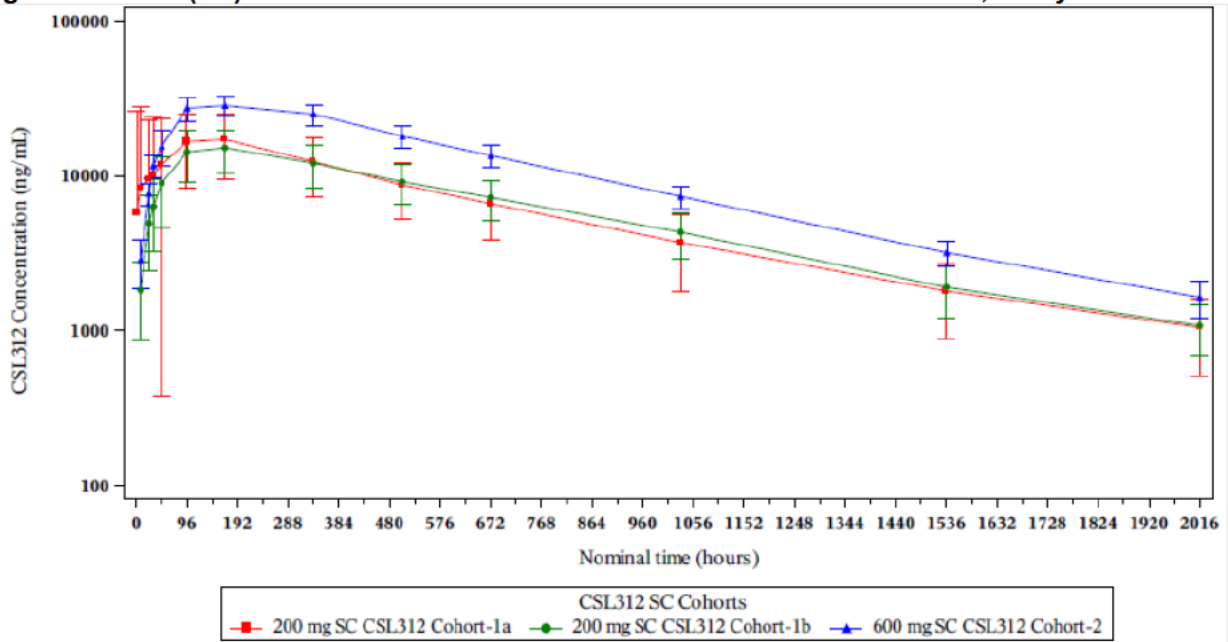
During analysis, it was noted that one subject in Cohort 1a, a Japanese subject who received 200 mg SC garadacimab, presented with much higher garadacimab concentrations from 1 to 48 h postdose relative to other subjects (subject (b) (6)). Garadacimab concentrations for this subject began at 69.3 µg/mL at 1 h postdose, peaked at 69.8 µg/mL at 8 h postdose and then declined to 41.2 µg/mL by 48 h postdose (data derived from Listing 16.2.5.2, Appendix 16.2.6, CSR for study 1003). In Cohort 1a, all remaining subjects (11/12, 92%) had garadacimab concentrations below the limit of quantitation at 1 h postdose, and the median concentrations at 8 and 48 h postdose were 2.9 and 7.2 µg/mL, respectively (data derived from Table 14.4.1.1.1, CSR for study 1003).

The Applicant notes that the reason for these higher values in subject (b) (6) has not been identified. However, an additional analysis was performed in which data from this subject were excluded for comparison.

PK Results

Mean (SD) garadacimab concentration-time profiles by dose group for SC cohorts are shown in [Figure 30](#). PK parameters by dose group are shown in [Table 74](#). Across SC cohorts, T_{max} was approximately 6 to 7 days, and the mean half-life was approximately 18 to 19 days. These data are consistent with observations in study 1001. Between doses of 200 and 600 mg SC, C_{max} and AUC_{0-inf} increased approximately two-fold for a three-fold increase in dose.

Figure 30. Mean (SD) Garadacimab Concentration-Time Profiles for SC Cohorts, Study 1003



Source: Figure 11-1, Clinical Study Report for study 1003.
Abbreviations: CSL312, garadacimab; SC, subcutaneous

Table 74. Summary of Garadacimab PK Parameters by Dose in SC Cohorts, Study 1003

Parameter (Unit)	Cohort 1a Japanese 200 mg SC CSL312 N = 12	Cohort 1b Caucasian 200 mg SC CSL312 N = 13	Cohort 2 Japanese 600 mg SC CSL312 N = 4
AUC_{0-inf} (h•µg/mL)			
Number of Subjects with Data	12	12	4
Mean (SD)	11,926 (5843)	11,920 (3611)	21,774 (2943)
Median	11,505	12,413	21,068
Min, Max	3354, 24,290	5667, 16,230	19,057, 25,901
AUC_{0-last} (h•µg/mL)			
Number of Subjects with Data	12	13	4
Mean (SD)	11,283 (5512)	10,555 (4018)	20,751 (2682)
Median	11,058	11,403	20,285
Min, Max	3045, 22,585	2629, 15,351	18,046, 24,387
C_{max} (µg/mL)			
Number of Subjects with Data	12	13	4
Mean (SD)	21.2 (17.0)	15.4 (4.7)	29.5 (4.8)
Median	18.4	14.8	30.8
Min, Max	6.9, 69.8	7.1, 21.5	22.7, 33.6
t_{1/2} (h)			
Number of Subjects with Data	12	12	4
Mean (SD)	424 (72)	457 (56)	427 (38)
Median	449	454	431
Min, Max	270, 527	368, 543	387, 460
T_{max} (h)			
Number of Subjects with Data	12	13	4
Median	169	168	145
Min, Max	8, 171	96, 340	96, 145
CL/F (L/h)			
Number of Subjects with Data	12	12	4
Mean (SD)	0.022 (0.014)	0.019 (0.007)	0.028 (0.004)
Median	0.017	0.016	0.028
Min, Max	0.01, 0.06	0.01, 0.04	0.02, 0.03
V_z/F (L)			
Number of Subjects with Data	12	12	4
Mean (SD)	12.5 (5.8)	12.1 (4.3)	17.2 (2.6)
Median	10.0	11.1	16.2
Min, Max	6.3, 23.2	7.6, 22.0	15.4, 20.8

AUC_{0-inf} = area under the curve from time 0 extrapolated to infinity; AUC_{0-last} = area under the curve from time 0 to the last measurable concentration; CL/F = apparent clearance; C_{max} = maximum concentration; Max = maximum; Min = minimum; N = number of subjects assigned to the treatment; SC = subcutaneous; SD = standard deviation; t_{1/2} = terminal elimination half-life; T_{max} = time of maximum concentration; V_z/F = apparent volume of distribution.

Source: Table 11-3, Clinical Study Report for study 1003.
Abbreviation: CSL312, garadacimab

Statistical analysis comparing PK parameters among Japanese and Caucasian subjects at the 200 mg SC dose are shown in [Table 75](#) (including all subjects) and [Table 76](#) (excluding one subject with high concentrations). When all subjects were considered, the C_{max} and AUC_{0-inf} in Japanese subjects were approximately 17% higher and 7% lower, respectively, relative to Caucasian subjects. Upon exclusion of subject (b) (6), only C_{max} and AUC were impacted. The C_{max} and AUC_{0-inf} in Japanese subjects was approximately 3% higher and 14%

lower, respectively, relative to Caucasian subjects. Overall, the data suggested that the PK of garadacimab was comparable between Japanese and Caucasian subjects.

Table 75. Pharmacokinetics Comparison of Japanese and Caucasian Subjects (All Subjects), Study 1003

Parameter	Geometric LSM		Geometric LSM Ratio ^a	90% CI (%) ^a
	Japanese Subjects N = 12	White Subjects N = 13		
C _{max} (µg/mL)	17.1	14.6	1.17	0.82, 1.67
AUC _{0-inf} (µg•h/mL)	10,567	11,346 ^a	0.93	0.68, 1.28

AUC_{0-inf} = area under the plasma concentration-time curve extrapolated to infinity; CI = confidence interval;

C_{max} = maximum plasma concentration; CSR = clinical study report; LSM = least squares mean.

^a n = 12; pharmacokinetic parameter not calculated for 1 subject due to insufficient pharmacokinetic timepoints in terminal phase because subject was lost to follow-up.

Source: Module 5.3.4.1, Study CSL312_1003 CSR, [Table 11-6](#)

Source: Table 3, Summary of Clinical Pharmacology.

Table 76. Pharmacokinetics Comparison of Japanese and Caucasian Subjects (Excluding One Subject With Extreme Values), Study 1003

Parameter	Geometric LSM		Geometric LSM Ratio ^a	90% CI (%) ^a
	Japanese Subjects N = 11	White Subjects N = 13		
C _{max} (µg/mL)	15.1	14.6	1.03	0.76, 1.39
AUC _{0-inf} (µg•h/mL)	9797	11,346 ^a	0.86	0.64, 1.17

AUC_{0-inf} = area under the plasma concentration-time curve extrapolated to infinity; CI = confidence interval;

C_{max} = maximum plasma concentration; CSR = clinical study report; LSM = least squares mean.

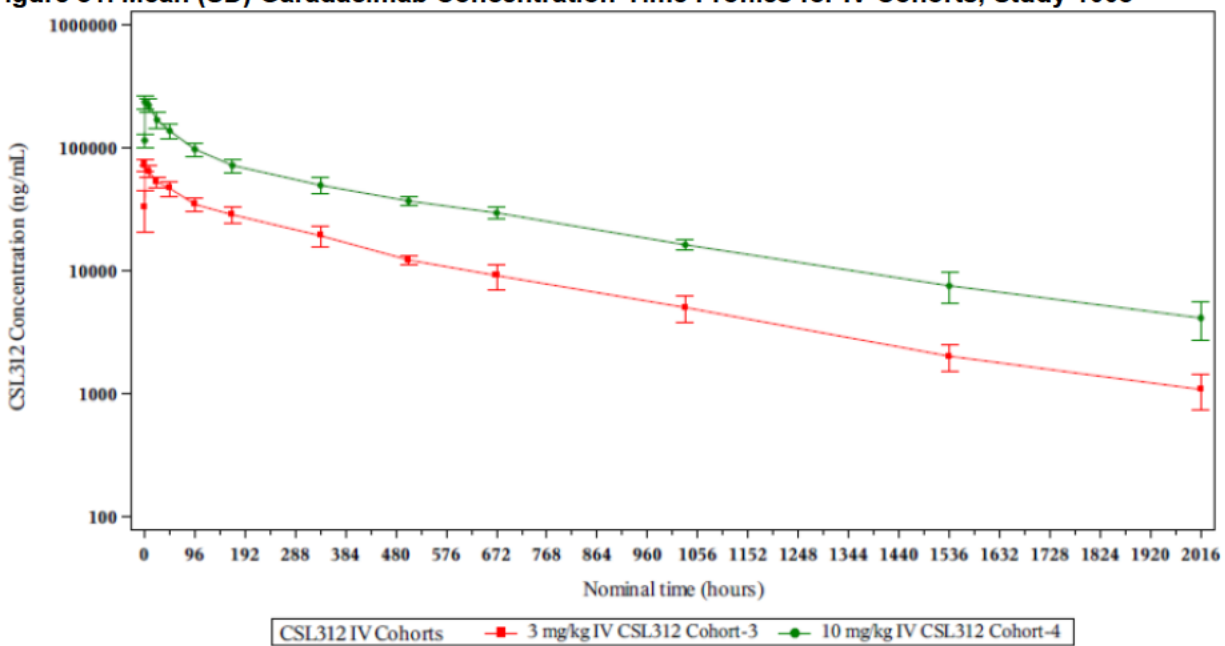
^a n = 12; pharmacokinetic parameter not calculated for 1 subject due to insufficient pharmacokinetic timepoints in terminal phase because subject was lost to follow-up.

Source: Module 5.3.4.1, Study CSL312_1003 CSR, [Table 11-7](#)

Source: Table 4, Summary of Clinical Pharmacology.

Mean (SD) garadacimab concentration-time profiles by dose group for IV cohorts are shown in [Figure 31](#). The median T_{max} was 4.5 h in the 3 mg/kg cohort and 1 h (approximate end of the infusion) in the 10 mg/kg cohort. The mean half-life was 17.4 days and 18.7 days in the 3 mg/kg and 10 mg/kg cohorts, respectively. Summaries of C_{max} and AUC are shown in [Table 77](#). The C_{max} increased 3.2-fold and the AUC_{0-last} and AUC_{0-inf} increased about 3-fold for a 3.3-fold increase in dose.

Figure 31. Mean (SD) Garadacimab Concentration-Time Profiles for IV Cohorts, Study 1003



Source: Figure 11-2, Clinical Study Report for study 1003.
Abbreviations: CSL312, garadacimab; IV, intravenous

Table 77. Summary of Garadacimab PK Parameters by Dose in IV Cohorts, Study 1003

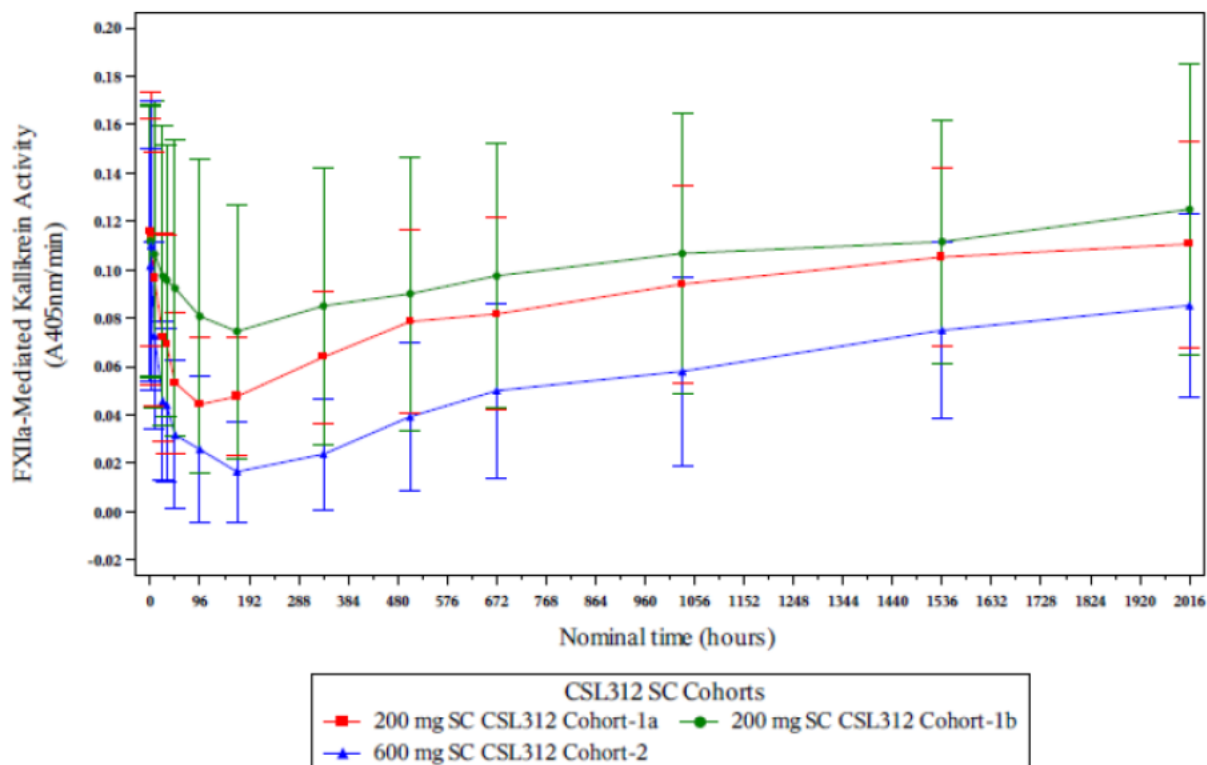
Parameter (Unit)	Cohort 3 Japanese 3 mg/kg IV CSL312 N = 4	Cohort 4 Japanese 10 mg/kg IV CSL312 N = 4
AUC_{0-inf} (h•µg/mL)		
Number of Subjects with Data	4	4
Mean (SD)	20,416 (2911)	61,142 (3785)
Median	19,124	59,511
Min, Max	18,649, 24,769	58,795, 66,753
AUC_{0-last} (h•µg/mL)		
Number of Subjects with Data	4	4
Mean (SD)	19,756 (2795)	58,381 (3761)
Median	18,644	57,755
Min, Max	17,830, 23,907	54,638, 63,375
C_{max} (µg/mL)		
Number of Subjects with Data	4	4
Mean (SD)	72.5 (7.42)	233 (29.9)
Median	71.6	241
Min, Max	64.6, 82.1	190, 259

Source: Adapted from Table 11-5, Clinical Study Report for study 1003.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSL312, garadacimab; IV, intravenous; PK, pharmacokinetics

PD Results

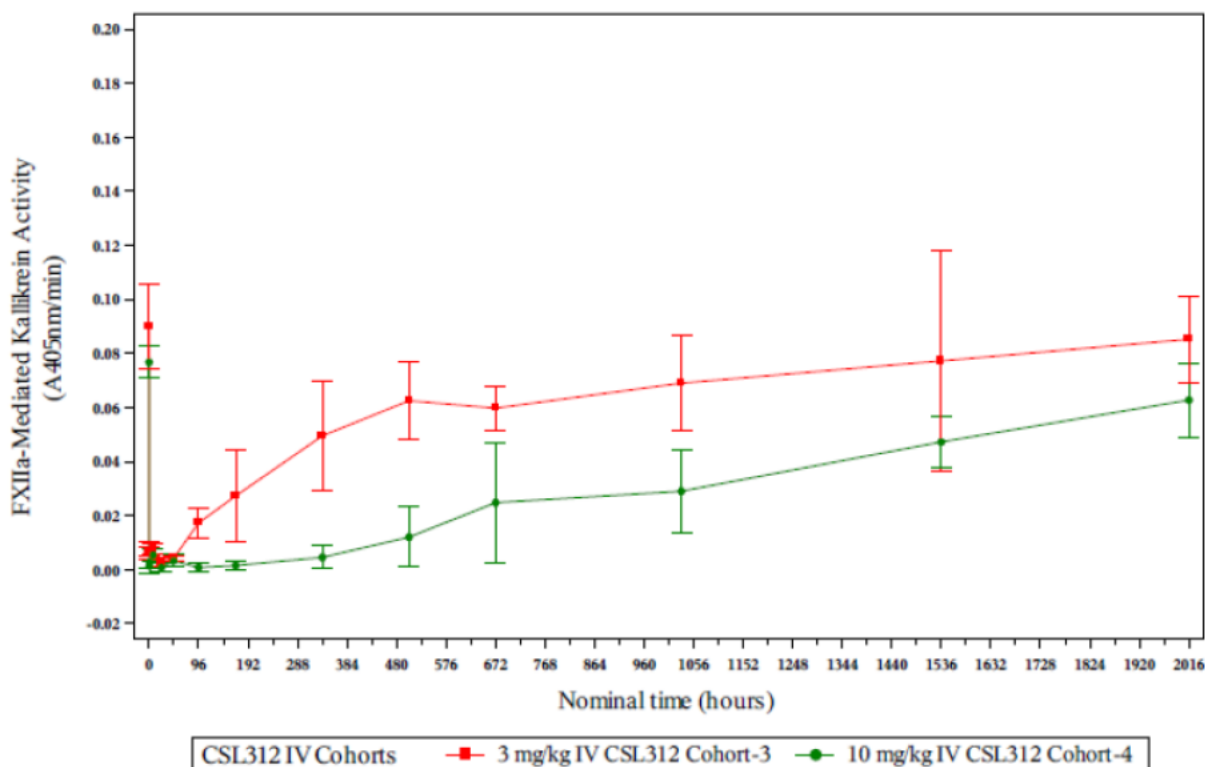
FXIIa-mediated kallikrein activity was assessed as a PD marker. Garadacimab showed dose-dependent inhibition of FXIIa-mediated kallikrein activity (Figure 32 and Figure 33). In SC cohorts, the time of peak response was approximately correlated with the garadacimab T_{max} . Mean inhibition was greater in Japanese relative to Caucasian subjects. However, there was large variability in measured kallikrein activity in both cohorts. Among SC cohorts, the most potent inhibition was observed at the 600 mg dose. The 3 and 10 mg/kg IV cohorts showed inhibition of FXIIa-mediated kallikrein activity. Activity returned to baseline by about Day 64 for the 200 mg SC and 3 mg/kg IV cohorts, whereas activity did not return to baseline by Day 85 for the 600 mg SC or 10 mg/kg IV cohorts. In study 1001, a return to baseline in FXIIa-mediated kallikrein activity was observed by Day 85 for cohorts receiving 10 mg/kg IV. The differences observed across studies may be due to variability of PD.

Figure 32. Mean (SD) FXIIa-Mediated Kallikrein Activity by Dose in SC Cohorts, Study 1003



Source: Figure 11-4, Clinical Study Report for study 1003.
Abbreviations: CSL312, garadacimab; SC, subcutaneous

Figure 33. Mean (SD) FXIIa-Mediated Kallikrein Activity by Dose in IV Cohorts, Study 1003



Source: Figure 11-5. Clinical Study Report for study 1003.
Abbreviations: CSL312, garadacimab; IV, intravenous; PK, pharmacokinetics

Immunogenicity Results

No subject in the study developed garadacimab ADAs.

14.2.4. Trial 2001 (Dose-Ranging Trial in Subjects With HAE)

Title

A multicenter, randomized, placebo-controlled, parallel-arm trial to investigate the efficacy, PKs, and safety of garadacimab in subjects with hereditary angioedema.

Objectives

The primary objective was to evaluate the efficacy of garadacimab in the prevention of HAE attacks in subjects with C1-INH HAE. Characterization of PK in subjects with HAE was included as a secondary objective, and evaluation of PD was an exploratory objective.

Trial Design

Trial 2001 was designed as a multicenter, randomized, placebo-controlled, parallel-arm trial in subjects with HAE (N=50) (Figure 65). Following a 4- to 8-week Run-in Period, subjects entered

Treatment Period 1, which lasted for approximately 13 weeks. The first 32 subjects with C1-INH HAE (i.e., Type I or II HAE) were randomized 1:1:1:1 to one of the following treatments:

- Garadacimab: 40 mg IV loading dose, then 75 mg SC Q4W beginning 1 week later.
- Garadacimab: 100 mg IV loading dose, then 200 mg SC Q4W beginning 1 week later.
- Garadacimab: 300 mg IV loading dose, then 600 mg SC Q4W beginning 1 week later.
- Placebo IV, then placebo SC Q4W beginning 1 week later.

These doses were selected based on a PK/PD model developed to quantify the relationship between garadacimab concentrations and FXIIa-mediated kallikrein activity from data in healthy subjects in study 1001. Based on the model, dosages of 75, 200, and 600 mg Q4W were predicted to result in at least 75% of subjects reaching percentage inhibitions of FXIIa-mediated kallikrein activity of ≥ 30 , ≥ 50 , and ≥ 90 %, respectively. IV loading doses were selected to yield exposures similar to those after SC doses based on approximate 50% bioavailability, but with achievement of earlier T_{max} . The Q4W dosing interval was based on an observed 19-day half-life in study 1001.

After the first 32 subjects with C1-INH HAE were randomized, up to an additional 8 subjects were assigned to an open-label arm in which all subjects received garadacimab at a dosage of 400 mg SC every 2 weeks (Q2W). These subjects did not receive an initial IV loading dose.

Up to 10 eligible subjects with FXII/plasminogen (PLG) HAE (i.e., Type III HAE with normal C1-esterase inhibitor and genetically confirmed factor XII or PLG gene mutation) were assigned to a separate open-label arm in which all subjects received garadacimab beginning with a 300 mg IV loading dose followed by 600 mg SC Q4W beginning 1 week later.

All subjects in Treatment Period 1 were eligible for participation in Treatment Period 2, which was conducted in an open-label manner and lasted for at least 44 weeks. Subjects were assigned to treatment as follows:

- C1-INH HAE subjects who received 75 mg SC Q4W or received open-label 400 mg SC Q2W in Treatment Period 1 were randomized 1:1 to 200 or 600 mg SC Q4W.
- C1-INH HAE subjects who received 200 mg SC Q4W in Treatment Period 1 continued on 200 mg SC Q4W.
- C1-INH HAE subjects who received 600 mg SC Q4W in Treatment Period 1 continued on 600 mg SC Q4W.
- FXII/PLG HAE subjects who received 600 mg SC Q4W in Treatment Period 1 continued on 600 mg SC Q4W.

All C1-INH HAE subjects who were receiving the 600-mg dose in Treatment Period 2 had their dose reduced to 200 mg SC Q4W at the next scheduled study visit, effective with Protocol Amendment 2.

IV and SC doses were administered using a 100 mg/mL formulation in a vial presentation. In blinded arms, doses were volume-normalized to maintain the blind. IV doses were given as an infusion at a volume of 3 mL over 3 min. SC doses were administered at a volume of 6 mL in Treatment Period 1, or at a volume of 2 mL or 6 mL for doses of 200 or 600 mg, respectively, in

Treatment Period 2. The preferred site of injection for SC doses was the abdomen, although another anatomic location could have been used at the discretion of the investigator.

The study enrolled male or female subjects aged 18 to 65 years with a diagnosis of C1-INH HAE or FXII/PLG HAE.

Routine prophylaxis to prevent HAE attacks with the use of C1-INH products or antifibrinolytics was prohibited during the Run-in Period and during the Treatment Periods. In addition, the following were prohibited during the 3 months before Screening and at any time during the study: angiotensin-converting enzyme inhibitors, and anticoagulants or antiplatelets.

Permitted therapies included prescribed medications required for management of acute or chronic medical conditions, and therapies to treat any AEs experienced during the study. Oral contraceptives or hormonal replacement therapy were permitted if taken at a stable dose in the 3 months prior to Screening. On-demand HAE therapy was permitted at any time during the study for the treatment of HAE attacks, including plasma-derived or recombinant C1-INH, icatibant, and ecallantide.

For additional details on the design of Study 2001, refer to Section [15.3](#).

PK, PD, and Immunogenicity Sampling

Treatment Period 1

C1-INH HAE and FXII/PLG HAE Subjects Receiving Drug Q4W

Blood samples to assess PK and PD were collected at predose on Day 1 and Weeks 1, 5, and 9. Postdose samples were collected on Day 1 at Hours 0.5, 4, and 8; and on Days 66 (~72 h after the Week 9 dose), 70, 77, 84, 91, and 186. Note that for subjects who participated in Treatment Period 2, the Day 91 (Week 13) visit was the first visit of Treatment Period 2, and no sample would be collected at the follow-up visit on Day 186.

Samples for coagulation labs were collected predose on Day 1 and on Days 29, 57, and 85.

Immunogenicity samples were collected at predose on Day 1, and on Day 91.

C1-INH HAE Subjects Receiving Drug Q2W

Blood samples to assess PK and PD were collected at predose on Day 1 and Weeks 3, 5, 7, 9, and 11. Postdose samples were collected on Days 64, 77, 85, and 180. Note that for subjects who participated in Treatment Period 2, the Day 85 visit was the first visit of Treatment Period 2, and no sample would be collected at the follow-up visit on Day 180.

Samples for coagulation labs were collected predose on Day 1 and on Days 35, 63, and 91.

Immunogenicity samples were collected at predose on Day 1, and on Day 85.

Treatment Period 2

Blood samples to assess PK and PD were collected at predose on Day 85 or 91 (Week 13, day depends on whether subjects received garadacimab SC Q4W or Q2W), and at Weeks 17, 21, 33, 45, 57, and 70. Samples for coagulation labs were collected at the same time points, with the exception of Week 70.

Immunogenicity samples were collected at predose on Day 85 or 91, and at Week 57.

Subject Disposition and Demographics

A total of 52 C1-INH subjects entered the Run-in Period and 38 subjects completed the Run-in Period and were assigned to one of the treatment arms as follows:

- Eight subjects received blinded placebo.
- Nine subjects received blinded garadacimab 75 mg SC Q4W.
- Eight subjects received blinded garadacimab 200 mg SC Q4W.
- Seven subjects received blinded garadacimab 600 mg SC Q4W.
- Six subjects received open-label garadacimab 400 mg SC Q2W.

All the 38 subjects completed Treatment Period 1 and entered Treatment Period 2. Twenty subjects received 200 mg SC Q4W and eighteen subjects received 600 mg SC Q4W. See Section [16.1](#) for additional details.

All the 20 subjects assigned to 200 mg SC Q4W completed Treatment Period 2. Two of these subjects had doses uptitrated to 400 mg Q4W during the study. Note that per protocol, dose increases were allowed at the discretion of the Investigator for subjects who experienced ≥ 3 HAE attacks within an 8-week period. A third subject who had originally been assigned to receive 600 mg SC Q4W was downtitrated to 200 mg SC Q4W and later uptitrated to 400 mg SC Q4W. The median (range) time to dose uptitration for all subjects was 142 (63, 167) days.

Of 18 subjects assigned to 600 mg SC Q4W, 16 completed Treatment Period 2, with two discontinuations prior to downtitration. Of a total of 18 subjects originally assigned to 600 mg SC Q4W, 16 were downtitrated to a dose of 200 mg Q4W, 12 of whom were downtitrated due to Protocol Amendment 2. Of the four subjects who were downtitrated to 200 mg Q4W prior to Protocol Amendment 2, one subject had the dose decreased remotely following remote re consent before the next scheduled visit. The remaining three subjects had doses reduced as action taken due to AEs as follows:

- One subject ((b) (6)) had mild rash.
- One subject ((b) (6)) had moderate headache and photopsia.
- One subject ((b) (6)) had mild dyspnea at rest and palpitations.

A total of seven FXII/PLG HAE subjects entered the Run-in Period and six subjects completed the Run-in Period and were assigned to treatment in Treatment Period 1. The six subjects comprised three subjects with FXII HAE and three subjects with PLG HAE. Of the six subjects, five completed Treatment Period 1, with one discontinuation (FXII HAE subject) due to lack of efficacy. Three subjects, all with PLG HAE, did not respond to treatment and completed the study after Treatment Period 1. The remaining two subjects, both with FXII HAE, were considered responders to therapy. These subjects entered and completed Treatment Period 2.

Across all treatment groups in Treatment Period 1, the median (interquartile range) body weight was as follows (data derived from Tables 14.1.3.1.1.1 and 14.1.3.1.1.2, CSR for Trial 2001):

- Placebo (n=8): 80.4 (77.8, 87.5) kg
- 75 mg Q4W (n=9): 96.3 (55.3, 100) kg
- 200 mg Q4W (n=8): 96.5 (81.9, 107) kg
- 600 mg Q4W (n=7): 74.4 (59.0, 85.5) kg
- Open-label 400 mg Q2W (n=6): 85.0 (73.0, 87.0) kg
- FXII/PLG HAE (n=6): 70.7 (56.5, 89.3) kg

Dose Response for Efficacy

The primary endpoint of the study was the time-normalized number of monthly HAE attacks on treatment with 200 or 600 mg garadacimab compared to placebo in Treatment Period 1. The time-normalized number of HAE attacks per month in subjects with C1-INH HAE by dose cohort in Treatment Period 1 is shown in [Table 78](#). A reduction relative to placebo in the mean time-normalized number of monthly HAE attacks was observed for all dosages evaluated in Treatment Period 1. No additional numerical reduction in the time-normalized number of monthly HAE attacks was observed in the 600 mg Q4W and 400 mg Q2W dosing groups compared to the 200 mg Q4W dosing group. See Section [16.1](#) for additional details. This trend continued into Treatment Period 2 in which the mean (SD) time-normalized number of HAE attacks per month was 0.08 (0.18) and 0.22 (0.35) for subjects receiving 200 mg Q4W and 600 mg Q4W, respectively (data derived from Table 11-6, CSR for Trial 2001). Data from Treatment Period 2 should be interpreted with caution as it was conducted in an open-label manner.

Table 78. Time-Normalized Number of HAE Attacks per Month by Dose Cohort in C1-INH HAE Subjects (Treatment Period 1), Trial 2001

	Placebo ^c q4wk N = 8	75 mg ^c CSL312 q4wk N = 9	200 mg ^c CSL312 q4wk N = 8	600 mg ^c CSL312 q4wk N = 7	400 mg ^c CSL312 q2wk N = 6
Number of Evaluable Subjects	8	9	8	7	6
Time-normalized Number of HAE Attacks per Month					
Mean (SD)	4.24 (1.801)	0.48 (1.057)	0.05 (0.127)	0.35 (0.407)	0.14 (0.222)
Median	4.61	0.00	0.00	0.34	0.00
Min, Max	1.40, 7.16	0.00, 3.26	0.00, 0.36	0.00, 1.05	0.00, 0.43
95% Confidence Interval	2.74, 5.75	- 0.33, 1.29	- 0.06, 0.15	- 0.02, 0.73	- 0.09, 0.38
P-value for Treatment Comparisons					
200 mg CSL312 vs Placebo ^a			< 0.001		
600 mg CSL312 vs Placebo ^a				< 0.001	
600 mg CSL312 vs 200 mg CSL312 ^b				0.082	
Percent Reduction in Time-normalized Number of HAE Attacks per Month Relative to Placebo					
Mean	–	88.68	98.94	91.68	–
Median	–	100.0	100.0	92.62	–

C1-INH HAE = hereditary angioedema with C1-esterase inhibitor deficiency; HAE = hereditary angioedema; ITT = intent-to-treat; max = maximum; min = minimum; N = number of subjects randomized / assigned to the treatment; q2wk = administered every 2 weeks; q4wk = administered every 4 weeks; SD = standard deviation.

- a Treatment comparisons were done using a 2-sided Mann-Whitney test at alpha = 0.025.
- b The treatment comparison was done using a 2-sided Mann-Whitney test at alpha = 0.05. This was an exploratory comparison.
- c The placebo, 75 mg, 200 mg, and 600 mg treatment arms were randomized and blinded; the 400 mg treatment arm was nonrandomized open-label.

Source: Table 11-5, Clinical Study Report for trial 2001.

PK Analysis

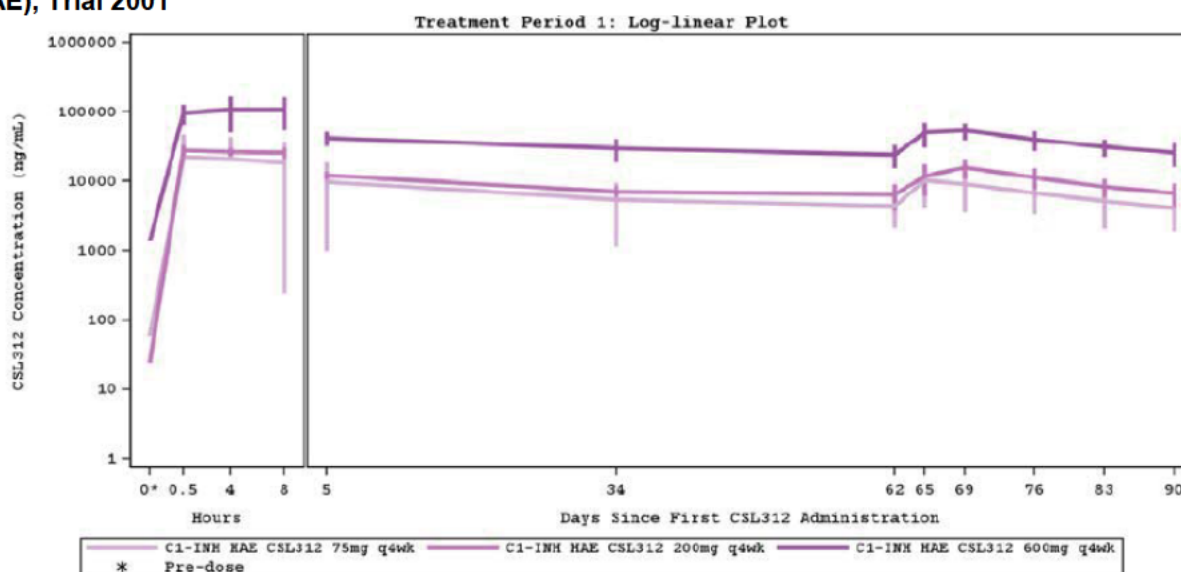
The 38 C1-INH subjects who received garadacimab in Treatment Periods 1 and 2 were included in the PK population, which comprised all subjects for whom at least one measurable concentration of garadacimab was reported. All the six FXII/PLG HAE subjects were included in the PK population in Treatment Period 1. Both FXII/PLG HAE subjects were included in the PK population in Treatment Period 2.

PK Results

Treatment Period 1

Mean (SD) garadacimab concentration-time profiles by dose group for blinded cohorts (i.e., 75, 200, or 600 mg Q4W with IV loading doses of 40, 100, and 300 mg, respectively) are shown in [Figure 34](#), for the open-label C1-INH cohort (i.e., 400 mg Q2W with no IV loading dose) in [Figure 35](#), and for the FXII/PLG HAE cohort (300 mg IV then 600 mg Q4W) in [Figure 36](#). For all cohorts that received an IV loading dose, peak concentrations were reached after the end of IV infusion. Following the beginning of SC dosing, plasma concentrations declined, with steady state reached after three doses (approximately Day 35, Week 5). In subjects receiving 400 mg SC Q2W with no IV loading dose, steady state appears to have been reached by Day 56 (Week 8).

Figure 34. Mean (SD) Garadacimab PK Profiles in Treatment Period 1 in Blinded Cohorts (C1-INH HAE), Trial 2001



C1-INH HAE = hereditary angioedema with C1-esterase inhibitor deficiency; PK = pharmacokinetic(s); q4wk = administered every 4 weeks; SD = standard deviation.

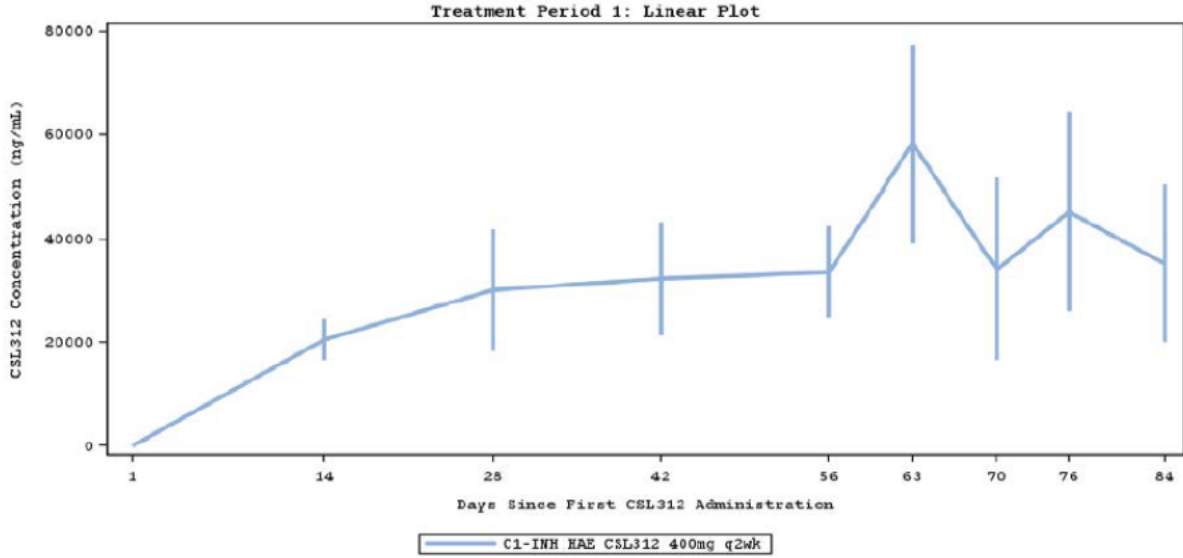
Note: The x-axis denotes the elapsed time in days since first CSL312 administration at time 0, which corresponds to Visit Day 1. Values below limit of quantification pre-dose are set to 0.

Source: Figure 11-1, Clinical Study Report for trial 2001.

Subjects in the 75, 200, and 600 mg q4wk cohorts all received IV loading doses of 40, 100 or 300 mg, respectively. SC doses were administered beginning approximately 1 week after the loading dose.

Abbreviations: CSL312, garadacimab; IV, intravenous; SC, subcutaneous

Figure 35. Mean (SD) Garadacimab PK Profiles in Treatment Period 1 in the Open-Label Cohort (C1-INH HAE), Trial 2001



C1-INH HAE = hereditary angioedema with C1-esterase inhibitor deficiency; PK = pharmacokinetic(s);
q2wk = administered every 2 weeks.

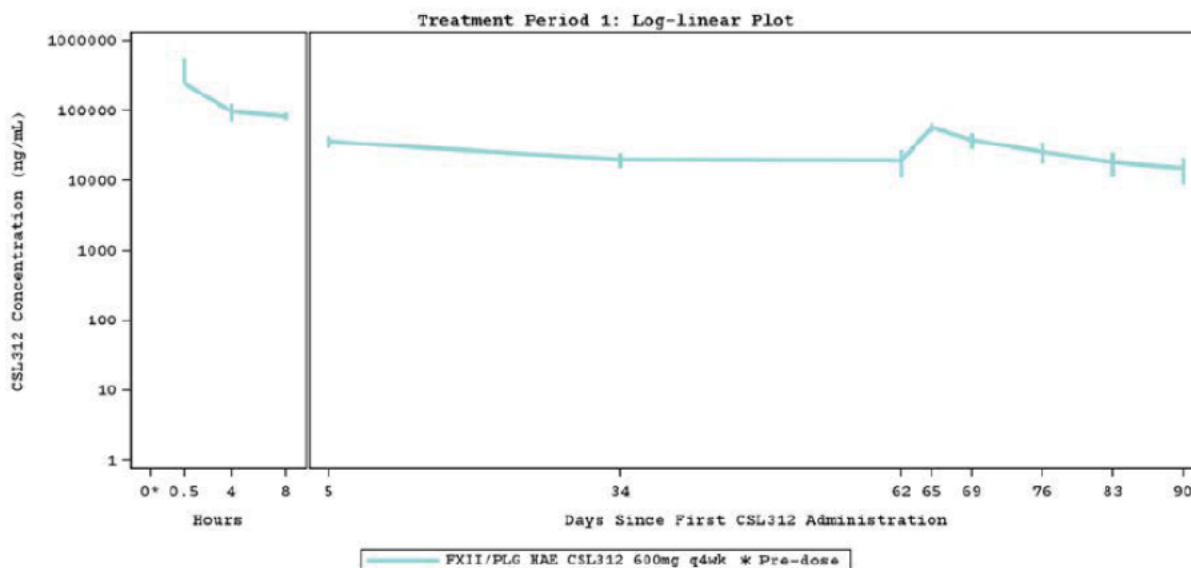
Note: The x-axis denotes the elapsed time in days since first CSL312 administration at time 0, which corresponds to Visit Day 1. Values below limit of quantification pre-dose are set to 0.

Source: Figure 11-2, Clinical Study Report for trial 2001.

Note that all subjects in this cohort received garadacimab at a dosage of 400 mg SC q2wk with no IV loading dose.

Abbreviations: CSL312, garadacimab; IV, intravenous; SC, subcutaneous

Figure 36. Mean (SD) Garadacimab PK Profiles in Treatment Period 1 in Subjects with FXII/PLG HAE, Trial 2001



FXII / PLG HAE = hereditary angioedema with normal C1-esterase inhibitor and factor XII or plasminogen gene mutation; PK = pharmacokinetic(s); q4wk = administered every 4 weeks.

Note: The x-axis denotes the elapsed time in days since first CSL312 administration at time 0, which corresponds to Visit Day 1. Values below limit of quantification pre-dose are set to 0.

Source: Figure 11-4, Clinical Study Report for trial 2001.

Note that all subjects in this cohort received garadacimab beginning with an IV loading dose of 300 mg, followed by 600 mg SC q4wk beginning approximately 1 week later.

Abbreviations: CSL312, garadacimab; IV, intravenous; SC, subcutaneous

A summary of steady state PK parameters following SC dosing in blinded treatment arms (C1-INH HAE subjects) and in subjects with FXII/PLG HAE is shown in [Table 79](#). Across all treatment groups, median T_{max} was approximately 6 to 7 days postdose, and the mean half-life ranged from 14.5 to 18.5 days. These values are consistent with those reported for healthy subjects following a single SC dose in studies 1001, 1003, and 1004. C_{max} and area under the concentration-time curve during the dosing interval appeared to increase in a slightly less-than-dose proportional manner between doses of 75 and 600 mg, with 5.3-fold and 5.9-fold increases, respectively, for an 8-fold increase in dose. There was no apparent difference in garadacimab exposure between subjects with C1-INH HAE and subjects with FXII/PLG HAE.

Table 79. Steady-State PK Parameters Following SC Dosing of Garadacimab (Day 63), Trial 2001

Location in CTD Study No.	Study Objective Design	Subjects: Number (M/F) Type Age (y) Mean (Range)	Treatment Day N	PK Parameters					
				Median (Min, Max)		Arithmetic Mean (SD)			
				t_{max} (h)	C_{max} ($\mu\text{g/mL}$)	AUC_{0-12h} ($\mu\text{g}\cdot\text{h/mL}$)	CL/F (L/h)	V_z/F (L)	$t_{1/2}$ (h)
Module 5.3.5.1 Study 2001	Evaluate the efficacy of garadacimab in the prevention of HAE attacks in subjects with C1-INH HAE. Randomized, placebo-controlled, parallel-arm	Period 1 Blinded: 32 (14/18) Subjects with C1-INH HAE 40.3 (20, 65)	Garadacimab SC 75 mg Q4W Day 63 N = 9	143 (45.4, 196)	10.6 (6.09)	4510 (2420)	0.0198 (0.0079)	10.6 (5.10)	412 (97.0)
			Garadacimab SC 200 mg Q4W Day 63 N = 8	166 (116, 218)	15.9 (5.22)	7170 (2410)	0.0303 (0.0084)	17.0 (4.78)	394 (85.6)
			Garadacimab SC 600 mg Q4W Day 63 N = 7	166 (72.4, 188)	56.4 (15.9)	26,500 (8150)	0.0246 (0.0079)	17.1 (6.67)	444 (44.0)
		Period 1 Open-label: 6 (0/6) Subjects with FXII / PLG HAE 41.5 (SD = 7.71)	Garadacimab SC 600 mg Q4W Day 63 N = 6	146 (70.4, 334)	43.0 (17.9)	18,800 (8380)	0.0375 (0.0171)	16.8 (7.83)	348 (106)

Source: Table 12, Summary of Clinical Pharmacology.

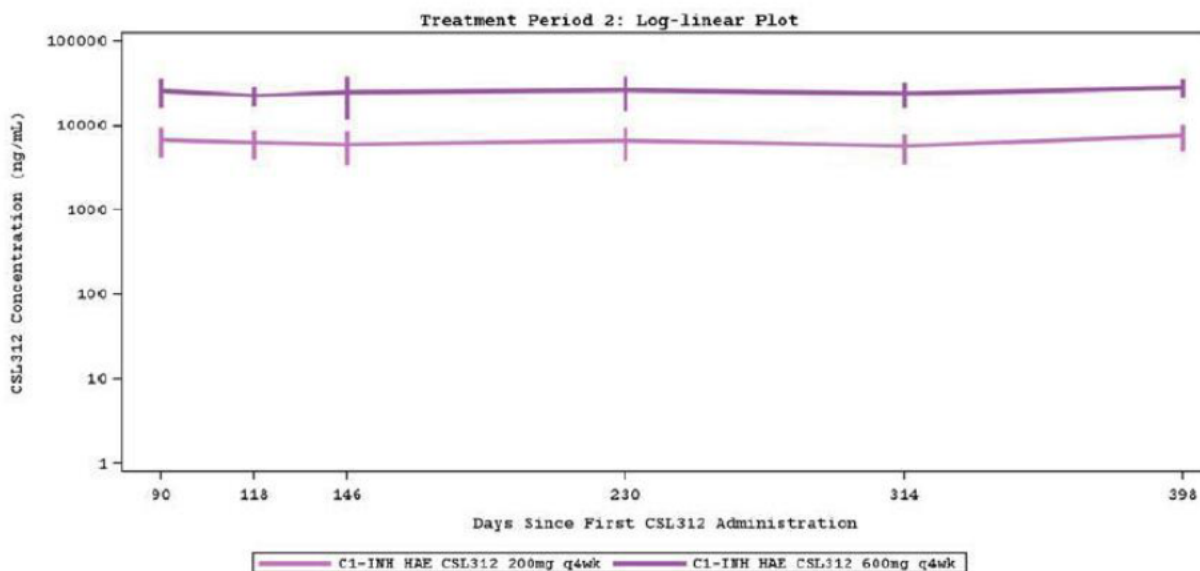
The half-life estimate should be interpreted with caution due to the time course of the terminal phase of the PK profile being less than three estimated half-lives.

Abbreviations: AUC, area under the concentration-time curve; C1-INH, C1-esterase inhibitor; CL/F, apparent clearance; C_{max} , maximum plasma concentration; CTD, common technical document; F, female; HAE, hereditary angioedema; M, male; PK, pharmacokinetics; PLG, plasminogen; Q4W, every 4 weeks; SC, subcutaneous; $T_{1/2}$, half-life; T_{max} , time to maximum plasma concentration; V_z/F , apparent volume of distribution

Treatment Period 2

Mean (SD) garadacimab concentration-time profiles for subjects receiving the same dose as in Treatment Period 1 are shown in [Figure 37](#). Steady-state trough concentrations remained consistent throughout Treatment Period 2.

Figure 37. Mean (SD) Garadacimab PK Profiles in Treatment Period 2 Among Subjects Receiving the Same Dose in Treatment Period 1, Trial 2001



C1-INH HAE = hereditary angioedema with C1-esterase inhibitor deficiency; PK = pharmacokinetic;
q4wk = administered every 4 weeks.

Source: Figure 11-3, Clinical Study Report for trial 2001.

All subjects received garadacimab at a dosage of 200 or 600 mg SC Q4W immediately after the end of Treatment Period 1. Only subjects who were already receiving 200 or 600 mg SC q4wk in Treatment Period 1 are represented above.

PD Results

FXIIa-mediated kallikrein activity was assessed as a PD marker. In the blinded treatment arms, garadacimab showed dose-dependent inhibition of FXIIa-mediated kallikrein activity ([Table 80](#)). Following administration of the IV loading dose, inhibition of FXIIa-mediated kallikrein activity was observed within 8 h postdose. Inhibition at all doses was maintained at trough throughout the Treatment Period, with the lowest activity observed among subjects receiving 600 mg Q4W. Changes in FXIIa-mediated kallikrein activity were comparable between C1-INH and FXII/PLG HAE subjects who received 300 mg IV then 600 mg SC Q4W.

Table 80. FXIIa-Mediated Kallikrein Activity (Delta A₄₀₅ nm/min) Over Time at Select Time Points in Treatment Period 1 (C1-INH Blinded and FXII/PLG Open-Label Treatment Arms), Trial 2001

Time Point	Placebo	75 mg Q4W	200 mg Q4W	600 mg Q4W	600 mg Q4W
	C1-INH (N=8)	C1-INH (N=9)	C1-INH (N=8)	C1-INH (N=7)	FXII/PLG (N=6)
Day 1, predose	0.18 (0.07)	0.14 (0.06)	0.16 (0.04)	0.12 (0.05)	0.14 (0.04)
Day 1, 8 h postdose	0.16 (0.06)	0.06 (0.04)	0.03 (0.02)	0.005 (0.002)	0.009 (0.006)
Week 1 (Day 6)	0.17 (0.06)	0.10 (0.04)	0.11 (0.03)	0.02 (0.03)	0.04 (0.02)
Week 5 (Day 35)	0.17 (0.05)	0.13 (0.04)	0.13 (0.04)	0.06 (0.04)	0.07 (0.04)
Week 9 (Day 63)	0.17 (0.06)	0.12 (0.03)	0.13 (0.04)	0.06 (0.04)	0.07 (0.04)
Week 10 (Day 70)	0.13 (0.04)	0.11 (0.04)	0.10 (0.04)	0.02 (0.01)	0.03 (0.03)
Week 13 (Day 91)	0.17 (0.05)	0.12 (0.04)	0.14 (0.04)	0.06 (0.05)	0.07 (0.03)

Source: Reviewer-generated table adapted from Tables 14.2.3.3.2.1 and 14.2.3.3.2.5, Clinical Study Report for trial 2001.

Doses of garadacimab or placebo were administered on Day 1, Week 1, Week 5, and Week 9. Samples collected at those time points were predose.

All treatment arms with C1-INH HAE subjects were conducted in a blinded manner. The treatment arm with FXII/PLG HAE subjects was conducted in an open-label manner.

Abbreviations: A, absorbance; C1-INH, C1-esterase inhibitor; FXII, Factor XII; PLG, plasminogen; Q4W, every 4 weeks

For C1-INH HAE subjects who received 400 mg SC Q2W without an IV loading dose, mean (SD) FXIIa-mediated kallikrein activity decreased from 0.20 (0.05) on Day 1 (predose) to 0.09 (0.07) at Week 3, 0.07 (0.03) at Week 9, 0.04 (0.05) at Week 10, 0.08 (0.03) at Week 11, 0.04 (0.04) at Week 12, and 0.06 (0.04) at Week 13 (data derived from Table 14.2.3.3.2.2, CSR for Trial 2001). Decreases in activity were observed after the first dose and maintained throughout the Treatment Period. Note that doses were dispensed on Day 1 and Weeks 3, 5, 7, 9, and 11. Thus, measurements at Weeks 10 and 12 occurred postdose. The lower mean activity at those time points may thus be attributed to higher plasma garadacimab concentrations.

Dose-dependent inhibition in FXIIa-mediated kallikrein activity was maintained in Treatment Period 2. From Week 17 onwards, mean (SD) FXIIa-mediated kallikrein activity ranged from 0.14 (0.04) to 0.17 (0.06) for the 200 mg SC Q4W arm, and from 0.8 (0.05) to 0.10 (0.05) for the 600 mg SC Q4W arm (data derived from Table 14.2.3.3.2.3, CSR for Trial 2001). Values observed for the 200 mg SC Q4W arm were similar to baseline levels for all treatment arms.

Activated Partial Thromboplastin Time

Per the Applicant, the normal range for aPTT values is between 24.3 and 43.4 seconds. During Treatment Period 1, in the 75 and 200 mg Q4W treatment arms, mean aPTT values post-first dose fell within this range at all time points (mean [SD] values range from 24.88 [3.23] to 28.26 [3.01] seconds). In these cohorts, maximum values did not exceed the upper limit of normal. No difference from placebo was apparent.

In the 600 mg Q4W cohort, mean post-first dose values were in general higher than those in the 75 and 200 mg Q4W cohorts (mean [SD] values range from 42.02 [17.8] to 47.95 [29.1] seconds). In the 600 mg Q4W treatment arms, the mean aPTT was above normal range on Days 35 and 63 with a mean [SD] value of 47.50 [31.69] seconds. Although mean values did not exceed the upper limit of normal on Day 91, maximum values indicate that at least some subjects exceeded the normal range. Per the Applicant, this prolongation in Treatment Period 1 was observed in three subjects (data derived from Table 14.2.3.3.7.1, CSR for Trial 2001).

In the 400 mg Q2W treatment arm, the mean aPTT was within normal range at all time points. Maximum values fell within the normal range at all time points except for the Day 85 time point

(mean [SD] aPTT at this time point was 36.38 [11.65] seconds) (data derived from Table 14.2.3.3.7.2, CSR for Trial 2001).

In Treatment Period 2, the mean aPTT was within the normal range at all time points for the 200 mg Q4W cohort (mean [SD] values range from 26.85 [4.22] to 28.68 [6.62] seconds). Maximum values exceeded normal range at Week 57. In the 600 mg Q4W cohort, mean values were in general higher than those in the 200 mg Q4W cohort (mean [SD] values range from 31.33 [10.7] to 44.3 [34.6] seconds). Maximum values exceeded normal range at all time points (data derived from Table 14.2.3.3.7.3, CSR for Trial 2001).

Immunogenicity Results

No subject treated with garadacimab tested positive for ADAs during Treatment Period 1. One subject randomized to placebo tested positive for ADAs at week 13 (i.e., the end of Treatment Period 1). This subject received 200 mg Q4W garadacimab in Treatment Period 2. No ADAs were detected in subsequent visits.

Note that immunogenicity samples were collected on Day 1, Week 13, and Week 57. Due to the sampling scheme, subjects with transient ADAs may not have been captured. Regardless, the data suggest that subjects likely did not have persistent ADAs.

Also note that the drug tolerance of the ADA assay is adequate up to 30 µg/mL garadacimab (refer to Office of Pharmaceutical Quality executive summary review dated August 26, 2024). At ADA sample collection time points, there were six subjects with seven samples with garadacimab concentrations exceeding 30 µg/mL, including three subjects who received 400 mg Q2W (concentrations of 46.0 to 54.1 µg/mL at Day 85) and three subjects who received 600 mg Q4W (one with a concentration of 31.4 µg/mL at Day 91, one with a concentration of 43.7 µg/mL at Day 91 and 36.5 µg/mL at Week 57, and one with a concentration of 32.0 µg/mL at Week 57).

14.2.5. Trial 3001 (Phase 3 Efficacy Trial in Subjects With Type I and II HAE)

Title

A multicenter, double-blind, randomized, placebo-controlled, parallel-arm trial to investigate the efficacy and safety of SC administration of garadacimab in the prophylactic treatment of HAE.

Study Design

For a detailed description of the design of trial 3001, refer to Section [6.2.1](#).

Trial 3001 was designed as a multicenter, double-blind, randomized, placebo-controlled, parallel-arm trial in adolescent and adult subjects with HAE. Following a Run-in Period of up to 2 months, subjects were randomized 3:2 to receive either garadacimab or placebo during the 6-month Treatment Period. Subjects on garadacimab received a 400 mg SC loading dose (administered as 2×200 mg) followed by 200 mg SC once monthly beginning on Day 31. Randomization was stratified by age (≤17 years or >17 years).

SC doses were administered using a 170 mg/mL solution in 1.2 mL PFS-NSD devices. SC injections were administered as 1×1.2 mL (200 mg) or 2×1.2 mL (400 mg) in the abdomen.

The 200-mg dose was selected based on efficacy, safety, PK, and PD observed in Treatment Period 1 of trial 2001, with support from exposure-response (E-R) modeling. An E-R model was constructed to simulate HAE attack rates over various garadacimab concentrations. The median predicted minimum daily average garadacimab concentrations at steady state following a 200 mg SC once monthly regimen corresponded to 90% relative risk reduction in HAE attack rate. Increasing the dose beyond 200 mg was not predicted to result in further reduction in HAE attack rate.

In end-of-Phase Two Meeting Minutes dated October 17, 2020 in DARRTS under IND 139936 (reference ID: 4687429), the Agency noted that the proposed dose and dose interval are supported by the phase 2 dose-ranging trial (2001), but noted that a different formulation from that used in 2001 will be used. As a result, the choice of the proposed dose and dosing interval was left at the risk and discretion of the Applicant. In addition, the Agency also requested that the Applicant provide justification for use of a loading dose.

The trial enrolled male or female subjects aged ≥ 12 years with a diagnosis of clinically confirmed C1-INH HAE (i.e., Type I or II HAE). No subject with FXII/PLG HAE diagnosis (i.e., HAE with normal C1-esterase inhibitor and genetically confirmed factor XII or PLG gene mutation) was enrolled in this trial.

For adults, use of C1-INH products, androgens, antifibrinolytics, or other small-molecule medications for routine prophylaxis against HAE within 2 weeks prior to the Run-in Period was exclusionary. For adolescents aged 12 to 17 years, use of long-term prophylactic therapy for HAE before screening was exclusion. Subjects were also excluded if they used lanadelumab within 3 months prior to the Run-in Period, or use of systemically absorbed estrogen-containing medications (e.g., oral contraceptives or hormone replacement therapy) or angiotensin-converting enzyme inhibitors within 4 weeks prior to the Run-in Period.

Permitted therapies included prescribed medications required for management of acute or chronic medical conditions, and therapies to treat any AEs experienced during the trial. On-demand HAE therapy was permitted at any time during the trial for the treatment of HAE attacks, including plasma-derived or recombinant C1-INH, icatibant, and ecallantide.

PK, PD, and Immunogenicity Sampling

Blood samples to assess PK and PD (i.e., FXIIa-mediated kallikrein activity) were collected on Days 1, 31, 62, 91, 121, 151, 182 (Month 7, end of the Treatment Period), and 242 (final follow-up visit).

Samples for coagulation labs were collected at Screening, predose on Day 1, and on Days 91 and 182 (Month 7, end of the Treatment Period).

Immunogenicity samples were collected on Day 1, and on Days 91 and 182.

Subject Disposition and Demographics

For details, see Section 6.2.4. A total of 76 subjects entered the Run-in Period and 65 subjects completed the Run-in Period and were randomized to treatment, including 39 who received garadacimab and 26 subjects who received placebo. One subject in the placebo arm was randomized to blinded treatment in error and never received study treatment. Of the remaining 64 subjects, 61 completed treatment and 60 completed the study. Three subjects, all in the

placebo group, discontinued treatment due to withdrawal. Of 60 subjects who completed the study, 57 entered open-label extension study 3002, comprising 36 subjects who received garadacimab and 21 subjects who received placebo.

Among adult subjects randomized to garadacimab, the median (range) body weight at Screening was 79 (58.4, 140) kg. The study enrolled six adolescent subjects ranging in age from 12 to 17 years. Four adolescents received garadacimab and two received placebo. Among adolescent subjects receiving garadacimab, the median (range) age was 15 (12, 17) years, and the median (range) body weight at Screening was 60.3 (54.3, 79) kg.

PK Analysis

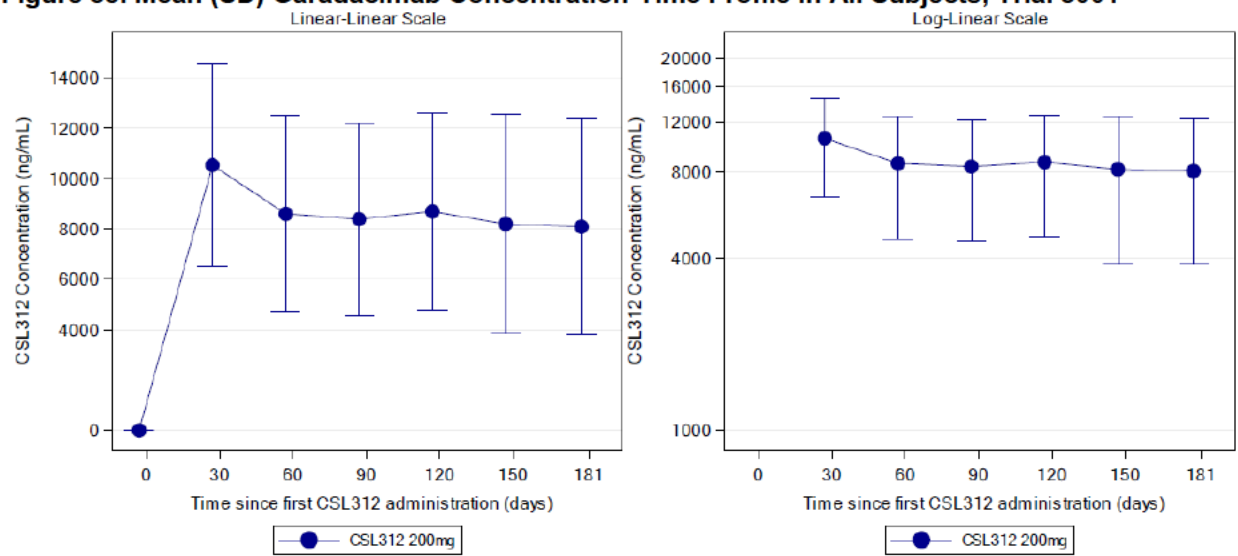
All the 39 subjects who received garadacimab were included in the PK population, which comprised all the subjects with at least one measurable concentration of garadacimab.

Plasma concentrations were summarized by nominal time points and plotted on linear and semilogarithmic scales. Noncompartmental analysis was not conducted. PK data were included in analyses of population PK, PK/PD, and E-R.

PK Results

The mean (SD) garadacimab concentration-time profile for all subjects is shown in [Figure 38](#). Following administration of the SC loading dose, the highest trough concentrations were observed on Day 30 prior to the second dose (mean [SD]=10,533 [4004] ng/mL). Plasma concentrations declined by Day 60 (prior to administration of the third dose) and remained consistent for the remainder of the Treatment Period. Mean (SD) trough concentrations from Day 60 through the remainder of the Treatment Period ranged from 8087 (4277) ng/mL to 8692 (3934) ng/mL. Steady-state for C_{trough} was reached by Day 60. This behavior is similar to observations in trial 2001, in which subjects received an IV loading dose prior to initiation of SC dosing.

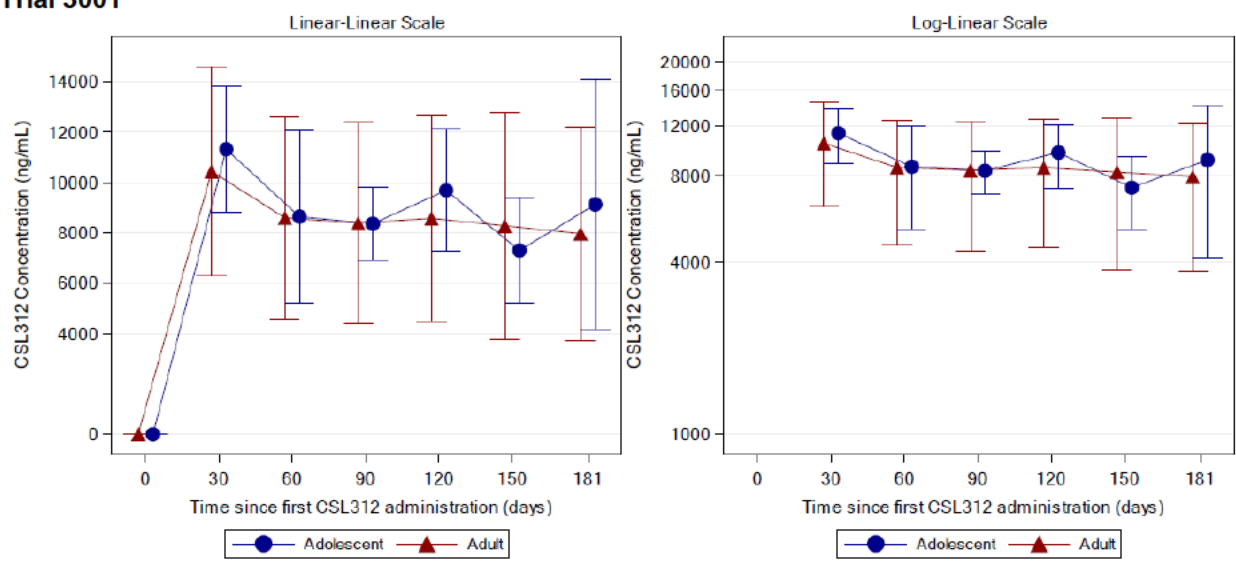
Figure 38. Mean (SD) Garadacimab Concentration-Time Profile in All Subjects, Trial 3001



Source: Figure 14.2.5.2.1, Clinical Study Report for trial 3001.
Abbreviation: CSL312, garadacimab

The mean (SD) garadacimab concentration-time profiles for adults versus adolescents are shown in [Figure 39](#). The PK of garadacimab in adolescents appears consistent with that in adults. The mean (SD) garadacimab trough concentrations in adolescents from Day 60 through the remainder of the Treatment Period ranged from 7297 (2085) ng/mL to 9688 (2421) ng/mL. In adults, trough concentrations ranged from 7969 (4257) ng/mL to 8593 (4006) ng/mL (data derived from Table 14.2.5.1.2, CSR for trial 3001).

Figure 39. Mean (SD) Garadacimab Concentration-Time Profiles in Adults Versus Adolescents, Trial 3001



Source: Figure 14.2.5.2.3, Clinical Study Report for trial 3001.
Abbreviation: CSL312, garadacimab

The final pooled population PK model was used to simulate steady state PK parameters for all subjects in trial 3001. Refer to Section [14.5](#) for additional details on the population PK analysis. Parameter estimates are shown in [Table 81](#). Exposure following the initial 400 mg SC loading dose was also predicted using the final population PK model. The mean (SD) model predicted AUC_{τ} and $C_{\max}$ following the 400 mg SC loading dose were 13700 (4140) ng*h/mL and 28.5 (9.0) $\mu\text{g/mL}$. Garadacimab exposure after the loading dose is thus about 133% of that at steady state following administration of 200 mg SC once monthly (refer to Applicant's response to IR, submitted September 20, 2024).

Table 81. Summary of Model-Predicted Garadacimab Pharmacokinetics in Subjects With HAE, Trial 3001

Metric	Mean (SD)	Geometric Mean (%CV)	Median (Range)
AUC _{tau,ss} (µg•h/mL)	10,300 (3380)	9770 (40.7)	9290 (4340, 18,200)
C _{max,ss} (µg/mL)	21.2 (6.58)	20.2 (38.3)	20.0 (9.64, 34.7)
C _{min,ss} (µg/mL)	9.30 (3.73)	8.53 (55.6)	8.86 (2.12, 20.2)
t _{max} (hours)	—	—	137 (91.0, 175)
CL/F (L/hr)	0.0217 (0.00793)	0.0205 (40.7)	0.0215 (0.0110, 0.0460)
V _c /F (L)	7.42 (4.20)	6.62 (57.7)	6.02 (3.04, 22.8)
t _{1/2} (hours)	445 (97.4)	434 (25.0)	434 (244, 669)

AUC_{tau,ss} = area under the plasma concentration-time curve in 1 dosing interval at steady state; CL/F = apparent systemic clearance; C_{max,ss} = maximum plasma concentration at steady state; C_{min,ss} = minimum plasma concentration at steady state; CV = coefficient of variation; HAE = hereditary angioedema; Q1M = once monthly; SC = subcutaneous; SD = standard deviation; t_{1/2} = terminal half-life; t_{max} = time to reach maximum plasma concentration; V_c/F = apparent volume of the central compartment.

Note: N = 39 subjects from Study 3001.

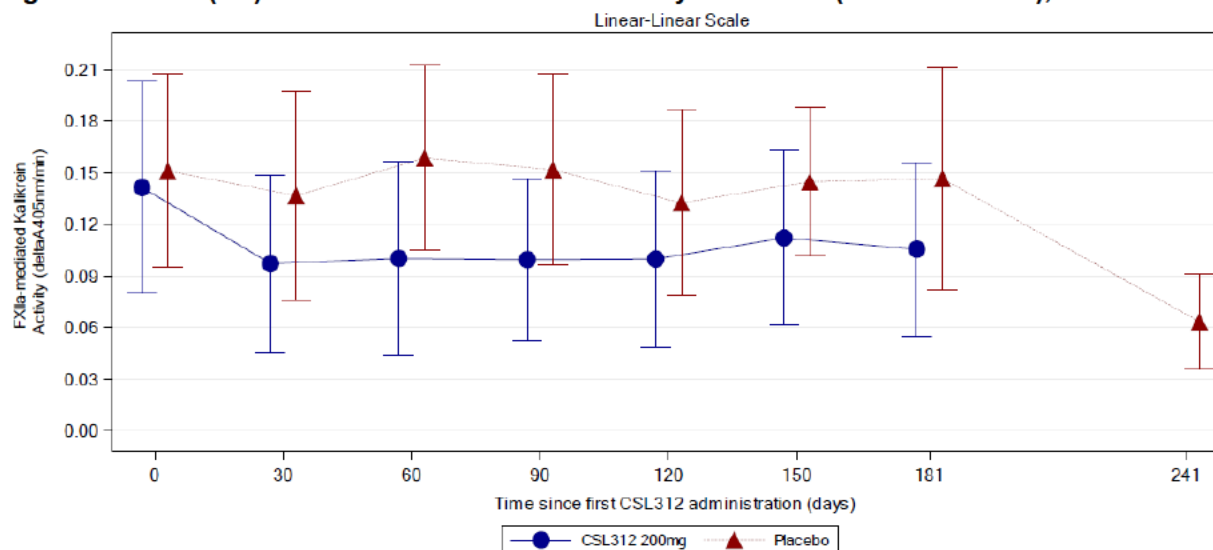
Source: Module 5.3.3.5, CSL0507F-Report-PKPD, Table S11

Source: Table 6, Summary of Clinical Pharmacology.

PD Results

FXIIa-mediated kallikrein activity was assessed as a PD marker. FXIIa-mediated kallikrein activity over time as an absolute value and a percentage of baseline is shown in [Figure 40](#) and [Figure 41](#), respectively. At predose time points, approximately 20% inhibition of FXIIa-mediated kallikrein activity was observed.

Figure 40. Mean (SD) FXIIa-Mediated Kallikrein Activity Over Time (Absolute Value), Trial 3001

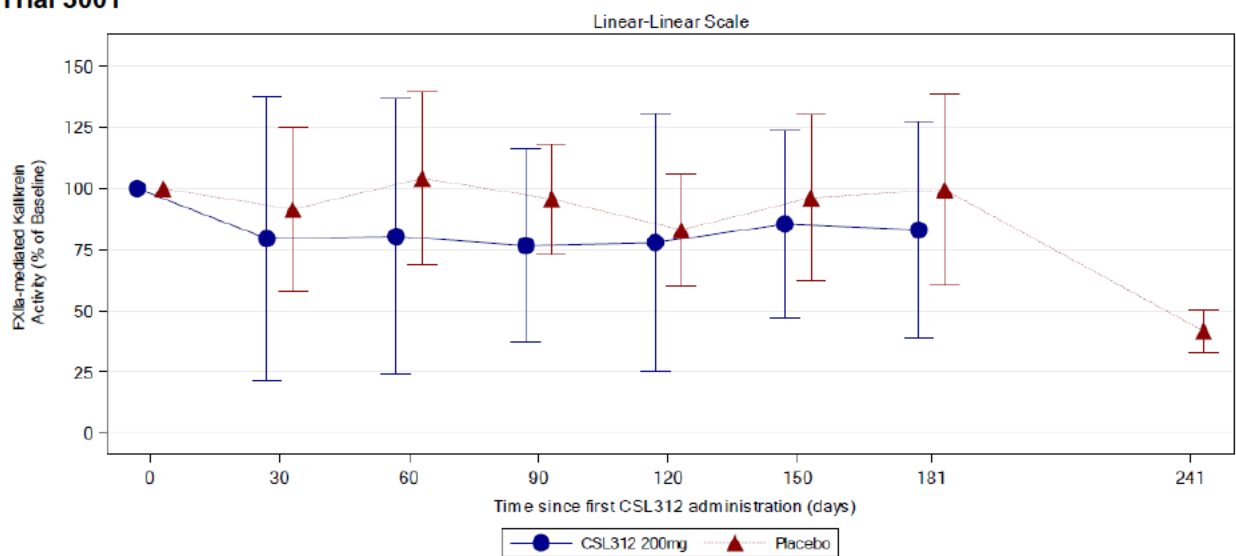


Source: Figure 14.2.6.2.2, Clinical Study Report for trial 3001.

Note that there were only two evaluable subjects at Day 242 as most subjects had either discontinued the trial or completed the trial and entered open-label study 3002.

Abbreviations: CSL312, garadacimab; FXIIa, activated Factor XII

Figure 41. Mean (SD) FXIIa-Mediated Kallikrein Activity Over Time (Percentage of Baseline), Trial 3001



Source: Figure 14.2.6.2.3, Clinical Study Report for trial 3001.

Note that there were only two evaluable subjects at Day 242 as most subjects had either discontinued the trial or completed the trial and entered open-label study 3002.

Abbreviations: CSL312, garadacimab; FXIIa, activated Factor XII

Activated Partial Thromboplastin Time

Per the Applicant, the normal range for aPTT values is between 24.3 and 43.4 seconds. For subjects in the garadacimab arm, there was little change in mean aPTT values throughout the Treatment Period. Mean (SD) aPTT at baseline, Day 91, and Day 182 were 29.26 (9.07) seconds, 28.84 (5.59) seconds, and 33.36 (19.8) seconds, respectively (data derived from Table 14.3.4.4, CSR for trial 3001). There were three subjects noted to have aPTT prolongation following administration of garadacimab:

- One adult subject with aPTT values of 59.4 and 95.5 seconds on Days 91 and 182, respectively.
- One adolescent subject (aged 17 years) with an aPTT of 67 seconds on Day 182, and
- One adult subject with an aPTT of 126 seconds on Day 182.

The C_{trough} values from these three subjects at the four time points listed above were not outliers or consistently at the higher end of the distribution of population C_{trough} values observed from trial 3001 (see Section 7.7.1).

Immunogenicity Results

Two subjects in the garadacimab arm tested positive for ADAs, including one subject at baseline (prior to receiving garadacimab) and one subject on Day 182, both with a titer value of 10. The subject who tested positive at baseline did not have detectable antibodies at subsequent visits.

14.2.6. Study 3002 (Long-Term Open-Label Extension Study in Subjects With HAE)

Title

An open-label study to evaluate the long-term safety and efficacy of garadacimab in the prophylactic treatment of hereditary angioedema.

Study Design

For a detailed description of the study design of 3002, refer to Sections [7.6.2](#) and [15.2](#).

Study 3002 is ongoing. An interim CSR was provided with a data cutoff of February 13, 2023 for all subjects, and May 22, 2023 for adolescent subjects (i.e., when 8/10 adolescents had ≥ 12 months of exposure).

Study 3002 was designed as a multicenter, open-label, phase 3b study in adolescent and adult subjects with HAE. This study enrolled rollover subjects with HAE from studies 2001 and 3001, as well as newly enrolled subjects with Type I or Type II HAE. All subjects received garadacimab. Rollover subjects continued to receive garadacimab at a dosage of 200 mg SC once monthly. Following a Run-in Period, garadacimab-naïve subjects received a 400 mg SC loading dose (2 $\times$ 200 mg) followed by 200 mg SC once monthly beginning one month later. Each subject was to receive garadacimab for at least 12 months.

SC doses were administered using a 170 mg/mL solution in 1.2 mL prefilled syringe or AI devices. SC injections were administered as 1 $\times$ 1.2 mL (200 mg) or 2 $\times$ 1.2 mL (400 mg) in the abdomen.

The study enrolled male or female subjects aged ≥ 12 years with a diagnosis of clinically confirmed C1-INH HAE (i.e., Type I or II HAE). Criteria regarding washout of prior medications and use of concomitant medications is similar to that from trial 3001.

PK, PD, and Immunogenicity Sampling

For subjects from 3001 and all naïve subjects, blood samples to assess PK and PD (i.e., FXIIa-mediated kallikrein activity) were collected on Days 1, 31, 61, and 91; Months 6, 9, 12, 18, 24, and 30; and at the end-of-treatment visit.

For subjects from 2001, blood samples to assess PK and PD were collected on Days 1 and 91; Months 6, 12, 18, 24, and 30; and at the end-of-treatment visit.

Additional PK/PD samples were collected in a subset of garadacimab-naïve subjects to characterize the PK of the loading dose. Following administration of the loading dose on Day 1, samples were collected on Days 7, 14, 21, and 30.

For adolescent subjects, additional PK/PD samples were collected following the Month 3 (Day 91) dose on Days 3, 7, 14, 21, and 30 (predose prior to the next dose).

Samples for coagulation labs were collected at Screening, predose on Day 1, and on Days 91, 181, 361 (Month 12), 541 (Month 18), 721 (Month 24), 901 (Month 30), and at the end-of-treatment visit. Rollover subjects from 2001 did not have a sample collected on Day 91.

For all subjects, immunogenicity samples were collected on Day 1, and at Months 6, 12, and 24 and at the end-of-treatment visit.

Subject Disposition and Demographics

For details, see Section [7.6.2](#). A total of 92 subjects rolled over from trials 2001 and 3001. From 2001, 35 subjects were enrolled, including 2 subjects with FXII HAE diagnosis (normal C1-INH with FXII gene mutation). From 3001, 57 subjects were enrolled, including 21 subjects who had received placebo and were therefore considered garadacimab-naïve. A total of 77 subjects with Type I or II HAE who were not previously enrolled in 2001 or 3001 entered the Run-in Period, and 69 subjects entered the Treatment Period.

One hundred sixty-one subjects entered the Treatment Period, including 90 who were garadacimab-naïve and 71 who were previously treated. Of these, 147 subjects are ongoing. Three subjects completed the study, and 11 prematurely discontinued. One hundred nineteen of the one hundred sixty-one subjects had at least 12 months of exposure to garadacimab.

Among all subjects, the median (range) body weight at baseline was 78.3 (45.0, 131) kg. The study enrolled 10 adolescents ranging in age from 13 to 17 years. Five adolescents rolled over from trial 3001 (n=3 received garadacimab and n=2 received placebo), and the remaining 5 were newly enrolled garadacimab-naïve subjects. Among adolescents, the median (range) age was 14.5 (13, 17) years, and the median (range) body weight at baseline was 55.7 (45.2, 88) kg.

PK Analysis

All 161 subjects who received garadacimab were included in the PK population, which was comprised of all subjects with at least one measurable concentration of garadacimab.

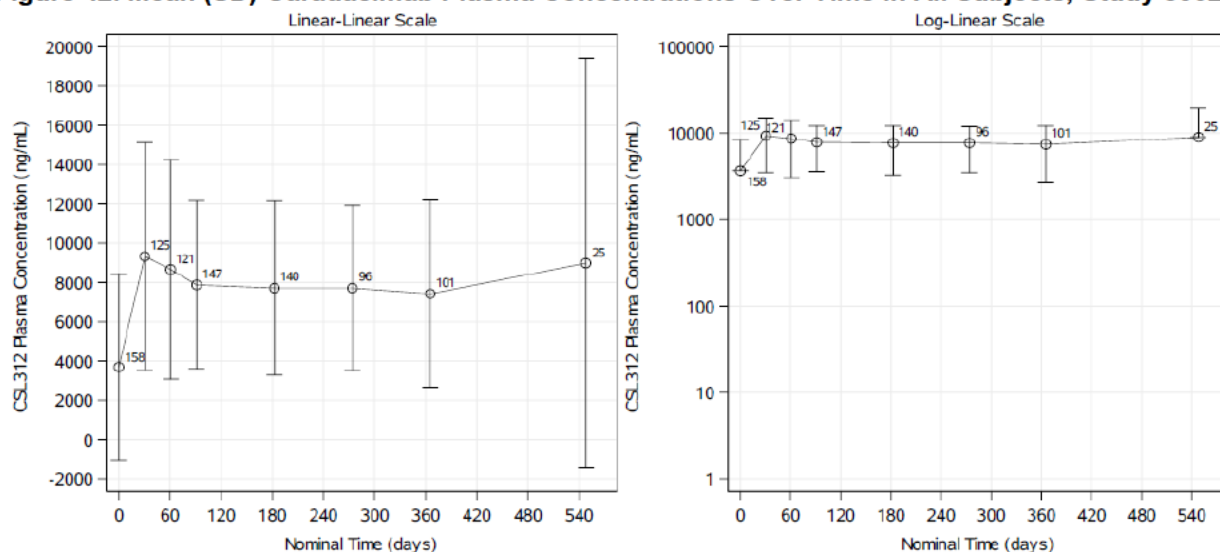
Plasma concentrations were summarized by nominal time points and plotted. PK parameters were derived for the PK subgroup of garadacimab-naïve subjects who had additional samples taken following the loading dose (n=15). These included T_{max} , C_{max} , and AUC_{0-30} .

Noncompartmental analysis was not conducted. PK data were included in analyses of population PK, PK/PD, and E-R.

PK Results

The mean (SD) garadacimab concentration-time profile for all subjects up to the time of data cutoff is shown in [Figure 42](#). At the time of data cutoff, PK data up to 12 months were available for 101 subjects. Most subjects (n=140) had data up to 6 months. From Month 3 through Month 12, mean (SD) steady-state trough concentrations ranged from 7429 (4759) ng/mL to 7882 (4276) ng/mL. Note that data shown include trough concentration data for all subjects (i.e., rollover and garadacimab-naïve subjects). Higher plasma concentrations with greater variability are observed at Month 1 and Month 2 due to some subjects receiving the loading dose.

Figure 42. Mean (SD) Garadacimab Plasma Concentrations Over Time in All Subjects, Study 3002



Source: Figure 14.2.7.1, Clinical Study Report for study 3002.

The x-axis denotes the elapsed time in days since first garadacimab administration.

Number next to each point represents the number of subjects contributing to data at that time point.

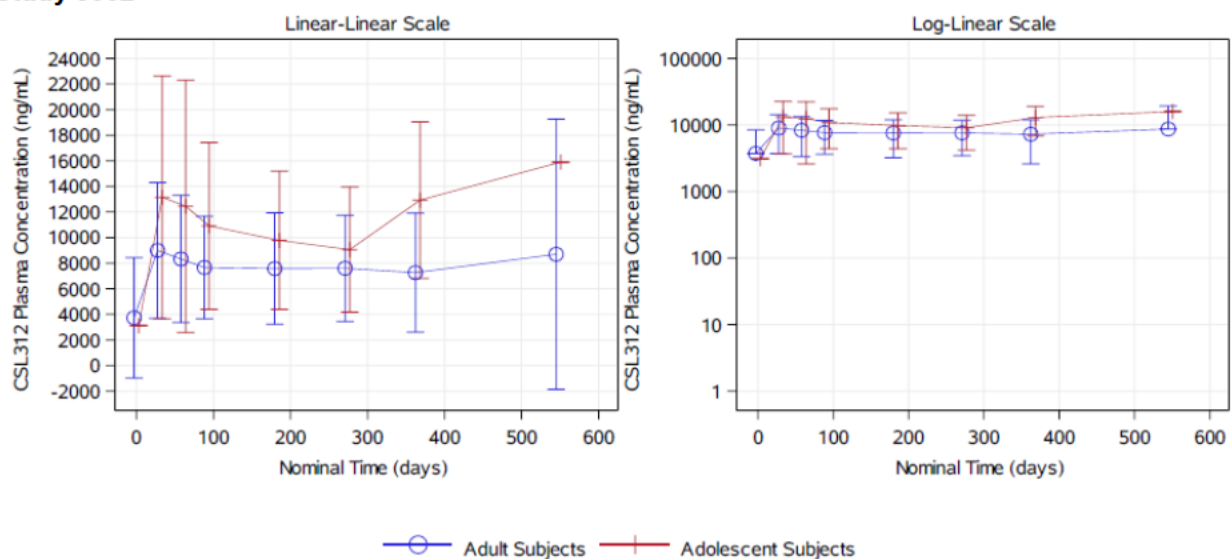
Only predose measurements scheduled for all subjects are displayed.

Abbreviation: CSL312, garadacimab

Additional PK samples were collected following administration of the 400 mg SC loading dose in a subgroup of garadacimab-naïve subjects (n=15). Peak concentrations were achieved on Day 7 postdose. The mean (SD) C_{max} was 24.5 (11.0) $\mu\text{g/mL}$, and the mean (SD) AUC_{0-30} was 10685 (5064) $\mu\text{g}\cdot\text{h/mL}$. These values are comparable to model-predicted steady state PK parameters from trial 3001 (mean [SD] C_{max} =21.2 [6.6] $\mu\text{g/mL}$; mean [SD] $AUC_{\tau,ss}$ =10,300 (3380) $\mu\text{g}\cdot\text{h/mL}$). Refer to [Table 81](#).

The mean (SD) garadacimab concentration-time profiles for adults (N=151) versus adolescents (N=10) are shown in [Figure 43](#). Garadacimab trough concentrations in adolescents were greater than those in adults, possibly due to lower body weight in adolescent subjects. The mean (SD) garadacimab trough concentrations from Month 3 through Month 12 are summarized in [Table 82](#). From Month 3 through Month 12, garadacimab trough concentrations were 1.2- to 1.8-fold greater in adolescents than in adults. Exposure was 1.8-fold greater at Month 12, a time point at which only three adolescent subjects provided data. Data at Month 12 should therefore be interpreted with caution.

Figure 43. Mean (SD) Garadacimab Concentration-Time Profiles in Adults Versus Adolescents, Study 3002



Source: Figure 14.2.7.2, Clinical Study Report for study 3002.

The x-axis denotes the elapsed time in days since first garadacimab administration.

Only predose measurements scheduled for all subjects are displayed.

Abbreviations: CSL312, garadacimab

Table 82. Mean (SD) Steady-State Garadacimab Trough Concentrations (ng/mL) From Month 3 Through Month 12 in Adults and Adolescents

Time Point	N	Adults (N=151)	N	Adolescents (N=10)	Fold-Change (Adolescents versus Adults)
Month 3	137	7660 (4011)	10	10915 (6522)	1.42
Month 6	131	7577 (4347)	9	9780 (5404)	1.29
Month 9	88	7598 (4153)	8	9056 (4890)	1.19
Month 12	98	7261 (4649)	3	12927 (6117)	1.78

Source: Reviewer-generated table adapted from Table 14.2.7.2, Clinical Study Report for study 3002.

Fold-change was calculated by dividing mean adolescent exposure by mean adult exposure.

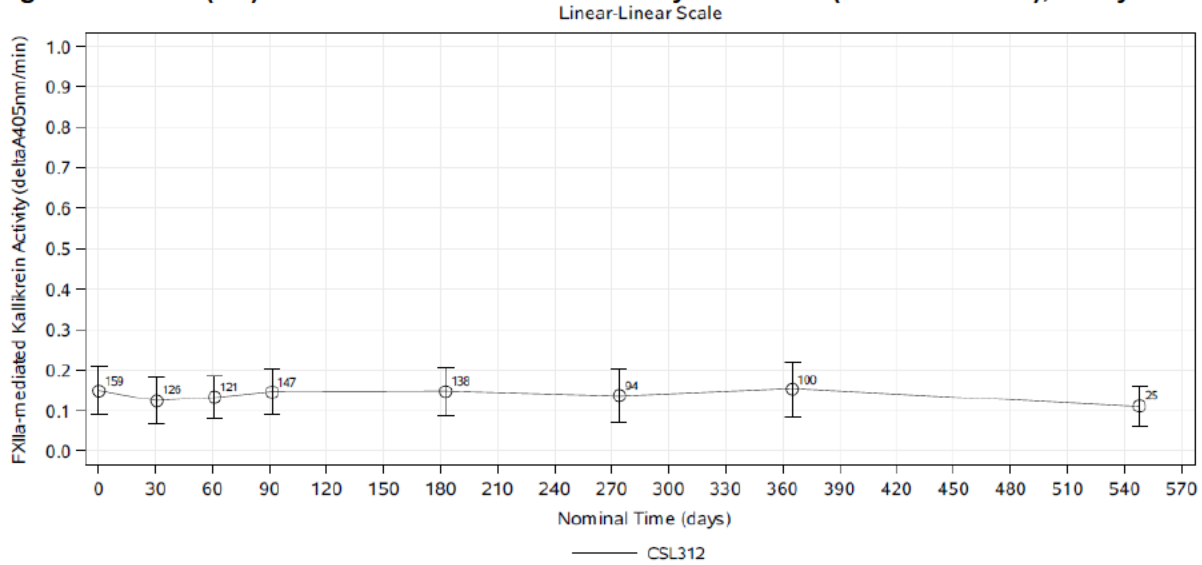
Adolescent subjects also had additional samples collected following the Month 3 dose, at 3, 7, 14, 21, and 30 days postdose. Peak concentrations were achieved in 3 to 7 days postdose with mean (SD) plasma concentrations at those time points of 21,948 (15,406) ng/mL and 21,652 (11,488) ng/mL, respectively. These values are approximately 1.4-fold greater than the observed steady state C_{max} following 200 mg SC Q4W in trial 2001 (mean [SD] C_{max} =15.9 [5.2] μ g/mL) and 2.6-fold lower than the observed steady state C_{max} following 600 mg SC Q4W in trial 2001 (mean [SD] C_{max} =56.4 [15.9] μ g/mL). Refer to [Table 79](#). The observed values are also comparable to the model-predicted steady state C_{max} from trial 3001 (mean [SD] C_{max} =21.2 [6.6] μ g/mL). Refer to [Table 81](#).

PD Results

FXIIa-mediated kallikrein activity was assessed as a PD marker. At the time of data cutoff, data up to Month 12 were available for 100 of 161 subjects. Baseline data were defined as Day 1 of study 3002 for garadacimab-naïve subjects and as baseline of the parent study for rollover subjects. FXIIa-mediated kallikrein activity over time for all subjects as absolute values and percentages of baseline is shown in [Figure 44](#) and [Figure 45](#), respectively. At predose time

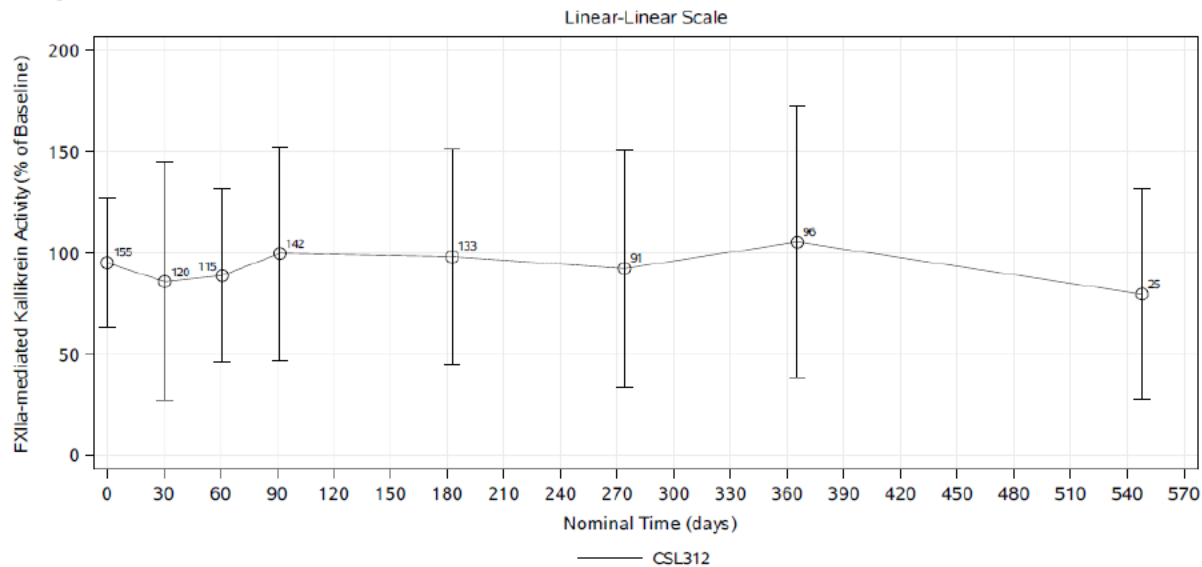
points, little to no inhibition of FXIIa-mediated kallikrein activity relative to baseline was observed.

Figure 44. Mean (SD) FXIIa-Mediated Kallikrein Activity Over Time (Absolute Value), Study 3002



Source: Figure 14.2.9.1, Clinical Study Report for study 3002.
 The x-axis denotes the elapsed time in days since first garadacimab administration.
 Nominal time 0 shows data from Day 1 of study 3002.
 Abbreviations: CSL312, garadacimab; FXIIa, activated Factor XII

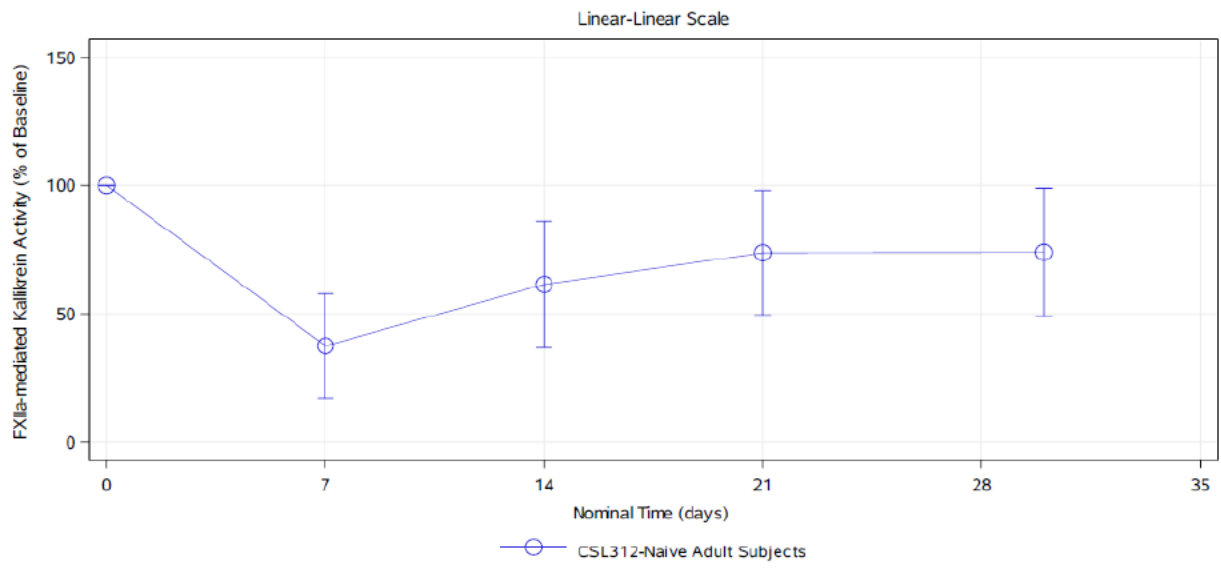
Figure 45. Mean (SD) FXIIa-Mediated Kallikrein Activity Over Time (Percentage of Baseline), Study 3002



Source: Figure 14.2.9.1, Clinical Study Report for study 3002.
 The x-axis denotes the elapsed time in days since first garadacimab administration.
 Nominal time 0 shows data from Day 1 of study 3002
 The percent of baseline calculation uses Day 1 of study 3002 for garadacimab-naïve subjects, and baseline of the previous study for rollover subjects.
 Abbreviations: CSL312, garadacimab; FXIIa, activated Factor XII

FXIIa-mediated kallikrein activity was also evaluated in a subset of garadacimab-naïve subjects who had additional samples collected after the loading dose (n=15). FXIIa-mediated kallikrein activity over 30 days postdose in garadacimab-naïve subjects is shown in [Figure 46](#). Concentration-dependent inhibition was observed with approximately 40% of baseline activity observed on Day 7, the time of peak concentration. By Day 30, approximately 75% of baseline activity was observed. Note that the values of 40% and 75% were visually estimated from [Figure 46](#).

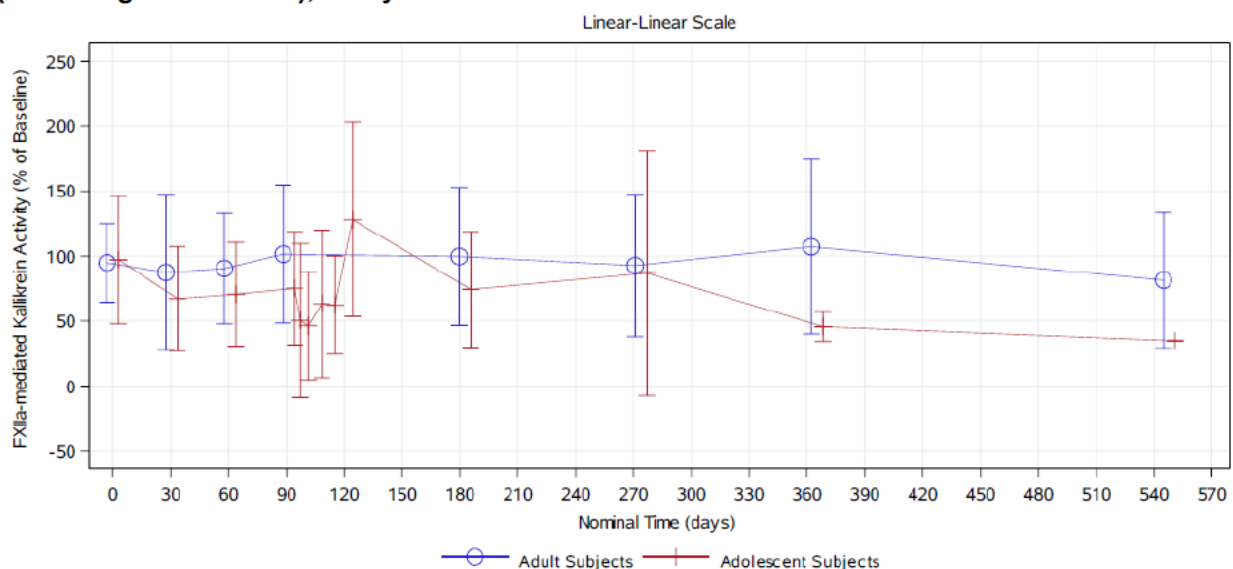
Figure 46. Mean (SD) FXIIa-Mediated Kallikrein Activity Over Time Following the Loading Dose in Garadacimab-Naïve Subjects (Percentage of Baseline), Study 3002



Source: Figure 14.2.9.2, Clinical Study Report for study 3002.
The x-axis denotes the elapsed time in days since first garadacimab administration.
Nominal time 0 shows data from Day 1 of study 3002.
The percent of baseline calculation uses Day 1 of study 3002 for garadacimab-naïve subjects.
Abbreviations: CSL312, garadacimab; FXIIa, activated Factor XII

This trend of concentration-dependent inhibition of FXIIa-mediated kallikrein activity was corroborated by data in adolescent subjects who had additional samples collected following the Month 3 dose. FXIIa-mediated kallikrein activity in adults and adolescents over time is shown in [Figure 47](#). At the time of peak concentration on Days 3 to 7 following the Month 3 dose (administered on Day 90), inhibition to about 50% activity was observed. Throughout the Treatment Period, activity appeared similar between adults and adolescents.

Figure 47. Mean (SD) FXIIa-Mediated Kallikrein Activity Over Time in Adults and Adolescents (Percentage of Baseline), Study 3002



Source: Figure 14.2.9.2, Clinical Study Report for study 3002.

The x-axis denotes the elapsed time in days since first garadacimab administration.

Nominal time 0 shows data from Day 1 of study 3002.

The percent of baseline calculation uses Day 1 of study 3002 for garadacimab-naïve subjects and baseline of the previous study for rollover subjects.

Abbreviations: CSL312, garadacimab; FXIIa, activated Factor XII

Activated Partial Thromboplastin Time

Per the Applicant, the normal range for aPTT values is between 24.3 and 43.4 seconds. Mean (SD) aPTT at baseline was 29.46 (11.1) seconds. From Month 3 through Month 12, mean (SD) aPTT ranged from 28.55 (3.76) to 30.73 (11.3) seconds. There were 21/161 subjects (13.0%) with 25 cases of aPTT prolongation during the study, including 5 cases at Screening, 5 cases at Day 1, 6 cases at Month 3, 8 cases at Month 6, and 1 case at Month 12. Values above normal range ranged between 45.1 and 126.0 seconds. Most cases were transient (i.e., occurring at a single time point), except in three subjects who had prolongation at multiple time points, including before the first dose of study treatment. Prolongation of aPTT was observed in three adolescent subjects (data derived from Listing 16.2.8.5.1, CSR for study 3002). In two cases, prolongation was observed at Screening only. In the remaining case, prolongation was observed transiently at Month 6.

- One adolescent subject ((b) (6), aged 13 years) had aPTT above normal range at Screening only (61.2 seconds). On Day 1 and Month 6, this subject had an aPTT below the normal range.
- One adolescent subject ((b) (6), aged 14 years) had aPTT above normal range at Month 6 (55.2 seconds). The aPTT value was within the normal range at Month 12.
- One adolescent subject ((b) (6), aged 15 years) had aPTT above the normal range at Screening only (101.6 seconds). Values were within the normal range at all other time points (Day 1, Month 3, and Month 6).

Immunogenicity Results

Five subjects tested positive for ADAs, including the following:

- One rollover subject from 3001. This subject tested positive on Day 182 (end of 3001 and baseline of 3002) with a titer value of 10. This subject also tested positive at Month 6 with a titer value of 160.
- Three subjects tested positive at Month 12, each with a titer value of 10.
- One subject tested positive at the End-of-Treatment visit after 5 months of treatment with a titer value of 320.

14.3. Bioanalytical Method Validation and Performance

14.3.1. PK Bioanalytical Methods

Overall, bioanalytical methods to quantitate garadacimab concentrations in clinical study samples were determined to be acceptable.

Garadacimab concentrations were determined using an enzyme-linked immunosorbent assay. Briefly, an anti-idiotypic antibody specific to garadacimab was coated on a microtiter plate. Following addition of plasma samples, garadacimab is bound to the anti-idiotypic antibody. Bound garadacimab is detected using a commercial antihuman lambda chain specific IgG antibody conjugated with horseradish peroxidase. Application of an appropriate substrate produces a blue color in proportion to the number of complexes formed. The bioanalytical method was performed in two laboratories:

- CSL Research and Clinical Bioanalytics
 - Studies 1001 and 1003, and trial 2001
 - Procedure RnD-SOP-000053053 (manual method) was used in 1001, 1003, and 2001
 - Procedure RnD-SOP-000053165 (automated method) was used in 1001. Partial validation was conducted to support use of an automated Tecan EVO200 platform. Assay principle and format is unchanged from the manual method
 - The method was revalidated for use in 1003 and 2001 due to exhaustion of stocks and standards (reported in RnD-VAL-000141302)
- (b) (4)
 - Study 1004, trial 3001, and study 3002
 - Procedure TP80240 was used in 1004 and 3002
 - Procedure TP80003 was used in 3001

Because subjects from trial 2001 rolled into study 3002, concordance testing was performed to compare bioanalytical method performance across the two laboratories.

Note that for the assay used for 1001 (CSL Research), the reported assay range is 1.25 to 100 ng/mL in 1% human plasma based on 100-fold dilution (i.e., 125 to 10,000 ng/mL in PK samples prior to dilution). For the assay used for 1003 and 2001 (CSL Research) following

revalidation, the assay range is 1 to 100 ng/mL in 1% human plasma (100 to 10,000 ng/mL in PK samples prior to dilution).

The assay range for the method used in 1004 and 3002 (TP80240) ranged from 1.01 to 111 ng/mL in 1% human plasma (i.e., 101 to 11100 ng/mL in PK samples prior to dilution). The assay range for the method used in 3001 (TP80003) ranged from 10.6 to 111 ng/mL in 1% human plasma (1060 to 11100 ng/mL in PK samples prior to dilution). The validation report for TP80003 notes that initial evaluations of selectivity at a concentration of 1.01 ng/mL did not meet acceptance criteria. Thus, the lower limit of quantification for TP80003 was increased to 10.6 ng/mL, a concentration at which selectivity evaluations were acceptable.

Assay procedures TP80240 and TP80003 are very similar, and the key differences include extension of the standard curve in TP80240 to accommodate a wider analytical range, and assessment of the lower limit of quantification. The Applicant conducted a full revalidation to support the wider analytical range. Refer to the Applicant's Information Request Response dated February 20, 2024.

Table 83. PK Method Validation for TP80240

Bioanalytical method review summary	Method validation adequate to support results in studies 1004 and 3002		
Materials used for calibration curve, QCs & concentration	CSL312 (garadacimab) drug product, Lot #AR20201109, 10 mg/mL, supplied by client (assumed CSL)		
Validated assay range	1.01 ng/mL (LLOQ) to 111 ng/mL (ULOQ) in human plasma		
Minimum required dilutions (MRDs)	1:100		
Source & lot of reagents (LBA)	CSL312 Anti-Idiotypic Antibody 4D3.7, Lot #HM20190313A, 8.26 mg/mL, CSL Mouse α -Human lambda light chain, (b) (4), 0.45 mg/mL, (b) (4)		
Regression model & weighting	5-parameter fit with $1/y^2$ weighting		
Validation parameters	Method validation summary		Acceptability
Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to ULOQ	11	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.2 to 3.1%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	$\leq 5.6\%$	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	-5.3 to 2.0%	Yes
	Interbatch %CV	$\leq 13.2\%$	Yes
	Percent total error (TE)	$\leq 15.2\%$	Yes
Selectivity & matrix effect	Ten lots of human plasma were evaluated both unspiked and spiked with garadacimab at the LLOQ (1.01 ng/mL) and high QC (80 ng/mL). 80% and 100% met acceptance criteria at the LLOQ and high QC, respectively.		Yes
Hemolysis effect	No observed effect in 5 lots of hemolyzed matrix		Yes
Lipemic effect	No observed effect in 5 lots of lipemic matrix		Yes
Dilution linearity, parallelism & Hook effect	Acceptance criteria met for dilutions ranging from 1:100 to 1:1,000,000. No hook effect was observed for samples at concentrations up to 500,000 ng/mL		Yes
Bench-top/process stability	Stable in human plasma at room temperature for 24 h, and for up to 72 h under refrigeration.		Yes

Freeze-thaw stability	Established for up to 5 freeze-thaw cycles	Yes
Long-term storage	Established stability in human plasma at -80°C for 241 days	Yes

Source: Bioanalytical report V1382005P4.

Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantification; QC, quality control; ULOQ, upper limit of quantification

Table 84. PK Method Validation for TP80003

Bioanalytical method			
review summary	Method validation adequate to support results in trial 3001		
Materials used for calibration curve, QCs & concentration	CSL312 (garadacimab) drug product, Lot #AR20201109 and P100188689, 10 mg/mL, supplied by client (assumed CSL)		
Validated assay range	10.6 ng/mL (LLOQ) to 111 ng/mL (ULOQ) in human plasma		
Minimum required dilutions (MRDs)	1:100		
Source & lot of reagents (LBA)	CSL312 Anti-Idiotypic Antibody 4D3.7, Lot #HM20190313A, RF15-331, PTS1420\LC 4034, 8.26 mg/mL, CSL Mouse α -Human lambda light chain, (b) (4) 0.8 mg/mL, (b) (4)		
Regression model & weighting	4-parameter fit with $1/y^2$ weighting		
Validation parameters	Method validation summary		Acceptability
Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to ULOQ	5 or 7 ^a	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.8 to 2.7%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	$\leq 6.6\%$	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 3 QCs ^b	-2.3 to 0.0%	Yes
	Interbatch %CV	$\leq 4.8\%$	Yes
	Percent total error (TE)	$\leq 6.4\%$	Yes
Selectivity & matrix effect	20 lots of human plasma were evaluated both unspiked and spiked with garadacimab at the LLOQ (10.6 ng/mL) and high QC (80 ng/mL). 80% and 100% met acceptance criteria at the LLOQ and high QC, respectively.		Yes
Hemolysis effect	No observed effect in 5 lots of hemolyzed matrix		Yes
Lipemic effect	No observed effect in 5 lots of lipemic matrix		Yes
Dilution linearity & hook effect	Acceptance criteria met for dilutions ranging from 1:100 to 1:20,000. No hook effect was observed for samples at concentrations up to 500,000 ng/mL		Yes

Bench-top/process stability	Stable in human plasma at room temperature for 169.5 h, and for up to 166.75 h under refrigeration.	Yes
Freeze-thaw stability	Established for up to 5 freeze-thaw cycles	Yes
Long-term storage	Established stability in human plasma at -80°C for 46 days. Note that in method TP80240, stability in human plasma at -80°C was established for up to 241 days.	Yes

Source: Bioanalytical report V1382005P3.

^a Standard curves were initially developed using nine calibrators between 1.01 and 111 ng/mL. An LLOQ of 1.01 ng/mL was determined for procedure TP80240. In TP80003, initial evaluations of selectivity at 1.01 ng/mL did not meet acceptance criteria. Thus, the LLOQ was increased to 10.6 ng/mL. Prior to the investigation, there were 5 standard calibrators between the LLOQ and ULOQ (10.6, 19.1, 34.3, 61.7, and 111 ng/mL). After the investigation, there were 7 standard calibrators between the LLOQ and ULOQ (10.6, 17.3, 25.1, 36.4, 52.8, 76.6, and 111 ng/mL). Reported accuracy and precision results represent data across all runs between the LLOQ and ULOQ.

^b Accuracy and precision were determined for 5 QCs assuming an LLOQ of 1.01 ng/mL. QC concentrations were 1.01, 3.00, 40.0, 80.0, and 111 ng/mL. As the assay LLOQ is 10.6 ng/mL, values are reported for 3 QCs of 40.0, 80.0, and 111 ng/mL. Note that acceptance criteria were met at concentrations of 1.01 and 3.00 ng/mL (%bias ≤4.7%, %CV ≤9.1%, %TE ≤21.1%).

Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantification; QC, quality control; ULOQ, upper limit of quantification

Table 85. PK Method Validation for RnD-SOP-000053053

Report Number and Title: Module 5.3.1.4, REP-007315 [formerly REP-19829] (manual method), CSL312 Pharmacokinetic Assay Validation Report			
Assay Procedure: RnD-SOP-000053053 (manual method)			
	Acceptance criteria	Summary of result	Source location in validation report
System suitability	RE and CV < 20% for 7 out of 9 non-zero standards (excluding anchor points)	RE: -1.6% to 1.1% CV: 1.34% to 3.24%	Tables 2, 3
Selectivity	RE and CV < 20% for 80% of samples	RE: -14.2% to 22.9% CV: 4.7% to 19.0%	Table 4
Dilutional linearity	RE < 30%	RE: -6.9% to 25.4%	Table 5
Range	Determined by the acceptable range for accuracy and precision	1.25 to 100 ng/mL	Section 7.4
Accuracy	RE < 20% (< 25% for LLOQ/ULOQ)	Repeatability: -23.3% to 1.7% Inter-assay precision: -12.7% to 0.7% Inter-operative precision: -12.5% to -0.1%	Tables 6, 7, 8
Intermediate precision / repeatability	CV < 20% (< 25% for ULC/UHC)	Repeatability: 2.9% to 10.0% Inter-assay precision: 4.4% to 22.1% Inter-operative precision: 7% to 20%	Tables 6, 7, 8
Quantitation limit	Quantitatively determined with acceptable precision and accuracy	LLOQ: 125 ng/mL Minimum required dilution: 100	Section 7.7
Robustness	CV and RE < 20%	Freeze / thaw cycles: 5 freeze / thaw cycles Plate coating time: Up to 72 hours at 4°C	Tables 9, 10

Source: Table 3, Summary of Biopharmaceutical Studies.

Note: The minimum required dilution (MRD) of the assay is 1:100. Standard curves used a five-parameter curve fit without weighting.

Precision and accuracy were demonstrated by interpolating the concentration of five controls and examining the relative error (RE) and coefficient of variation (CV). Based on the concentrations of the controls (i.e., 1.25, 5, 40, 80, and 100 ng/mL), the range of the assay was shown to be 1.25 to 100 ng/mL.

Acceptance criteria of relative error <30% for dilutional linearity is not considered with FDA's Guidance for Industry, *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022). The calculated mean concentration should be within 20% of the nominal concentration. The observed relative error of 25.4% was derived from 1/6 individual plasma lots. Among the remaining five lots, relative error ranged from -6.9 to 11.4%.

Repeatability refers to three sets of controls assayed on one plate; interassay precision refers to three sets of controls assayed on a different plate and performed on different days by one operator; interoperator precision refers to three sets of controls assayed on three separate days by two different operators.

Abbreviations: LLOQ, lower limit of quantification; PK, pharmacokinetics

Table 86. PK Method Validation for RnD-SOP-000053165

Report Number and Title: Module 5.3.1.4, REP-007341 [formerly REP-20231] (Automated version), Automated CSL312 Pharmacokinetic Assay Validation Report			
Assay Procedure: RnD-SOP-000053165 (automated method)			
	Acceptance criteria	Summary of result	Source location in validation report
System suitability	RE and CV < 20% for 7 out of 9 non-zero standards (excluding anchor points)	RE: -23.84% to 10.4% CV: 2.84% to 22.86%	Tables 2, 3
Range	Determined by the acceptable range for accuracy and precision	1.25 to 100 ng/mL	Section 7.2
Accuracy	RE < 20% (< 25% for LLOQ/ULOQ)	Repeatability: -18.43% to 4.11% Inter-assay precision: -7.51% to 9.80% Inter-operative precision: -1.64% to 13.49%	Tables 4, 5, 6
Intermediate precision / repeatability	CV < 20% (< 25% for ULC/UHC)	Repeatability: 2.51% to 18.79% Inter-assay precision: 1.62% to 10.49% Inter-operative precision: 1.81% to 7.23%	Tables 4, 5, 6
Quantitation limit	Quantitatively determined with acceptable precision and accuracy	LLOQ: 125 ng/mL Minimum required dilution: 100	Section 7.5

Source: Table 3, Summary of Biopharmaceutical Studies.

The minimum required dilution (MRD) of the assay is 1:100. Standard curves used a five-parameter curve fit without weighting. Precision and accuracy were demonstrated by interpolating the concentration of five controls and examining the relative error (RE) and coefficient of variation (CV). Based on the concentrations of the controls (i.e., 1.25, 5, 40, 80, and 100 ng/mL), the range of the assay was shown to be 1.25 to 100 ng/mL.

The mean relative error of -23.84% and %CV of 22.8% were both assessed for a theoretical concentration of 1.01 ng/mL, which is below the LLOQ of 1.25 ng/mL. The mean % relative error and %CV for theoretical values in between the assay limits ranges from -9.2 to 10.4% and 2.8 to 8.5%, respectively.

Repeatability refers to three sets of controls assayed on one plate; interassay precision refers to three sets of controls each assayed on independent assay runs on the automated platform; interoperative precision is included in error and refers to evaluation of overlapping process iterations meaning three sets of controls assayed on overlapping process iterations on the automated platform. Abbreviations: LLOQ, lower limit of quantification; PK, pharmacokinetics

Table 87. PK Method Validation for RnD-VAL-000141302

Report Number and Title: Module 5.3.1.4, RnD-VAL-000141302, CSL312 Pharmacokinetic Assay Validation Report Assay Procedure: RnD-SOP-000053053			
	Acceptance criteria	Summary of result	Source location in validation report
System suitability	RE and CV $\leq$ 20% for 7 out of 9 non-zero standards (excluding anchor points)	RE: -12% to 3% CV: 0.6% to 2.5%	Tables 2, 3
Selectivity	RE and CV $\leq$ 20% for 80% of samples	RE: -13% to 40% CV: 1% to 8%	Table 4
Dilutional linearity	RE $\leq$ 30%	RE: -13% to 18%	Table 5
Range	Determined by the acceptable range for accuracy and precision	1 to 100 ng/mL	Section 7.4
Accuracy	RE $\leq$ 20% (< 25% for ULPC/UHPC)	RE: -14% to -1%	Table 6
Intermediate precision / repeatability	CV $\leq$ 20% (< 25% for ULPC/UHPC)	Repeatability (CV): 2.1% to 12.9% Inter-assay precision (CV): 2% to 24% Inter-operative precision (CV): 0.2% to 16%	Tables 7, 8, 9
Quantitation limit	Quantitatively determined with acceptable precision and accuracy	LLOQ: 100 ng/mL Minimum required dilution: 100	Section 7.7
Robustness	CV and RE < 20%	<u>Freeze / thaw cycles:</u> 6 freeze / thaw cycles <u>Plate coating time:</u> Up to 72 hours at 2°C to 8°C <u>Ambient temperature stability:</u> 7 days	Tables 10B, 11, 12

Source: Table 3, Summary of Biopharmaceutical Studies.

Note: Precision and accuracy were demonstrated by interpolating the concentration of five controls and examining the relative error (RE) and coefficient of variation (CV). Based on the concentrations of the controls (i.e., 1, 5, 40, 80, and 100 ng/mL), the range of the assay was shown to be 1 to 100 ng/mL.

The relative error of 40% under selectivity was noted as not meeting acceptance criteria. This value was obtained in 1 out of 5 replicates at a concentration of 200 µg/mL. Across all remaining replicates (n=9), the relative error ranged from -13 to 17%.

Acceptance criteria of relative error <30% for dilutional linearity is not consistent with FDA's guidance for industry, *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022). The calculated mean concentration should be within 20% of the nominal concentration. The observed relative error for dilutional linearity meets acceptance criteria.

Repeatability refers to three sets of controls assayed on one plate; interassay precision refers to three sets of controls assayed on a different plate and performed on different days by one operator; interoperator precision refers to three sets of controls assayed on three separate days by two different operators.

Abbreviations: LLOQ, lower limit of quantification; PK, pharmacokinetics

In response to the Agency's inquiry, the Applicant submitted an amended bioanalytical method validation report for method RnD-VAL-000141302 (v. 8.0, submitted on February 20, 2024). The following information was provided on selectivity, benchtop stability and long-term stability:

- Selectivity was assessed in plasma from subjects with HAE (N=20 lots). Individual lots were spiked with garadacimab at concentrations of 1, 5, and 80 ng/mL. Note that 10 lots were spiked at 5 ng/mL, while 10 separate lots (N=20 total) were spiked at 1 and 80 ng/mL. At all concentrations, the %RE and %CV were <20% for at least 8/10 lots.
- Sample stability in 100% pooled healthy human plasma (sodium citrate) at temperatures $\leq$ -60°C is established for up to 3 years, 5 months and 25 days (~41 months).
- Long-term stability in plasma from subjects with HAE is ongoing. Samples are spiked with garadacimab at concentrations of 15,000 and 7,500 ng/mL. Per the Applicant, at the time of response (i.e., February 20, 2024), 10 months stability assessment has been completed and shown to pass acceptance criteria.

Concordance testing was performed using trial samples from trial 2001 in support of study 3002 as subjects from 2001 were permitted to rollover into 3002. Samples were initially measured using assay procedure RnD-SOP-000053053 (CSL Research) and then measured using assay procedure TP80240 (b) (4). Of 35 samples, 31 (88.6%) fell within 30% of the mean value. The results of concordance testing support the comparability of the method across both laboratories.

In-Study Bioanalysis Reports

Bioanalytical method performance in study 1004 is described in report RnD-SUP-000564586. The Division submitted a request to the Office of Study Integrity and Surveillance to conduct an inspection of the bioanalytical site for study 1004. Refer to the Office of Study Integrity and Surveillance review submitted in DARRTS dated December 5, 2023. Per the Office of Study Integrity and Surveillance inspection summary, a two-item Form FDA 483 was issued for under-reporting of sample reanalysis and inaccurate reporting of study activities for study 1004. Nevertheless, based on the inspectional findings and the firm’s responses, it was concluded that the observations were unlikely to have an impact on study data reliability. The following recommendations were made:

- The reported value of one subject sample should be removed due to unacceptable variability between replicate wells (Subject (b) (6), Day 85 sample)
- Review division should verify that amendments to the in-study bioanalysis report should include revisions indicated in the firm’s responses.

In response to the Agency’s inquiry, the Applicant submitted the amended bioanalysis report RnD-SUP-000564586 on February 20, 2024. The submitted report contains the amendments indicated in the firm’s responses.

Table 88. Bioanalytical Method Performance in Study 1004

Assay passing rate	• 102/108 runs met the method acceptance criteria • Six runs were rejected due to QCs not passing acceptance criteria	Yes
Standard curve performance	• Cumulative accuracy (% bias) range: -2.7 to 3.1% • Cumulative precision (% CV): ≤6.5%	Yes
QC performance	Across all passing runs, QC performance met acceptance criteria based on at least 2/3 of the total QCs and at least 50% at each concentration level falling within ±20% of the nominal values • Cumulative accuracy (% bias) range: -1.0 to 2.9% • Cumulative precision (% CV): ≤9.8% • Percent total error (%TE): ≤12.7%	Yes
Method reproducibility	Incurred sample reanalysis was performed for 165/1698 samples (9.7%). 148/165 samples (89.7%) met the acceptance criteria based on percent difference ≤30% of the mean.	Yes

Repeat analysis	Sample analysis was repeated for the following reasons: • Original result was above the ULOQ • Original result was below the LLOQ by dilution • Replicate analysis %CV was >20%	Yes
Study sample analysis/ stability	All samples were stored at -80°C until analysis. Per the Applicant, samples were not processed beyond the established stability window of 241 days at -80°C.	

Source: Bioanalytical Report RnD-SUP-000564586 (amended version submitted February 20, 2024).
Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantification; QC, quality control; ULOQ, upper limit of quantification

Table 89. Bioanalytical Method Performance in Trial 3001

Assay passing rate	• 21/21 runs met the method acceptance criteria	Yes
Standard curve performance	• Cumulative accuracy (% bias) range: -2.7 to 3.8% • Cumulative precision (% CV): ≤4.7%	Yes
QC performance	Across all passing runs, QC performance met acceptance criteria based on at least 2/3 of the total QCs and at least 50% at each concentration level falling within ±20% of the nominal values • Cumulative accuracy (% bias) range: -6.0 to -3.3% • Cumulative precision (% CV): ≤10.9% • Percent total error (%TE): ≤16.9%	Yes
Method reproducibility	Incurred sample reanalysis was performed for 45/434 samples (10.4%). 43/45 samples (95.6%) met acceptance criteria based on percent difference ≤30% of the mean.	Yes
Repeat analysis	Sample analysis was repeated for the following reason: • Original result was above the ULOQ	Yes
Study sample analysis/ stability	All samples were stored at -80°C until analysis. Per the Applicant, samples were not processed beyond the established stability windows. The first receipt date and last analysis date are December 7, 2021 and May 25, 2022, respectively. Analysis is therefore covered by the established stability window of 241 days at -80°C.	

Source: Bioanalytical Report RnD-SUP-000559520.
Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantification; QC, quality control; ULOQ, upper limit of quantification

Table 90. Bioanalytical Method Performance in Study 3002

Assay passing rate	• 45/49 runs met the method acceptance criteria • Four runs were rejected due to QCs not meeting acceptance criteria	Yes
Standard curve performance	• Cumulative accuracy (% bias) range: -2.2 to 2.8% • Cumulative precision (% CV): ≤6.0%	Yes
QC performance	Across all passing runs, QC performance met acceptance criteria based on at least 2/3 of the total QCs and at least 50% at each concentration level falling within ±20% of the nominal values • Cumulative accuracy (% bias) range: 1.0 to 7.8% • Cumulative precision (% CV): ≤11.9% • Percentage total error (%TE): ≤19.7%	Yes

Method reproducibility	As the study is ongoing, incurred sample reanalysis was not conducted and is pending additional sample analysis.	Yes
Repeat analysis	Sample analysis was repeated for the following reason: Original result was above the ULOQ	Yes
Study sample analysis/ stability	All samples were stored at -80°C until analysis. Per the Applicant, samples were not processed beyond the established stability windows. The maximum period of storage between sample collection and analysis was 641 days. Analysis is not covered by the established stability window of 241 days at -80°C. However, per the amended validation report for RnD-VAL-000141302, stability in human plasma has been demonstrated for up to 41 months. Analysis is therefore covered by the established stability window at -80°C.	

Source: Interim Bioanalytical Report RnD-SUP-000566153 (through November 2022).
Abbreviations: CV, coefficient of variation; QC, quality control; ULOQ, upper limit of quantification

Table 91. Bioanalytical Method Performance in Study 1001

Assay passing rate	136/138 runs met the method acceptance criteria - Two runs were rejected due to curve failure	Yes
Standard curve performance	- Cumulative accuracy (% bias) range: -6.1 to 6.0% - Cumulative precision (% CV): ≤8.8% Standard curves were generated from 9 standards with concentrations ranging from 1.0 to 111 ng/mL. For 7 out of 9 standards, a minimum of duplicate wells must have a calculated concentration with a CV of ≤20%. The measured concentration for 7 of the 9 standards must be within 20% of theoretical concentration. The curve fit measured (R-value) must be ≥0.985. Note that the LLOQ for the method used in 1001 was 1.25 ng/mL. However standard curve samples went as low as 1.01 ng/mL. In most runs, standard curve samples at 1.01 ng/mL were either below the limit of quantitation or had unacceptable %bias. Thus, in most runs, the LLOQ could be considered the next standard of 1.81 ng/mL. In other runs (n = 5), standards at 1.81 ng/mL also had unacceptable %bias and thus the LLOQ in these runs was 3.3 ng/mL. Note that study 1001 was a single-dose study. The change in LLOQ is primarily expected to have affected measurement of samples with lower concentrations (i.e., samples at the very beginning and end of time course).	Yes

QC performance	Assay acceptance criteria is based on the following: a minimum of duplicate wells of at least 2 of the 3 controls must have a CV of $\leq 20\%$. The measured concentration must be within 20% of the theoretical (expected) concentration for 2 of the 3 controls. The Applicant indicates that 2 out of 3 QCs per level need to be included in the calculation of nominal value (within 20% of nominal). • Cumulative accuracy (% bias) range: 2.3 to 5.1% • Cumulative precision (% CV): $\leq 9.2\%$ • Percent total error (%TE): $\leq 14.1\%$ Note that in eight passing runs, the determined mean concentration for the low QC fell outside of acceptance criteria. In one passing run, the determined mean concentration for the medium QC fell outside of acceptance criteria. In five passing runs, the determined mean concentration for the high QC fell outside of acceptance criteria. As replicate data were not provided, accuracy and precision of these runs cannot be guaranteed (i.e., it is unclear whether at least 50% of QCs per level fell within $\pm 20\%$ of nominal values). Approximately 10% of the passing runs are impacted. There may thus be an impact on the study data reported. Results from study 1001 should be interpreted with caution.	No
Method reproducibility	Incurred sample reanalysis was performed for 187/1776 samples (10.5%). 158/187 samples (84.5%) met the acceptance criteria based on percent difference $\leq 30\%$ of the mean.	Yes
Repeat analysis	Sample analysis was repeated for the following reasons: • Sample out of on-plate range or dilution adjustment • Original result was outside of acceptance criteria • PK reasons • Interim data set repeat It is unclear what is meant by PK reasons. 20 samples were re-analyzed with re-analysis results reported for this rationale (10 samples each from two subjects). For both subjects, an unusual BLQ sample was observed (prior sample and following sample both were quantitated). Thus, it is likely that "PK reasons" refers to observation of unusual PK results.	Yes
Study sample analysis/ stability	All samples were stored at -80°C until analysis. Assays were conducted between December 2016 and November 2017. The report indicates that long-term stability at -80°C was established for up to 36 months. Per the amended validation report for RnD-VAL-000141302, stability in human plasma has been demonstrated for up to 41 months. Analysis is therefore covered by the established stability window at -80°C.	

Source: Bioanalytical Report REP-020166, Response to Information Request dated March 1, 2024.
 Note accuracy and precision of the standard are only reported for concentrations of 1.81, 3.27, 5.88, 10.58, 19.05, 34.29, 61.73, and 111.11 ng/mL.
 Percentage bias was calculated as the mean calculated concentration subtracted by theoretical concentration. The resulting value is divided by theoretical concentration and multiplied by 100 to obtain the value.
 Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantification; PK, pharmacokinetics; QC, quality control

Table 92. Bioanalytical Method Performance in Study 1003

Assay passing rate	65/65 runs met the method acceptance criteria	Yes
Standard curve performance	- Cumulative accuracy (% bias) range: -8.3 to 4.6% - Cumulative precision (% CV): ≤5.4% Standard curves were generated from 9 standards with concentrations ranging from 1.0 to 111 ng/mL. For 7 out of 9 standards, a minimum of duplicate wells must have a calculated concentration with a CV of ≤20%. The measured concentration for 7 of the 9 standards must be within 20% of theoretical concentration. The curve fit measured (R value) must be ≥0.985. Note that in most runs, standard curve samples at 1.01 ng/mL were either below the limit of quantitation or had unacceptable %bias. Thus, in most runs, the LLOQ could be considered the next standard of 1.81 ng/mL. In other runs (n=5), standards at 1.81 ng/mL also had unacceptable %bias and thus the LLOQ in these runs was 3.3 ng/mL. Note that study 1003 was a single-dose study. It is possible that the change in LLOQ may have affected measurements of samples with lower concentrations (i.e., at the very beginning and end of the time course). However, this is expected to have low impact on assessment of C_{max}, AUC, T_{max}, and half-life.	Yes
QC performance	Assay acceptance criteria is based on the following: a minimum of duplicate wells of at least 2 of the 3 controls must have a CV of ≤20%. The measured concentration must be within 20% of the theoretical (expected) concentration for 2 of the 3 controls. The Applicant indicates that 2 out of 3 QCs per level need to be included in the calculation of nominal value (within 20% of nominal). - Cumulative accuracy (% bias) range: -3.9 to 4.1% - Cumulative precision (% CV): ≤4.8% - Percentage total error (%TE): ≤8.9% Note that in one passing run, the determined mean concentration for the low QC fell outside of acceptance criteria. As replicate data were not provided, accuracy and precision of this run cannot be guaranteed (i.e., it is unclear whether at least 50% of QCs per level fell within ±20% of nominal values). As only a single run was impacted, it is not expected that there will be a major impact to the reported study data.	Yes
Method reproducibility	Incurred sample reanalysis was performed for 136/1140 samples (11.9%). 133/136 samples (97.8%) met acceptance criteria based on percent difference ≤30% of the mean.	Yes

Repeat analysis	Sample analysis was repeated for the following reasons: Yes • Sample out of on-plate range • Original result was outside of acceptance criteria • Dilution adjustment • PK reasons Refer to explanation of PK reasons in Table 91. This rationale was used for one sample (subject (b) (6), predose) where an original concentration of 2380 ng/mL was re-assayed as BLQ and reported as BLQ.
Study sample analysis/ stability	All samples were stored at -80°C until analysis. Assays were conducted between March 2021 and May 2021. The report indicates that long-term stability at -80°C was established for up to 36 months. Per the amended validation report for RnD-VAL-000141302, stability in human plasma has been demonstrated for up to 41 months. Analysis is therefore covered by the established stability window at -80°C.

Source: Bioanalytical Report REP-019487, Response to Information Request dated March 1, 2024.
The accuracy and precision of the standard are reported for concentrations of 1.81, 3.3, 5.9, 10.6, 19.1, 34.3, 61.7, and 111 ng/mL. Although samples at 1.01 ng/mL were also reported, most samples were either below the limit of quantitation or replicate wells had unacceptable %bias or %CV.
Percent bias was calculated as the mean calculated concentration subtracted by theoretical concentration. The resulting value is divided by theoretical concentration and multiplied by 100 to obtain the value.
Abbreviations: AUC, area under the concentration-time curve; BLQ, below the limit of quantification; C_{max}, maximum plasma concentration; CV, coefficient of variation; LLOQ, lower limit of quantification; PK, pharmacokinetics; QC, quality control; T_{max}, time to maximum plasma concentration; ULOQ, upper limit of quantification

Table 93. Bioanalytical Method Performance in Trial 2001

Assay passing rate	• 136/143 runs met the method acceptance criteria • Two runs were rejected due to use of an expired reagent • Three runs were rejected due to QCs not meeting acceptance criteria • Two runs were rejected due to operator error	Yes
Standard curve performance	• Cumulative accuracy (% bias) range: -9.7 to 5.8% • Cumulative precision (% CV): ≤8.4% Standard curves were generated from 9 standards with concentrations ranging from 1.0 to 111 ng/mL. For 7 out of 9 standards, a minimum of duplicate wells must have a calculated concentration with a CV of ≤20%. The measured concentration for 7 of the 9 standards must be within 20% of theoretical concentration. The curve fit measured (R-value) must be ≥0.985. Note that for some runs, standard curve samples at 1.01 ng/mL were either below the limit of quantitation or had unacceptable %bias. Thus, in some runs, the LLOQ could be considered the next standard of 1.81 ng/mL. In other runs (n=11), standards at 1.81 ng/mL also had unacceptable %bias and thus the LLOQ in these runs was 3.3 ng/mL. Note that trial 2001 was a multiple-dose trial with mean trough concentrations exceeding 4092 ng/mL across all cohorts. Therefore, the change in LLOQ is unlikely to affect concentrations measured in this study.	Yes

QC performance	Assay acceptance criteria is based on the following: a minimum of duplicate wells of at least 2 of the 3 controls must have a CV of $\leq 20\%$. The measured concentration must be within 20% of the theoretical (expected) concentration for 2 of the 3 controls. The Applicant indicates that 2 out of 3 QCs per level need to be included in the calculation of nominal value (within 20% of nominal). • Cumulative accuracy (% bias) range: 2.3 to 5.1% • Cumulative precision (% CV): $\leq 9.2\%$ • Percentage total error (%TE): $\leq 14.1\%$ Note that in three passing runs, the determined mean concentration for the low QC fell outside of acceptance criteria. As replicate data were not provided, accuracy and precision of these runs cannot be guaranteed (i.e., it is unclear whether at least 50% of QCs per level fell within $\pm 20\%$ of nominal values). As few runs are impacted, it is not expected that there will be a major impact to the reported study data.	Yes
Method reproducibility	• Incurred sample reanalysis was performed for 247/3365 samples (7.3%). This is greater than 10% of first 1000 samples and 5% of remaining samples ($100 + 2265 \times 0.05 = 213$). • 219/247 samples (88.7%) met acceptance criteria based on percent difference $\leq 30\%$ of the mean.	Yes
Repeat analysis	Sample analysis was repeated for the following reasons: • Sample out of on-plate range • Original result was outside of acceptance criteria • Detectable concentration in predose samples (note that in this scenario, samples were retested twice) • PK reasons Refer to explanation of PK reasons in Table 91. This rationale was used for one sample (subject (b) (6), Day 35) where an original concentration of 177 ng/mL was re-assayed as BLQ and reported as BLQ.	Yes
Study sample analysis/ stability	All samples were stored at -80°C until analysis. Assays were conducted between February 2019 and November 2021. The report indicates that long-term stability at -80°C was established for up to 36 months. Per the amended validation report for RnD-VAL-000141302, stability in human plasma has been demonstrated for up to 41 months. Analysis is therefore covered by the established stability window at -80°C.	

Source: Bioanalytical Report REP-019486.

Note accuracy and precision of the standard are reported for concentrations of 1.81, 3.3, 5.9, 10.6, 19.1, 34.3, 61.7, and 111 ng/mL. Although samples at 1.01 ng/mL were also reported, most samples were either below the limit of quantitation or replicate wells had unacceptable %bias or %CV.

Percent bias was calculated as the mean calculated concentration subtracted by theoretical concentration. The resulting value is divided by theoretical concentration and multiplied by 100 to obtain the value.

Abbreviations: AUC, area under the concentration-time curve; BLQ, below the limit of quantification; C_{max} , maximum plasma concentration; CV, coefficient of variation; LLOQ, lower limit of quantification; PK, pharmacokinetics; QC, quality control; T_{max} , time to maximum plasma concentration

14.3.2. PD Bioanalytical Methods

14.3.2.1. Activated Factor XII-Mediated Kallikrein Activity

To determine activated FXII-mediated kallikrein activity in clinical study samples, a chromogenic enzymatic assay was used to track inhibitory effects of garadacimab on the kallikrein-kinin system. Plasma samples are diluted in a reaction buffer containing dextran sulfate, an activator of the contact system. The chromogenic substrate (S2302), which is enzymatically cleaved by kallikrein and FXIIa, was used to monitor the amidolytic activity generated in plasma samples upon activation of the contact system. Substrate cleavage is monitored at an absorbance of 405 nm (A_{405}) with the change of absorbance per minute as the assay readout. Control plasma samples in the presence and absence of garadacimab or kallikrein were included to approximate clinical samples possessing high, medium, and low levels of amidolytic activity. Note that this assay did not use a calibration standard and thus the accuracy of the method was not determined. Amidolytic activity generated after ex vivo contact activation was reported as a continuous variable to track the level of inhibition by garadacimab. This means that the individual values themselves are not likely to be meaningful.

Note that there are limitations to the PD assay used to measure FXIIa-mediated kallikrein activity. First, the chromogenic substrate S2302 is not specifically cleaved by FXIIa, but rather is also cleaved by kallikrein. Although, presumably, inhibition of FXIIa should also inhibit downstream production of kallikrein. The second is that the method is semiquantitative, as noted above. Thus, individual values determined from the assay are not likely to be meaningful.

For phase 3 studies, validation was updated for phase 3 drug product and to incorporate frozen controls rather than controls prepared “in-assay.” Robustness was also assessed for use of standard cryovials compared to FluidX tubes.

- The same assay procedure RnD-SOP-000053087 was used for trials 2001 and 3001, and study 3002. All assays were performed by CSL Research and Clinical Bioanalytics
 - Validation report RnD-VAL-000148888 describes validation of the method in 2001
 - Validation report REP-019128 describes validation of the method in 3001 and 3002.

The range of the assay was determined by spiking kallikrein into prekallikrein-deficient plasma ([Table 94](#) and [Table 95](#)). For both validation reports, activity was found to increase at kallikrein concentrations up to 10 U/mL (RnD-VAL-000148888) or 5 U/mL (REP-019128). The Applicant hypothesizes that at higher kallikrein concentrations, amidolytic activity is so rapid that the majority of substrate cleavage occurs prior to initiation of the first absorbance time point of the kinetic read. Thus, the upper limits of the assay are defined at the maximum activity observed for each validation. The assay range is 0.003 to 0.371 $\Delta A_{405\text{nm}/\text{min}}$ for RnD-VAL-000148888 and 0.005 to 0.298 $\Delta A_{405\text{nm}/\text{min}}$ for REP-019128. In both reports, FXII-mediated kallikrein activity was measured in the plasma of subjects with HAE (n=6). In all cases, the mean activity fell within the assay range.

Table 94. Range of Kallikrein Activity in Spiked Pre-Kallikrein Deficient Plasma (RnD-VAL-000148888)

Kallikrein concentration (U/mL)	Mean Activity ($\Delta A_{405\text{nm}}/\text{min}$)	SD	%CV
20	0.153	0.006	4.12
10	0.371	0.012	3.14
5	0.316	0.006	2.01
2.5	0.206	0.002	0.85
1.25	0.119	0.003	2.32
0.625	0.059	0.001	1.73
0.313	0.030	0.002	5.02
0	0.003	0.000	9.12

Source: Table 2, Report RnD-VAL-000148888.
 Abbreviations: A, absorbance; CV, coefficient of variation; SD, standard deviation

Table 95. Range of Kallikrein Activity in Spiked Pre-Kallikrein Deficient Plasma (REP-019128)

Kallikrein concentration (U/mL)	Mean activity ($\Delta A_{405\text{nm}}/\text{min}$)	CV (%)
20	0.120	39.8
10	0.290	2.7
5	0.298	10.1
2.5	0.201	15.7
1.25	0.120	9.7
0.63	0.076	8.7
0.31	0.040	8.2
0	0.002	17.0

Source: Table 8, Report REP-019128nD-VAL-000148888.
 Abbreviations: A, absorbance; CV, coefficient of variation; SD, standard deviation

Table 96. PD Method Validation for Factor XII-Mediated Kallikrein Activity in 2001, 3001, and 3002

Report Number and Title: Module 5.3.1.4, RnD-VAL-000148888, FXIIa-mediated Kallikrein Activity Assay Validation Report Assay Procedure: RnD-SOP-000053087			
	Acceptance criteria	Summary of result	Source location in validation report
Range	Determined by the acceptable range for precision	0.003 to 0.371 ΔA_{405} nm/min	Section 7.2
Precision	CV $\leq$ 30% for 3 of the 4 controls	Intra-assay precision (CV): 4.60% to 8.58% Inter-assay precision (CV): 9.36% to 44.43%	Tables 5, 8
Robustness	As there are no coating steps and freeze / thaw cycles were not recommended, robustness analysis was confined to use of 2 different lots of the substrate. CV $\leq$ 30% for 3 of the 4 controls	CV: 0% to 8.54%	Table 9
Report Number and Title: Module 5.3.1.4, REP-019128, CSL312 FXIIa-mediated Kallikrein Activity Assay Validation Report Assay Procedure: RnD-SOP-000053087			
	Acceptance criteria	Summary of result	Source location in validation report
Range	Determined by the acceptable range for precision	0.005 to 0.298 ΔA_{405} nm/min	Section 5.5
Precision	CV $\leq$ 30% for 3 of the 4 controls	Intra-assay precision (CV): 1.9% to 4.2% Inter-assay precision (CV): 8.8% to 18.4% Inter-operator precision (CV): 8.3% to 16.3%	Tables 3, 5, 6
Robustness	As there are no coating steps and freeze / thaw cycles were not recommended, robustness analysis was confined to use of 2 different lots of the substrate. CV $\leq$ 30% for 3 of the 4 controls	Substrate lots (CV): 5.1% to 30.3% Tube types (cryovial and FluidX) (CV): 27.5%	Tables 10, 11

CV = coefficient of variation; FXIIa = activated Factor XII; HAE = hereditary angioedema.

Source: Table 7, Summary of Biopharmaceutical Studies.

Report RnD-VAL-000148888 (top) describes validation for the method in 2001. Report REP-019128 (bottom) describes validation for the method in 3001 and 3002

Specified criteria for precision under RnD-VAL-000148888 passed. The interassay precision of the medium control was 44.4%. All other controls had interassay precision that was $\leq$ 10.5%.

Specified criteria for robustness under REP-019128 passed. The precision of the low control was 30.3%. All other controls had interassay precision that was $\leq$ 12.6%.

Abbreviations: A, absorbance; PD, pharmacodynamics; SOP, standard operating procedure

In-Study Bioanalysis

FXII-mediated kallikrein activity is most relevant for studies in subjects with HAE. Thus, trials 2001 and 3001 and study 3002 were evaluated.

- Trial 2001 – REP-019486
- Trial 3001 – REP-020153
- Study 3002 – REP-020155

The following were observed:

- Trial 2001 – the %CV for QCs ranged from 12.3 to 26.7%
 - In three runs, the mean activity for the medium control was marked as being “unusually high” meaning values were $>$ 2-fold of the average. The %CV for these samples was $\leq$ 9.8%
- Trial 3001 – the %CV for QCs ranged from 22.5 to 29.0%

- Study 3002 – the %CV for QCs ranged from 21.3 to 48.0%
 - %CV for low controls was 39.6%. Across runs, assay values ranged from 0.004 to 0.015, a difference of 0.011. The high %CV observed is likely due to the low values which have a higher sensitivity to smaller changes in measured values.
 - %CV for maximum controls (samples spiked with 10 U/mL kallikrein) was 48.0% with assay values ranging from 0.020 to 0.281.

In report REP-020155 (in-study report for 3002), HAE sample stability was assessed with incurred sample analysis using stored samples from trials 2001 (n=31) and 3001 (n=57). Samples for 2001 were stored for 13 to 18 months, while samples for 3002 were stored for 6 to 13 months. A total of 62.5% (55/88) of retested samples were within 30% difference of the original value, including 21/31 samples (67.7%) from 2001 and 34/57 samples (59.6%) from 3001. The samples from 2001 were stored for a longer period of time than those from 3001 and the number of samples with a percent difference <30% was higher in 2001. This suggests that the method is prone to variability in measurements and the differences observed may not be due to stability issues.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Across clinical studies conducted in subjects with HAE who received garadacimab (n=173), a total of 5 subjects (2.9%) tested positive for treatment-emergent antidrug antibodies (TE-ADAs). Two subjects tested positive prior to receiving garadacimab treatment. These subjects exhibited low ADA titers (i.e., 10). No adolescent subject tested positive for TE-ADAs. Among subjects who received the proposed dosing regimen of garadacimab (400 mg SC loading dose on Day 1, then 200 mg SC once monthly) in trial 3001 and study 3002 (n=129; includes 39 garadacimab-treated subjects in 3001, 21 placebo-treated subjects in 3001 who rolled over to 3002, and 69 garadacimab-naïve subjects from 3002), the incidence of TE-ADAs was 3.9 % (5/129). Of six post-treatment ADA-positive samples, only two samples showed higher titers (160 and 320), whereas four samples showed lower titers (10). In addition, only one out of five TE-ADA positive subjects tested positive at more than one time point, indicating that most positive immunogenicity results were transient. In phase 1 single-dose studies conducted in healthy subjects (i.e., 1001, 1003, and 1004), no subjects tested positive for ADAs.

Note that the drug tolerance of the ADA assay is adequate up to 30 µg/mL garadacimab (refer to Office of Pharmaceutical Quality executive summary review dated August 26, 2024). In trial 3001, no subjects had garadacimab trough concentrations exceeding 30 µg/mL with median (range) trough concentrations from Day 60 through Day 180 ranging from 7.21 (1.26, 21.3) µg/mL to 8.27 (1.75, 17.9) µg/mL. In study 3002 at ADA sample collection time points, five subjects had garadacimab concentrations exceeding 30 µg/mL, including two subjects at Month 6 (concentrations of 34.1 and 37.7 µg/mL), and three subjects at Month 12 (concentrations of 31.9 to 33.4 µg/mL). There were few samples with garadacimab concentrations exceeding 30 µg/mL. As the ADA incidence was generally low, these observations are not expected to impact the overall assessment.

A summary of immunogenicity data are provided in [Table 97](#). TE-ADAs were observed in trial 3001 and study 3002 among subjects receiving the proposed TBM dosage. In trial 3001, one

subject tested positive for TE-ADAs on Day 182. This subject also tested positive during study 3002 at the Month 6 visit. The remaining four subjects tested positive during study 3002. Pretreatment ADAs were detected in an additional two subjects, one from trial 2001 and one from trial 3001.

Table 97. Summary of Immunogenicity Data

ADA Positive Subjects	Study	Treatment	Positive Sample	Reciprocal Titer	
Positive Before Garadacimab Treatment (Pre-existing ADA)					
(b) (6) a	2001	Placebo	Week 13 (End of TP1)	10	
	3001	Garadacimab	Day 1 Visit	10	
Positive After Garadacimab Treatment (Treatment-emergent ADA)					
(b) (6) c	3001	Garadacimab	Day 182 (End of Treatment Visit)	10	
	3002	Garadacimab	Month 6 Visit	160	
	d	3002	Garadacimab	Month 12 Visit	10
		3002	Garadacimab	End of Treatment ^e	320
		3002	Garadacimab	Month 12 Visit	10
		3002	Garadacimab	Month 12 Visit	10

ADA = antidrug antibody; TP1 = treatment period 1.

^a Subject tested positive during placebo treatment at the end of TP1 in Study 2001 and rolled over to Study 3002 (not ADA positive in Study 3002; data cutoff on 13 February 2023).

^b Subject tested positive before the start of garadacimab treatment and rolled over to Study 3002 (not ADA positive in Study 3002; data cutoff on 13 February 2023).

^c This subject rolled over from Study 3001 and was ADA positive in Studies 3001 and 3002.

^d This subject rolled over from Study 3001 (not ADA positive in Study 3001).

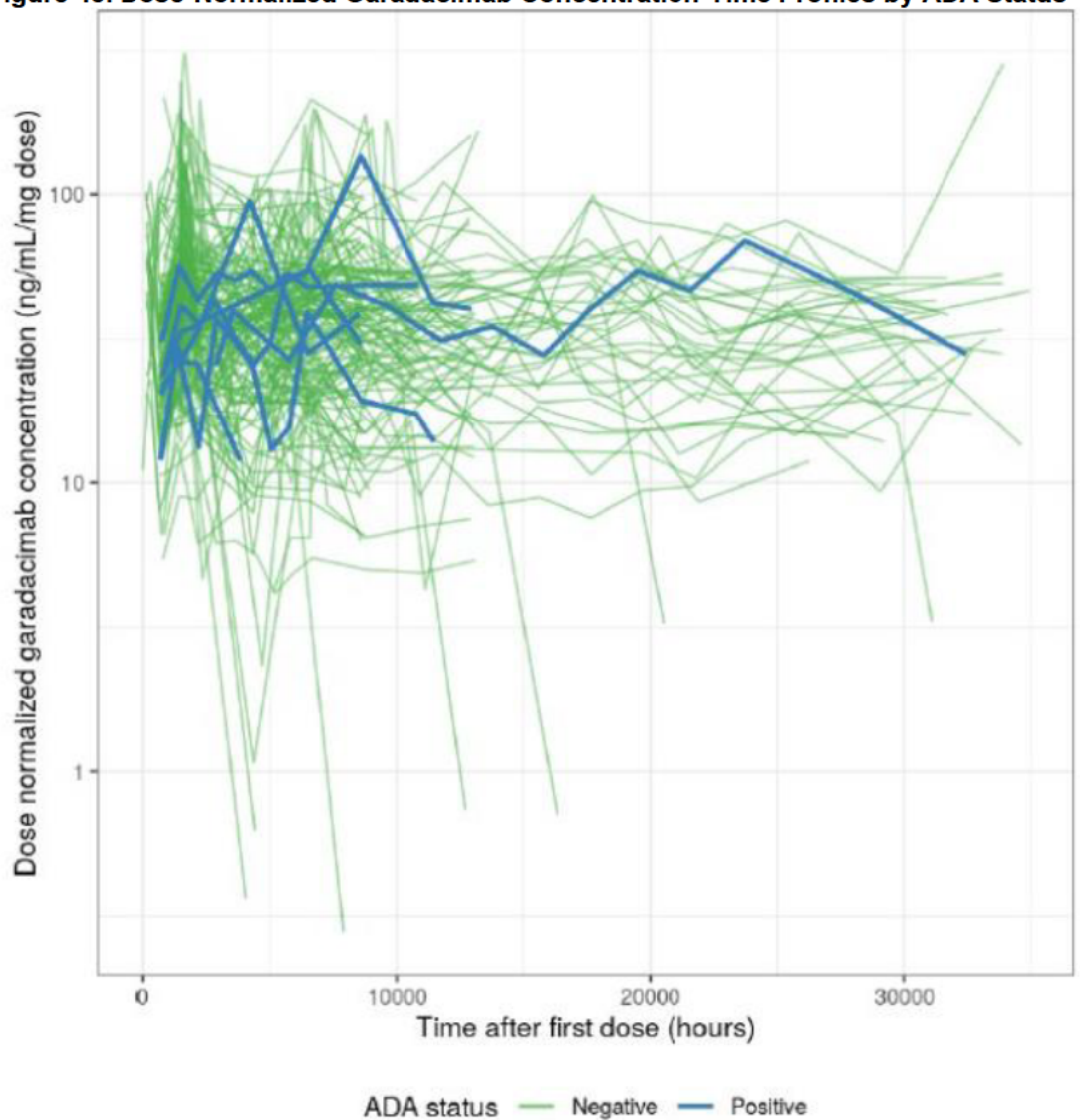
^e Subject discontinued from the study due to injection site reaction about 40 days after the last dose of garadacimab (400 mg loading dose followed by 4 doses of 200 mg garadacimab).

Source: Table 8, Integrated Summary of Immunogenicity.

Note that an assay to measure neutralizing antibodies is still in development. Thus, at the time of review, data on the incidence of neutralizing antibodies are not available.

Individual dose-normalized garadacimab concentration-time profiles by ADA status are shown in [Figure 48](#). Overall, there was no apparent impact of ADAs on the PK of garadacimab. Individual concentration-time profiles indicate that garadacimab concentrations among subjects who tested positive for ADAs were within the range of concentrations observed among subjects who were negative for ADAs.

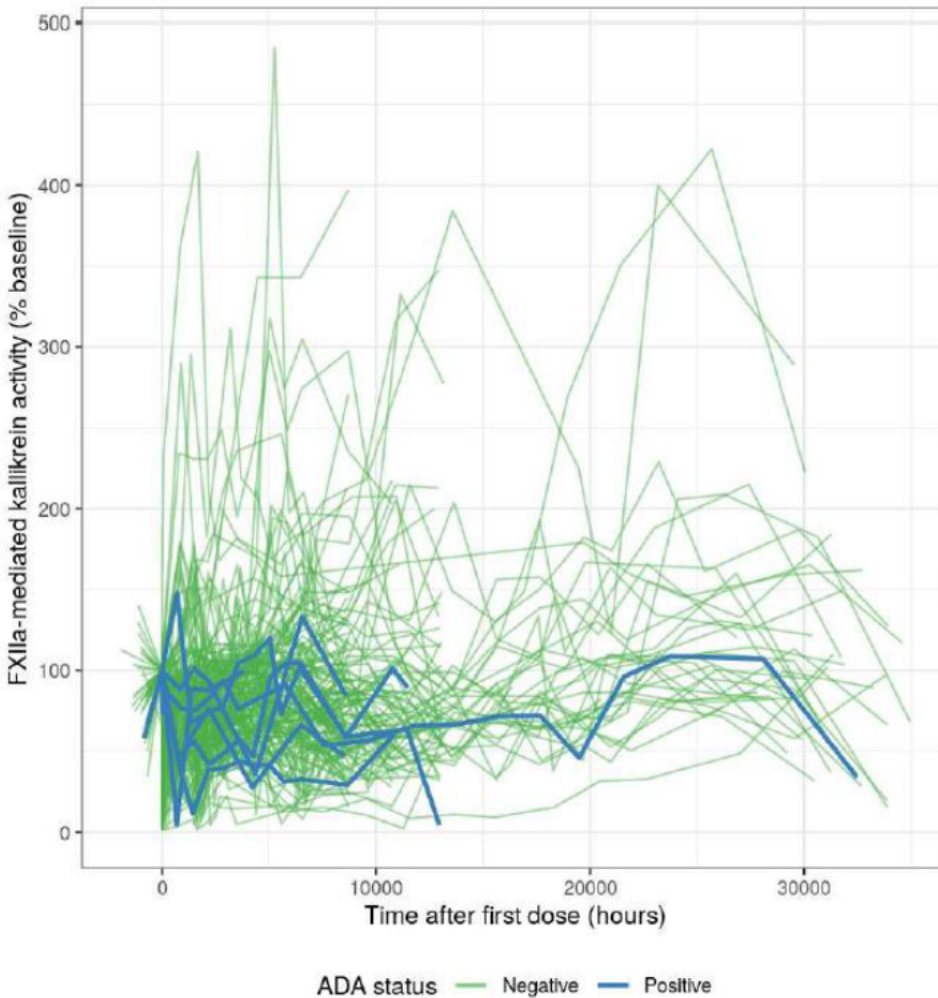
Figure 48. Dose-Normalized Garadacimab Concentration-Time Profiles by ADA Status



Source: Figure 3, Integrated Summary of Immunogenicity.
ADA-positive includes all subjects who tested positive for ADAs, including pretreatment and posttreatment.
Abbreviation: ADA, antidrug antibody

The impact of ADAs on PD was assessed by comparing FXII-mediated kallikrein activity by ADA status (Figure 49). There was no apparent difference in the percent change from baseline in FXII-mediated kallikrein activity among ADA-positive subjects relative to subjects who did not develop ADAs. As noted in Sections 14.2.5 and 14.2.6, after accounting for variability, little change from baseline in FXII-mediated kallikrein activity was observed at predose timepoints. As all subjects with TE-ADAs were derived from trial 3001 and study 3002, in which FXII-mediated kallikrein activity was measured at time points associated with garadacimab trough concentrations, the data are not sufficiently sensitive for determining whether ADAs had an impact on PD.

Figure 49. Percentage Change From Baseline in FXII-Mediated Kallikrein Activity Over Time by ADA Status



Source: Figure S124, Population PK/PD Report.

ADA-positive includes all subjects who tested positive for ADAs, including pretreatment and posttreatment.

Abbreviations: ADA, antidrug antibody; PD, pharmacodynamics; PK, pharmacokinetics

A summary of efficacy data in subjects with HAE who tested positive for ADAs (both pretreatment and treatment-emergent) is shown in [Table 98](#). Among all subjects, there was a reduction in the number of HAE attacks per month during the Treatment Period relative to that during the Run-in Period. The observed efficacy in ADA-positive subjects was consistent with that observed for the overall population. Overall, there was no apparent impact of ADAs on the efficacy of garadacimab.

Table 98. Efficacy Data in ADA-Positive Subjects and the Overall Population

ADA Positive Subjects	Study	Treatment	HAE Attack Rate in ADA Positive Subjects		HAE Attack Rate in Overall Population (Mean)		
			Attacks per Month During Run-in	Attacks per Month During TP	Attacks per Month During Run-in	Attacks per Month During TP	
(b) (6) ^a	3001	Garadacimab	2.9	0.0	3.07	0.27	
	3001	Garadacimab	1.22	0.0			
	(b) (6) ^b	3002	Garadacimab	1.2	0.0	4.7	0.16
		3002	Garadacimab	5.2	0.0		
		3002	Garadacimab	1.7	0.2		
		3002	Garadacimab	2.0	0.0		
		3002	Garadacimab	1.3	0.0		
			Attacks per Month During TP1	Attacks per Month During TP2	Attacks per Month During TP1	Attacks per Month During TP2	
(b) (6) ^d	2001	Placebo	4.51 ^e	0.05	4.24 ^e	0.08	

ADA = antidrug antibody; HAE = hereditary angioedema; TP = treatment period; TP1 = treatment period 1; TP2 = treatment period 2.

^a Subject tested positive before the start of garadacimab treatment and rolled over to Study 3002 (not ADA positive in Study 3002; data cutoff on 13 February 2023).

^b Subject rolled over from Study 3001 and was ADA positive in Studies 3001 and 3002.

^c This subject rolled over from Study 3001 (not ADA positive in Study 3001).

^d Subject tested positive during placebo treatment at the end of TP1 in Study 2001 and rolled over to Study 3002 (not ADA positive in Study 3002; data cutoff on 13 February 2023).

^e Attacks per months during the placebo period as subject was randomized to placebo during TP1; randomized to 200 mg garadacimab during TP2.

Source: Table 9, Integrated Summary of Immunogenicity.

In two TE-ADA-positive subjects ((b) (6)), no treatment-emergent adverse events (TEAEs) were reported. One TE-ADA-positive subject ((b) (6)) reported three TEAEs, all of which were judged as not related to treatment, including upper respiratory tract infection, increased blood creatinine, and COVID-19. All TEAEs occurred prior to detection of ADAs. One TE-ADA-positive subject ((b) (6)) reported four TEAEs, including injection site pruritus, injection site erythema, pyrexia, and myalgia. Only the injection site reactions were deemed related to treatment. All TEAEs occurred prior to detection of ADAs. The remaining TE-ADA-positive subject ((b) (6)), who tested positive for ADAs at the End of Treatment visit, discontinued from the study due to injection site irritation of moderate intensity deemed related to treatment. Prior to detection of ADAs, this subject also experienced treatment-related AEs of erythema and injection site erythema. Notably, this subject also presented with the highest titer ADAs.

In general, TE-ADAs did not impact the safety of garadacimab. For one subject who discontinued prematurely due to moderate injection site irritation and presented with the highest titer ADAs, the impact of ADAs on safety cannot be ruled out. Overall, few subjects with HAE

tested positive for ADAs across the garadacimab development program, precluding a definitive assessment of the impact of ADAs on safety.

14.5. Pharmacometrics Assessment

14.5.1. Population PK Analysis

14.5.1.1. Executive Summary

The Applicant submitted a population PK report entitled “Population PK-PD Modeling and Simulation of Garadacimab in Subjects with Hereditary Angioedema” to support the application of garadacimab for the treatment of adolescents and adults with HAE. The population PK and PK-PD models in this report were developed using data from two phase 1 studies, one phase 2 study, and two phase 3 studies.

In general, the Applicant’s population PK and PK-PD models adequately characterize the PK/PD (FXIIa-mediated kallikrein activity) of garadacimab, and the model-predicted real time concentrations of garadacimab are adequate for use in E-R analysis. In the final model, PK was described by a two-compartment model with first-order absorption and elimination, and PD was described by a direct effect sigmoidal maximal-efficacy model. None of the covariates (e.g., age, sex, race, body weight, renal impairment, Japanese ethnicity, Chinese ethnicity, baseline serum creatinine, baseline alanine aminotransferase, baseline bilirubin, baseline FXIIa-mediated kallikrein activity) were likely to have clinically meaningful impact on garadacimab exposure and PD response. The recommended dosage for garadacimab in patients with HAE is supported by the population PK/PK-PD analyses results as well as those of the other analyses (i.e., clinical efficacy, safety, and E-R analyses).

14.5.1.2. PPK Assessment Summary

Table 99. PPK Summary

General Information	
Objectives of PPK analysis	• Develop a population pharmacokinetic (PK) model with pooled data from study 1001, study 1003, trial 2001, trial 3001, and study 3002. • Evaluate the impact of specific covariates on PK and assess the need for dose-adjustments for certain subgroups of patients. • Develop a population pharmacokinetic-pharmacodynamic (PKPD) model for FXIIa-mediated kallikrein activity with data from study 1001, study 1003, trial 2001, trial 3001, and study 3002. • Evaluate the impact of specific covariates on pharmacodynamics (PD). • Perform simulations to confirm dose selection.
Study included	Study 1001, study 1003, trial 2001, trial 3001, and study 3002

General Information	
Dose(s) included	Single dose: • IV: 0.1, 0.3, 1, 3, 10 mg/kg • SC: 1, 3, 10 mg/kg; 200 or 600 mg Multiple doses: • 40 mg IV loading followed by 75 mg Q4W SC; • 100 mg IV loading followed by 200 mg Q4W SC; • 300 mg IV loading followed by 600 mg Q4W SC; • 400 mg Q2W SC; • 200 or 600 mg Q4W SC; • 400 mg SC loading followed by 200 mg monthly SC
Population included	PopPK dataset: Healthy subjects and subjects with hereditary angioedema who received garadacimab. PopPK-PD dataset: Healthy subjects and subjects with hereditary angioedema who received garadacimab or placebo.
Population characteristics (Table 101)	General PopPK dataset: • Age: median 39 yr (range: 12-73, 5.4% subj ≥65 yr, 0% subj ≥75 yr) • Weight median 76 kg (range 43.3-153.2 kg) • 110 (45.5%) male • Race: white: 182 (75.2%); black, of African heritage or African American: 4 (1.7%); Asian: 52 (21.5%); other: 4 (1.7%) PopPK-PD dataset: • Age: median 37.5 yr (range: 12-73, 4.6% subj ≥65 yr, 0% subj ≥75 yr) • Weight median 75.9 kg (range 43.3-153.2 kg) • 110 (48.8%) male • Race: White: 195 (75.0%); black, of African heritage or African American: 5 (1.9%); Asian: 55 (21.2%); other: 5 (1.9%)
	Organ Impairment PopPK dataset: • Renal (eGFR, based): n (%) in each category - normal: 211 (87.2%), mild: 29 (12.0%), moderate: 2 (0.8%) PopPK-PD dataset: • Renal (eGFR, based): n (%) in each category - normal: 225 (86.5%), mild: 33 (12.7%), moderate: 2 (0.8%)
	Pediatrics (if any) PopPK dataset: • Age: median 15 yr (range: 12-17, 0% subj ≤2 yr, 0% subj ≤6 yr, 9.1% subj ≤12 yr) • Weight: median 57.8 kg (range: 43.3-153.2) PopPK-PD dataset: • Age: median 15 yr (range: 12-17, 0% subj ≤2 yr, 0% subj ≤6 yr, 9.1% subj ≤12 yr) • Weight: median 57.8 kg (range: 43.3-153.2)
Nos. of subjects, PK samples, and BLQ	PopPK dataset: • 2623 PK samples from 242 subjects; 63 of 2623 (2.4%) postdose PK samples were BLQ PopPK-PD dataset: • 3184 PD samples from 262 subjects; 21 of 3184 (0.7%) pre-/postdose PD samples were BLQ

General Information		
Sampling schedule	Rich sampling	Study 1001 • IV: Predose and 0.5, 1, 6, 12, 24 and 48 h postdose, and Days 4, 7, 14, 21, 28, 35, 56, and 84. • SC: Predose and 1, 6, 12, 24, 32 and 48 h postdose, and Days 4, 7, 14, 21, 28, 35, 56, and 84. Study 1003 • Part A (SC): Predose and 1, 8, 24, 32 and 48 h postdose, and Days 4, 7, 14, 21, 28, 43, 64, and 84. • Part B (IV): Predose and 0.5, 1, 8, 24, 48 h postdose, and Days 4, 7, 14, 21, 28, 43, 64, and 84.
	In ITT population	Trial 2001 • TP1 Q4W: Predose and 0.5, 4, 8 h and 5, 34, 62, 65, 69, 76, 83, 90, and 185* days. • TP1 Q2W: Predose and 14, 28, 42, 56, 63, 70, 76, 84, and 179 days. • TP2: 84/90 days (last TP1 visit) and 118, 146, 230, 314, 398, and 493** days. Trial 3001 • Predose, and 30, 60, 90, 120, 150, 181, and 241*** days. (C_{trough}) Study 3002 • Garadacimab-naïve and trial 3001 subjects: Predose; Days 30, 60, 90, 180, 270, 360, 540, 720, and 900; EOT (1 month after last garadacimab dose); and Follow-up Visit (2 months after EOT). • Trial 2001 subjects: Predose; Days 90, 180, 360, 540, 720, and 900; EOT (1 month after last garadacimab dose); and Follow-up Visit (2 months after EOT). • PK subgroup (subset of garadacimab -naïve adult subjects): +7, +14, +21, +30 days following the first garadacimab dose. • Additional adolescent PK sampling: +3, +7, +14, +21, +30 days following fourth garadacimab dose (at Day 90).
Covariates evaluated	Static	Baseline age, baseline weight, sex, ethnicity (Japanese versus non-Japanese, Asian versus non-Asian, Chinese versus non-Chinese), population (healthy or subject with HAE), HAE subtypes (Healthy, Type I, Type II, FXII/PLG HAE), Formulation, baseline aspartate transaminase (AST), baseline alanine aminotransferase (ALT), baseline bilirubin (BILI), baseline creatinine clearance, baseline serum creatinine (SCR), baseline estimated glomerular filtration rate (eGFR), baseline FXIIa-mediated kallikrein activity, albumin, renal function, age group (adolescent, adult, elderly), race, HAE treatment used prior to study entry, U.S. or non-U.S.
	Time-varying	ADA status, rescue medications or concomitant medications (analgesics, antihistamines, or anti-inflammatory/antirheumatics)
Final Model	Summary	Acceptability [FDA's Comments]
Software and version	NONMEM® version 7.5	Acceptable
Estimation algorithm	FOCE	Acceptable

General Information		
Model structure	PopPK - Two-compartment model with first-order absorption and elimination. - The effects of body weight on all clearance and volume terms were estimated. - The effects of Japanese ethnicity (Japanese versus non-Japanese), Chinese ethnicity (Chinese versus non-Chinese), subject status (healthy versus HAE subject), baseline serum creatinine (SCR), baseline alanine aminotransferase (ALT) and baseline bilirubin (BILI) on clearance were estimated. - IIV was estimated on CL, V2 and F1 with a full Ω block. - Residual variability included a proportional term. PopPK-PD - A direct effect sigmoidal E_{max} model. - The effect of baseline FXIIa-mediated kallikrein activity on the EC_{50} and E_0 parameters was estimated. - IIV was estimated on EC_{50}, E_0 and GAMMA. - Residual variability included a proportional term and an additive term.	Acceptable
Model parameter estimates	PopPK: Table 102 PopPK-PD: Table 103	Acceptable
Uncertainty and variability (RSE, IIV, shrinkage, bootstrap)	PopPK - The RSE for all parameters except SCR on CL were <50%. The RSE for SCR on CL was >100%. Shrinkage (%) on IIV for CL, V2, and F1 are 28.7, 25.2, and 43.3, respectively. PopPK-PD - The RSE for all parameters except EC_{50}-E_0 covariance and GAMMA-EC_{50} covariance were <30%. The RSE for all the parameters were <50%. Eta-shrinkage for EC_{50}, E_0, and GAMMA were 20.2%, 14.7%, and 27%.	Acceptable. The high RSE for SCR on CL suggested the effect of SCR cannot be estimated precisely with the available data. The RSE for other parameters are reasonable.
BLQ for parameter accuracy	BLQ PK data and BLQ PD data were disregarded.	Acceptable
GOF, VPC	PopPK: Figure 50, Figure 51 PopPK-PD: Figure 52, Figure 53	Acceptable
Significant covariates and clinical relevance	PopPK: Figure 54 PopPK-PD: Figure 55	Acceptable
Analysis based on simulation (optional)	PopPK: Table 104, Figure 56	Acceptable
Labeling Language	Description	Acceptability [FDA's Comments]
12.3 PK	(b) (4)	The proposed labeling is acceptable upon the Applicant and FDA reaching agreements to the FDA-recommended

General Information



(b) (4) revisions to the labeling.

Source: Module 5.3.3.5, Population Pharmacokinetic / Pharmacodynamic Analysis Report.
Abbreviations: ADA, antidrug antibody; BLQ, below the limit of quantification; C1-INH, C1-esterase inhibitor; CL, clearance; CSL312, garadacimab; C_{trough}, lowest plasma concentration; E₀, baseline effect; EC₅₀, half-maximal effective concentration; eFGFR, baseline estimated glomerular filtration rate; E_{max}, maximum efficacy; EOT, end of treatment; F1, bioavailability; FXIIa, activated Factor XII; HAE, hereditary angioedema; IIV, interindividual variation; ITT, intent-to-treat; IV, intravenous; PopPK, population pharmacokinetics; Q2W, every 2 weeks; Q4W, every 4 weeks; RSE, root square error; SC, subcutaneous; V₂, volume of the peripheral compartment

Table 100. Applicant-Summary of Baseline Characteristics and Laboratory Values in the Dataset, Stratified by Study of The PopPK Dataset

A: Continuous covariates by study of the PopPK dataset

Variable	n	Mean	Median	SD	Min / Max
Study: CSL312-1001					
Age (years)	32	27.1	24.9	6.26	19.2 / 41.1
FXIIa-mediated kallikrein activity (A405nm/min)	32	0.101	0.107	0.0337	0.0455 / 0.156
Aspartate aminotransferase (U/L)	32	20.8	20.0	5.56	12.0 / 39.0
Alanine aminotransferase (U/L)	32	21.6	21.5	8.90	10.0 / 47.0
Bilirubin ($\mu\text{mol/L}$)	32	11.1	10.5	4.03	6.00 / 22.0
Creatinine clearance (mL/min)	32	131	132	20.7	89.9 / 167
Serum creatinine (mg/dL)	32	0.943	0.932	0.105	0.768 / 1.19
Albumin (g/L)	32	41.9	42.0	2.14	36.0 / 46.0
eGFR (mL/min/1.73m ²)	32	112	113	12.2	82.2 / 130
Weight (kg)	32	78.1	75.7	10.3	59.7 / 102
Study: CSL312-1003					
Age (years)	37	38.3	41.0	10.6	18.0 / 55.0
FXIIa-mediated kallikrein activity (A405nm/min)	37	0.106	0.102	0.0461	0.0430 / 0.274
Aspartate aminotransferase (U/L)	37	18.0	17.0	3.73	10.0 / 30.0
Alanine aminotransferase (U/L)	37	16.5	14.0	6.77	6.00 / 34.0
Bilirubin ($\mu\text{mol/L}$)	37	7.39	6.80	3.46	3.40 / 18.8
Creatinine clearance (mL/min)	37	116	116	22.2	83.2 / 166
Serum creatinine (mg/dL)	37	0.740	0.699	0.154	0.499 / 1.10
Albumin (g/L)	37	45.8	46.0	2.54	40.0 / 51.0
eGFR (mL/min/1.73m ²)	37	113	113	12.1	80.9 / 134
Weight (kg)	37	64.9	62.4	10.3	51.3 / 90.5
Study: CSL312-2001 TP1					
Age (years)	39	39.5	39.0	12.6	21.0 / 65.0
FXIIa-mediated kallikrein activity (A405nm/min)	39	0.153	0.163	0.0571	0.0420 / 0.265
Aspartate aminotransferase (U/L)	39	20.9	19.0	8.40	9.00 / 40.0
Alanine aminotransferase (U/L)	39	24.6	18.0	18.3	6.00 / 85.0
Bilirubin ($\mu\text{mol/L}$)	39	6.46	6.00	3.02	3.00 / 18.0
Creatinine clearance (mL/min)	39	136	129	54.7	40.5 / 335
Serum creatinine (mg/dL)	39	0.828	0.836	0.181	0.508 / 1.22
Albumin (g/L)	39	46.5	47.0	3.18	41.0 / 54.0
eGFR (mL/min/1.73m ²)	39	101	104	18.3	57.1 / 136
Weight (kg)	39	85.2	83.4	24.0	45.5 / 135

Study: CSL312-2001 TP2					
Age (years)	40	39.8	39.0	13.1	20.0 / 65.0
FXIIa-mediated kallikrein activity (A405nm/min)	40	0.159	0.166	0.0573	0.0440 / 0.265
Aspartate aminotransferase (U/L)	40	20.7	18.5	8.34	9.00 / 40.0
Alanine aminotransferase (U/L)	40	24.8	18.0	17.8	7.00 / 85.0
Bilirubin ($\mu\text{mol/L}$)	40	6.75	6.00	3.01	3.00 / 18.0
Creatinine clearance (mL/min)	40	138	128	51.9	68.8 / 335
Serum creatinine (mg/dL)	40	0.813	0.814	0.173	0.508 / 1.22
Albumin (g/L)	40	46.9	47.0	2.95	42.0 / 54.0
eGFR (mL/min/1.73m ²)	40	104	105	16.8	62.1 / 136
Weight (kg)	40	85.2	83.2	21.2	52.6 / 135
Study: CSL312-3001					
Age (years)	50	42.5	41.5	16.8	12.0 / 69.0
FXIIa-mediated kallikrein activity (A405nm/min)	50	0.145	0.140	0.0580	0.0260 / 0.260
Aspartate aminotransferase (U/L)	50	21.8	19.0	12.3	5.00 / 91.0
Alanine aminotransferase (U/L)	50	23.1	18.0	18.4	8.00 / 114
Bilirubin ($\mu\text{mol/L}$)	50	8.22	7.65	3.17	2.80 / 17.5
Creatinine clearance (mL/min)	50	129	119	43.8	66.8 / 222
Serum creatinine (mg/dL)	50	0.772	0.751	0.176	0.411 / 1.14
Albumin (g/L)	50	43.4	43.0	2.56	38.0 / 49.0
eGFR (mL/min/1.73m ²)	50	107	107	20.4	54.2 / 150
Weight (kg)	50	78.0	76.3	19.3	43.3 / 138
Study: CSL312-3002					
Age (years)	161	41.6	42.0	15.2	12.0 / 73.0
FXIIa-mediated kallikrein activity (A405nm/min)	159	0.161	0.171	0.0558	0.0260 / 0.293
Aspartate aminotransferase (U/L)	161	22.4	19.0	11.4	9.00 / 91.0
Alanine aminotransferase (U/L)	161	25.2	19.0	19.8	7.00 / 117
Bilirubin ($\mu\text{mol/L}$)	161	8.86	8.00	6.51	2.80 / 74.9
Creatinine clearance (mL/min)	161	134	127	53.0	66.8 / 556
Serum creatinine (mg/dL)	161	0.770	0.751	0.160	0.411 / 1.22
Albumin (g/L)	161	44.1	44.0	2.91	38.0 / 54.0
eGFR (mL/min/1.73m ²)	161	107	107	17.6	54.2 / 157
Weight (kg)	161	80.7	79.0	20.3	43.3 / 153

B: Categorical covariates by study of the PopPK dataset

	Study					
	CSL312-1001	CSL312-1003	CSL312-2001 TP1	CSL312-2001 TP2	CSL312-3001	CSL312-3002
Anti-drug antibodies						
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
No Result	32 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Negative	0 (0.0)	37 (100.0)	39 (100.0)	40 (100.0)	49 (98.0)	159 (98.8)
Positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.6)
Renal function						
Baseline eGFR >= 90 mL/min/1.73m2	31 (96.9)	35 (94.6)	28 (71.8)	32 (80.0)	43 (86.0)	136 (84.5)
60 =< Baseline eGFR < 90 mL/min/1.73m2	1 (3.1)	2 (5.4)	10 (25.6)	8 (20.0)	6 (12.0)	24 (14.9)
30 =< Baseline eGFR < 60 mL/min/1.73m2	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)	1 (2.0)	1 (0.6)
15 =< Baseline eGFR < 30 mL/min/1.73m2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Baseline eGFR < 15 mL/min/1.73m2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age group						
Adolescent (<=17 years)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (10.0)	11 (6.8)
Adult (>17 to <65 years)	32 (100.0)	37 (100.0)	38 (97.4)	39 (97.5)	39 (78.0)	137 (85.1)
Elderly (>= 65 years)	0 (0.0)	0 (0.0)	1 (2.6)	1 (2.5)	6 (12.0)	13 (8.1)
Sex						
Female	0 (0.0)	21 (56.8)	25 (64.1)	23 (57.5)	30 (60.0)	101 (62.7)
Male	32 (100.0)	16 (43.2)	14 (35.9)	17 (42.5)	20 (40.0)	60 (37.3)
Race						
Caucasian	26 (81.2)	13 (35.1)	35 (89.7)	35 (87.5)	42 (84.0)	133 (82.6)
Black or African American	1 (3.1)	0 (0.0)	1 (2.6)	1 (2.5)	1 (2.0)	2 (1.2)
Asian	4 (12.5)	24 (64.9)	3 (7.7)	3 (7.5)	5 (10.0)	23 (14.3)
Other	1 (3.1)	0 (0.0)	0 (0.0)	1 (2.5)	2 (4.0)	3 (1.9)
Asian or non-Asian						
Asian	4 (12.5)	24 (64.9)	3 (7.7)	3 (7.5)	5 (10.0)	23 (14.3)
Non-Asian	28 (87.5)	13 (35.1)	36 (92.3)	37 (92.5)	45 (90.0)	138 (85.7)
Study						
	CSL312-1001	CSL312-1003	CSL312-2001 TP1	CSL312-2001 TP2	CSL312-3001	CSL312-3002
Japanese or non-Japanese						
Japanese	0 (0.0)	24 (64.9)	0 (0.0)	0 (0.0)	5 (10.0)	12 (7.5)
Non-Japanese	32 (100.0)	13 (35.1)	39 (100.0)	40 (100.0)	45 (90.0)	149 (92.5)
Chinese or non-Chinese						
Chinese	0 (0.0)	0 (0.0)	1 (2.6)	1 (2.5)	0 (0.0)	9 (5.6)
Non-Chinese	32 (100.0)	37 (100.0)	38 (97.4)	39 (97.5)	50 (100.0)	152 (94.4)
Healthy or patient with HAE						
Healthy	32 (100.0)	37 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patient with HAE	0 (0.0)	0 (0.0)	39 (100.0)	40 (100.0)	50 (100.0)	161 (100.0)
HAE treatment used prior to study entry						
No	32 (100.0)	37 (100.0)	28 (71.8)	29 (72.5)	46 (92.0)	133 (82.6)
Yes	0 (0.0)	0 (0.0)	11 (28.2)	11 (27.5)	4 (8.0)	28 (17.4)
HAE subtypes						
Healthy	32 (100.0)	37 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Type I	0 (0.0)	0 (0.0)	32 (82.1)	36 (90.0)	45 (90.0)	145 (90.1)
Type II	0 (0.0)	0 (0.0)	1 (2.6)	2 (5.0)	5 (10.0)	14 (8.7)
FXII/PLG HAE	0 (0.0)	0 (0.0)	6 (15.4)	2 (5.0)	0 (0.0)	2 (1.2)
US vs Non-US						
US	0 (0.0)	37 (100.0)	9 (23.1)	10 (25.0)	14 (28.0)	36 (22.4)
Non-US	32 (100.0)	0 (0.0)	30 (76.9)	30 (75.0)	36 (72.0)	125 (77.6)

Source: Applicant's Population PK Report, Tables S4 and S5.

Abbreviations: A, absorbance; CSL312, garadacimab; eGFR, estimated glomerular filtration rate; FXII/PLG HAE, hereditary angioedema with normal C1-esterase inhibitor and factor XII or plasminogen gene mutation; HAE, hereditary angioedema; max, maximum; min, minimum; n, number of records summarized; PK, pharmacokinetics; PopPK, population pharmacokinetics; SD, standard deviation; TP, Treatment Period; summary is count (percentage) for categorical variables

Table 101. Applicant Summary of Baseline Characteristics and Laboratory Values in the Dataset, Stratified by Study of the PopPK-PD Dataset

A: Continuous covariates by study of the PopPK-PD dataset

Variable	n	Mean	Median	SD	Min / Max
Study: CSL312-1001					
Age (years)	48	27.4	25.4	6.43	19.2 / 44.0
FXIIa-mediated kallikrein activity (A405nm/min)	48	0.101	0.108	0.0333	0.0368 / 0.156
Aspartate aminotransferase (U/L)	48	20.3	20.0	5.04	12.0 / 39.0
Alanine aminotransferase (U/L)	48	20.6	19.0	8.40	8.00 / 47.0
Bilirubin ($\mu\text{mol/L}$)	48	10.7	10.0	3.62	6.00 / 22.0
Creatinine clearance (mL/min)	48	128	126	23.1	85.8 / 196
Serum creatinine (mg/dL)	48	0.958	0.944	0.101	0.768 / 1.19
Albumin (g/L)	48	41.7	42.0	2.14	36.0 / 46.0
eGFR (mL/min/1.73m ²)	48	111	112	12.1	82.2 / 130
Weight (kg)	48	78.0	74.8	12.1	56.5 / 117
Study: CSL312-1003					
Age (years)	37	38.3	41.0	10.6	18.0 / 55.0
FXIIa-mediated kallikrein activity (A405nm/min)	37	0.106	0.102	0.0461	0.0430 / 0.274
Aspartate aminotransferase (U/L)	37	18.0	17.0	3.73	10.0 / 30.0
Alanine aminotransferase (U/L)	37	16.5	14.0	6.77	6.00 / 34.0
Bilirubin ($\mu\text{mol/L}$)	37	7.39	6.80	3.46	3.40 / 18.8
Creatinine clearance (mL/min)	37	116	116	22.2	83.2 / 166
Serum creatinine (mg/dL)	37	0.740	0.699	0.154	0.499 / 1.10
Albumin (g/L)	37	45.8	46.0	2.54	40.0 / 51.0
eGFR (mL/min/1.73m ²)	37	113	113	12.1	80.9 / 134
Weight (kg)	37	64.9	62.4	10.3	51.3 / 90.5
Study: CSL312-2001 TP1					
Age (years)	44	40.0	39.0	12.8	20.0 / 65.0
FXIIa-mediated kallikrein activity (A405nm/min)	44	0.153	0.160	0.0588	0.0420 / 0.265
Aspartate aminotransferase (U/L)	44	20.4	18.5	8.06	9.00 / 40.0
Alanine aminotransferase (U/L)	44	23.6	17.0	17.4	6.00 / 85.0
Bilirubin ($\mu\text{mol/L}$)	44	6.55	6.00	2.98	3.00 / 18.0
Creatinine clearance (mL/min)	44	136	128	52.3	40.5 / 335
Serum creatinine (mg/dL)	44	0.821	0.836	0.173	0.508 / 1.22
Albumin (g/L)	44	46.5	47.0	3.09	41.0 / 54.0
eGFR (mL/min/1.73m ²)	44	102	104	17.8	57.1 / 136
Weight (kg)	44	84.9	83.2	22.7	45.5 / 135
Study: CSL312-2001 TP2					
Age (years)	40	39.8	39.0	13.1	20.0 / 65.0
FXIIa-mediated kallikrein activity (A405nm/min)	40	0.159	0.166	0.0573	0.0440 / 0.265
Aspartate aminotransferase (U/L)	40	20.7	18.5	8.34	9.00 / 40.0
Alanine aminotransferase (U/L)	40	24.8	18.0	17.8	7.00 / 85.0

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Bilirubin ($\mu\text{mol/L}$)	40	6.75	6.00	3.01	3.00 / 18.0
Creatinine clearance (mL/min)	40	138	128	51.9	68.8 / 335
Serum creatinine (mg/dL)	40	0.813	0.814	0.173	0.508 / 1.22
Albumin (g/L)	40	46.9	47.0	2.95	42.0 / 54.0
eGFR (mL/min/1.73m ²)	40	104	105	16.8	62.1 / 136
Weight (kg)	40	85.2	83.2	21.2	52.6 / 135
Study: CSL312-3001					
Age (years)	64	41.2	41.0	15.9	12.0 / 69.0
FXIIa-mediated kallikrein activity (A405nm/min)	64	0.145	0.147	0.0594	0.0120 / 0.261
Aspartate aminotransferase (U/L)	64	21.0	19.0	11.1	5.00 / 91.0
Alanine aminotransferase (U/L)	64	22.0	18.0	16.5	8.00 / 114
Bilirubin ($\mu\text{mol/L}$)	64	8.47	8.10	3.30	2.80 / 17.5
Creatinine clearance (mL/min)	64	138	122	70.2	66.8 / 556
Serum creatinine (mg/dL)	64	0.772	0.751	0.173	0.411 / 1.14
Albumin (g/L)	64	43.5	43.0	2.62	38.0 / 49.0
eGFR (mL/min/1.73m ²)	64	108	109	20.3	54.2 / 157
Weight (kg)	64	80.4	77.2	21.9	43.3 / 153
Study: CSL312-3002					
Age (years)	161	41.6	42.0	15.2	12.0 / 73.0
FXIIa-mediated kallikrein activity (A405nm/min)	159	0.161	0.171	0.0558	0.0260 / 0.293
Aspartate aminotransferase (U/L)	161	22.4	19.0	11.4	9.00 / 91.0
Alanine aminotransferase (U/L)	161	25.2	19.0	19.8	7.00 / 117
Bilirubin ($\mu\text{mol/L}$)	161	8.86	8.00	6.51	2.80 / 74.9
Creatinine clearance (mL/min)	161	134	127	53.0	66.8 / 556
Serum creatinine (mg/dL)	161	0.770	0.751	0.160	0.411 / 1.22
Albumin (g/L)	161	44.1	44.0	2.91	38.0 / 54.0
eGFR (mL/min/1.73m ²)	161	107	107	17.6	54.2 / 157
Weight (kg)	161	80.7	79.0	20.3	43.3 / 153

B: Categorical covariates by study of the PopPK-PD dataset

	Study					
	CSL312-1001	CSL312-1003	CSL312-2001 TP1	CSL312-2001 TP2	CSL312-3001	CSL312-3002
Anti-drug antibodies						
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
No Result	48 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Negative	0 (0.0)	37 (100.0)	44 (100.0)	40 (100.0)	63 (98.4)	159 (98.8)
Positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.6)
Renal function						
Baseline eGFR $\geq$ 90 mL/min/1.73m ²	44 (91.7)	35 (94.6)	33 (75.0)	32 (80.0)	54 (84.4)	136 (84.5)
60 $\leq$ Baseline eGFR < 90 mL/min/1.73m ²	4 (8.3)	2 (5.4)	10 (22.7)	8 (20.0)	9 (14.1)	24 (14.9)
30 $\leq$ Baseline eGFR < 60 mL/min/1.73m ²	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	1 (0.6)
15 $\leq$ Baseline eGFR < 30 mL/min/1.73m ²	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Baseline eGFR < 15 mL/min/1.73m ²	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age group						
Adolescent ($\leq$ 17 years)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (9.4)	11 (6.8)
Adult (>17 to <65 years)	48 (100.0)	37 (100.0)	43 (97.7)	39 (97.5)	52 (81.2)	137 (85.1)
Elderly ($\geq$ 65 years)	0 (0.0)	0 (0.0)	1 (2.3)	1 (2.5)	6 (9.4)	13 (8.1)
Sex						
Female	0 (0.0)	21 (56.8)	27 (61.4)	23 (57.5)	38 (59.4)	101 (62.7)
Male	48 (100.0)	16 (43.2)	17 (38.6)	17 (42.5)	26 (40.6)	60 (37.3)
Race						
Caucasian	37 (77.1)	13 (35.1)	39 (88.6)	35 (87.5)	55 (85.9)	133 (82.6)
Black or African American	2 (4.2)	0 (0.0)	1 (2.3)	1 (2.5)	1 (1.6)	2 (1.2)
Asian	7 (14.6)	24 (64.9)	3 (6.8)	3 (7.5)	6 (9.4)	23 (14.3)
Other	2 (4.2)	0 (0.0)	1 (2.3)	1 (2.5)	2 (3.1)	3 (1.9)
Asian or non-Asian						
Asian	7 (14.6)	24 (64.9)	3 (6.8)	3 (7.5)	6 (9.4)	23 (14.3)
Non-Asian	41 (85.4)	13 (35.1)	41 (93.2)	37 (92.5)	58 (90.6)	138 (85.7)

Source: Applicant's Population PK Report, Tables S19 and S20.

Abbreviations: A, absorbance; CSL-312, garadacimab; eGFR, estimated glomerular filtration rate; FXII/PLG HAE, hereditary angioedema with normal C1-esterase inhibitor and factor XII or plasminogen gene mutation; HAE, hereditary angioedema; max, maximum; min, minimum; n, number of records summarized; PD, pharmacodynamics; PK, pharmacokinetics; PopPK, population pharmacokinetics; SD, standard deviation; TP, Treatment Period; summary is count (percentage) for categorical variables

Table 102. Applicant Parameter Estimates and SE From Final Population PK Model

			Estimate	95% CI	
Structural model parameters					
CL (L/h)	$\exp(\theta_1)$	Clearance	0.00664	0.00573, 0.00769	
V2 (L)	$\exp(\theta_2)$	Central compartment volume of distribution	2.37	1.77, 3.17	
F1	θ_3	Absolute bioavailability	0.387	0.344, 0.431	
Q (L/h)	$\exp(\theta_4)$	Intercompartmental clearance	0.00685	0.00588, 0.00799	
V3 (L)	$\exp(\theta_5)$	Peripheral compartment volume of distribution	1.41	1.34, 1.50	
KA (1/h)	$\exp(\theta_6)$	First-order absorption rate constant	0.00824	0.00763, 0.00889	
Covariate effect parameters					
CL Q ~ WT	θ_7	Weight effect on CL and Q	1.16	0.963, 1.36	
V2 V3 ~ WT	θ_8	Weight effect on V2 and V3	0.843	0.657, 1.03	
CL ~ JPN	$\exp(\theta_9)$	Japanese effect on CL	1.27	1.11, 1.44	
CL ~ CHN	$\exp(\theta_{10})$	Chinese effect on CL	1.02	0.861, 1.21	
CL ~ PAT	$\exp(\theta_{11})$	Patient effect on CL	1.05	0.952, 1.17	
CL ~ SCR	θ_{12}	Serum creatinine effect on CL	-0.0343	-0.214, 0.146	
CL ~ ALT	θ_{13}	Alanine aminotransferase effect on CL	-0.0773	-0.148, -0.00670	
CL ~ BILI	θ_{14}	Bilirubin effect on CL	-0.136	-0.203, -0.0692	
			Estimate	95% CI	Shrinkage (%)
Interindividual variance parameters					
IIV-CL	$\Omega_{(1,1)}$	0.175 [CV%=43.8]	0.0980, 0.253	28.7	
IIV-V2	$\Omega_{(2,2)}$	0.717 [CV%=102]	0.442, 0.991	25.2	
IIV-F1	$\Omega_{(3,3)}$	0.359 [SD=0.135]	0.209, 0.510	43.3	
Interindividual covariance parameters					
V2-CL	$\Omega_{(2,1)}$	0.263 [Corr=0.743]	0.0961, 0.430	-	
F1-CL	$\Omega_{(3,1)}$	0.154 [Corr=0.614]	0.0578, 0.251	-	
F1-V2	$\Omega_{(3,2)}$	0.174 [Corr=0.342]	-0.0970, 0.444	-	
Residual variance					
Proportional	$\Sigma_{(1,1)}$	0.0395 [CV%=19.9]	0.0383, 0.0407	8.27	

Source: Applicant's Population PK Report, Tables S9 and S10.

Confidence intervals=estimate±1.96 SE; CV% of log-normal omegas=sqrt(exp(estimate) - 1) 100; CV% of sigma=sqrt(estimate) 100. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; CI, confidence interval; CL, clearance; CV, coefficient of variation; corr, correlation coefficient; CV, coefficient of variation; SD, standard deviation; IIV, interindividual variation; PK, pharmacokinetics; SCR, serum creatinine; SE, standard error

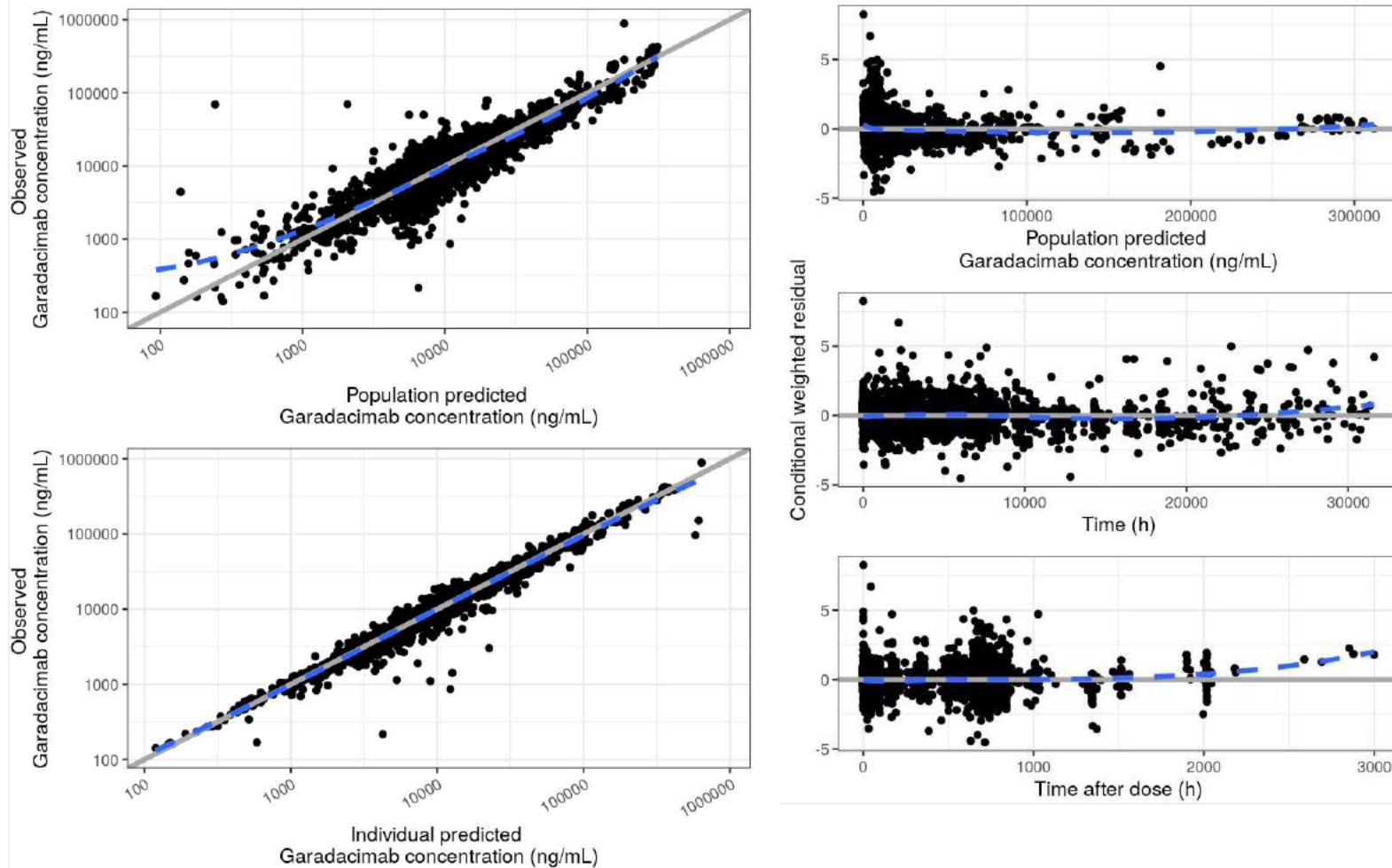
Table 103. Applicant-Parameter Estimates and SE From Final Population PK-PD Model

			Estimate	95% CI	
Structural model parameters					
EMAX (unitless)	$\exp(\theta_1)$	Maximal inhibitory effect of drug	0.988	0.981, 0.996	
EC50 (ng/mL)	$\exp(\theta_2)$	Concentration that causes half-maximal effect	17600	16400, 18800	
E0 (% baseline)	$\exp(\theta_3)$	Initial level of FXIIa-mediated kallikrein activity	98.8	94.9, 103	
GAMMA (unitless)	$\exp(\theta_4)$	Shape parameter	2.05	1.88, 2.23	
Covariate effect parameters					
E0 ~ BLPD	θ_5	Baseline FXIIa-mediated kallikrein activity effect on E0	-0.262	-0.308, -0.217	
EC50 ~ BLPD	θ_6	Baseline FXIIa-mediated kallikrein activity effect on EC50	0.269	0.124, 0.413	
			Estimate	95% CI	Shrinkage (%)
Interindividual variance parameters					
IIV-EC50	$\Omega_{(2,2)}$	0.168 [CV%=42.8]	0.119, 0.217	20.2	
IIV-E0	$\Omega_{(3,3)}$	0.0268 [CV%=16.5]	0.0219, 0.0317	14.7	
IIV-GAMMA	$\Omega_{(4,4)}$	0.150 [CV%=40.2]	0.0876, 0.212	27.0	
Interindividual covariance parameters					
EC50-E0	$\Omega_{(3,2)}$	0.0148 [Corr=0.221]	0.00160, 0.0280	-	
GAMMA-E0	$\Omega_{(4,2)}$	0.0846 [Corr=0.533]	0.0441, 0.125	-	
GAMMA-EC50	$\Omega_{(4,3)}$	0.0254 [Corr=0.400]	0.00647, 0.0442	-	
Residual variance					
Proportional	$\Sigma_{(1,1)}$	0.0577 [CV%=24.0]	0.0556, 0.0597	6.15	
Additive	$\Sigma_{(2,2)}$	6.01 [SD=2.45]	4.42, 7.61	6.15	

Source: Applicant's Population PK Report, Tables S23 and S24.

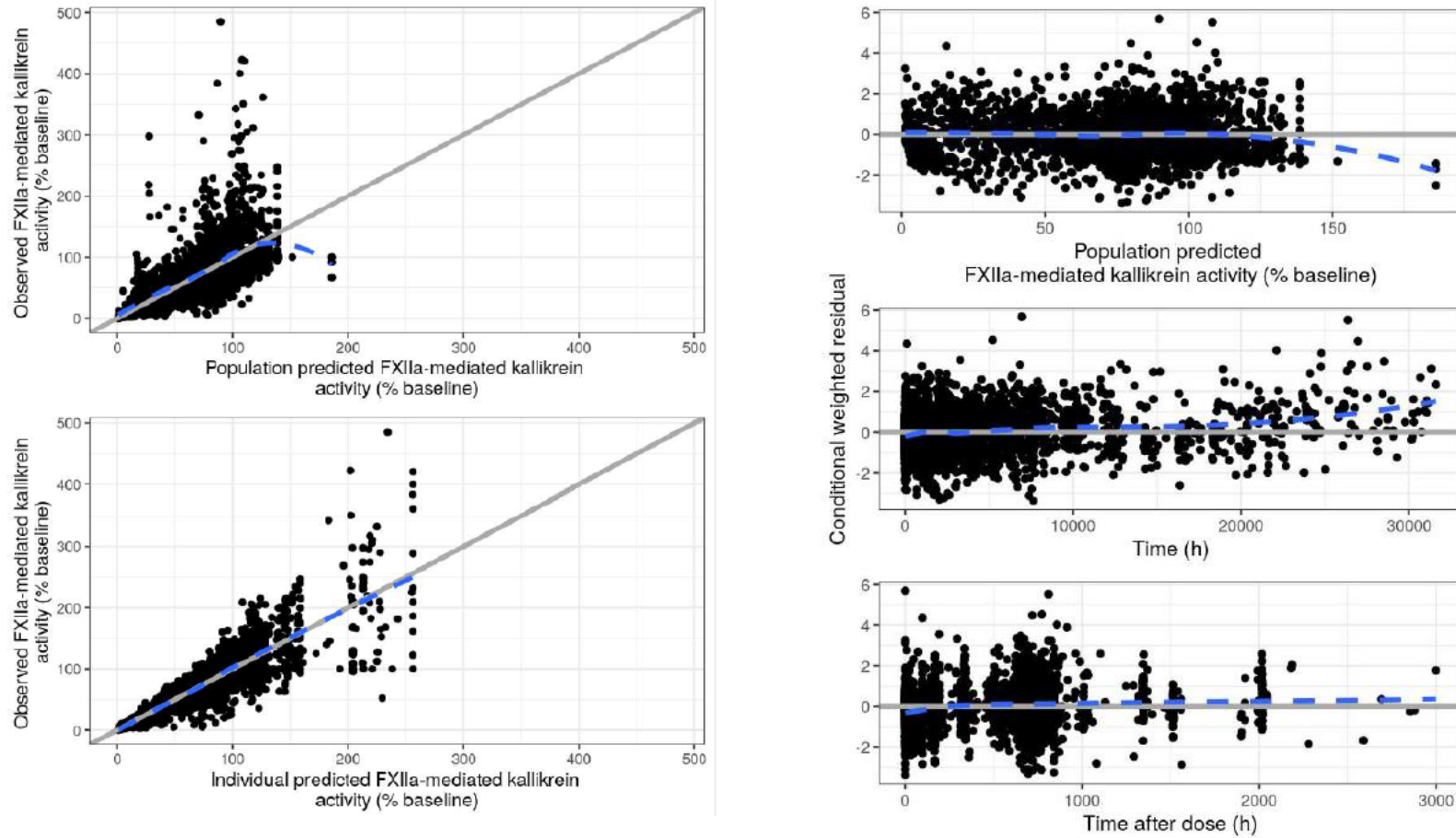
Abbreviations: A, absorbance; CSL-312, garadacimab; eGFR, estimated glomerular filtration rate; FXII/PLG HAE, hereditary angioedema with normal C1-esterase inhibitor and factor XII or plasminogen gene mutation; HAE, hereditary angioedema; max, maximum; min, minimum; n, number of records summarized; PK, pharmacokinetics; PopPK, population pharmacokinetics; SD, standard deviation; TP, Treatment Period; summary is count (percentage) for categorical variables

Figure 50. Applicant-Goodness-of-Fit Plots for the Final Population PK Model



Source: Applicant's Population PK Report, Figures S51 and S55.
Observed values are indicated by solid black circles. The line of identity (solid grey) is included as a reference ($x=y$). Solid black circles represent the individual residual values associated with each observation record. The solid horizontal grey line (residuals=0) was included for reference. The dashed blue line represents a LOESS smooth through the data.
Abbreviations: LOESS, locally reweighted scatterplot smoothing; PK, pharmacokinetics

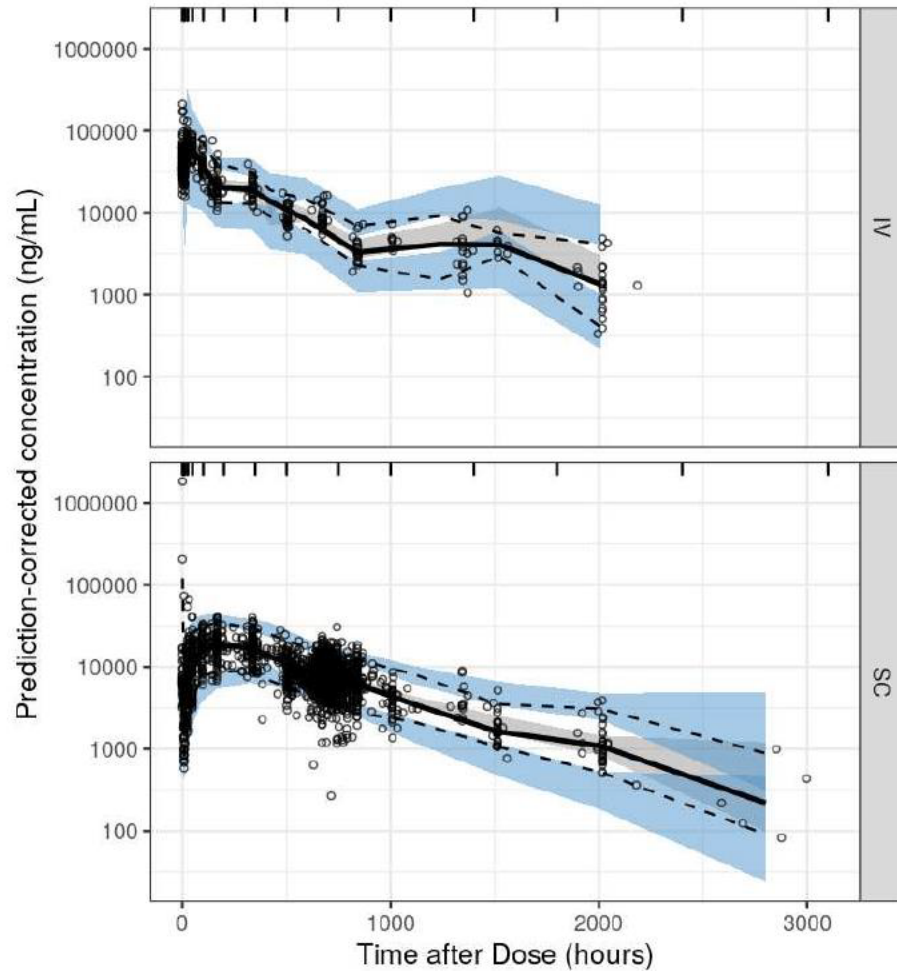
Figure 51. Applicant Goodness-of-Fit Plots for the Final Population PK-PD Model



Source: Applicant's Population PK Report, Figures S143 and S148.

Observed values are indicated by solid black circles. The line of identity (solid grey) is included as a reference ($x=y$). Solid black circles represent the individual residual values associated with each observation record. The solid horizontal grey line (residuals=0) was included for reference. The dashed blue line represents a LOESS smooth through the data. Abbreviations: LOESS, locally reweighted scatterplot smoothing; PD, pharmacodynamics; PK, pharmacokinetics

Figure 52. Applicant VPC of the Final Population PK Model, Stratified by Administration Route

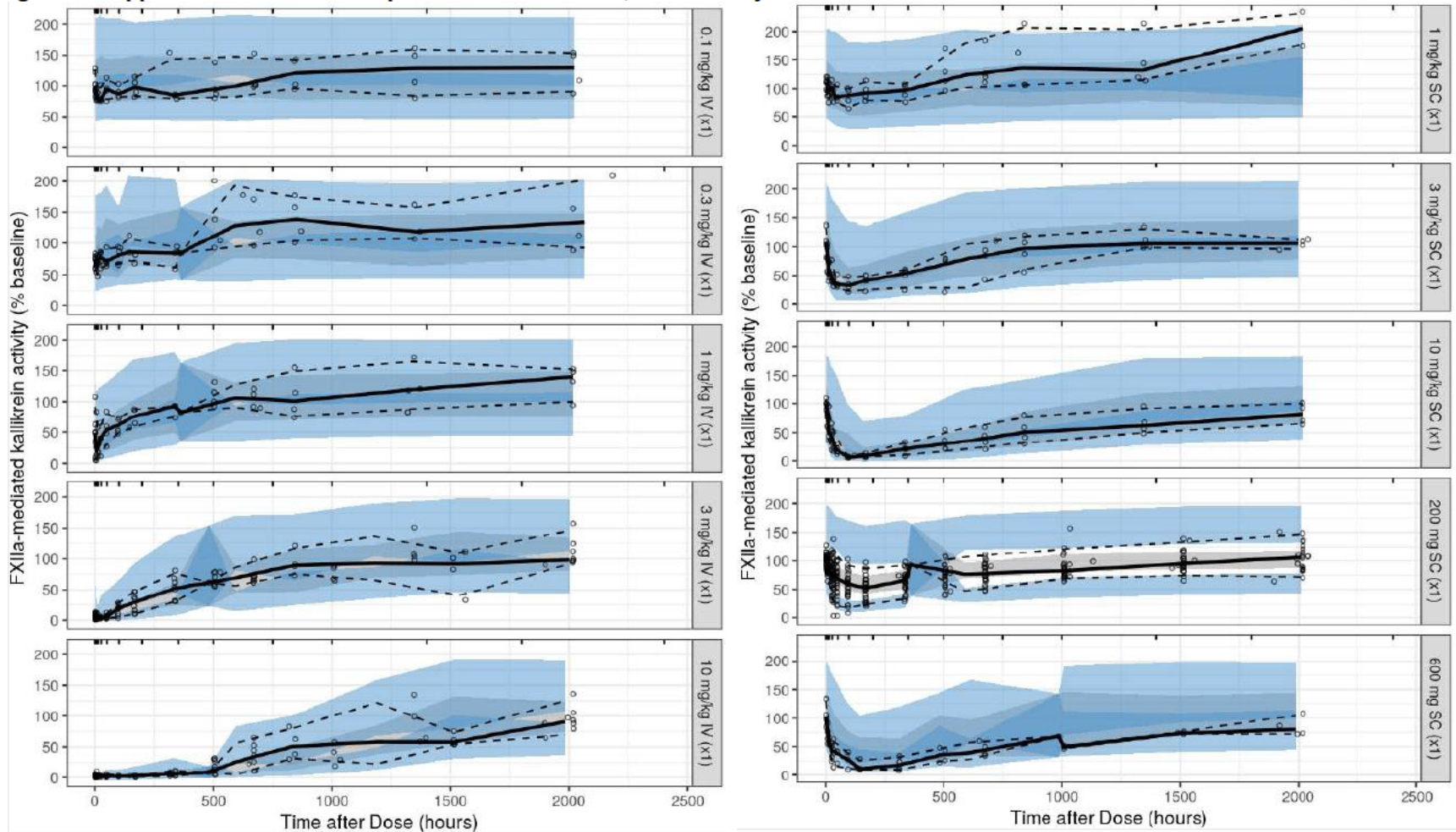


Source: Applicant's Population PK Report, Figure S113.

Black lines represent the median (solid), 5th and 95th percentiles (dashed) of the observed data. Blue and grey shaded regions represent the 95% confidence intervals of the corresponding (i.e., 5th, 50th, and 95th) percentiles. The points are observed garadacimab concentrations.

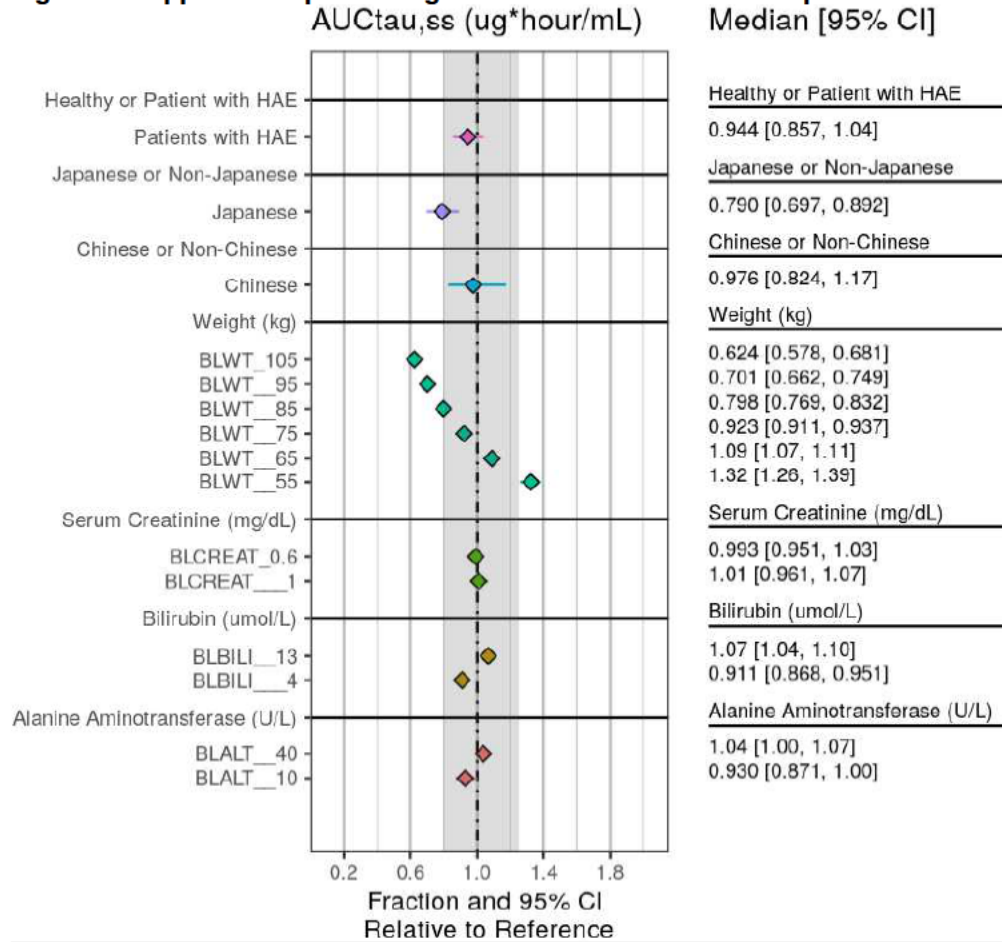
Abbreviations: PK, pharmacokinetics; VPC, visual predictive check

Figure 53. Applicant-VPC of Final Population PK-PD Model, Stratified by Administration Route and Dose Level



Source: Applicant's Population PK Report, Figure S162.
 Black lines represent the median (solid), 5th and 95th percentiles (dashed) of the observed data. Blue and grey shaded regions represent the 95% confidence intervals of the corresponding (i.e., 5th, 50th, and 95th) percentiles. The points are observed FXIIa-mediated kallikrein activity.
 Abbreviations: FXIIa, activated Factor XII; PD, pharmacodynamics; PK, pharmacokinetics; VPC, visual predictive check

Figure 54. Applicant Impact of Significant PK Covariates on Exposure

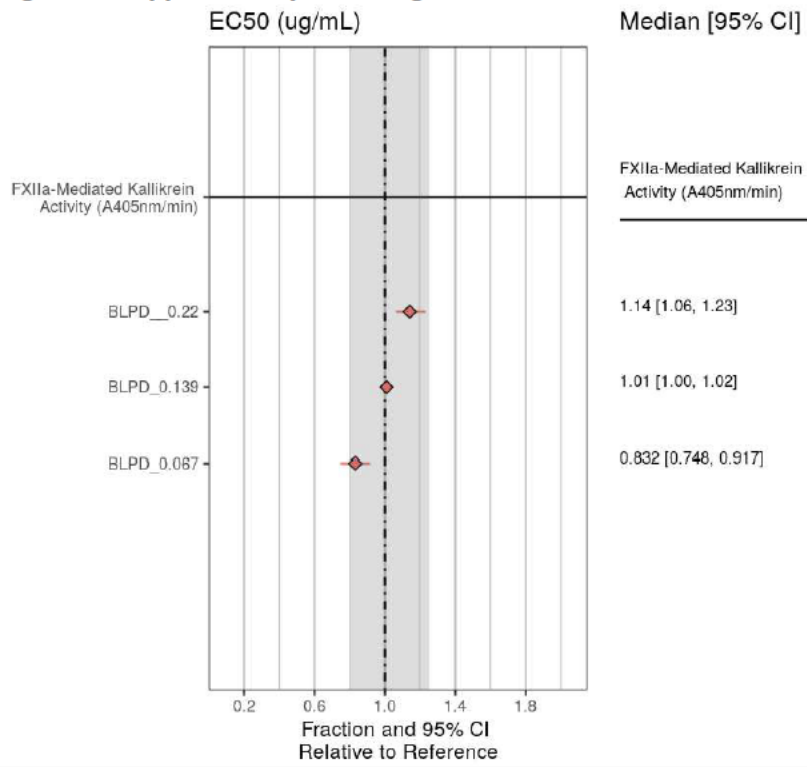


Source: Applicant's Population PK Report, Figure S82.

The covariates in the model were visualized by varying single covariates individually while keeping all other conditions constant (*ceteris paribus*). Results are presented relative to a reference subject, i.e., a non-Japanese, non-Chinese, healthy volunteer with baseline weight of 70 kg, baseline SCR of 0.75 mg/dL, baseline ALT of 25 U/L and baseline BILI of 8µmol/L. The colored diamonds represent the median and the solid horizontal lines represent the 95% confidence interval. The grey shaded reference range of 80-125% was analogous to the region of practical equivalence (ROPE). For continuous covariates, the upper and lower values used in the simulations were determined based on the 10th and 90th percentiles in the observed dataset.

Abbreviations: AUC, area under the concentration-time curve; BLWT, baseline weight (kg), BLCREAT, baseline serum creatinine (mg/dL), BLBILI, baseline bilirubin (µmol/L), BLALT, baseline alanine aminotransferase (U/L), HAE, hereditary angioedema, CI, confidence interval; PK, pharmacokinetics

Figure 55. Applicant Impact of Significant PD Covariates on EC₅₀



Source: Applicant's Population PK Report, Figure S165.

The covariates in the model were visualized by varying single covariates individually while keeping all other conditions constant (*ceteris paribus*). Results are presented relative to a reference subject, i.e., a subject with a baseline FXIIa-mediated kallikrein activity of 0.134 A_{405nm/min}. The colored diamonds represent the median and the solid horizontal lines represent the 95% confidence interval. The grey shaded reference range of 80%-125% was analogous to the region of practical equivalence (ROPE). For continuous covariates, the upper and lower values used in the simulations were determined based on the 10th and 90th percentiles in the observed dataset.

Abbreviations: A, absorbance; BLPD, baseline FXIIa-mediated kallikrein activity (A405nm/min); CI, confidence interval, EC₅₀, concentration that causes half-maximal effect; FXIIa, activated Factor XII; PD, pharmacodynamics; PK, pharmacokinetics

Table 104. Applicant-Simulated PK and PD Metrics in Adolescent and Adult Subjects Receiving a 400 mg SC Loading Dose Followed by 200 mg SC Q1M Maintenance Doses

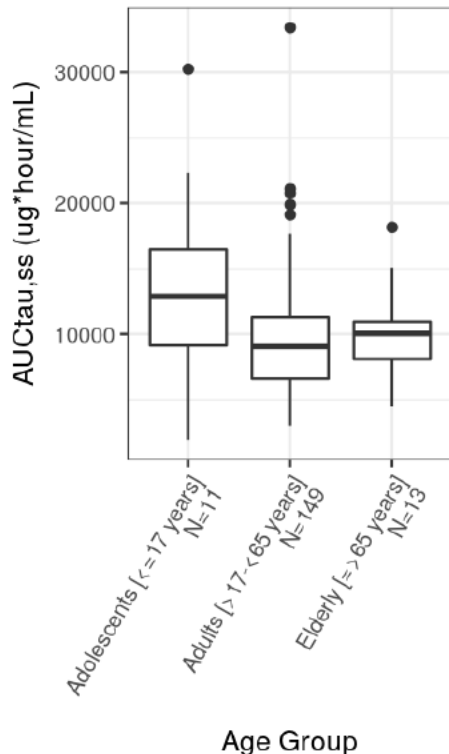
Metric	Mean (SD)	Geometric mean (%CV)	Median (90% CI)
Adolescents (12-17 years) and Adults (> 17 years), N = 20000			
AUC _{tau,SS} (µg*hr/mL)	11900 (5940)	10600 (60.9)	10700 (4810, 23100)
C _{max,SS} (µg/mL)	23.9 (12.9)	21.0 (66.5)	21.1 (9.02, 48.4)
C _{min,SS} (µg/mL)	9.80 (5.37)	8.56 (69.0)	8.61 (3.56, 20.1)
T _{max} (hours)	141 (31.4)	137 (28.4)	144 (84.0, 186)
CL/F (L/hr)	0.0211 (0.0106)	0.0188 (60.9)	0.0188 (0.00865, 0.0416)
V2/F (L)	8.94 (8.90)	6.33 (130)	6.36 (1.61, 25.1)
T _{1/2} (hours)	501 (170)	478 (34.7)	466 (308, 810)
Nadir of FXIIa mediated kallikrein activity (% baseline)	45.8 (28.0)	36.6 (110)	40.4 (9.24, 98.9)
Adolescents (12-17 years), N = 10000			
AUC _{tau,SS} (µg*hr/mL)	13700 (6670)	12300 (60.9)	12500 (5480, 26400)
C _{max,SS} (µg/mL)	27.3 (14.4)	24.0 (66.8)	24.4 (10.0, 54.7)
C _{min,SS} (µg/mL)	11.5 (6.04)	10.1 (67.3)	10.3 (4.23, 23.0)
T _{max} (hours)	143 (31.4)	139 (28.0)	146 (84.0, 186)
CL/F (L/hr)	0.0183 (0.00945)	0.0163 (60.9)	0.0160 (0.00758, 0.0365)
V2/F (L)	8.14 (8.12)	5.74 (130)	5.75 (1.46, 22.7)
T _{1/2} (hours)	524 (173)	501 (33.9)	489 (323, 838)
Nadir of FXIIa mediated kallikrein activity (% baseline)	40.7 (27.0)	31.5 (119)	34.6 (7.39, 93.3)
Adults (> 17 years), N = 10000			
AUC _{tau,SS} (µg*hr/mL)	10100 (4400)	9200 (53.5)	9280 (4480, 18300)
C _{max,SS} (µg/mL)	20.5 (10.0)	18.4 (60.3)	18.6 (8.36, 39.7)
C _{min,SS} (µg/mL)	8.08 (3.91)	7.23 (61.3)	7.36 (3.21, 15.4)
T _{max} (hours)	140 (31.4)	136 (28.7)	142 (84.0, 186)
CL/F (L/hr)	0.0239 (0.0110)	0.0217 (53.5)	0.0216 (0.0109, 0.0447)
V2/F (L)	9.73 (9.55)	6.97 (127)	6.98 (1.82, 26.8)
T _{1/2} (hours)	478 (163)	456 (34.5)	444 (296, 777)
Nadir of FXIIa mediated kallikrein activity (% baseline)	50.9 (28.2)	42.4 (93.5)	46.5 (12.6, 104)

Source: Applicant's Population PK Report, Table S25.

Dosing regimen: 400 mg SC loading dose + 200 mg SC Q1M.

Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance; CI, confidence interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CV, coefficient of variation; FXIIa, activated Factor XII; PK, pharmacokinetics; Q1M, once monthly; SC, subcutaneous; SD, standard deviation; SS, steady state; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration; V2/f, xxx

Figure 56. Applicant-Simulated PK Exposure Metrics Versus Age Group for Subjects With HAE Using Empirical Bayes Estimates (EBE)



Source: Applicant's Population PK Report, Figure S94.
Median values are designated by a solid line in the center of the box. Boxes indicate the interquartile range (IQR) with whiskers extending to 1.5×IQR.
Abbreviations: AUC_{tau,ss}, area under the concentration-time curve during the dosing interval at steady state; CL, clearance, HAE, hereditary angioedema; PK, pharmacokinetics; V₂, central compartment volume of distribution,

The Applicant's population PK/PK-PD analyses are acceptable. Overall, the final population PK and PK-PD models are adequate to characterize the PK/PD profile of garadacimab as indicated in the Applicant's diagnostic plots. The FDA reviewer was able to repeat and verify the Applicant's analysis with no significant discordance identified. The population PK model excluding data from study 1001, which had an issue in the bioanalysis of samples, did not suggest any changes in conclusions regarding the intrinsic factors in the proposed drug label. The reviewer agrees with the Applicant's conclusion regarding the effect of covariates on garadacimab exposure and FXIIa-mediated kallikrein activity. FDA accepted the labeling language in Section 12.3 of the prescribing information (PI) related to PK parameters and effect of covariates (age, [REDACTED], race, body weight, renal impairment, [REDACTED] (b) (4)

14.5.1.3. PPK Review Issues

No substantive issue.

14.5.1.4. Reviewer's Independent Analysis

Reviewer's independent analysis was not performed.

14.5.2. Exposure-Response Analysis

14.5.2.1. ER (Efficacy) Executive Summary

A time-varying Poisson process model with a maximum inhibition (E-R) relationship generally described the efficacy endpoint (HAE attack rate) in subjects with HAE who received either garadacimab or placebo in the phase 2 trial (2001) and phase 3 studies (3001 and 3002). None of the covariates (e.g., age, Japanese, Chinese, male, prior treatment, the use of concomitant medications [analgesic, anti-inflammatory and antirheumatic, antihistamine, antibacterials] and rescue medications [plasma-derived and recombinant C1-INH or icatibant], body weight, obesity) were likely to have clinically meaningful impact on the effectiveness of garadacimab in reducing HAE attack. Dose adjustments due to the forementioned covariates are not needed.

14.5.2.2. ER (Efficacy) Assessment Summary

Table 105. ER (Efficacy) Summary

General Information	
Goal of ER analysis	Develop an exposure-response (ER) model for garadacimab and hereditary angioedema (HAE) attacks with data from trial 2001, trial 3001, and study 3002 • Explore effects of covariates on the HAE attack rate and/or drug activity. • Explore the impact of rescue medication use on the HAE attack rate. Perform simulations to confirm efficacy of a 400 mg (2x200 mg) subcutaneous (SC) loading dose followed by 200 mg once monthly SC dose.
Study included	Trial 2001, trial 3001, and study 3002
Endpoint	HAE attack rate
No. of subjects (total, and with individual pharmacokinetics [PK])	177
Population characteristics (Table 106)	General • Age: median 41 yr (range 12-73 yr) • Weight: median 79.2 kg (range 43.3-153 kg) • 64 (36.2%) male • 147 (83.1%) White, 3 (1.7%) black, of African heritage or African American, 24 (13.6%) Asian, 3 (1.7%) other Pediatrics (if any) • Age: median 15 yr (range: 12-17 yr, 0% subj ≤2 yr, 0% subj ≤6 yr, 9.1% subj ≤12 yr) • Weight: median 57.8 kg (range: 43.3-153.2 kg)
Dose(s) included	• 40 mg IV loading followed by 75 mg Q4W SC; • 100 mg IV loading followed by 200 mg Q4W SC; • 300 mg IV loading followed by 600 mg Q4W SC; • 400 mg Q2W SC; • 200 or 600 mg Q4W SC; • 400 mg SC loading followed by 200 mg monthly SC
Exposure metrics explored (range)	Real time concentration

General Information		
Covariates evaluated	Baseline age, baseline weight, sex, ethnicity (Japanese versus non-Japanese, Asian versus non-Asian, Chinese versus non-Chinese), HAE subtypes (healthy, Type I, Type II, FXII/PLG HAE), Baseline attack rate, HAE prophylaxis treatment used prior to study entry, Class of HAE acute treatment used prior to study entry (three drug classes: complement C1 esterase inhibitors, B2 receptor antagonists (icatibant acetate), and other rescue medication)	
Final Model Parameters	Summary	Acceptability [FDA's Comments]
Model structure	A time-varying Poisson process model with a maximum inhibition exposure-response relationship	Acceptable
Model parameter estimates	Table 107	Acceptable
Model evaluation	Figure 57	Acceptable
Covariates and clinical relevance	Figure 58	Acceptable
Simulation for specific population	Not applicable	N/A
Visualization of E-R relationships	Figure 59	Acceptable
Overall clinical relevance for ER	Population simulations based on the final model suggested the monthly HAE attack rate and HAE relative risk decreased with increasing exposure ($AUC_{tau,ss}$, $C_{min,ss}$, and $C_{max,ss}$). More than 70% of subjects who received 200 mg SC monthly maintenance dose were projected to have 90% reduction in relative risk at steady state; more than 85% subjects who received 400 mg SC loading dose were projected to have 90% reduction in relative risk after the first dose. The recommended dose regimen as implemented in trial 3001 and study 3002 is appropriate for prevention ¹ of HAE attacks in subjects 12 yr and older.	Acceptable
Labeling Language	Description	Acceptability [FDA's Comments]
12.2 Pharmacodynamics	Not applicable	N/A

Source: Module 5.3.3.5, Exposure-Response Analysis Report.

Abbreviations: AUC, area under the concentration-time curve; C_{max} , maximum plasma concentration; C_{min} , minimum plasma concentration; FXII/PLG, Factor XII/plasminogen; N/A, not applicable; Q2W, every 2 weeks; Q4W, every 4 weeks; yr, year

Table 106. Applicant-Summary of Baseline Characteristics and Laboratory Values in the Dataset Stratified by Study

A: Continuous covariates by study

Variable	n	Mean	Median	SD	Min / Max
Study: CSL312_2001					
Age (years)	44	40.0	39.0	12.8	20.0 / 65.0
Weight (kg)	44	84.9	83.2	22.7	45.5 / 135
Rate of HAE attacks in run-in (HAE attacks per week)	44	1.02	0.830	0.545	0.170 / 2.95
Study: CSL312_3001					
Age (years)	64	41.2	41.0	15.9	12.0 / 69.0
Weight (kg)	64	80.4	77.2	21.9	43.3 / 153
Rate of HAE attacks in run-in (HAE attacks per week)	64	0.601	0.500	0.379	0.200 / 2.33
Study: CSL312_3002 (CSL312-naive subjects only)					
Age (years)	69	41.2	42.0	15.7	13.0 / 73.0
Weight (kg)	69	79.7	78.0	18.3	45.0 / 125
Rate of HAE attacks in run-in (HAE attacks per week)	69	0.671	0.510	0.522	0.130 / 3.11
All data					
Age (years)	177	40.9	41.0	15.0	12.0 / 73.0
Weight (kg)	177	81.2	79.2	20.8	43.3 / 153
Rate of HAE attacks in run-in (HAE attacks per week)	177	0.733	0.610	0.508	0.130 / 3.11

B: Categorical covariates by study

	Study			Summary n = 177
	CSL312_2001 n = 44	CSL312_3001 n = 64	CSL312_3002 naive subjects n = 69	
Race				
Caucasian	39 (88.6)	55 (85.9)	53 (76.8)	147 (83.1)
Black or African American	1 (2.3)	1 (1.6)	1 (1.4)	3 (1.7)
Asian	3 (6.8)	6 (9.4)	15 (21.7)	24 (13.6)
Other	1 (2.3)	2 (3.1)	0 (0.0)	3 (1.7)
Asian or non-Asian				
Asian	3 (6.8)	6 (9.4)	15 (21.7)	24 (13.6)
Non-Asian	41 (93.2)	58 (90.6)	54 (78.3)	153 (86.4)
Chinese or non-Chinese				
Chinese	1 (2.3)	0 (0.0)	9 (13.0)	10 (5.6)
Non-Chinese	43 (97.7)	64 (100.0)	60 (87.0)	167 (94.4)
Japanese or non-Japanese				
Japanese	0 (0.0)	6 (9.4)	6 (8.7)	12 (6.8)
Non-Japanese	44 (100.0)	58 (90.6)	63 (91.3)	165 (93.2)
Sex				
Female	27 (61.4)	38 (59.4)	48 (69.6)	113 (63.8)
Male	17 (38.6)	26 (40.6)	21 (30.4)	64 (36.2)
HAE treatment used prior to study entry				
No	31 (70.5)	58 (90.6)	57 (82.6)	146 (82.5)
Yes	13 (29.5)	6 (9.4)	12 (17.4)	31 (17.5)
HAE subtypes				
Healthy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Type I	36 (81.8)	56 (87.5)	65 (94.2)	157 (88.7)
Type II	2 (4.5)	8 (12.5)	4 (5.8)	14 (7.9)
FXII/PLG HAE	6 (13.6)	0 (0.0)	0 (0.0)	6 (3.4)

Source: Applicant's ER Report, Tables S5 and S6.

Summary is count (percentage) for categorical variables.

Abbreviations: CSL312, garadacimab; ER, exposure-response; FXII/PLG, Factor XII/plasminogen; HAE, hereditary angioedema; n, number of records summarized, SD, standard deviation, min, minimum, max, maximum

Table 107. Applicant Parameter Estimates From the Final ER Model

			Estimate	95% CI	
Structural model parameters					
BL hazard (1/h)	$\exp(\theta_1)$	Baseline HAE attack hazard	0.00440	0.00381, 0.00510	
EC50 (ng/mL)	$\exp(\theta_2)$	Concentration at half of the maximal effect	303	160, 533	
Placebo	$\exp(\theta_3)$	Placebo effect	0.728	0.621, 0.849	
I _{max}	$\exp(\theta_4)/(1 + \exp(\theta_4))$	Maximum inhibition of the HAE attack hazard	1	FIXED	
Hill	$\exp(\theta_5)$	Hill coefficient	1.00	FIXED	
Covariate effect parameters					
BL HAE hazard ~ Age (years)	$\exp(\theta_8)$	Age effect on BL HAE hazard	1.01	1.00, 1.01	
EC50 ~ Age (years)	$\exp(\theta_9)$	Age effect on EC50	0.987	0.961, 1.01	
BL HAE hazard ~ Japanese	$\exp(\theta_{12})$	Japanese effect on BL HAE hazard	0.789	0.486, 1.21	
EC50 ~ Japanese	$\exp(\theta_{13})$	Japanese effect on EC50	4.26	0.781, 19.5	
BL HAE hazard ~ Chinese	$\exp(\theta_{14})$	Chinese effect on BL HAE hazard	0.487	0.285, 0.868	
EC50 ~ Chinese	$\exp(\theta_{15})$	Chinese effect on EC50	1.05	0.125, 6.29	
BL HAE hazard ~ Male	$\exp(\theta_{16})$	Male effect on BL HAE hazard	1.05	0.861, 1.29	
EC50 ~ Male	$\exp(\theta_{17})$	Male effect on EC50	0.479	0.191, 1.25	
BL HAE hazard ~ Prior treatment	$\exp(\theta_{18})$	Prior treatment effect on BL HAE hazard	1.28	0.967, 1.66	
EC50 ~ Prior treatment	$\exp(\theta_{19})$	Prior treatment effect on EC50	1.53	0.464, 4.69	
BL HAE hazard ~ FXII HAE type	$\exp(\theta_{20})$	FXII HAE type effect on BL HAE hazard	0.946	0.593, 1.51	
EC50 ~ FXII HAE type	$\exp(\theta_{21})$	FXII HAE type effect on EC50	451	56.2, 5020	
			Estimate	95% CI	Shrinkage (%)
Interindividual variance parameters					
IIV-BL HAE attack hazard	$\Omega_{(1,1)}$	0.206 [CV%=47.9]	0.142, 0.289	28.6	
IIV-EC50	$\Omega_{(2,2)}$	4.95 [CV%=1.18e+03]	3.20, 7.37	22.7	
Interindividual covariance parameters					
BL HAE attack hazard - EC50	$\Omega_{(2,1)}$	0.0445 [Corr=0.0407]	-0.228, 0.327	-	

Source: Applicant's ER Report, Tables S29 and S30.

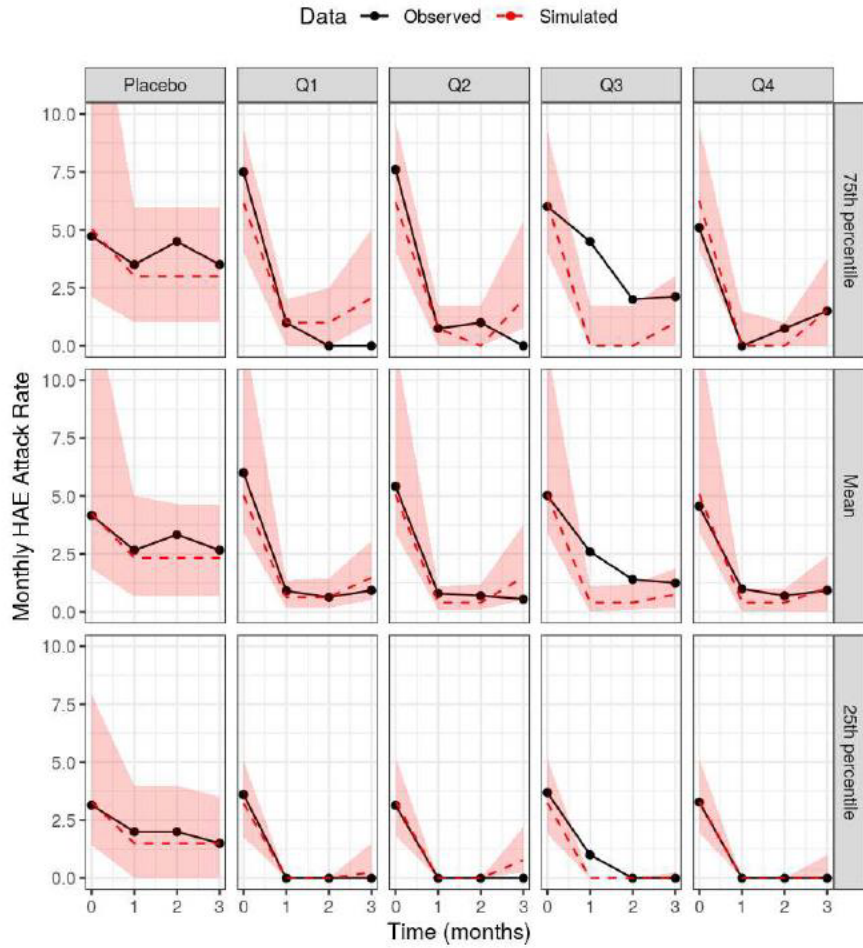
Confidence intervals based on 2.5th and 97.5th percentiles of sampling importance sampling resample.

CV% of log-normal omegas= $\sqrt{\exp(\text{estimate}) - 1}$ 100.

Abbreviations: BL, baseline; CI, confidence interval; corr, correlation coefficient; CV, coefficient of variation; ER, exposure-response; FXII, Factor XII; HAE, hereditary angioedema

Figure 57. Applicant-Final Model VPC: Monthly HAE Attack Rate Versus Time Stratified by Study and Quartiles of $AUC_{\tau,ss}$ at 3 Months

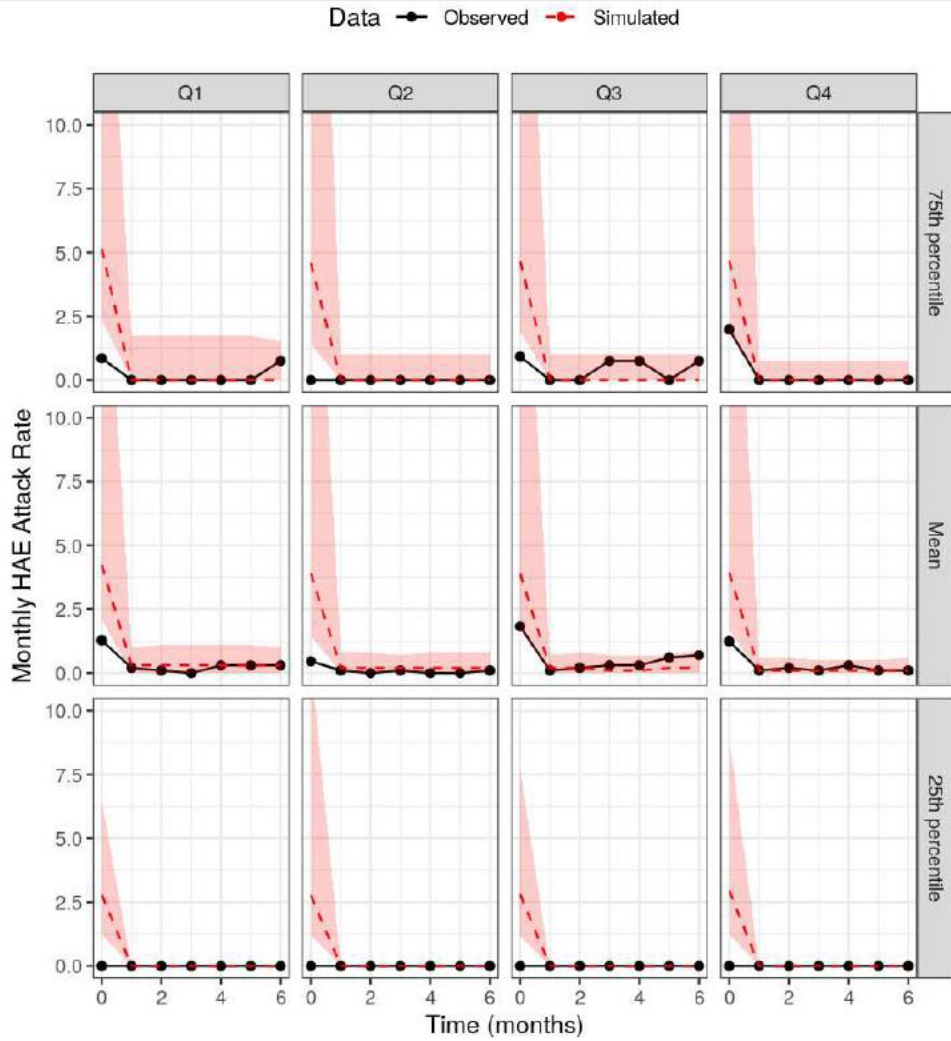
A: Trial 2001 Treatment Period 1 stratified by quartiles of $AUC_{\tau,ss}$ at 3 months



Source: Applicant's ER Report, Figure S74.

Abbreviations: AUC, area under the concentration-time curve; CSL312, garadacimab; HAE, hereditary angioedema; Q, quartile; VPC, visual predictive check

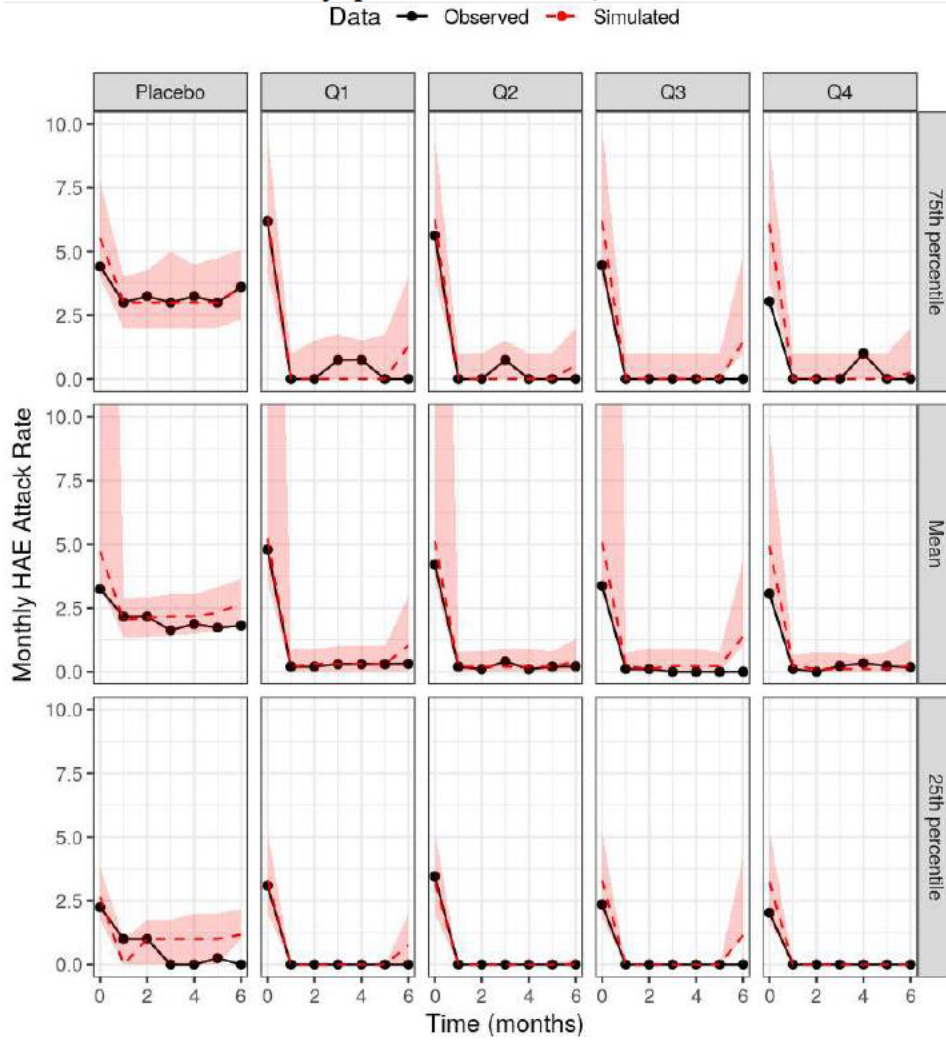
B: Trial 2001 Treatment Period 2 stratified by quartiles of $AUC_{\tau,ss}$ at 3 months



Source: Applicant's ER Report, Figure S76.

Abbreviations: AUC, area under the concentration-time curve; CSL312, garadacimab; HAE, hereditary angioedema; Q, quartile

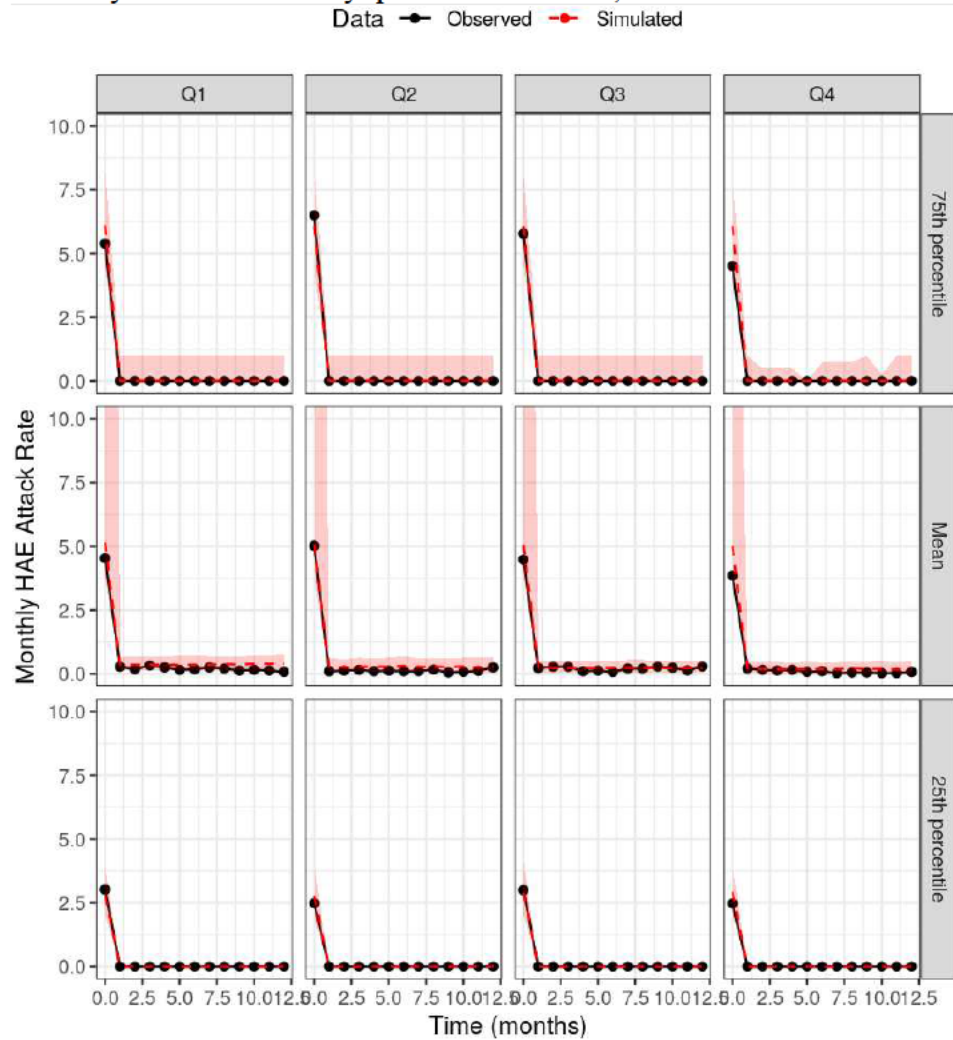
C: Trial 3001 stratified by quartiles of $AUC_{\tau_{ss}}$ at 3 months



Source: Applicant's ER Report, Figure S78.

Abbreviations: AUC, area under the concentration-time curve; CSL312, garadacimab; HAE, hereditary angioedema; Q, quartile

D: Study 3002 stratified by quartiles of $AUC_{\tau_{0.5,ss}}$ at 3 months

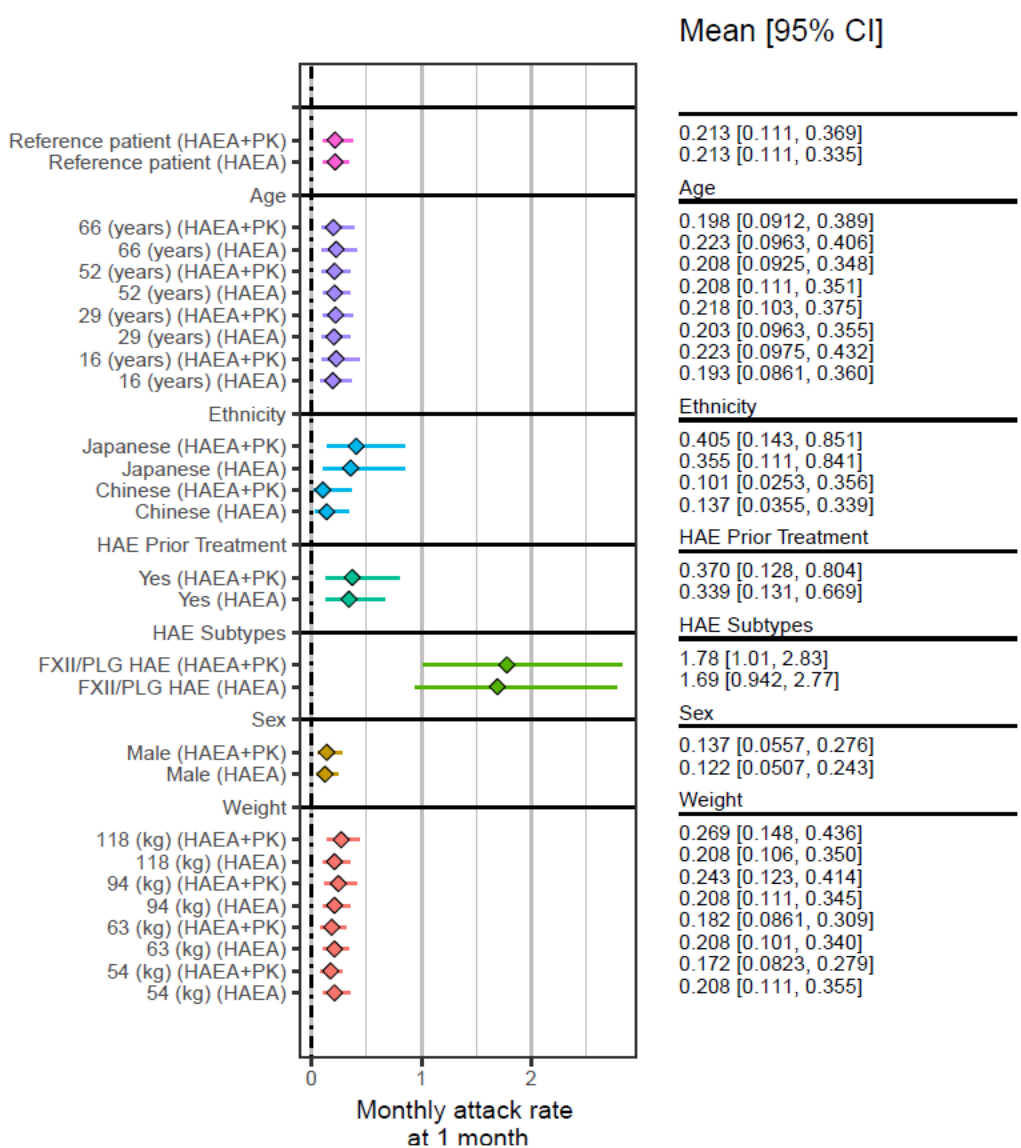


Source: Applicant's ER Report, Figure S80.

The lines represent the mean, 25th or 75th percentiles of the observed (solid black) and simulated (dashed red) data. The red shaded regions represent the 95% confidence intervals of the corresponding mean and percentiles.

Abbreviations: AUC, area under the concentration-time curve; CSL312, garadacimab; HAE, hereditary angioedema; Q, quartile

Figure 58. Applicant-Forest Plots: Conditional Simulations of Monthly Attack Rate at Month 1 With Fixed Covariate Levels

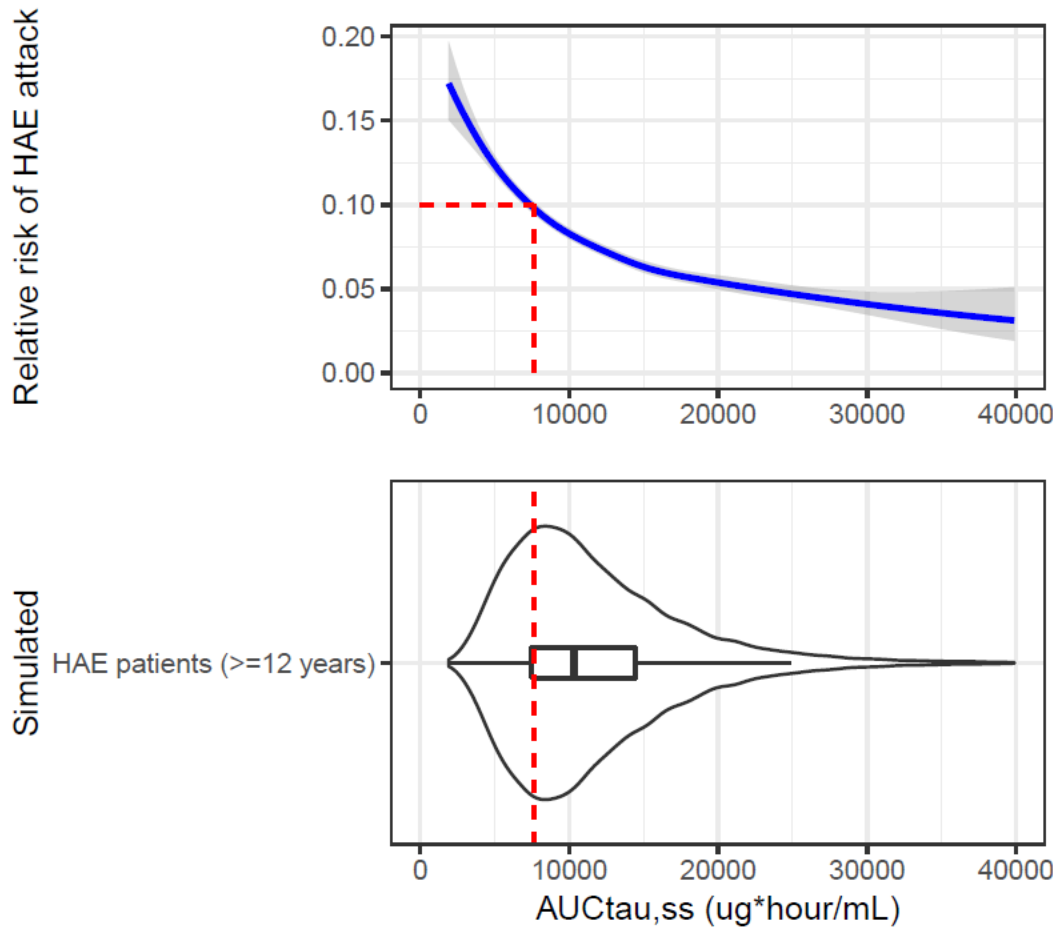


Source: Applicant's ER Report, Figure S156.

Points and lines indicate the mean and 95% PI for the mean monthly attack rate. Covariates are fixed at the indicated levels in either the HAE attack model alone (HAEA), in which case PK assumes the reference patient, or in both the HAEA and PK model. PK is simulated at steady-state with a SC 400 mg loading dose and 200 mg SC once monthly maintenance dose. Continuous covariate levels correspond to the 5th, 25th, 50th, 75th, and 95th percentiles of the covariate in the analysis population.

Abbreviations: CI, confidence interval; ER, exposure-response; FXII/PLG, Factor XII/plasminogen; HAE, hereditary angioedema; PK, pharmacokinetics; SC, subcutaneous

Figure 59. Applicant Population Simulations: HAE Relative Risk by $AUC_{\tau,ss}$ in the Adolescent and Adult Populations



Source: Applicant's ER Report, Figure S162.

In the top panel, the simulated mean HAE relative risk is shown as the blue line with an approximate 95% CI for the mean in grey. The second panel shows the density of simulated $AUC_{\tau,ss}$ in which the boxplot indicates the 25th, 50th, and 75th percentiles with whiskers extending to 1.5× IQR. The dashed red line indicates the exposure threshold corresponding to a 10% relative risk of HAE attack.

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; ER, exposure-response; FXII/PLG, Factor XII/plasminogen; HAE, hereditary angioedema; IQR, interquartile range

14.5.2.3. ER (Safety) Executive Summary

Given a favorable safety and tolerability profile for garadacimab, the Applicant did not conduct exposure-response analysis for safety.

14.5.2.4. ER (Safety) Assessment Summary

Exposure-response (safety) analysis was not conducted as garadacimab has a favorable safety and tolerability profile.

In general, the Applicant's E-R analyses for garadacimab are considered acceptable for the purpose of supporting analyses objectives. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

14.5.2.5. ER Review Issues

No substantive issue.

14.5.2.6. Reviewer's Independent Analysis

Reviewer's independent analysis was not performed.

14.6. Pharmacogenetics

See Section [6.3.2](#).

15. Additional Study/Trial Design Information

15.1. Trial 3001: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Arm Study To Investigate the Efficacy and Safety of Subcutaneous Administration of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema

Applicant:	CSL Behring, LLC
Drug name:	CSL312 (garadacimab)
Indication:	Prophylaxis to prevent attacks of HAE in subjects 12 years and older
Source of information:	CSL312_3001 Clinical Study Protocol (dated August 4, 2020); CSL312_3001 Clinical Study Report (dated October 6, 2022; submitted June 28, 2023); CSL312_3001 Statistical Analysis Plan (dated April 21, 2021)
Trial identifier:	VANGUARD
Protocol number:	CSL312_3001
Clinical phase:	Phase 3
EudraCT number:	2020-000570-25
IND number:	139936
ClinicalTrial.gov identifier:	NCT 04656418
Ethics:	The clinical study protocol and all amendments were approved by the independent ethics committees/institutional review boards of the participating centers. The study was carried out in accordance with the ICH of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice guidelines, and the ethical principles that have their origin in the Declaration of Helsinki.
Trial centers:	Germany, Israel, United States, Canada, Netherlands, Japan, and Hungary
Planned duration of main phase:	6 months
Trial status:	Completed
Trial start date:	January 27, 2021
Trial completion date:	June 7, 2022

Applicant:	CSL Behring, LLC
Data of database lock:	June 24, 2022

15.1.1. Definition and Collection of HAE Attacks, Trial 3001

The following items pertaining to an acute HAE attack event, including start and end dates and times, were recorded by subjects during the study in an eDiary: HAE attack onset and resolution, HAE symptoms (with location), use of on-demand therapy or medical assistance to treat HAE symptoms, and interference with daily activities. Participants were encouraged to notify and report HAE attacks to the study site within 72 h of symptom onset. HAE attacks were confirmed by the investigator after reviewing the eDiary data at each visit and collecting any additional missing or relevant information. Per the clinical study protocol (dated August 4, 2020), investigator-confirmed HAE attacks were defined as meeting all of the following criteria:

- Associated with at least one symptom or location (see [Table 108](#)).
- Separated from the previous attack by a minimum of 24 h without symptoms.
- Consisted of symptoms typical of an HAE attack and not just prodromal symptoms.
- Lacked an alternative cause for the symptoms.
- Lacked use of on-demand medication to only treat prodromal symptoms.

Table 108. Symptoms and Locations Associated With an HAE Attack

	Peripheral Attack Symptoms (cutaneous)	Abdominal Attack Symptoms	Laryngeal Attack Symptoms
Locations	• head • face (external): lips, nose, cheeks or eyes • neck • arms/hands • chest, shoulder or back • external abdominal area • external genitourinary areas (buttocks) • legs/Feet • Others	• internal abdomen (including, but not limited to, the intestine, the bladder, and / or testicles or uterus) • internal genitourinary (including, but not limited to, the penis and/or scrotum, or the labia and/or vulva)	Face internal or upper airway/throat • tongue / palate/inside mouth • nasal cavity • throat / voice box • uvula • larynx
Symptoms	• pain / discomfort • skin swelling • itching / irritation • tight skin • burning • redness / rash	• pain / cramping / discomfort • vomiting/nausea • abdominal swelling / bloating /tightness / hard stomach • diarrhea • gassy • low blood pressure • pass out/feel dizzy	• difficult breathing (dyspnea), speaking, or swallowing • voice change • stridor / wheezing • throat tightening • turning blue

Source: Clinical Study Protocol (dated August 4, 2020), Table 1, p. 113.
 Abbreviations: HAE, hereditary angioedema

15.1.2. Data and Safety Monitoring Committee, Trial 3001

An independent data monitoring committee (IDMC) was established to monitor the safety and efficacy data generated during the trial. The IDMC was comprised of an independent, unblinded statistician and independent clinical specialists in the fields of HAE management who have experience in clinical trials. The IDMC reviewed accumulating data during the study in an unblinded manner to advise on the further conduct of the study. No success or futility thresholds were established for IDMC reviews (the Applicant would not stop the study unless a major safety issue was identified). No safety concerns were identified during the IDMC meetings, and the IDMC recommended that the study continue as planned.

15.1.3. Sample Size Considerations, Trial 3001

The Applicant determined that 40 subjects (allocated 3:2 to garadacimab: placebo) with C1-INH (Type I or Type II) HAE completing the 6-month Treatment Period would be needed to achieve a power of approximately 90% via a two-sided Wilcoxon test at $\alpha=5\%$. Monthly HAE attack rates of 0.3125 and 1.3 were assumed for the garadacimab and placebo arms (equivalent to a 76% reduction relative to placebo) and were assumed to be Poisson distributed (the assumed monthly attack rates were used as the two means of the Poisson distributions).

The assumed attack rate for the garadacimab arm was based on the results of Treatment Period 1 in the phase 2 trial (2001; see Section [16.1](#)), where the mean of the individual attack rates for the 24 subjects who were administered 75 mg, 200 mg, or 600 mg garadacimab was calculated as 0.3125 attacks per month. To be conservative, the mean attack rate of the three pooled doses was used instead of the mean attack rate for only the 200 mg garadacimab arm, as the 200 mg garadacimab arm showed the highest treatment effect among the three doses. The assumed attack rate for the placebo arm was based on a publication of a prior phase 3 study of lanadelumab (not conducted by the Applicant) for the prevention of HAE attacks ([Banerji et al. 2018](#)), where an attack rate of 0.3 attacks per week was assumed (which is equivalent to 1.3 attacks per month).

The Applicant performed the sample size calculation for this study using the “proc power” procedure in SAS (version 9.4), which uses the O’Brien-Castelloe approach to compute the approximate power. The randomization ratio of 3:2 was implemented by using “GROUPNS=(24 16)”, resulting in a total sample size of 40, which was the lowest one reaching a power of 90%.

To allow for sufficient safety data, to increase the likelihood of adolescents entering the study, and to have at least 40 subjects reaching the end of the study, an additional 20 subjects were planned to be randomized (for a total planned sample size of about 60 subjects). The Applicant also aimed to randomize approximately 5 adolescent subjects and approximately 5 Japanese subjects among the 60 total subjects.

The study included a total of 64 subjects (39 on garadacimab and 25 on placebo) and met the Applicant’s main enrollment goal (though one subject on placebo was excluded from efficacy analyses due to receiving less than 30 days of study treatment). The Applicant also met their other enrollment goals (6 adolescent subjects and 6 Japanese subjects were included in the study).

The sample size for this phase 3 trial was comparable to prior similar HAE programs and was generally reasonable, as HAE is a rare condition.

15.1.4. Changes to the Planned Analyses, Trial 3001

The Applicant made the following changes prior to database lock in relation to the prespecified analyses in the original clinical study protocol (dated August 4, 2020):

1. Estimand definitions were updated to reflect the potential impact of the COVID-19 pandemic

No subjects discontinued treatment or the study as a result of the COVID-19 pandemic.

1. Comparison of the distribution of responses to therapy (via the Subject's Global Assessment of Response to Therapy (SGART)) between the garadacimab and placebo arms at the end of the 6-month Treatment Period used data at Visit Day 182 only. A two-sided chi-squared test at $\alpha=5\%$ was used. If a subject's SGART value at Visit Day 182 was missing, then the subject was not included in the exploratory analysis.
2. Definitions for H02 and H04 were modified.
3. For the primary estimand, the intercurrent event of early discontinuation due or not due to COVID-19 was removed.

The Applicant removed this intercurrent event per FDA feedback, as the Agency did not consider this to be an intercurrent event.

1. Exploratory analyses of patient-reported outcome endpoints (the angioedema quality of life, EQ-5D-5L, Work Productivity and Activity Impairment, and Investigator's Global Assessment of Response to Therapy) were conducted in the intent-to-treat (ITT) Analysis Set rather than the Safety Analysis Set.

No changes were made to the Applicant's prespecified analyses after database lock. However, the following additional analyses were conducted after database lock:

1. The time-normalized number of HAE attacks within 3 months before Screening for subjects with and without HAE prophylaxis during 3 months before Screening (for HAE history using the ITT Analysis Set).
2. The time-normalized number of HAE attacks during the 3 months before Screening or start of HAE prophylaxis (for HAE history using the ITT Analysis Set).
3. The time-normalized number of HAE attacks per month for the first and second 3 months of treatment in the ITT Analysis Set using a generalized linear model for count data assuming a Poisson distribution.
4. The time-normalized number of HAE attacks per month requiring on-demand therapy in the ITT Analysis Set using a Poisson modeled structured similarly to the Applicant's sensitivity analysis for the primary endpoint described in Section [6.2.3.2](#), where the baseline attack rate only included HAE attacks that required on-demand therapy during the Run-in Period.
5. The time-normalized number of moderate or severe HAE attacks per month in the ITT Analysis Set using a Poisson modeled structured similarly to the Applicant's sensitivity analysis for the primary endpoint described in Section [6.2.3.2](#), where the baseline attack rate only included HAE attacks that were moderate or severe during the Run-in Period.

The results of analyses #4 and #5 above were submitted by the Applicant at the Agency's request during the review cycle. The results of these analyses can be found in Section [6.2.4.5](#).

15.1.5. Protocol Amendments, Trial 3001

The original clinical study protocol (dated August 4, 2020) had no substantial amendments and had one administrative amendment (dated December 8, 2020) that only added clarification of an exclusion criterion related to use of contraception. A Japanese version of the protocol (dated January 15, 2021) was created to include study sites in Japan, which contained several minor administrative adjustments required for compliance with local regulations in Japan.

None of the above changes substantially impacted the study design or results.

15.1.6. Safety Assessments, Trial 3001

Safety assessments included AE reporting, laboratory parameters (clinical chemistry, hematology, coagulation, urinalysis), vital signs, physical examinations, and EKG testing according to the Schedules of Assessments (see [Figure 60](#) and [Figure 61](#)). Labs were collected at baseline and Months 3 and 6. Subjects had an additional lab collection on Day 1 if baseline labs were collected more than 90 days prior to the first dose of garadacimab administration. Pregnancy tests, urinalyses, and hematology, chemistry, and coagulation labs were processed at a central laboratory. Overall, the safety monitoring in trial 3001 was adequate to inform the safety profile of garadacimab for the proposed use.

Study Period	Treatment Period ^a						End of Treatment Period ^{b,c}	Follow-up ^d /Final Visit
	1	2	3	4	5	6		
Month	1 / 1	31 / 2	61 / 3	91 / 4	121 / 5	151 / 6	182	242
Visit Day / Dose Number	1 / 1	31 / 2	61 / 3	91 / 4	121 / 5	151 / 6	182	242
Visit Window (Days)	NA	± 4d	± 4d	± 4d	± 4d	± 4d	± 4d	-14d
Confirm access to on-demand HAE medication ^e	X	X	X	X	X	X	X	
IRT investigational product kit assignment	X	X	X	X	X	X		
SC administration of investigational product	X ^g	X ^h	X ^h	X ^h	X ^h	X ^h		
Investigational product accountability	X	X	X	X	X	X		
Offer subject option to enroll in Study CSL312_3002						X ⁱ		

Angioedema QoL = Angioedema Quality of Life; C1-INH = C1-esterase inhibitor; C4 = complement C4; d = day; ECG = electrocardiogram; eCOA = electronic clinical outcomes assessment; eDiary = electronic diary; EQ-5D-5L = EuroQoL-Group 5-Dimension 5-Level; FXII = Factor XII; FXIIa = activated Factor XII; HAE = hereditary angioedema; ICF = informed consent form; IGART = Investigator's Global Assessment of Response to Therapy; IRT = interactive response technology; NA = not applicable; PK / PD = pharmacokinetic / pharmacodynamics; PRO = patient-reported outcomes; SC = subcutaneous; SGART = Subject's Global Assessment of Response to Therapy; WPAL:GH = Work Productivity and Activity Impairment: General Health.

^a Treatment Period Visits had ± 4 day window, with a maximum of 33 days between any 2 consecutive doses.

^b The Day 182 End of Treatment Period Visit corresponded to the first day of the open-label phase 3b study for subjects rolling over into Study CSL312_3002. Subjects entered Study CSL312_3002 after completing the Day 182 assessments and signing the ICF for Study CSL312_3002. Subjects who did not enter Study CSL312_3002 were required to complete the Day 242 study visits after completing the Day 182 assessments.

^c Subjects who terminated early from the study (ie, before Day 182) underwent the assessments specified for the End of Treatment Visit (Day 182), if possible.

^d Subjects who did not enter Study CSL312_3002 were required to complete the Follow-up Visit. The in-person Follow-up Visit could have been waived in place of a telephone contact during which information about adverse events and concomitant therapies / medications was collected. If the Follow-up Visit was conducted as an in-person visit, then a blood draw for assessment of PK / PD and immunogenicity occurred, as well as collection of information about adverse events, concomitant therapies / medications.

^e Subjects were eligible to exit in the Run-in Period and enter the Treatment Period after completing at least 1 month of the Run-in Period and experiencing at least 2 HAE attacks. C1-INH functional activity and antigen, and C4 antigen concentration levels were confirmed before randomization into the Treatment Period. Eligibility was confirmed before randomization and any study assessments were performed.

^f The urine test for beta-human chorionic gonadotropin was performed for sexually active women of childbearing potential (only). A serum pregnancy test was performed by the site if urine result was inconclusive.

^g A physical examination was conducted per the investigator's standard procedure and also included assessment of unilateral pain and / or swelling of the lower extremities for the purpose of screening for deep vein thrombosis.

^h At visits, administration of investigational product occurred after physical examinations, vital signs, body weight, and pregnancy tests were completed.

ⁱ Standard 12-lead ECGs were performed.

^j Assessments could have been omitted if Screening / Run-in Period assessments occurred within the previous 3 months.

^k Blood samples for potential future assessment of HAE biomarkers were obtained during the Treatment Period. These samples were stored for potential testing of HAE biomarkers and will be destroyed within 5 years after completion of the study or used for future research on HAE. These samples were not collected in adolescents.

^l Blood sample for PK included CSL312 concentration and blood sample for PD included FXII concentration and FXIIa-mediated kallikrein activity.

^m Blood sample for binding antibodies (inhibitory and non-inhibitory) specific to FXIIa inhibitor monoclonal antibody (anti-CSL312).

ⁿ The following patient-related outcomes were entered at specified study site visits before any other interaction with the subject about their health status and before review of the eDiary: Angioedema QoL, EQ-5D-5L, WPAL:GH, and SGART.

^o Investigator completed IGART in RAVE. Subjects completed SGART.

^p Only applicable for subjects who did not roll over to Study CSL312_3002.

^q The eDiary was collected and deactivated on Day 182 for subjects rolling over to Study CSL312_3002 and on Day 242 for all other subjects. For subjects who terminated the study early, the eDiary was deactivated and collected either on date of early termination or at the Follow-up Visit as applicable. If the Follow-up Visit was conducted remotely, the device should have been returned to the site.

^r Berinert was the suggested on-demand medication for use during this study. Subjects could use the on-demand medication of their choice to treat HAE attacks experienced during the study if that medication had previously been shown to be effective.

^s The first dose of investigational product was a loading dose consisting of either 2 SC injections of 200 mg CSL312 each for a total of 400 mg CSL312 (Active Arm) or 2 SC injections of volume-matched placebo (Placebo Arm) administered by the investigator or delegate at the study site.

^t Investigational product administration consisting of either 1 200 mg CSL312 SC injection (Active Arm) or 1 SC injection of volume-matched placebo (Placebo Arm) could have been self-administered by the subject under the supervision of the investigator or delegate at the study site.

Source: Phase 3 Clinical Trial Protocol, p. 13.

15.1.7. Grading of Adverse Events, Trial 3001

Table 109. Grading Scale for Adverse Event Severity in Trial 3001

Severity	Definition
Mild	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Source: CDISC SDTM Severity Intensity Scale for Adverse Event Terminology, phase 3 Clinical Trial Protocol, p. 80.
Abbreviations: AE, adverse event; CDISC, Clinical Data Interchange Standards Consortium; SDTM, Study Data Tabulation Model

15.2. Study 3002: An Open-Label Study To Evaluate the Long-Term Safety and Efficacy of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema

Applicant:	CSL Behring, LLC
Drug name:	Garadacimab
Indication:	Prophylaxis to prevent attacks of HAE in subjects 12 years and older
Source of information:	CSL312_3002 Interim Clinical Study Report (dated August 10, 2023); CSL312_3002 Statistical Analysis Plan (dated June 25, 2021)
Trial identifiers	
Protocol number:	CSL312_3002
Clinical phase:	Phase 3b (open-label study)
EudraCT number:	2020-003918-12
IND number:	139936
ClinicalTrial.gov identifier:	NCT04739059
Ethics:	The clinical study protocol and all amendments were approved by the independent ethics committees/institutional review boards of the participating centers. The study was carried out in accordance with the ICH of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice guidelines.
Trial centers:	Australia (4 centers), Canada (5 centers), Czech Republic (2 centers), Germany (5 centers), Hong Kong (1 center), Hungary (1 center), Israel (1 center), Japan (10 centers), Netherlands (1 center), New Zealand (1 center), Russia (1 center), Spain (2 centers), Taiwan (1 center), and the United States (12 centers)
Planned duration of main phase:	At least 12 months
Trial status:	Ongoing

Applicant:	CSL Behring, LLC
Trial start date:	March 29, 2021
Trial completion date:	November 2025 (anticipated)
Date of database lock:	February 13, 2023 (all subjects except adolescents); May 22, 2023 (adolescents only)

15.2.1. Study Design, Study 3002

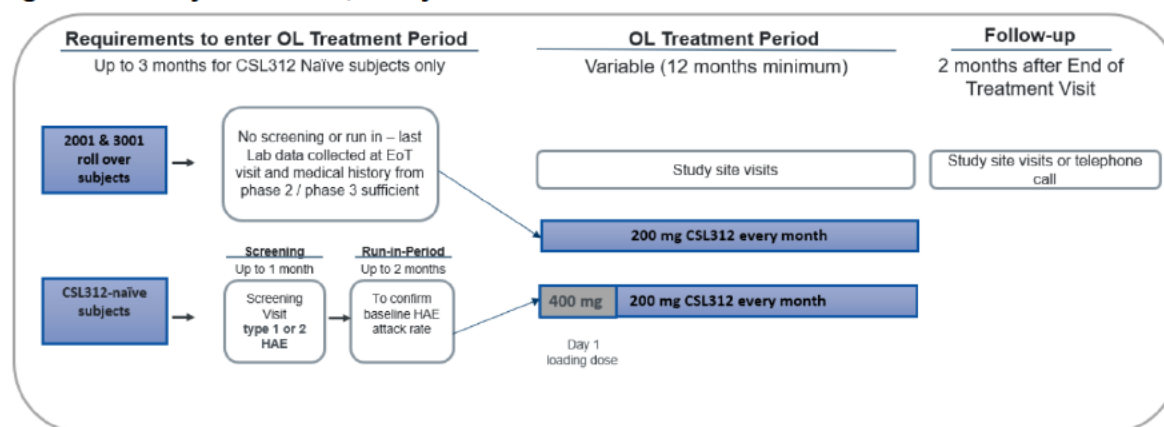
Study 3002 was a multicenter, open-label, phase 3b study to investigate the long-term safety and efficacy of garadacimab when administered once monthly for at least 12 months. Subjects eligible to participate in this study were:

- Subjects from the phase 2 trial (2001).
- Subjects from the phase 3 trial (3001).
- Garadacimab-naïve subjects (i.e., newly enrolled subjects with C1-INH [Type I or Type II] HAE).

The study comprised four periods (see [Figure 62](#)):

- Screening Period (up to 1 month; for garadacimab-naïve subjects).
- Run-in Period (up to 2 months; for garadacimab-naïve subjects).
- Treatment Period (12 months minimum; open-label).
- Follow-up Period (2 months after End of Treatment [EoT] Visit).

Figure 62. Study Schematic, Study 3002



Source: Interim Clinical Study Report (dated August 10, 2023), Figure 9-1, p. 19.
Abbreviations: CSL312, garadacimab; EoT, end of treatment; HAE, hereditary angioedema; OL, open-label

Following informed consent, garadacimab-naïve subjects underwent a Screening Period of up to 1 month to determine eligibility for enrollment in the study. Screened subjects who met all inclusion criteria, and none of the exclusion criteria, entered the Run-in Period. If a subject did not meet the criteria for entering the Run-in Period within 30 days, the subject could have been rescreened once.

After Screening, eligible subjects entered the Run-in Period lasting at least 1 month and up to 2 months to confirm underlying disease status and to assess eligibility for participation in the Treatment Period. The first day of the Run-in Period could have occurred on the same day as Screening. Subjects had to experience ≥ 2 HAE attacks during the Run-in Period to be eligible to enter the Treatment Period. Subjects who experienced ≥ 2 HAE attacks during the required first month of the Run-in Period could immediately enter the Treatment Period. Subjects who did not experience an HAE attack during the first month of the Run-in Period remained in the Run-in Period for up to 2 months, during which time they were required to experience ≥ 2 HAE attacks to be eligible to enter the Treatment Period. If a subject was unable to enter the Treatment Period after Day 60, then approval from the Applicant was required for the subject to extend the Run-in Period for another month to enter the Treatment Period within 3 months. Subjects were prohibited from using routine prophylaxis to prevent HAE attacks during the Run-in Period; however, subjects could have used on-demand HAE therapy (i.e., C1-INH replacement or icatibant or ecallantide) to treat HAE attacks if the medication was previously shown to be effective. Subjects who did not meet the minimum HAE attack rate during the Run-in Period or were otherwise determined to be ineligible due to Screening assessments were considered Run-in failures and were not rescreened.

Subjects meeting all eligibility criteria entered the Treatment Period after the Run-in Period. If a subject was unable to enter the Treatment Period after Day 60, then approval from the Applicant was required for the subject to enter the Treatment Period. During the Treatment Period, subjects were assigned to 200 mg garadacimab administered SC once per month. For garadacimab-naïve subjects, a loading dose of 400 mg garadacimab (two 200 mg doses) was administered SC on Visit Day 1, then 200 mg per month in subsequent months. The Treatment Period had a variable duration for individual subjects; however, each subject received garadacimab for at least 12 months.

For the Follow-up Period, subjects were contacted approximately two months after their EoT Visit to complete final study assessments.

For details regarding the collection and reporting of HAE data, and the investigator confirmation of HAE attacks, see Section [15.1.1](#).

15.2.1.1. Sample Size Assumptions, Study 3002

Approximately 150 subjects (including 8 Japanese subjects) were planned to be enrolled in the study, with a minimum of 100 subjects having at least 12 months of exposure to garadacimab. Since this was an open label, single-arm study with no control arm, the sample size for this study was not based on a formal calculation but on the International Council for Harmonisation guidance, *E1A The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* ([October 1995](#)). The Applicant claimed that a sample size of 100 subjects would allow for the observation of ≥ 1 AE with a probability of 3% at a 95% confidence level.

15.2.2. Schedule of Assessments, Study 3002

During the Treatment Period of study 3002, subjects received garadacimab 200 mg SC every month. Study visits, vitals, physical examinations, laboratory monitoring, and AE monitoring for

rollovers and garadacimab-naïve subjects are shown in [Figure 63](#) and [Figure 64](#). The trial 3001 rollovers and garadacimab-naïve subjects received laboratory assessments on Day 1, Month 3, Month 6, Month 12, and every 6 months thereafter ([Figure 63](#)). The trial 2001 rollover subjects received laboratory assessments on Day 1, Month 6, Month 12, and every 6 months thereafter ([Figure 64](#)). The laboratory assessments were collected at 6-month intervals for the trial 2001 rollovers as those subjects had already received garadacimab every 4 weeks for about 1 year. The laboratory analyses were conducted at a central laboratory. The schedules of assessments are acceptable for a phase 3, open-label extension study.

Figure 63. Schedule of Assessments for Rollover Subjects from Parent Trial 3001 and Garadacimab-Naïve Subjects, Study 3002

Study Period	Treatment Period										EoT ^a	Final Visit ^b / Follow-up (2 months after EoT Visit)
	Month	1	2	3	6	9	12	18	24	30		
Visit Day	1	31	61	91	181	271	361	541	721	901		
Visit Window (Days)		± 4d ^c	± 4d ^c	± 4d ^c	± 4d ^c	± 4d ^c	± 4d ^c	± 4d ^c	± 4d ^c	± 4d ^c		± 7d
Study center visit	X	X	X	X	X	X	X	X	X	X	X	
Written informed consent for CSL312_3001 subjects	X											
Confirm eligibility for Treatment Period ^d	X											
Physical examination ^e	X	X	X	X	X	X	X	X	X	X	X	
Vital signs including body weight and height ^f	X	X	X	X	X	X	X	X	X	X	X	
SGART and IGART ^g							X		X			
TSQM II (subjects ≥ 18 years), Angioedema-QoL (subjects ≥ 18 years) & WPAI:GH (subjects ≥ 16 years) ^h	X			X	X	X	X	X	X			
Urine collection for urinalysis (central lab)	X				X		X	X	X	X	X	
Blood Draws ⁱ (central lab)	Hematology / Biochemistry / Coagulation	X			X	X		X	X	X	X	X
	Retention sample for HAE biomarkers ^j	X	X	X	X	X	X	X	X	X	X	X
	Pharmacokinetics / Pharmacodynamics	X	X	X	X	X	X	X	X	X	X	X
	Immunogenicity	X				X		X		X		X
Pregnancy test ^k	X	X	X	X	X	X	X	X	X	X	X	
PRO / eCOA tablet training	X											
Review of eDiary instructions with subject	X											
Review eDiary data and assess / document HAE attacks	X	X	X	X	X	X	X	X	X	X	X	X
eDiary deactivation ^l												X
Confirm access to on-demand HAE medication ^m	X	X	X	X	X	X	X	X	X	X		
IRT CSL312 kit assignment	X	X	X	X	X	X	X	X	X	X		
Accountability of CSL312	X	X	X	X	X	X	X	X	X	X	X	
Administration of CSL312 at site ^{n,o}	X	X	X	X								

Primary Endpoint: frequency of TEAEs.

Secondary Endpoints: The secondary objectives of this study were to evaluate long-term safety and efficacy, including patient-reported assessment of response to therapy.

- Serious adverse events
- Deaths
- Related TEAEs
- TEAEs leading to study discontinuation
- TEAEs by severity
- Anti-garadacimab antibodies
- Laboratory findings reported as an AE
- Adverse events of special interest (thromboembolic events, abnormal bleeding events, and severe hypersensitivity including anaphylaxis events)
- TEAEs among C1-INH subjects
- Time-normalized number of HAE attacks per month
- Reduction in the monthly attack rate during the Treatment Period compared to the Run-in Period
- Time-normalized number of HAE attacks per month requiring on-demand treatment
- Time-normalized number of moderate and/or severe HAE attacks per month
- SGART responses of *good* or *excellent* at the end of the Treatment Period

The exploratory objectives of this study were to evaluate the efficacy and quality-of-life (QoL) associated with the use of garadacimab in subjects with HAE. PK and PD were also assessed.

Exploratory Endpoints

- Time to first HAE attack after Day-1 administration (after Day-14 administration for garadacimab-naïve subjects).
- Quality-of-life questionnaires:
 - Angioedema Quality of Life Questionnaire.
 - Work Productivity and Activity Impairment: General Health.
 - Treatment Satisfaction for Medication Questionnaire II.
 - Investigator’s Global Assessment of Response to Therapy.
- PK/PD parameters.

15.2.4. Analysis Populations, Study 3002

The following analysis sets were defined by the Applicant in the final statistical analysis plan (statistical analysis plan (SAP); version 1.0; dated June 25, 2021):

Screened Analysis Set: All subjects who provided written informed consent.

All Treated Subjects Analysis Set: All subjects in the Screened Analysis Set who were assigned to treatment. The All-Treated Subjects (ATS) Analysis Set was analyzed using the treatment to which the subject was assigned, regardless of the treatment actually received. This was the main set used for efficacy analyses.

Safety Analysis Set: All subjects in the ATS Analysis Set who received at least 1 dose of investigational product. The Safety Analysis Set was analyzed using the actual treatment received (the actual treatment was planned to be garadacimab for all subjects, but the dose level could have been incremented from the initially planned 200 mg). This was the main set used for safety analyses.

Per Protocol Analysis Set: All subjects in the ATS Analysis Set who received at least one dose of investigational product and who complied with the protocol. Decisions regarding exclusion from the Per Protocol Analysis Set were planned to be made and documented before database lock.

15.2.5. Time Point Description, Study 3002

AEs, HAE attacks, laboratory data, vital signs, and other measurements were assigned to the Applicant-defined study periods shown below in [Table 110](#).

Table 110. Definitions of Study Periods (Study 3002)

Period	Start Date	End Date
Screening Period	Date of Informed Consent	Run-in Period Start Date
Run-in Period	Run-in Period Start Date	Day 1 Visit date of the Treatment Period or Date of Run-in Non-completion [whichever is first]
Treatment/Efficacy evaluation period	Date of Day 1 Visit of Treatment Period	Date of End of Treatment Visit or End of Study date [whichever is first]
Treatment/Efficacy evaluation period for up-titrated doses	Date of Day 1 Visit of Treatment Period (for 200mg CSL312) or Date of Dose Uptitration (for 400mg or 600 mg CSL312, respectively)	Date of next Dose Uptitration (from CRF) – 1 Day or Date of End of Treatment Visit or End of Study date [whichever is first]
Follow-up	Date of End of Treatment Visit	Date of Final/ Follow-up Visit
Safety Evaluation Period	Date and start time of First CSL312 Administration as entered in the eDiary	Date of Final/ Follow-up Visit

Source: Statistical Analysis Plan (version 1.0; dated June 25, 2021), Table 3, p. 27.
Abbreviations: CRF, case report form; CSL312, garadacimab

The efficacy periods for up-titrated doses only existed for subjects who had a dose increase. The safety evaluation period consisted of the Treatment/Efficacy evaluation period plus the Follow-

up period. Screening and Run-in periods were not performed for rollover subjects (instead, relevant endpoint data, such as HAE attacks during the Run-in Period, were used from trials 2001 and 3001). The durations of the Treatment/Efficacy and Safety evaluation periods (in days) were calculated as: End Date – Start Date + 1 Day. The durations of the Screening, Run-in, and Follow-up periods (in days) were calculated as: End Date – Start Date.

15.2.6. Primary Analysis Description, Study 3002

The primary endpoint of TEAEs was provided as number of subjects, percentage of subjects, and number of events. The TEAE rates per injection and per subject-year were also reported.

15.2.7. Secondary Efficacy Analysis Description, Study 3002

The secondary efficacy endpoints were analyzed using the ATS Analysis Set. The time-normalized number of HAE attacks was also analyzed using the Per Protocol Analysis Set.

For all analyses considering HAE attacks, only investigator-confirmed attacks were used. Subjects entered HAE symptoms into an eDiary (with the start and end date and time), along with location of HAE symptoms, use of on-demand therapy to treat HAE symptoms, and interference of HAE symptoms with daily activities. The investigator confirmed HAE attacks based on a review of the eDiary, relevant medical history, and physician judgment.

For garadacimab-naïve subjects, HAE attacks with a start date on or after the first day of the Run-in Period but prior to the date and time of the first study drug administration were counted for the Run-in Period. For subjects from the phase 2 (2001) or phase 3 (3001) trial, the number of HAE attacks during the Run-in Period of the previous study was used. HAE attacks with a start date and time after the first study drug administration through the EoT Visit were counted for the Treatment Period and were included in the efficacy analyses.

The time-normalized number of HAE attacks per month were calculated per subject as:

$$[\text{number of HAE attacks} \div \text{length of subject treatment in days}] \times 30.4375$$

Length of subject treatment in days was calculated as the duration of the Treatment/Efficacy evaluation period defined in [Table 110](#).

The time-normalized number of HAE attacks per month were summarized descriptively using the mean and median with corresponding 95% CIs.

Reduction in HAE attack rate during the Treatment Period compared to the Run-in Period was summarized descriptively as a percent reduction per subject, calculated as:

$$100\% \times (1 - [\text{time-normalized number of HAE attacks per month during treatment} \div \text{time-normalized number of HAE attacks per month during the Run-in Period}]).$$

The number and percentage of responders and nonresponders were also presented with corresponding 95% CIs. A subject was classified as a responder if their percent reduction in HAE attacks during treatment compared to the Run-in Period was $\geq 50\%$. The number and percentage of subjects with reductions of $\geq 70\%$, $\geq 90\%$, and 100% (i.e., attack-free during

treatment) were also reported with associated 95% CIs. Exact Clopper-Pearson CIs were used for all percentages.

The time-normalized number of HAE attacks per month requiring on-demand therapy was summarized descriptively, calculated per subject as:

$$\frac{\text{[number of HAE attacks requiring on-demand therapy]}}{\text{length of subject treatment in days}} \times 30.4375.$$

Length of subject treatment in days was calculated as the duration of the Treatment/Efficacy evaluation period defined in [Table 110](#).

The time-normalized number of moderate and/or severe HAE attacks per month was calculated and analyzed similarly to the total time-normalized number of HAE attacks per month (described above).

Finally, SGART results were presented descriptively by study visit where assessed. The number and percentage of subjects with each rating (“none”, “poor”, “fair”, “good”, or “excellent”) were reported, along with cumulative responses (“poor or better”, “fair or better”, and “good or excellent”). A two-sided 95% CI was reported for the percentages for each cumulative response category. An exploratory Friedman test at $\alpha=5\%$ was conducted to compare the percentage of subjects with responses of “good” or “excellent” between Visit Day 361 and Visit Day 721.

15.2.8. Sensitivity and Supportive Statistical Analyses Description, Study 3002

To evaluate the impact of the COVID-19 pandemic on the primary endpoint (safety), the overview of TEAEs was repeated as a sensitivity analysis excluding all TEAEs related to COVID-19. As a supportive analysis, a summary table of the TEAEs associated with COVID-19 was reported for subjects with C1-INH (Type I or Type II) HAE.

As supplementary analyses, all secondary endpoints (efficacy), except SGART, were assessed over time in 3-month (91-day) time windows with the first window starting on the Month 1, Day 1 Visit. The time-normalized number of HAE attacks and the time-normalized number of HAE attacks requiring on-demand therapy were also assessed from Visit Day 1 until Visit Day 31 of the Treatment Period. This was repeated for moderate and severe HAE attacks.

15.2.9. Changes to the Planned Analyses, Study 3002

The Applicant did not report any major changes to the analyses described in the final statistical analysis plan (SAP; version 1.0; dated June 25, 2021).

For the secondary safety endpoints, the Applicant planned to present tables for the C1-INH (Type I or Type II) HAE subjects, the non-C1-INH HAE subjects, and overall. Instead, only the summary of the TEAEs were presented for the three groups above, and all other secondary safety endpoints were presented for the overall study population only.

15.2.10. Interim Analyses, Study 3002

An initial interim analysis was planned to be conducted when approximately 100 subjects had 12 months of exposure to garadacimab in study 3002 alone or across all three studies (i.e., trials 2001 and 3001 and study 3002).

Results from a second interim analysis, completed after approximately 119 subjects had at least 12 months of exposure to garadacimab in study 3002 alone or across all three studies, are presented in the Applicant's Interim Clinical Study Report (dated August 10, 2023). The data cutoff dates for the second interim analysis were February 13, 2023 (for all subjects except adolescents) and May 22, 2023 (for adolescents).

Additional interim analyses were conducted on an as-needed basis to support regulatory activities. The results of the interim analyses were not intended to be used for stopping or adapting the study or adjusting the sample size.

15.2.11. Data and Safety Monitoring Committee, Study 3002

An IDMC was established to monitor the safety and efficacy data generated during the study. The IDMC reviewed accumulating data from the ongoing study. No success or futility thresholds were set for IDMC reviews. The Applicant planned to continue the trial unless a safety issue that warranted study termination was confirmed. The composition, activities, analysis, responsibilities, and timing of meetings of the IDMC were outlined in the IDMC Charter.

15.3. Trial 2001: A Multicenter, Randomized, Placebo-Controlled, Parallel-Arm Study To Investigate the Efficacy, Pharmacokinetics, and Safety of CSL312 in Subjects With Hereditary Angioedema

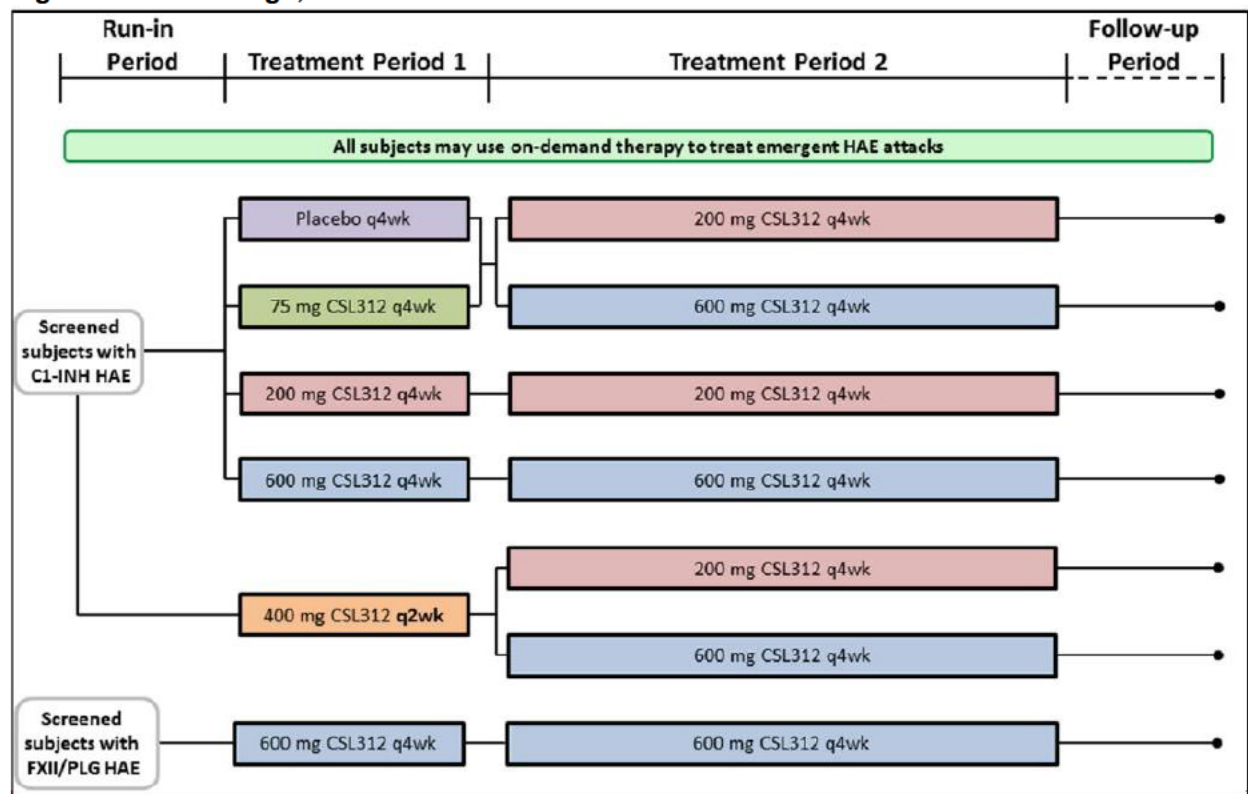
Applicant:	CSL Behring, LLC
Drug name:	Garadacimab
Indication:	Prophylaxis to prevent attacks of HAE in subjects 12 years and older
Source of information:	CSL312_2001 Clinical Study Protocol (dated May 30, 2018); CSL312_2001 Study Report (dated May 30, 2022); CSL312_2001 Statistical Analysis Plan (dated June 19, 2020)
Protocol number:	CSL312_2001
Clinical phase:	Phase 2
EudraCT number:	2018-000605-24
IND number:	139936
ClinicalTrial.gov identifier:	NCT03712228
Ethics:	The clinical study protocol and all amendments were approved by the independent ethics committees/institutional review boards of the participating centers. The study was carried out in accordance with the ICH of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice guidelines.

Applicant:	CSL Behring, LLC
Trial centers:	Australia, Canada, Germany, Israel, and the United States
Planned duration of main phase:	Treatment Period 1: 13 weeks Treatment Period 2: 44 weeks
Trial status:	Completed
Trial start date:	October 29, 2018
Trial completion date:	October 15, 2021
Data of database lock:	December 6, 2021

15.3.1. Trial Design, Trial 2001

Results from this study support the efficacy of garadacimab in preventing HAE attacks. This was a two-period (Treatment Periods 1 and 2), multicenter (10 U.S. sites and 9 ex-U.S. sites), randomized, placebo-controlled, parallel-group, dose-ranging, phase 2 trial among 38 adult subjects (20 to 65 years of age) with C1-INH (Type I or Type II) HAE or FXII/PLG (Type III) HAE. Treatment Period 1 was the randomized (1:1:1:1), double-blind, placebo-controlled, dose-ranging portion of the study, and Treatment Period 2 was an open-label portion (see [Figure 65](#)). Before entering the trial, subjects with Type I or Type II HAE had to demonstrate ≥ 4 HAE attacks over a consecutive 2-month period during the 3 months prior to Screening.

Figure 65. Trial Design, Trial 2001



Source: Study Report (dated May 30, 2022), Figure 9-1, p. 22
 Abbreviations: C1-INH, C1 esterase inhibitor; CSL312, garadacimab; FXII, Factor XII; HAE, hereditary angioedema; PLG, plasminogen; q2wk, once every 2 weeks; q4wk, once every 4 weeks

Subjects who provided written informed consent were screened for their eligibility to enter the Run-in Period. Screening was completed within 28 days before the first day of the Run-in Period.

After Screening, eligible subjects entered the Run-in Period, which lasted a minimum of 4 weeks and up to 8 weeks, to confirm their underlying disease status and to assess their eligibility for participation in Treatment Period 1. Subjects were not permitted to use routine prophylaxis to prevent HAE attacks during the Run-in Period, but subjects could use on-demand HAE therapy (i.e., C1-INH replacement or icatibant or ecallantide) to treat emerging HAE attacks. Subjects completed the Run-in Period and could begin Treatment Period 1 when the following criteria were met:

- Subjects with C1-INH (Type I or Type II) HAE must have experienced ≥ 2 HAE attacks within a consecutive 4-week period during the Run-in Period.
- Subjects with FXII/PLG (Type III) HAE must have experienced ≥ 1 HAE attack during the Run-in Period.

Subjects entered Treatment Period 1 no later than 14 days after the Week 9 (Day 57) telephone contact during the Run-in Period. If this was not possible for the subject, then approval was required from the Applicant.

In Treatment Period 1, 32 subjects were randomized 1:1:1:1 to receive 75 mg, 200 mg, or 600 mg garadacimab SC every 4 weeks for 13 weeks, or matched placebo. Additional subjects (N=6) were assigned to 400 mg garadacimab SC Q2W for 13 weeks (open-label). Subjects documented HAE attack onset, symptoms, and use of on-demand medications in an eDiary. During each visit, the Investigator reviewed the eDiary and documented HAE attacks.

Outside of the planned randomization algorithm, six subjects with Type III HAE were enrolled. These six subjects consisted of three subjects with FXII mutation and three with PLG mutation. Once the FXII/PLG (Type III) HAE subjects satisfied all Run-in Period criteria, they were directly assigned to receive 600 mg garadacimab SC every 4 weeks (open-label).

All subjects who participated in Treatment Period 1 were able to participate in Treatment Period 2, which lasted 44 weeks and was extended up until another garadacimab study was opened for subjects to join or until the current study was discontinued. In Treatment Period 2 (open-label), subjects either continued on their regimen (if they were already assigned to 200 mg or 600 mg garadacimab SC every 4 weeks in Treatment Period 1) or were moved to the 200 mg and 600 mg garadacimab arms. After the first planned interim analysis, it was determined that there was no difference in efficacy between the 200 mg and 600 mg garadacimab arms, but there were significantly more injection site reactions in the 600 mg garadacimab arm. Therefore, a protocol amendment in March 2020 reassigned all Type I and Type II HAE subjects to 200 mg garadacimab every 4 weeks. Subjects with Type III HAE continued on 600 mg garadacimab every 4 weeks.

The overall design was generally reasonable for a proof of concept, dose-ranging trial in a development program for an HAE prophylactic therapy.

15.3.2. Schedule of Assessments, Trial 2001

In Treatment Period 1 of trial 2001, subjects received garadacimab 75 mg or 200 mg or 600 mg or placebo SC every 4 weeks or 400 mg Q2W for 3 months. During Treatment Period 2 (open-label), subjects received garadacimab 600 mg or 200 mg SC every 4 weeks. Study visits, vitals, physical exams, laboratory monitoring, and AE monitoring are shown in [Table 111](#), [Table 112](#), [Table 113](#), and [Table 114](#). The laboratory analyses were conducted at a central lab. The schedules of assessments are acceptable for a phase 2, dose-ranging trial.

15.3.3. Eligibility Criteria, Trial 2001

Key inclusion and exclusion criteria for this trial are summarized below. These criteria appear reasonable for a phase 2 HAE trial.

Key Inclusion Criteria

- Adults 18 to 65 years of age.
- A diagnosis of C1-INH (Type I or Type II) HAE or FXII/PLG (Type III) HAE as demonstrated by clinical history consistent with HAE (SC or mucosal, nonpruritic swelling episodes without accompanying urticaria) and supportive laboratory values:
 - C1-INH antigen concentration or function activity <50% of the lower limit of the reference range and C4 antigen concentration below the lower limit of the reference range (for subjects with Type I or Type II HAE).
 - HAE-associated FXII or PLG gene mutation (for subjects with Type III HAE).
- For baseline HAE attack rate:
 - Four or more HAE attacks over a consecutive 2-month period during the 3 months before Screening, as documented in the subject's medical record (for subjects with Type I or Type II HAE).
 - One or more HAE attack during the 3 months before screening, as documented in the subject's medical record (for subjects with Type III HAE).
 - For subjects on prophylactic HAE therapy, documentation of baseline HAE attack rate prior to prophylactic HAE therapy was accepted.
- Willing to cease the use of C1-INH products, androgens, or antifibrinolytics for routine prophylaxis against HAE attacks on the first day of the Run-in Period, after being assessed by the investigator to be able to adequately manage on-demand treatments of HAE attacks without assistance.

Key Exclusion Criteria

- History of clinically significant arterial or venous thrombosis, or current clinically significant prothrombotic risk (including presence of a central venous access device).
- History of uncontrolled, abnormal bleeding events due to a coagulopathy, or a current clinically significant coagulopathy, or clinically significant risks for bleeding events.
- Had any preplanned surgeries during the trial that had an inherent clinically significant risk for thrombotic events or bleeding.
- Had an incurable malignancy.
- For subjects with Type I or Type II HAE, a clinically significant history of poor response to C1-INH therapy for the management of HAE.
- Female subjects with Type I or Type II HAE who initiated or changed dose of any hormonal contraceptive regimen or hormone replacement therapy (i.e., estrogen/progesterone products) within 3 months before Screening.

- Known hypersensitivity to the investigational product or any of its excipients.

15.3.4. Primary and Secondary Objectives and Endpoints, Trial 2001

Primary Objectives and Endpoints

The primary objective of this study was to evaluate the dose and efficacy of garadacimab in the prevention of HAE attacks in subjects with C1-INH (Type I or Type II) HAE. The primary endpoint was the time-normalized number of investigator-confirmed HAE attacks per month during the blinded, placebo-controlled portion of the study (Treatment Period 1). The primary endpoint was calculated per subject as:

$$[\text{number of HAE attacks} \div \text{length of subject's evaluation period in days}] \times 30.4375.$$

A subject's evaluation period depended on whether the subject received an IV loading dose. All 32 subjects with Type I or Type II HAE who were assigned to 75 mg, 200 mg, or 600 mg garadacimab, or matched placebo, in Treatment Period 1 received an IV loading dose. For these subjects, their evaluation periods were from Day 6, or the date of first SC administration of the investigational product, until Day 91 or the Study Completion Visit date (whichever occurred first).

The additional six subjects who were assigned to 400 mg garadacimab Q2W (open-label) in Treatment Period 1 did not receive an IV loading dose. For these subjects, their evaluation periods were from Day 15, or the date of second SC administration of the investigational product, until Day 85 or the Study Completion Visit date (whichever occurred first).

Secondary Objectives and Endpoints

The secondary objectives of this study included evaluation of the efficacy of garadacimab in subjects with C1-INH (Type I or Type II) HAE. The secondary efficacy endpoints included:

- Number and percentage of subjects with Type I or Type II HAE who had a $\geq 50\%$ reduction in the time-normalized number of HAE attacks per month during Treatment Period 1 compared to the Run-in Period.
- Number and percentage of subjects with Type I or Type II HAE who were attack-free during Treatment Period 1.
- Number, time-normalized number (per month), and percentage of mild, moderate, and severe HAE attacks in subjects with Type I or Type II HAE during Treatment Period 1.
- Number, time-normalized number (per month), and percentage of mild, moderate, and severe HAE attacks treated with on-demand therapy in subjects with Type I or Type II HAE during Treatment Period 1.

15.3.5. Statistical Analysis Plan, Trial 2001

The final statistical analysis plan (SAP; version 2.0) is dated June 19, 2020. The analysis sets defined by the Applicant for this study included the following:

Screening Population: All subjects who provided written informed consent and underwent any study screening procedure.

ITT Population: All subjects who provided informed consent, underwent any study screening procedure, and was assigned to treatment in Treatment Period 1 or to treatment in Treatment Period 2, regardless of whether they received the investigational product. The ITT Analysis Set was analyzed using the treatment to which the subject was assigned in Treatment Period 1, in Treatment Period 2 at Week 13, or 200 mg after dose reduction from 600 mg following Amendment 2 in Treatment Period 2 (only applicable for C1-INH [Type I or Type II] HAE subjects), regardless of the actual treatment received. This was the main set used for efficacy analyses. Subjects with FXII/PLG (Type III) HAE were not included.

Safety Population: All subjects who provided informed consent, were assigned to treatment in Treatment Period 1 or to treatment in Treatment Period 2 and received at least 1 dose or partial dose of the investigational product. The Safety Population was based on the actual treatment received and was the main set used for safety analyses.

Per Protocol Population: All subjects in the ITT Analysis Set, excluding subjects who had a significant protocol violation. Protocol violations leading to exclusion from the Per Protocol Population were reviewed and agreed upon prior to conducting each of the interim analyses and before database lock.

15.3.6. Analysis of the Primary Endpoint, Trial 2001

The primary analysis tested for a difference in the time-normalized number of HAE attacks per month during Treatment Period 1 between 200 mg garadacimab versus placebo and between 600 mg garadacimab versus placebo at a full alpha level of 5%. A two-sided Mann-Whitney test was used for both comparisons (each at $\alpha=2.5\%$ to account for multiple testing). An exploratory Mann-Whitney test was conducted to compare 200 mg garadacimab and 600 mg garadacimab at $\alpha=5\%$. No testing was done for the 75 mg and 400 mg garadacimab arms.

Handling of Missing Data

While strategies for addressing missing data were prespecified in the final SAP, no missing data occurred for the primary endpoint. Therefore, no missing data or sensitivity analyses were conducted by the Applicant.

Subgroup Analyses

Subgroup analyses for the primary endpoint were not prespecified in the protocol or final SAP or submitted by the Applicant.

15.3.7. Analysis of the Secondary Endpoint, Trial 2001

All secondary endpoints in Section [15.3.3](#) were investigated exploratorily via descriptive statistics. No statistical testing was conducted for these endpoints.

15.3.8. Data and Safety Monitoring Committee, Trial 2001

An IDMC was established to monitor safety, efficacy, and PK/PD data generated during the trial. The IDMC was comprised of independent clinical specialists in HAE with experience in clinical trials. The IDMC reviewed accumulating data from the ongoing study in an unblinded manner. No safety concerns were identified during the IDMC meetings, and the IDMC recommended that the study continue as planned.

15.3.9. Sample Size Considerations, Trial 2001

The Applicant determined that seven subjects with C1-INH (Type I or Type II) HAE assigned to each tested treatment arm (200 mg garadacimab, 600 mg garadacimab, or placebo) were needed to reach about 82% power for the comparisons of 200 mg garadacimab versus placebo and 600 mg garadacimab versus placebo in Treatment Period 1, under the following assumptions:

- Alpha=2.5% for each comparison using two-sided Mann-Whitney tests.
- The time-normalized number of HAE attacks per month was 2.9 in the placebo arm (derived from a previous HAE trial [3001] conducted by the Applicant, where the lower bound of the distribution-free 95% CI for the median in the first placebo Treatment Period was used).
- The time-normalized number of HAE attacks per month was 0.6 in the garadacimab arms (derived from a previous HAE trial [3001] conducted by the Applicant, where the upper bound of the distribution-free 95% CI for the median of the combined active Treatment Periods was used).
- The time-normalized HAE attack rates follow a Poisson distribution, where the lower and upper bounds of the 95% CIs for the medians are used as the rate parameters.
- Randomization allocation is equal.

The 75 mg garadacimab arm was included for PK/PD reasons and was not expected to yield maximum clinical efficacy. The sample size of seven subjects with Type I or Type II HAE for this arm was not driven by an efficacy comparison or power calculation, but to maintain study blinding and consistency with the other treatment arms. No testing for efficacy was planned for the 75 mg garadacimab arm versus placebo.

An additional 1 subject with Type I or Type II HAE was planned to be added to each of the four treatment arms above to account for dropouts during Treatment Period 1, resulting in eight subjects with Type I or Type II HAE planned per treatment arm. A total of 32 subjects with Type I or Type II HAE were randomized to the blinded, placebo-controlled portion of the study (Treatment Period 1).

An additional eight subjects with Type I or Type II HAE were planned to be assigned to 400 mg garadacimab Q2W (open-label) and an additional 10 subjects with FXII/PLG (Type III) HAE were planned to be assigned to 600 mg garadacimab every 4 weeks (open-label). A power calculation was not performed for these two treatment arms; they were included for informational purposes only and were not planned to be tested against placebo. In the study,

there were six subjects with Type I or Type II HAE in the 400 mg garadacimab arm (open-label) and six subjects with Type III HAE in the 600 mg garadacimab arm (open-label).

Overall, a total of up to 40 subjects with Type I or Type II HAE were planned to be assigned to treatment in Treatment Period 1. In the study, a total of 38 subjects with Type I or Type II HAE were enrolled.

Treatment Period 2 was open-label and comprised subjects from Treatment Period 1. Therefore, no sample size calculations were performed for Treatment Period 2.

15.3.10. Protocol Amendments, Trial 2001

The original protocol (dated May 30, 2018) had two substantial amendments: Amendment 1 (dated December 18, 2018) and Amendment 2 (dated March 20, 2020).

Amendment 1 included updates to pregnancy testing, acceptable methods of contraception and use of routine (long-term) HAE prophylaxis, and the duration of the Follow-up Period (extended to 85 days), and clarifications were made to the statistical methods (before database lock).

In Amendment 2, all subjects with C1-INH (Type I or Type II) HAE receiving 600 mg garadacimab in Treatment Period 2 had their doses decreased to 200 mg, and corresponding edits were made to the Statistical Analyses and Methods section of the protocol (before database lock).

Additionally, Contingency Amendment 1 (dated April 9, 2020) was produced in response to the COVID-19 pandemic, which allowed all subjects in Treatment Period 2 to substitute a research center visit with a remote telephone or video conference.

15.3.11. Changes to the Planned Analyses, Trial 2001

The original SAP (SAP; version 1.0; dated April 1, 2020) was modified to include updates to align with Amendment 2 and Contingency Amendment 1 of the original protocol (described above). All changes are reflected in the final SAP (version 2.0; dated June 19, 2020) and were generally reasonable.

16. Efficacy

16.1. Durability of Treatment Effect, Study 3002

A total of 161 subjects (151 adults and 10 adolescents) were enrolled in an open-label extension study (3002), of which 90 (56%) were garadacimab-naïve (69 new subjects and 21 subjects from trial 3001) and 71 (44%) were previously treated with garadacimab (35 subjects from trial 2001 and 36 subjects from trial 3001). Of the 161 subjects, 145 (90%) had Type I HAE, 14 (9%) had Type II HAE, and 2 (1%) had Type III HAE. The mean duration of garadacimab treatment was 14 months (range: 3 to 21 months), with 119 subjects (74%) having received garadacimab for ≥ 12 months. As shown in [Table 115](#), the mean time-normalized number of HAE attacks per month was 0.16 (95% CI=0.1, 0.22), which is generally consistent with the primary analysis

results from the pivotal study ([Table 10](#)). This treatment effect was sustained in 55 subjects (34%) who received garadacimab for >15 months (mean=0.15; 95% CI=0.05, 0.25). However, because of the lack of a control arm and blinding, these results should be interpreted with caution.

Table 115. HAE Attack Rate, Study 3002

Variable	Garadacimab (N=161)
Total number of HAE attacks during the Treatment Period	330
Time-normalized number of HAE attacks per month	
Mean (SD)	0.16 (0.37)
95% CI	0.1, 0.22
Median (min, max)	0 (0, 1.9)

Source: Statistical reviewer; Interim Clinical Study Report (dated August 10, 2023), Table 11-2, p. 77.

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; max, maximum; min, minimum; N, total number of subjects; SD, standard deviation

16.2. Results of Statistical Analyses, Trial 2001

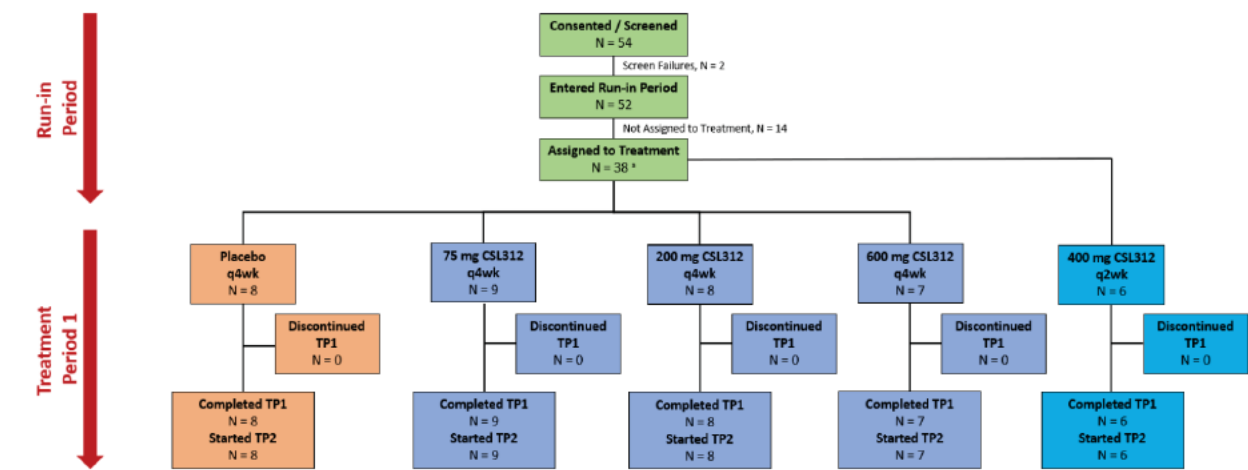
This section summarizes subject disposition, baseline demographics and clinical characteristics, and the primary and secondary efficacy results.

Subject Disposition

Disposition information is provided in [Figure 66](#). A total of 54 subjects were screened, of which 2 were screen failures due to not having a clinical diagnosis of C1-INH (Type I or Type II) HAE and reasons related to use of contraception or hormone replacement therapy. Of the 52 subjects who entered the Run-in Period, 14 failed to meet all Run-in Period completion criteria and were not assigned to treatment. A total of 38 subjects with Type I or Type II HAE were randomized in Treatment Period 1, and 6 additional subjects with FXII/PLG (Type III) HAE received 600 mg garadacimab once every 4 weeks (open-label). All 38 subjects on blinded treatment completed Treatment Period 1.

Overall, the subject disposition is generally reasonable for a phase 2 HAE trial. For further information regarding the Type III HAE subjects, see Section [6.3.2](#).

Figure 66. Subject Disposition, Trial 2001



Source: Study Report (dated May 30, 2022), Figure 10-1, p. 83.
 Abbreviations: N, number of subjects; q2wk, once every 2 weeks; q4wk, once every 4 weeks; TP1, Treatment Period 1

Baseline Demographics and Clinical Characteristics

The demographics and clinical characteristics of the ITT set at baseline are summarized in [Table 116](#). Imbalances in age, sex, race, and ethnicity are noted across the treatment arms. Due to the small size of the trial (HAE is a rare condition), these imbalances are expected. This trial was only powered to detect a difference between 200 mg garadacimab versus placebo and between 600 mg garadacimab versus placebo; as such, a sample size of seven to eight subjects per treatment arm was established (see Section [15.3.8](#) for more details). The baseline demographics and clinical characteristics of the subjects in this study are generally reflective of the overall HAE population and are generally reasonable for a phase 2 HAE trial.

Table 116. Baseline Demographics and Clinical Characteristics (ITT Analysis Set, Treatment Period 1), Trial 2001

Demographic/ Clinical Characteristic	Garadacimab 600 mg (q4wk) (N=7)	Garadacimab 200 mg (q4wk) (N=8)	Garadacimab 75 mg (q4wk) (N=9)	Placebo (q4wk) (N=8)	Blinded Overall (N=32)	Garadacimab 400 mg (q2wk) (N=6)
Sex, n (%)						
Female	5 (71.4)	2 (25)	7 (77.8)	4 (50)	18 (56.3)	3 (50)
Male	2 (28.6)	6 (75)	2 (22.2)	4 (50)	14 (43.8)	3 (50)
Age (years)						
Mean (SD)	30.4 (15.5)	39.5 (10.7)	48.1 (7.6)	41 (12.6)	40.3 (12.8)	37.2 (18)
Median (min, max)	24 (21, 65)	38.5 (26, 54)	46 (39, 61)	39.5 (20, 55)	39.5 (20, 65)	30.5 (21, 64)
Race, n (%)						
Asian	2 (28.6)	0 (0)	0 (0)	0 (0)	2 (6.3)	1 (16.7)
Black or African American	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)
Multiple	0 (0)	0 (0)	0 (0)	1 (12.5)	1 (3.1)	0 (0)
White	5 (71.4)	8 (100)	9 (100)	7 (87.5)	29 (90.6)	4 (66.7)
Ethnicity, n (%)						
Hispanic or Latino	0 (0)	0 (0)	0 (0)	1 (12.5)	1 (3.1)	1 (16.7)
Not Hispanic or Latino	7 (100)	8 (100)	9 (100)	7 (87.5)	31 (96.9)	5 (83.3)
BMI (kg/m ²)						
Mean (SD)	25.9 (4)	30.5 (6.6)	29.2 (9.6)	28.9 (4.1)	28.7 (6.6)	30.3 (9.8)
Median (min, max)	25.9 (20.7, 30.3)	29.7 (23.2, 44.6)	28 (18.6, 48.3)	28.6 (23.8, 36.5)	28.8 (18.6, 48.3)	26.7 (23, 49.2)
Location, n (%)						
United States	2 (28.6)	0 (0)	2 (22.2)	4 (50)	8 (25)	2 (33.3)
ex-United States	5 (71.4)	8 (100)	7 (77.8)	4 (50)	24 (75)	4 (66.7)
HAE Type, n (%)						
Type I	7 (100)	7 (87.5)	9 (100)	7 (87.5)	30 (93.8)	6 (100)
Type II	0 (0)	1 (12.5)	0 (0)	1 (12.5)	2 (6.3)	0 (0)
Prior use of HAE prophylaxis, n (%)	3 (42.9)	1 (12.5)	6 (66.7)	1 (12.5)	11 (34.3)	1 (16.7)

Source: Statistical reviewer; Study Report (dated May 30, 2022), Table 11-1 (p. 91) and Table 11-3 (p. 96).

The placebo arm and the 75 mg, 200 mg, and 600 mg garadacimab arms were blinded; the 400 mg garadacimab arm was open-label

Abbreviations: BMI, body mass index; HAE, hereditary angioedema; ITT, intent-to-treat; max, maximum; min, minimum; N, number of subjects in the ITT population; n, number of subjects with the respective demographic or clinical characteristic; q2wk, once every 2 weeks; q4wk, once every 4 weeks; SD, standard deviation

Primary Efficacy Results

The primary efficacy endpoint was the time-normalized number of HAE attacks per month during Treatment Period 1. This endpoint is consistent with the phase 3 trial (3001) and previous programs for HAE prophylaxis. The calculation of the time-normalized number of HAE attacks per month during Treatment Period 1 is provided in Section [15.3.3](#).

The primary efficacy results are shown in [Table 117](#). The mean time-normalized number of HAE attacks per month during Treatment Period 1 was lowest in the 200 mg garadacimab arm (mean=0.05; 95% CI: -0.06, 0.15) compared to placebo (mean=4.24; 95% CI: 2.74, 5.75), with a reduction in the mean of 98.9% relative to placebo. The mean time-normalized number of HAE attacks per month during Treatment Period 1 was also considerably lower in the 600 mg garadacimab arm (mean=0.35; 95% CI: -0.02, 0.73) compared to placebo (mean=4.24; 95% CI: 2.74, 5.75), with a reduction in the mean of 91.7% relative to placebo. These results signify an improvement in both the 200 mg and 600 mg garadacimab arms compared to placebo. Further, there was a statistically significant difference (Mann-Whitney p-value <0.001) in the rank sums of the time-normalized number of HAE attacks per month in the 200 mg garadacimab and placebo arms (i.e., the rank sum in the 200 mg garadacimab arm was significantly lower than the placebo arm, assuming that a higher rank indicates a worse outcome). A similar conclusion can be made for the 600 mg garadacimab arm versus placebo (Mann-Whitney p-value=0.001).

Finally, in an exploratory analysis, there was no statistical difference between the 200 mg and 600 mg garadacimab arms (Mann-Whitney p-value=0.085).

Table 117. Primary Efficacy Results (ITT Analysis Set, Treatment Period 1), Trial 2001

Analysis Statistic	Garadacimab 600 mg (q4wk) (N=7)	Garadacimab 200 mg (q4wk) (N=8)	Garadacimab 75 mg (q4wk) (N=9)	Placebo (q4wk) (N=8)	Garadacimab 400 mg (q2wk) (N=6)
	Time-normalized number of HAE attacks per month				
Mean (SD)	0.35 (0.41)	0.05 (0.13)	0.48 (1.06)	4.24 (1.80)	0.14 (0.22)
95% CI	-0.02, 0.73	-0.06, 0.15	-0.33, 1.29	2.74, 5.75	-0.09, 0.38
Median (min, max)	0.34 (0, 1.05)	0 (0, 0.36)	0 (0, 3.26)	4.61 (1.40, 7.16)	0 (0, 0.43)
Percentage reduction relative to placebo					
Mean	91.7	98.9	88.7	-	-
Median	92.6	100	100	-	-
P-value					
200 mg garadacimab versus placebo ^a	-	<0.001	-	-	-
600 mg garadacimab versus placebo ^a				-	-
600 mg garadacimab versus 200 mg garadacimab ^b	0.001	-	-	-	-
	0.085	-	-		

Source: Statistical reviewer; Study Report (dated May 30, 2022), Table 11-5, p. 104-105.

Abbreviations: ITT, intent-to-treat; max, maximum; min, minimum; N, number of subjects in the ITT Analysis Set; q2wk, once every 2 weeks; q4wk, once every 4 weeks; SD, standard deviation

Secondary Efficacy Results

[Table 118](#) shows the number and percentage of subjects with C1-INH (Type I or Type II) HAE who had a $\geq 50\%$ reduction in the time-normalized number of HAE attacks per month during Treatment Period 1 compared to the Run-in Period. All garadacimab arms outperformed placebo on this endpoint. All subjects in the 75 mg, 200 mg, and 400 mg garadacimab arms had a reduction of at least 50%. Most subjects (86%) in the 600 mg garadacimab arm also met this endpoint. No subjects on placebo achieved a $\geq 50\%$ reduction.

Table 118. Secondary Efficacy Analysis: Subjects With a $\geq 50\%$ Reduction in the Time-Normalized Number of HAE Attacks per Month Compared to the Run-in Period (ITT Analysis Set, Treatment Period 1), Trial 2001

Analysis Statistic	Garadacimab 600 mg (q4wk) (N=7)	Garadacimab 200 mg (q4wk) (N=8)	Garadacimab 75 mg (q4wk) (N=9)	Placebo (q4wk) (N=8)	Garadacimab 400 mg (q2wk) (N=6)
Reduction of $\geq 50\%$, n (%)	6 (85.7)	8 (100)	9 (100)	0 (0)	6 (100)
95% CI ^a	48.7, 99.3	67.6, 100	70.1, 100	0, 32.4	61, 100

Source: Statistical reviewer; Study Report (dated May 30, 2022), Table 14.2.2.1.1, pp. 571-572.

^a Calculated for the percentage of subjects using Wilson's asymptotic confidence limits

The placebo arm and the 75 mg, 200 mg, and 600 mg garadacimab arms were blinded; the 400 mg garadacimab arm was open-label.

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; N, number of subjects in the ITT Analysis Set; n, number of subjects meeting the criteria; q2wk, once every 2 weeks; q4wk, once every 4 weeks

The number and percentage of subjects with Type I or Type II HAE who were attack-free during Treatment Period 1 are presented in [Table 119](#). All garadacimab arms outperformed placebo on this endpoint. The majority of subjects in the 75 mg, 200 mg, and 400 mg garadacimab arms did not experience any HAE attacks during Treatment Period 1. A total of 3/7 subjects (43%) in the 600 mg garadacimab arm were attack-free during Treatment Period 1. No subjects on placebo met this endpoint.

Table 119. Secondary Efficacy Analysis: Number of Attack-Free Subjects (ITT Analysis Set, Treatment Period 1), Trial 2001

Analysis Statistic	Garadacimab 600 mg (q4wk) (N=7)	Garadacimab 200 mg (q4wk) (N=8)	Garadacimab 75 mg (q4wk) (N=9)	Placebo (q4wk) (N=8)	Garadacimab 400 mg (q2wk) (N=6)
Number of attack-free subjects, n (%)	3 (42.9)	7 (87.5)	5 (55.6)	0 (0)	4 (66.7)
95% CI ^a	15.8, 75	52.9, 99.4	26.7, 81.1	0, 32.4	30, 90.3

Source: Statistical reviewer; Study Report (dated May 30, 2022), Table 11-9, p. 114.

^a Calculated for the percentage of subjects using Wilson's asymptotic confidence limits

The placebo arm and the 75 mg, 200 mg, and 600 mg garadacimab arms were blinded; the 400 mg garadacimab arm was open-label.

Abbreviations: CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the ITT Analysis Set; n, number of attack-free subjects; q2wk, once every 2 weeks; q4wk, once every 4 weeks

[Table 120](#) shows the number and percentage of mild, moderate, and severe HAE attacks among subjects with Type I or Type II HAE during Treatment Period 1, in addition to the time-normalized number of moderate and severe HAE attacks per month. There was a total of 117 HAE attacks during Treatment Period 1, of which 95 (81%), 7 (6%), and 1 (1%) were experienced by subjects on placebo, 600 mg garadacimab, and 200 mg garadacimab, respectively. Of the 117 HAE attacks, 39 (33%) were mild, 57 (49%) were moderate, and 21 (18%) were severe, with most of the moderate and severe HAE attacks occurring in the placebo

arm. Among the blinded arms, the fewest HAE attacks occurred among subjects on 200 mg garadacimab (one moderate attack from one subject) and 600 mg garadacimab (two mild attacks from two subjects, four moderate attacks from two subjects, and one severe attack from one subject). Furthermore, the mean time-normalized number of moderate and severe HAE attacks per month were considerably lower in all the garadacimab arms compared to placebo, with the 200 mg garadacimab arm yielding the most favorable results.

Table 120. Secondary Efficacy Analysis: Number of Moderate and Severe HAE Attacks (ITT Analysis Set, Treatment Period 1), Trial 2001

Analysis Statistic	Garadacimab	Garadacimab	Garadacimab	Placebo	Garadacimab
	600 mg (q4wk) (N=7)	200 mg (q4wk) (N=8)	75 mg (q4wk) (N=9)	(q4wk) (N=8)	400 mg (q2wk) (N=6)
Total number of HAE attacks	7	1	12	95	2
HAE attacks ^a , n (%)					
Mild	2 (28.6)	0 (0)	3 (25)	32 (33.7)	2 (100)
Moderate	4 (57.1)	1 (100)	9 (75)	43 (45.3)	0 (0)
Severe	1 (14.3)	0 (0)	0 (0)	20 (21.1)	0 (0)
Subjects with ≥1 attack ^b , n (%)					
Mild	2 (28.6)	0 (0)	3 (33.3)	7 (87.5)	2 (33.3)
Moderate	2 (28.6)	1 (12.5)	1 (11.1)	8 (100)	0 (0)
Severe	1 (14.3)	0 (0)	0 (0)	5 (62.5)	0 (0)
Time-normalized number of moderate HAE attacks per month					
Mean (SD)	0.2 (0.35)	0.05 (0.13)	0.36 (1.09)	1.93 (1.4)	0 (0)
Median (min, max)	0 (0, 0.72)	0 (0, 0.36)	0 (0, 3.26)	1.74 (0.35, 4.71)	0 (0, 0)
95% CI	-0.12, 0.52	-0.06, 0.15	-0.47, 1.2	0.76, 3.11	0, 0
Time-normalized number of severe HAE attacks per month					
Mean (SD)	0.05 (0.14)	0 (0)	0 (0)	0.89 (1.36)	0 (0)
Median (min, max)	0 (0, 0.36)	0 (0, 0)	0 (0, 0)	0.37 (0, 3.94)	0 (0, 0)
95% CI	-0.07, 0.18	0, 0	0, 0	-0.25, 2.03	0, 0

Source: Statistical reviewer; Study Report (dated May 30, 2022), Table 11-11, pp. 116-117.

^a Percentages based on the total number of HAE attacks.

^b Percentages based on the number of subjects in each treatment arm.

The placebo arm and the 75 mg, 200 mg, and 600 mg garadacimab arms were blinded; the 400 mg garadacimab arm was open-label.

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; max, maximum; min, minimum; N, number of subjects in the ITT Analysis Set; n, number of occurrences; q2wk, once every 2 weeks; q4wk, once every 4 weeks

The number and percentage of mild, moderate, and severe HAE attacks requiring on-demand therapy among subjects with Type I or Type II HAE during Treatment Period 1 is presented in [Table 121](#), in addition to the time-normalized number of moderate and severe HAE attacks per month requiring on-demand therapy. A total of 104/117 HAE attacks (89%) required on-demand therapy during Treatment Period 1, of which 89 (86%), 3 (3%), and 1 (1%) were experienced by subjects on placebo, 600 mg garadacimab, and 200 mg garadacimab, respectively. Of the 104 HAE attacks requiring on-demand therapy, 29 (28%) were mild, 54 (52%) were moderate, and 21 (20%) were severe, with most of the moderate and severe HAE attacks requiring on-demand therapy occurring in the placebo arm. Among the blinded arms, the fewest HAE attacks requiring

on-demand therapy occurred in the 200 mg garadacimab arm (one moderate attack from one subject) and the 600 mg garadacimab arm (two moderate attacks from one subject and one severe attack from one subject). Furthermore, the mean time-normalized number of moderate and severe HAE attacks per month requiring on-demand therapy was considerably lower in all the garadacimab arms compared to placebo, with the 200 mg garadacimab arm yielding the most favorable results.

Table 121. Secondary Efficacy Analysis: Number of Moderate and Severe HAE Attacks Requiring On-Demand Therapy (ITT Analysis Set, Treatment Period 1), Trial 2001

Analysis Statistic	Garadacimab	Garadacimab	Garadacimab	Placebo	Garadacimab
	600 mg (q4wk) (N=7)	200 mg (q4wk) (N=8)	75 mg (q4wk) (N=9)	(q4wk) (N=8)	400 mg (q2wk) (N=6)
Total number of HAE attacks requiring on-demand therapy	3	1	11	89	0
HAE attacks requiring on-demand therapy ^a , n (%)					
Mild	0 (0)	0 (0)	2 (18.2)	27 (30.3)	0 (0)
Moderate	2 (66.7)	1 (100)	9 (81.8)	42 (47.2)	0 (0)
Severe	1 (33.3)	0 (0)	0 (0)	20 (22.5)	0 (0)
Subjects with ≥1 HAE attack requiring on-demand therapy ^b , n (%)					
Mild	0 (0)	0 (0)	2 (22.2)	6 (75)	0 (0)
Moderate	1 (14.3)	1 (12.5)	1 (11.1)	7 (87.5)	0 (0)
Severe	1 (14.3)	0 (0)	0 (0)	5 (62.5)	0 (0)
Time-normalized number of moderate HAE attacks per month requiring on-demand therapy					
Mean (SD)	0.1 (0.27)	0.05 (0.13)	0.36 (1.09)	1.89 (1.46)	0 (0)
Median (min, max)	0 (0, 0.72)	0 (0, 0.36)	0 (0, 3.26)	1.74 (0, 4.71)	0 (0, 0)
95% CI	-0.15, 0.36	-0.06, 0.15	-0.47, 1.2	0.67, 3.11	0, 0
Time-normalized number of severe HAE attacks per month requiring on-demand therapy					
Mean (SD)	0.05 (0.14)	0 (0)	0 (0)	0.89 (1.36)	0 (0)
Median (min, max)	0 (0, 0.36)	0 (0, 0)	0 (0, 0)	0.37 (0, 3.94)	0 (0, 0)
95% CI	-0.07, 0.18	0, 0	0, 0	-0.25, 2.03	0, 0

Source: Statistical reviewer; Study Report (dated May 30, 2022), Table 14.2.2.5.1 (pp. 664-671) and Table 14.2.2.5.2 (pp. 676-683).

^a Percentages based on the total number of HAE attacks requiring on-demand therapy.

^b Percentages based on the number of subjects in each treatment arm.

The placebo arm and the 75, 200, and 600 mg garadacimab arms were blinded; the 400 mg garadacimab arm was open-label.

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; max, maximum; min, minimum; N, number of subjects in the ITT Analysis Set; n, number of subjects meeting the criteria; q2wk, once every 2 weeks; q4wk, once every 4 weeks

The primary and secondary efficacy results reported above support the Applicant's further investigation of the 200 mg garadacimab regimen in the phase 3 trial (3001) and provide additional supportive evidence of the effectiveness of garadacimab in preventing HAE attacks.

16.2.1. Interim Analyses, Trial 2001

The first planned interim analysis was conducted after all C1-INH (Type I or Type II) HAE subjects who received 75 mg, 200 mg, or 600 mg garadacimab every 4 weeks, or matched placebo, completed Treatment Period 1. Confirmatory tests of 200 mg garadacimab versus placebo and 600 mg garadacimab versus placebo were conducted. All efficacy results in Section [16.2](#) and safety assessments are based on the first interim analysis.

The second planned interim analysis was conducted after all subjects with Type I or Type II HAE assigned to receive 400 mg garadacimab Q2W and all subjects with FXII/PLG (Type III) HAE who were assigned to receive 600 mg garadacimab every 4 weeks completed Treatment Period 1. This interim analysis included subjects with all HAE subtypes (Type I, Type II, and Type III). These data are not shown as all the results are open-label.

The interim analyses above were planned to provide information on safety, efficacy, and PK/PD parameters for Type I, Type II, and Type III HAE.

17. Clinical Safety

17.1. Subgroup Analyses, Trial 3001

The review team conducted additional safety analyses by sex, age, race and geography using system organ class and preferred terms to assess for potential safety imbalances. These post hoc subgroup analyses conducted on a small population have limited interpretability. But overall, no imbalance was identified.

17.1.1. Treatment-Emergent Adverse Events by Sex

Table 122. Subgroup Analysis by Sex of TEAEs by SOC and PT, Safety Population, Trial 3001

SOC and PT	Garadacimab 200 mg		Placebo	
	Female (N=24)	Male (N=15)	Female (N=14)	Male (N=11)
Cardiac disorders	0	0	1 (7.1)	0
Cardiovascular disorder	0	0	1 (7.1)	0
Congenital, familial and genetic disorders	1 (4.2)	0	0	1 (9.1)
Hereditary angioedema	1 (4.2)	0	0	1 (9.1)
Eye disorders	2 (8.3)	1 (6.7)	0	0
Eczema eyelids	0	1 (6.7)	0	0
Visual impairment	2 (8.3)	0	0	0
Gastrointestinal disorders	6 (25.0)	2 (13.3)	5 (35.7)	1 (9.1)
Abdominal distension	0	0	0	1 (9.1)
Abdominal pain	1 (4.2)	1 (6.7)	0	0
Constipation	0	0	1 (7.1)	0
Dental caries	0	0	1 (7.1)	0
Diarrhea	0	2 (13.3)	1 (7.1)	0
Hemorrhoids	0	1 (6.7)	0	0
Nausea	0	0	2 (14.3)	1 (9.1)

SOC and PT	Garadacimab 200 mg		Placebo	
	Female (N=24)	Male (N=15)	Female (N=14)	Male (N=11)
General disorders and administration site conditions	2 (8.3)	2 (13.3)	8 (57.1)	1 (9.1)
Chest pain	0	0	1 (7.1)	0
Drug withdrawal syndrome	0	0	1 (7.1)	0
Fatigue	0	0	2 (14.3)	1 (9.1)
Feeling cold	0	1 (6.7)	0	0
Injection site erythema	0	1 (6.7)	2 (14.3)	0
Malaise	0	1 (6.7)	0	0
Non-cardiac chest pain	0	0	1 (7.1)	0
Pyrexia	1 (4.2)	0	2 (14.3)	0
Vaccination site reaction	0	0	1 (7.1)	0
Infections and infestations	11 (45.8)	4 (26.7)	4 (28.6)	4 (36.4)
Bronchitis	0	1 (6.7)	0	0
Conjunctivitis	1 (4.2)	1 (6.7)	0	0
COVID-19	0	0	2 (14.3)	2 (18.2)
Gastroenteritis viral	0	0	0	1 (9.1)
Gastrointestinal infection	2 (8.3)	0	0	1 (9.1)
Nasopharyngitis	2 (8.3)	1 (6.7)	1 (7.1)	0
Oral herpes	0	0	0	1 (9.1)
Sinusitis	2 (8.3)	0	0	0
Upper respiratory tract infection	4 (16.7)	1 (6.7)	1 (7.1)	1 (9.1)
Urinary tract infection	3 (12.5)	0	0	0
Injury, poisoning and procedural complications	3 (12.5)	2 (13.3)	0	1 (9.1)
Contusion	1 (4.2)	0	0	1 (9.1)
Fall	1 (4.2)	1 (6.7)	0	1 (9.1)
Limb injury	0	1 (6.7)	0	0
Investigations	2 (8.3)	2 (13.3)	2 (14.3)	1 (9.1)
Bacterial test positive	0	0	1 (7.1)	0
Crystal urine present	0	0	1 (7.1)	0
Occult blood positive	0	1 (6.7)	0	0
Protein urine present	0	0	1 (7.1)	0
Prothrombin fragment 1.2 increased	0	1 (6.7)	0	1 (9.1)
Urinary occult blood positive	0	0	1 (7.1)	0
Urinary sediment present	0	0	1 (7.1)	0
Urine leukocyte esterase positive	0	0	1 (7.1)	0
White blood cells urine positive	0	0	1 (7.1)	0
Musculoskeletal and connective tissue disorders	3 (12.5)	3 (20.0)	4 (28.6)	1 (9.1)
Arthralgia	0	1 (6.7)	1 (7.1)	0
Back pain	1 (4.2)	1 (6.7)	1 (7.1)	0
Bone pain	0	1 (6.7)	0	0
Muscle spasms	0	0	0	1 (9.1)
Pain in extremity	0	0	3 (21.4)	0
Periarthritis	0	0	1 (7.1)	0
Nervous system disorders	3 (12.5)	1 (6.7)	5 (35.7)	0
Dizziness	1 (4.2)	0	1 (7.1)	0
Headache	3 (12.5)	1 (6.7)	5 (35.7)	0
Psychiatric disorders	1 (4.2)	1 (6.7)	0	0
Depressed mood	0	1 (6.7)	0	0
Renal and urinary disorders	0	1 (6.7)	0	0
Hypertonic bladder	0	1 (6.7)	0	0

SOC and PT	Garadacimab 200 mg		Placebo	
	Female (N=24)	Male (N=15)	Female (N=14)	Male (N=11)
Reproductive system and breast disorders	1 (4.2)	0	1 (7.1)	0
Nipple pain	0	0	1 (7.1)	0
Respiratory, thoracic and mediastinal disorders	1 (4.2)	2 (13.3)	2 (14.3)	1 (9.1)
Cough	0	1 (6.7)	0	0
Oropharyngeal pain	1 (4.2)	1 (6.7)	1 (7.1)	0
Sinus congestion	0	0	1 (7.1)	0
Throat irritation	0	0	0	1 (9.1)
Skin and subcutaneous tissue disorders	0	1 (6.7)	1 (7.1)	0
Erythema marginatum	0	0	1 (7.1)	0
Hyperhidrosis	0	1 (6.7)	0	0
Rash	0	0	1 (7.1)	0
Vascular disorders	0	0	0	1 (9.1)
Hypertension	0	0	0	1 (9.1)

Source: Clinical reviewer generated using OCS Analysis Studio, Custom Table Tool.

Columns – Dataset: Demographics; Filter: SAFFL='Y'.

Any AE – Dataset: Adverse Events; Filter: None.

SOC and PT – Dataset: Adverse Events; Filter: None; Percent Threshold: ≥5%.

Abbreviations: COVID-19, coronavirus disease 2019; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event

17.1.2. Treatment-Emergent Adverse Events by Age

Table 123. Subgroup Analysis by Age of TEAEs by SOC and PT, Safety Population, Trial 3001

SOC and PT	Garadacimab 200 mg			Placebo	
	<18 Years (N=4)	18-64 Years (N=29)	≥65 Years (N=6)	<18 Years (N=2)	18-64 Years (N=23)
Eye disorders	0	2 (6.9)	1 (16.7)	0	0
Eczema eyelids	0	0	1 (16.7)	0	0
Visual impairment	0	2 (6.9)	0	0	0
Gastrointestinal disorders	1 (25.0)	7 (24.1)	0	1 (50.0)	5 (21.7)
Abdominal distension	0	0	0	1 (50.0)	0
Abdominal pain	0	2 (6.9)	0	0	0
Abdominal pain lower	1 (25.0)	0	0	0	0
Diarrhea	0	2 (6.9)	0	0	1 (4.3)
Nausea	0	0	0	1 (50.0)	2 (8.7)
General disorders and administration site conditions	0	3 (10.3)	1 (16.7)	0	9 (39.1)
Fatigue	0	0	0	0	3 (13.0)
Injection site erythema	0	0	1 (16.7)	0	2 (8.7)
Pyrexia	0	1 (3.4)	0	0	2 (8.7)

SOC and PT	Garadacimab 200 mg			Placebo	
	<18 Years (N=4)	18-64 Years (N=29)	≥65 Years (N=6)	<18 Years (N=2)	18-64 Years (N=23)
Infections and infestations	1 (25.0)	12 (41.4)	2 (33.3)	1 (50.0)	7 (30.4)
Bronchitis	0	0	1 (16.7)	0	0
Conjunctivitis	0	2 (6.9)	0	0	0
COVID-19	0	0	0	1 (50.0)	3 (13.0)
Gastroenteritis viral	0	0	0	1 (50.0)	0
Gastrointestinal infection	0	2 (6.9)	0	0	1 (4.3)
Nasopharyngitis	1 (25.0)	1 (3.4)	1 (16.7)	0	1 (4.3)
Otitis externa	1 (25.0)	0	0	0	0
Sinusitis	0	2 (6.9)	0	0	0
Upper respiratory tract infection	0	5 (17.2)	0	0	2 (8.7)
Urinary tract infection	0	3 (10.3)	0	0	0
Injury, poisoning and procedural complications	0	5 (17.2)	0	0	1 (4.3)
Fall	0	2 (6.9)	0	0	1 (4.3)
Investigations	0	3 (10.3)	1 (16.7)	0	3 (13.0)
Occult blood positive	0	0	1 (16.7)	0	0
Musculoskeletal and connective tissue disorders	0	6 (20.7)	0	1 (50.0)	4 (17.4)
Back pain	0	2 (6.9)	0	0	1 (4.3)
Muscle spasms	0	0	0	1 (50.0)	0
Pain in extremity	0	0	0	0	3 (13.0)
Nervous system disorders	0	4 (13.8)	0	0	5 (21.7)
Headache	0	4 (13.8)	0	0	5 (21.7)
Respiratory, thoracic and mediastinal disorders	1 (25.0)	1 (3.4)	1 (16.7)	2 (100.0)	1 (4.3)
Cough	0	0	1 (16.7)	0	0
Oropharyngeal pain	1 (25.0)	1 (3.4)	0	1 (50.0)	0
Throat irritation	0	0	0	1 (50.0)	0

Source: Clinical reviewer generated using OCS Analysis Studio, Custom Table Tool.

Columns – Dataset: Demographics; Filter: SAFFL='Y'.

Any AE – Dataset: Adverse Events; Filter: None.

SOC and PT – Dataset: Adverse Events; Filter: None; Percent Threshold: ≥5%.

Abbreviations: COVID-19, coronavirus disease 2019; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event

17.1.3. Treatment-Emergent Adverse Events by Geographic Region, Trial 3001

Table 124. Subgroup Analysis by Geographic Region of TEAEs by SOC and PT, Safety, Population, Trial 3001

SOC and PT	Garadacimab 200 mg		Placebo	
	Outside U.S. (N=27)	U.S. (N=12)	Outside U.S. (N=16)	U.S. (N=9)
Cardiac disorders	0	0	1 (6.2)	0
Cardiovascular disorder	0	0	1 (6.2)	0
Congenital, familial and genetic disorders	1 (3.7)	0	0	0
Hereditary angioedema	1 (3.7)	0	0	0
Eye disorders	2 (7.4)	1 (8.3)	0	0
Eczema eyelids	1 (3.7)	0	0	0
Visual impairment	1 (3.7)	1 (8.3)	0	0

SOC and PT	Garadacimab 200 mg		Placebo	
	Outside U.S. (N=27)	U.S. (N=12)	Outside U.S. (N=16)	U.S. (N=9)
Gastrointestinal disorders	6 (22.2)	2 (16.7)	2 (12.5)	3 (33.3)
Abdominal distension	0	0	0	1 (11.1)
Abdominal pain	1 (3.7)	1 (8.3)	0	0
Abdominal pain lower	1 (3.7)	0	0	0
Constipation	0	0	0	1 (11.1)
Dental caries	0	0	1 (6.2)	0
Diarrhea	2 (7.4)	0	0	1 (11.1)
Dyspepsia	1 (3.7)	0	0	0
Food poisoning	0	1 (8.3)	0	0
Hemorrhoids	1 (3.7)	0	0	0
Nausea	0	0	1 (6.2)	1 (11.1)
Noninfective gingivitis	1 (3.7)	0	0	0
Toothache	1 (3.7)	0	0	0
General disorders and administration site conditions	3 (11.1)	1 (8.3)	6 (37.5)	3 (33.3)
Chest pain	0	0	1 (6.2)	0
Drug withdrawal syndrome	0	0	0	1 (11.1)
Fatigue	0	0	1 (6.2)	2 (22.2)
Feeling cold	1 (3.7)	0	0	0
Injection site bruising	0	1 (8.3)	0	0
Injection site erythema	1 (3.7)	0	2 (12.5)	0
Injection site pruritus	0	1 (8.3)	0	0
Malaise	1 (3.7)	0	0	0
Noncardiac chest pain	0	0	1 (6.2)	0
Pyrexia	1 (3.7)	0	2 (12.5)	0
Vaccination site reaction	0	0	0	1 (11.1)
Infections and infestations	8 (29.6)	5 (41.7)	4 (25.0)	3 (33.3)
Bronchitis	0	1 (8.3)	0	0
Conjunctivitis	1 (3.7)	1 (8.3)	0	0
COVID-19	0	0	2 (12.5)	1 (11.1)
Gastroenteritis viral	0	0	0	1 (11.1)
Gastrointestinal infection	2 (7.4)	0	1 (6.2)	0
Helicobacter infection	1 (3.7)	0	0	0
Nasopharyngitis	3 (11.1)	0	1 (6.2)	0
Oral herpes	0	0	1 (6.2)	0
Otitis externa	1 (3.7)	0	0	0
Pyelonephritis	0	1 (8.3)	0	0
Rhinitis	1 (3.7)	0	0	0
Sinusitis	0	2 (16.7)	0	0
Tooth infection	0	1 (8.3)	0	0
Upper respiratory tract infection	2 (7.4)	2 (16.7)	0	2 (22.2)
Urinary tract infection	0	2 (16.7)	0	0
Injury, poisoning and procedural complications	2 (7.4)	1 (8.3)	1 (6.2)	0
Arthropod bite	0	1 (8.3)	0	0
Contusion	0	0	1 (6.2)	0
Fall	1 (3.7)	0	1 (6.2)	0
Limb injury	1 (3.7)	0	0	0
Traumatic hematoma	1 (3.7)	0	0	0

SOC and PT	Garadacimab 200 mg		Placebo	
	Outside U.S. (N=27)	U.S. (N=12)	Outside U.S. (N=16)	U.S. (N=9)
Investigations	3 (11.1)	0	2 (12.5)	0
Bacterial test positive	0	0	1 (6.2)	0
Human papilloma virus test positive	1 (3.7)	0	0	0
Prothrombin fragment 1.2 increased	1 (3.7)	0	1 (6.2)	0
SARS-CoV-2 test positive	1 (3.7)	0	0	0
Urinary sediment present	0	0	1 (6.2)	0
Urine leukocyte esterase positive	0	0	1 (6.2)	0
White blood cells urine positive	0	0	1 (6.2)	0
Musculoskeletal and connective tissue disorders	2 (7.4)	3 (25.0)	3 (18.8)	2 (22.2)
Arthralgia	0	0	1 (6.2)	0
Back pain	1 (3.7)	1 (8.3)	0	1 (11.1)
Bone pain	1 (3.7)	0	0	0
Muscle spasms	0	0	0	1 (11.1)
Osteoporosis	0	1 (8.3)	0	0
Pain in extremity	0	0	2 (12.5)	0
Periarthritis	0	0	0	1 (11.1)
Rotator cuff syndrome	0	1 (8.3)	0	0
Systemic lupus erythematosus	0	1 (8.3)	0	0
Nervous system disorders	3 (11.1)	1 (8.3)	4 (25.0)	0
Dizziness	1 (3.7)	0	0	0
Headache	2 (7.4)	1 (8.3)	4 (25.0)	0
Psychiatric disorders	1 (3.7)	1 (8.3)	0	0
Anxiety	0	1 (8.3)	0	0
Depressed mood	1 (3.7)	0	0	0
Reproductive system and breast disorders	1 (3.7)	0	0	1 (11.1)
Menstruation delayed	1 (3.7)	0	0	0
Nipple pain	0	0	0	1 (11.1)
Respiratory, thoracic and mediastinal disorders	3 (11.1)	0	1 (6.2)	2 (22.2)
Cough	1 (3.7)	0	0	0
Oropharyngeal pain	2 (7.4)	0	0	1 (11.1)
Sinus congestion	0	0	1 (6.2)	0
Throat irritation	0	0	0	1 (11.1)
Skin and subcutaneous tissue disorders	1 (3.7)	0	1 (6.2)	0
Erythema marginatum	0	0	1 (6.2)	0
Hyperhidrosis	1 (3.7)	0	0	0
Rash	0	0	1 (6.2)	0
Vascular disorders	0	0	1 (6.2)	0
Hypertension	0	0	1 (6.2)	0

Source: OCS Analysis Studio, Custom Table Tool.

Columns – Dataset: Demographics; Filter: SAFFL='Y'.

Table Section 1 – Dataset: Adverse Events; Filter: TRTEMFL='Y'.

Abbreviations: COVID-19, coronavirus disease 2019; PT, preferred term; SARS-CoV-2, systemic acute respiratory syndrome coronavirus-2; SOC, system organ class; TEAE, treatment-emergent adverse event

17.1.4. Treatment-Emergent Adverse Events by Race, Trial 3001

Table 125. Subgroup Analysis by Race of TEAEs by SOC and PT, Safety Population, Trial 3001

SOC and PT	Garadacimab 200 mg				Placebo		
	Asian (N=4)	Native Hawaiian or Other Pacific Islander (N=1)	Other (N=1)	White (N=33)	Asian (N=2)	Black or African American (N=1)	White (N=22)
Cardiac disorders	0	0	0	0	0	0	1 (4.5)
Cardiovascular disorder	0	0	0	0	0	0	1 (4.5)
Congenital, familial and genetic disorders	0	0	0	1 (3.0)	0	1 (100.0)	0
Hereditary angioedema	0	0	0	1 (3.0)	0	1 (100.0)	0
Eye disorders	0	1 (100.0)	0	2 (6.1)	0	0	0
Eczema eyelids	0	1 (100.0)	0	0	0	0	0
Visual impairment	0	0	0	2 (6.1)	0	0	0
Gastrointestinal disorders	1 (25.0)	0	0	7 (21.2)	0	0	6 (27.3)
Abdominal distension	0	0	0	0	0	0	1 (4.5)
Abdominal pain	0	0	0	2 (6.1)	0	0	0
Abdominal pain lower	0	0	0	1 (3.0)	0	0	0
Constipation	0	0	0	0	0	0	1 (4.5)
Dental caries	0	0	0	0	0	0	1 (4.5)
Diarrhea	0	0	0	2 (6.1)	0	0	1 (4.5)
Dyspepsia	0	0	0	1 (3.0)	0	0	0
Food poisoning	0	0	0	1 (3.0)	0	0	0
Hemorrhoids	0	0	0	1 (3.0)	0	0	0
Nausea	0	0	0	0	0	0	3 (13.6)
Noninfective gingivitis	1 (25.0)	0	0	0	0	0	0
Toothache	0	0	0	1 (3.0)	0	0	0
General disorders and administration site conditions	1 (25.0)	0	0	3 (9.1)	1 (50.0)	0	8 (36.4)
Chest pain	0	0	0	0	0	0	1 (4.5)
Drug withdrawal syndrome	0	0	0	0	0	0	1 (4.5)
Fatigue	0	0	0	0	0	0	3 (13.6)
Feeling cold	0	0	0	1 (3.0)	0	0	0
Injection site bruising	0	0	0	1 (3.0)	0	0	0
Injection site erythema	0	0	0	1 (3.0)	0	0	2 (9.1)
Injection site pruritus	0	0	0	1 (3.0)	0	0	0
Malaise	0	0	0	1 (3.0)	0	0	0
Noncardiac chest pain	0	0	0	0	0	0	1 (4.5)
Pyrexia	1 (25.0)	0	0	0	1 (50.0)	0	1 (4.5)
Vaccination site reaction	0	0	0	0	0	0	1 (4.5)

SOC and PT	Garadacimab 200 mg				Placebo		
	Asian (N=4)	Native Hawaiian or Other Pacific Islander (N=1)	Other (N=1)	White (N=33)	Asian (N=2)	Black or African American (N=1)	White (N=22)
Infections and infestations	2 (50.0)	0	0	13 (39.4)	1 (50.0)	1 (100.0)	6 (27.3)
Bronchitis	0	0	0	1 (3.0)	0	0	0
Conjunctivitis	1 (25.0)	0	0	1 (3.0)	0	0	0
COVID-19	0	0	0	0	1 (50.0)	1 (100.0)	2 (9.1)
Gastroenteritis viral	0	0	0	0	0	0	1 (4.5)
Gastrointestinal infection	0	0	0	2 (6.1)	0	0	1 (4.5)
Helicobacter infection	0	0	0	1 (3.0)	0	0	0
Nasopharyngitis	0	0	0	3 (9.1)	0	0	1 (4.5)
Oral herpes	0	0	0	0	0	0	1 (4.5)
Otitis externa	0	0	0	1 (3.0)	0	0	0
Pyelonephritis	0	0	0	1 (3.0)	0	0	0
Rhinitis	0	0	0	1 (3.0)	0	0	0
Sinusitis	0	0	0	2 (6.1)	0	0	0
Tooth infection	0	0	0	1 (3.0)	0	0	0
Upper respiratory tract infection	1 (25.0)	0	0	4 (12.1)	0	0	2 (9.1)
Urinary tract infection	0	0	0	3 (9.1)	0	0	0
Injury, poisoning and procedural complications	0	0	0	5 (15.2)	0	0	1 (4.5)
Arthropod bite	0	0	0	1 (3.0)	0	0	0
Contusion	0	0	0	1 (3.0)	0	0	1 (4.5)
Fall	0	0	0	2 (6.1)	0	0	1 (4.5)
Limb injury	0	0	0	1 (3.0)	0	0	0
Traumatic hematoma	0	0	0	1 (3.0)	0	0	0
Investigations	1 (25.0)	0	0	3 (9.1)	1 (50.0)	0	2 (9.1)
Bacterial test positive	0	0	0	0	0	0	1 (4.5)
Crystal urine present	0	0	0	0	0	0	1 (4.5)
Human papilloma virus test positive	0	0	0	1 (3.0)	0	0	0
Occult blood positive	0	0	0	1 (3.0)	0	0	0
Protein urine present	0	0	0	0	0	0	1 (4.5)
Prothrombin fragment 1.2 increased	1 (25.0)	0	0	0	1 (50.0)	0	0
SARS-CoV-2 test positive	0	0	0	1 (3.0)	0	0	0
Urinary occult blood positive	0	0	0	0	0	0	1 (4.5)
Urinary sediment present	0	0	0	0	0	0	1 (4.5)
Urine leukocyte esterase positive	0	0	0	0	0	0	1 (4.5)
White blood cells urine positive	0	0	0	0	0	0	1 (4.5)

SOC and PT	Garadacimab 200 mg				Placebo		
	Asian (N=4)	Native Hawaiian or Other Pacific Islander (N=1)	Other (N=1)	White (N=33)	Asian (N=2)	Black or African American (N=1)	White (N=22)
Musculoskeletal and connective tissue disorders	1 (25.0)	0	0	5 (15.2)	0	0	5 (22.7)
Arthralgia	0	0	0	1 (3.0)	0	0	1 (4.5)
Back pain	1 (25.0)	0	0	1 (3.0)	0	0	1 (4.5)
Bone pain	0	0	0	1 (3.0)	0	0	0
Muscle spasms	0	0	0	0	0	0	1 (4.5)
Osteoporosis	0	0	0	1 (3.0)	0	0	0
Pain in extremity	0	0	0	0	0	0	3 (13.6)
Periarthritis	0	0	0	0	0	0	1 (4.5)
Rotator cuff syndrome	0	0	0	1 (3.0)	0	0	0
Systemic lupus erythematosus	0	0	0	1 (3.0)	0	0	0
Nervous system disorders	0	0	0	4 (12.1)	0	0	5 (22.7)
Dizziness	0	0	0	1 (3.0)	0	0	1 (4.5)
Headache	0	0	0	4 (12.1)	0	0	5 (22.7)
Psychiatric disorders	0	0	0	2 (6.1)	0	0	0
Anxiety	0	0	0	1 (3.0)	0	0	0
Depressed mood	0	0	0	1 (3.0)	0	0	0
Renal and urinary disorders	0	0	0	1 (3.0)	0	0	0
Hypertonic bladder	0	0	0	1 (3.0)	0	0	0
Reproductive system and breast disorders	0	0	0	1 (3.0)	0	0	1 (4.5)
Menstruation delayed	0	0	0	1 (3.0)	0	0	0
Nipple pain	0	0	0	0	0	0	1 (4.5)
Respiratory, thoracic and mediastinal disorders	0	0	0	3 (9.1)	0	0	3 (13.6)
Cough	0	0	0	1 (3.0)	0	0	0
Oropharyngeal pain	0	0	0	2 (6.1)	0	0	1 (4.5)
Sinus congestion	0	0	0	0	0	0	1 (4.5)
Throat irritation	0	0	0	0	0	0	1 (4.5)

SOC and PT	Garadacimab 200 mg				Placebo		
	Asian (N=4)	Native Hawaiian or Other Pacific Islander (N=1)	Other (N=1)	White (N=33)	Asian (N=2)	Black or African American (N=1)	White (N=22)
Skin and subcutaneous tissue disorders	0	0	0	1 (3.0)	0	0	1 (4.5)
Erythema marginatum	0	0	0	0	0	0	1 (4.5)
Hyperhidrosis	0	0	0	1 (3.0)	0	0	0
Rash	0	0	0	0	0	0	1 (4.5)
Vascular disorders	0	0	0	0	1 (50.0)	0	0
Hypertension	0	0	0	0	1 (50.0)	0	0

Source: OCS Analysis Studio, Custom Table Tool.

Columns – Dataset: Demographics; Filter: SAFFL='Y'.

Table Section 1 – Dataset: Adverse Events; Filter: SAFFL='Y'.

Abbreviations: COVID-19, coronavirus disease 2019; PT, preferred term; SARS-CoV-2, systemic acute respiratory syndrome coronavirus-2; SOC, system organ class; TEAE, treatment-emergent adverse event

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Drug resistance is not applicable.

20. Mechanism of Action/Drug Resistance

Not applicable.

21. Other Drug Development Considerations

Not applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

For this BLA 761367, two clinical investigators, Drs Joshua Jacobs and Timothy Craig, and the Applicant CSL Behring, LLC were inspected, covering two clinical studies: trial 3001 and study 3002. Based on the inspections, the studies appeared to have been adequately conducted, and the data generated by the clinical investigator sites and submitted by the Applicant appeared acceptable in support of this BLA.

During the clinical investigator inspections, the source records related to the primary efficacy endpoint and HAE attack characteristics (attack location, attack severity, on-demand therapies used (if any) and trigger for attack) were reviewed and verified against the Applicant's line listings for the subjects. The inspections did not identify discrepancies related to the documentation of the number of HAE attacks, which served as the basis for the primary efficacy endpoint.

During Dr Jacob's clinical site inspection, several discrepancies pertaining to the location of the HAE attack and attack trigger were identified when comparing the source documents with the Applicant's line listings. Some of the discrepancies were due to a limitation within the case report form and the electronic data capture system, which only allowed three entries per anatomical location. As a result, some of the attack locations were grouped into general body areas. See the Clinical Inspection Summary dated August 22, 2024, for additional details. The discrepancies related to the attack location and trigger did not affect the primary efficacy endpoint.

23. Labeling: Key Changes and Considerations

This PI review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant’s draft PI (Table 126). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 126. Key Labeling Changes and Considerations

Full PI Sections ¹	Rationale for Major Changes to FDA Revised PI ² Compared to Applicant’s Draft PI
1 INDICATIONS AND USAGE	No changes – the indication statement is consistent with other approved product labeling for HAE prophylactic therapies
2 DOSAGE AND ADMINISTRATION	The recommended dosage of ANDEMBRY is an initial loading dose of 400 mg (two 200 mg injections) administered subcutaneously on the first day of treatment followed by a maintenance dose of 200 mg administered subcutaneously every month. A preparation and administration instructions subsection were added to Section 2 to provide healthcare providers with instructions for the use of ANDEMBRY, which is intended for self-administration by the patient and/or caregiver. Therefore, the HCP are instructed to (b) (4) patients for subcutaneous injection technique.
4 CONTRAINDICATIONS	None – no changes
5 WARNINGS AND PRECAUTIONS	(b) (4) (b) (4) (b) (4)
6 ADVERSE REACTIONS	- The proposed label lacked information regarding the number of adult and adolescent subjects who had been exposed to garadacimab, specifically subjects who had served as the basis for the safety evaluation. The review team added language that the Clinical Trials Experience subsection reflects the safety of ANDEMBRY from the exposure of 161 adult and adolescent patients aged 12 years and older who received at least one dose of ANDEMBRY 200 mg subcutaneously. (b) (4) injection site reactions, which occurred more frequently in the placebo arm in trial 3001 (VANGUARD), as an adverse reaction. A revised adverse drugs reaction table included TEAEs that occurred with ≥7% frequency with garadacimab treatment and greater than placebo. - A new subheading for prolonged coagulation lab parameters was added to convey that abnormal aPTT and PT findings were observed in trial 3001 but were not associated with increased risk of bleeding, as this may be useful information for providers. Given that the lab tests are not clinically significant findings, the results were not added to the ADR table, but as a separate lab test subheading. This information was included in Section 6 rather than 12 because it was observed too infrequently to be considered a PD finding.

Full PI Sections ¹	Rationale for Major Changes to FDA Revised PI ² Compared to Applicant's Draft PI
7 DRUG INTERACTIONS	A Drug-Laboratory test interaction is provided because ANDEMBRY can prolong activated partial thromboplastin time (aPTT). The reagents used in the aPTT laboratory test initiates an intrinsic coagulation through the activation of FXII, inhibiting plasma FXIIa by ANDEMBRY and can prolong aPTT in the assay.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Exposure numbers in pediatric and geriatric patients were revised to reflect those in trial 3001; [REDACTED] (b) (4). Although exposure in geriatric patients was limited, the review team concluded that there were no differences in safety/effectiveness by age, consistent with other approved product labels.
10 OVERDOSAGE	This section is removed and omitted from the PI because no specific overdose data were available.
12 CLINICAL PHARMACOLOGY	[REDACTED] (b) (4) Observed PK data following a single 200 mg dose was added as it included rich PK sampling from the largest sample size across the Applicant's clinical program. Language was added to describe garadacimab exposure in adolescent patients relative to adult patients.
13 NONCLINICAL TOXICOLOGY	- Language was added to state that animal studies were not conducted to evaluate the carcinogenic or mutagenic potential of garadacimab-xxxx. - Language for fertility and reproductive performance was added based on animal data from mature male and female rabbits.
14 CLINICAL STUDIES	- New table inserted with patient demographics and baseline disease characteristics - Table 4 revised and [REDACTED] (b) (4) [REDACTED] (b) (4) was removed as this information is duplicative with the primary endpoint. - Result for the prespecified secondary endpoints of number of HAE attacks treated with on-demand medication and number of moderate or severe HAE attacks were [REDACTED] (b) (4). Although not multiplicity controlled, these are clinically relevant outcomes included in other HAE product labeling. - Prespecified secondary endpoints of proportion of patients with ≥50, 70, 90, 100% reduction during Treatment Period versus run-in were considered clinically meaningful and retained as labeling claims with revisions. These labeling claims are also included in other approved HAE product labels. [REDACTED] (b) (4)

Full PI Sections ¹	Rationale for Major Changes to FDA Revised PI ² Compared to Applicant's Draft PI
	(b) (4)
17 PATIENT COUNSELING INFORMATION	The self-administration counseling information was included in this section for HCP to instruct (b) (4) patients for self-administration of ANDEMBRY.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	- The strength of ANDEMBRY autoinjector was revised to reflect the total dose per volume (200 mg/1.2 mL) (b) (4) consistent with Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022). - The stability data in Section 16 was revised to reflect the appropriate in-use condition with sufficient data support.

Source: Reviewer generated using Applicant's draft PI

¹ Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.

² For the purposes of this document, the FDA revised PI is the PI that was conveyed in the final labeling IR of the review cycle. Abbreviations: FXII, Factor XII, HCP, healthcare professional; PI, Prescribing Information; PK, pharmacokinetics; PLLR, Pregnancy and Lactation Labelling; QTc, corrected QT interval

23.1. Approved Labeling Types

The following labeling documents were reviewed:

- Prescribing Information
- Patient Package Insert
- Instructions for Use
- Carton/container

The substantially complete PI, Patient Package Insert, and Instructions for Use will need to be reviewed by the labeling consultants (DMEPA, OPDP, and DMPP/Patient Labeling) during the resubmission review cycle.

24. Postmarketing Requirements and Commitments

Not applicable; however, no postmarketing requirements or commitments are needed based on the current review.

25. Financial Disclosure

Table 127. Covered Clinical Studies: 2001, 3001, and 3002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 31		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3 (b) (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: For study CSL312_2001, (b) (6) received payments totaling \$82,450 in compensation from CSLB grants, equipment, ongoing consultation, or honoraria. (b) (6) site had (b) (6) subjects consented. For study CSL312_3001, (b) (6) received payments totaling \$70,000 in compensation from CSLB grants, equipment, ongoing consultation or honoraria. (b) (6) site had (b) (6) subjects consented to the study. For study CSL312_3001, (b) (6) received payments totaling over \$50,000 in compensation from CSLB speaking fees and advisory honoraria. (b) (6) had (b) (6) subjects consented to the study. For study CSL312_3002, (b) (6) received payments totaling over \$25,000 in compensation from CSLB speaking fees and consulting arrangements. (b) (6) had (b) (6) subjects consented to the study. For study CSL312_3002, (b) (6) received payments totaling over \$50,000 in compensation from CSLB speaking fees and advisory honoraria. (b) (6) had (b) (6) subjects consented to the study. Significant payments of other sorts: see above Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator: None Sponsor of covered study: CSL Behring		
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): Not Applicable		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

Literature and Websites

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February, 2013, Guidance for Industry; Financial Disclosure by Clinical Investigators, accessed August 27, 2020, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/financial-disclosure-clinical-investigators>.

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27. Review Team

Table 128. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project managers	Nina Ton, Ladan Jafari, Brandi Wheeler
Nonclinical reviewer	Yu-Chen Tsai
Nonclinical team leader	Tim Robison
Division director (DPTII)	Andrew Goodwin
OCP reviewers	Amer Al-Khouja, Huali Wu, Joseph Roman
OCP team leaders	Yunzhao Ren, Jingyu Yu, Sarah Dorff
Deputy division director (DIIP/OCP)	Suresh Doddapaneni
Clinical reviewer	Canting Guo
Clinical team leader	Stacy Chin
Biometrics reviewer	Robert Tumasian
Biometrics team leader	Yongman Kim
Supervisory statistician (OB)	Weiya Zhang
Associate director for labeling	Jessica Lee
Cross-disciplinary team leader	Stacy Chin
Associate director for therapeutic review (DPACC)	Kelly Stone
Office deputy director (OII)	Kathleen Donohue

Abbreviations: DIIP, Division of Inflammation and Immune Pharmacology; DPACC, Division of Pulmonology, Allergy, and Critical Care; DPTII, Division of Pharmacology and Toxicology II; OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology; OII, Office of Immunology and Inflammation

Table 129. Additional Reviewers of Application

Office or Discipline	Names
OPQ	Arnold Seo, Lei Zhang (ATL), Yan Wang
OPMA	Hamet Touré, Virginia Carroll, Madushini Dharmasena, Candace Gomez-Broughton
OPQ Labeling	Diana Pei, Liming Lu
OPQ RBPM	Hannah Lee
DCOA	Ji Li, Onyekachukwu Illoh
OPDP	Quynh-Nhu Capasso, Adewale Adeleye
Patient Labeling	Mary Carroll, Marcia Williams
OSI	Suyoung Tina Chang, Phillip Kronstein
OSIS	Yiyue Zhang, Gopa Biswas
OSE/DEPI	Alice Cheng Chen, Mingfeng Zhang
OSE/DMEPA	Carlos Mena-Grillasca, Lissa Owens, Damon Birkemeier
OSE/DPV	Laura Kangas, Michelle Hines
OSE/DRM	Lindsey Crist, Jackie Sheppard
OSE SRPM	Cristina Attinello, Ameet Joshi
CDRH	Shruti Mistry, Janice Ferguson
Human Factors	Neha Kumar, Murewa Oguntimein
QT-IRT	Eliford Kitabi, Oluseyi Adeniyi
Clinical Data Scientists	Merve Kasap, Deangelo McKinley
Medical Editors	Quinn Laffin, Graeme O'May

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPMA, Office of Pharmaceutical Manufacturing Assessment; RBPM, Regulatory Business Process Manager; DCOA, Division of Clinical Outcomes Assessments; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSIS, Office of Study Integrity and Surveillance, OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPV, Division of Pharmacovigilance; DRM, Division of Risk Management; SRPM, Safety Regulatory Project Manager; CDRH, Center for Devices and Radiological Health; QT-IRT, QT Interdisciplinary Review Team

27.1. Reviewer Signatures

Table 27-130 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Tertiary Reviewer	Kelly Stone OII DPACC	Sections: All	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Kelly Stone Digitally signed by Kelly Stone Date: 10/4/2024 1:56 PM EDT GUID: 2024104175647				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Andrew Goodwin OII DPTII	Sections: 5.1, 7.1, 7.7, 13, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Andrew Goodwin Digitally signed by Andrew Goodwin Date: 10/4/2024 1:57 PM EDT GUID: 2024104175712				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Timothy Robison OII DPTII	Sections: 5.1, 7.1, 8.4, and 13.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	The nonclinical program is adequate to support approval. There are no outstanding nonclinical issues.

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Timothy Robison Digitally signed by Timothy Robison Date: 10/4/2024 2:05 PM EDT GUID: 202410418517				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Amer Al- Khouja OCP DIIP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Amer Al-Khouja Digitally signed by Amer Al-Khouja Date: 10/4/2024 2:13 PM EDT GUID: 2024104181353				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Phuong Ton ORO DROII	Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Phuong Ton Digitally signed by Phuong Ton Date: 10/4/2024 2:14 PM EDT GUID: 2024104181423				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Brandi Wheeler ORO DROII	Sections: Section 12 Summary of Regulatory History	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Brandi Wheeler Digitally signed by Brandi Wheeler Sign on behalf of Signing on behalf of Ladan Jafari Date: 10/4/2024 2:14 PM EDT GUID: 2024104181441				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/OBP) Discipline Primary Reviewer	Arnold Seo OPQAIH DPQAXIV	Sections: 9. Product Quality	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Arnold Seo Digitally signed by Arnold Seo Date: 10/4/2024 2:15 PM EDT GUID: 2024104181512				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Genomics Reviewer Discipline Primary Reviewer	Joseph Roman OCP DTPM	Sections: 6.3.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Joseph Roman Digitally signed by Joseph Roman Date: 10/4/2024 2:28 PM EDT GUID: 2024104182849				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Secondary Reviewer	Jingyu Yu OCP DPM	Sections: 6.3.4.	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
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		Date: 10/4/2024 2:32 PM EDT GUID: 2024104183220		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Stacy Chin OII DPACC	Sections: 1, 2, 3, 4, 6, 7, 10, 11, 15, 16, 17, 22, 23, 24, 25, 26	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	however, product quality and facility deficiencies preclude approval
Signature: Stacy Chin		Digitally signed by Stacy Chin		
		Date: 10/4/2024 2:36 PM EDT GUID: 2024104183642		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Stacy Chin OII DPACC	Sections: 23	Based on my assessment of the application: ☐ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Stacy Chin				
Digitally signed by Stacy Chin				
Date: 10/4/2024 2:37 PM EDT GUID: 2024104183724				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Robert Tumasian Iii OB DBIII	Sections: 6, 15-16, 23-26	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Robert Tumasian Iii				
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Date: 10/4/2024 2:40 PM EDT GUID: 202410418405				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Yongman Kim OB DBIII	Sections: 6, 15-16, 23-26	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Yongman Kim Digitally signed by Yongman Kim Date: 10/4/2024 2:55 PM EDT GUID: 2024104185546				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Canting Guo OII/CDER DPACC	Sections: 1, 2, 3, 4, 6, 7, 10, 11, 15, 16, 17, 22, 23, 24, 25, 26	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	From a clinical perspective, the clinical risk-benefit assessment is favorable and there are no deficiencies to preclude approval. I concur with OPQ and OPMA's recommendation for a CR due to microbiology, product quality and facility inspection deficiencies.
Signature: Canting Guo Digitally signed by Canting Guo Date: 10/4/2024 3:05 PM EDT GUID: 202410419515				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Jessica Lee OII DPACC	Sections: 23	Based on my assessment of the application: ☐ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Jessica Lee Digitally signed by Jessica Lee Date: 10/4/2024 3:20 PM EDT GUID: 202410419203				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/OBP) Discipline Secondary Reviewer	Lei Zhang OPQAIH DPQAXIV	Sections: 9	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Lei Zhang Digitally signed by Lei Zhang Date: 10/4/2024 3:40 PM EDT GUID: 2024104194022				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Yunzhao Ren OCP DIIP	Sections: 6.3.4.	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Yunzhao Ren Digitally signed by Yunzhao Ren Date: 10/4/2024 3:43 PM EDT GUID: 2024104194334				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Suresh Doddapaneni OCP DIIP	Sections: 6.3.4.	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Suresh Doddapaneni Digitally signed by Suresh Doddapaneni Date: 10/4/2024 5:34 PM EDT GUID: 2024104213425				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Huali Wu OCP DPM	Sections: 14.5	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Huali Wu Digitally signed by Huali Wu Date: 10/4/2024 7:16 PM EDT GUID: 2024104231615				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Ping Ji OCP DIIP	Sections: 6.3.4.	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Ping Ji Digitally signed by Ping Ji Date: 10/4/2024 8:00 PM EDT GUID: 20241050020				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/OBP) Discipline Tertiary Reviewer	Yan Wang OPQAIH DPQAXIV	Sections: 9	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
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		Date: 10/7/2024 9:09 AM EDT GUID: 202410713927		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Yu-Chen Tsai OII DPTII	Sections: 5, 13	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yu-Chen Tsai		Digitally signed by Yu-Chen Tsai		
		Date: 10/7/2024 10:12 AM EDT GUID: 2024107141258		

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/s/

STACY J CHIN
10/04/2024 02:38:27 PM

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KATHLEEN M DONOHUE
10/07/2024 11:02:08 AM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY BLA ASSESSMENT AND EVALUATION

Application Number*: 761367

Supporting Document Number/s: SDN 9 and 23

CDER Receipt Date: 10/13/2023 (SDN 9) and 3/28/2024 (SDN 23)

Sponsor: CSL Behring LLC

Product: Garadacimab

Pharmacologic Class: activated Factor XII (FXIIa) inhibitor
monoclonal antibody

Indication: Prophylaxis to prevent attacks of hereditary
angioedema (HAE)

Therapeutic area: Allergy and Immunology

Clinical Review Division: Division of Pulmonology, Allergy and
Critical Care (DPACC)

Pharm/Tox Division: Division of Pharm/Tox for Immunology and
Inflammation (DPT-II)

Reviewer: Yu-Chen Tsai, PhD

Supervisor/Team Leader: Timothy Robison, PhD, D.A.B.T.

Project Manager: Phuong Nina Ton

Purpose of Review: Other

Safety assessment of Extractables and
Leachables from the Container Closure
System (CCS), a prefilled syringe (PFS)

Reviewer Completion Date: June 5, 2024

Template Version: Sep 11, 2020

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY 3

 1.1 INTRODUCTION 3

 1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS 3

2 DRUG INFORMATION 4

 2.1 DRUG 4

 2.2 RELEVANT IND 5

 2.3 DRUG FORMULATION 6

 THE CONTAINER CLOSURE SYSTEM FOR CSL312 SFP 200MG (b) (4) 6

 (b) (4) 6

 2.4 COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN 7

 2.5 PROPOSED CLINICAL POPULATION AND DOSING REGIMEN 8

 2.6 REGULATORY BACKGROUND 8

3 STUDIES SUBMITTED 9

 3.1 STUDIES REVIEWED 9

 3.2 PREVIOUS REVIEWS REFERENCED 9

11 INTEGRATED SUMMARY AND SAFETY EVALUATION 9

 EXTRACTABLES 10

 LEACHABLES 12

 TOXICOLOGICAL RISK ASSESSMENT: (b) (4) 14

 TOXICOLOGICAL RISK ASSESSMENT: (b) (4) 15

 ELEMENTAL IMPURITIES 15

 OVERALL CONCLUSION 16

 REFERENCE 16

1 Executive Summary

1.1 Introduction

The Sponsor is developing CSL312 (garadacimab), an activated Factor XII (FXIIa) inhibitor monoclonal antibody for prophylaxis to prevent attacks of hereditary angioedema (HAE). CSL312 has been developed as a combination product incorporating a prefilled syringe which contains 200 mg of the formulated CSL312 active substance, defined as the CSL312 semi-finished product (SFP) 200 mg. Extractables and leachables studies were conducted with the container closure system that were evaluated in the present review.

1.2 Brief Discussion of Nonclinical Findings

Based on a Safety Concern Threshold (SCT) of (b) (4) µg/day, the Analytical Evaluation Threshold (AET) for CSL312 SFP 200mg was calculated to be (b) (4) µg/mL.

The PFS consists of (b) (4). CSL312 DP 200mg NSD contains one fixed dose for a single subcutaneous injection.

An extractable study was performed on (b) (4) rubber stopper. Eleven substances were identified at detectable levels as well as (b) (4). Compared to the qualification threshold (QT) of (b) (4) µg/day, which is applicable to non-genotoxic compounds, only the level of (b) (4) exceeded the QT. However, in both the initial and long-term leachable studies, (b) (4) was not observed above the AET.

To assess potential leachables in CSL312 SFP 200mg (PFS), a leachable profiling study was performed on one batch (batch P100172586) shortly after its production. In addition, to monitor leachables that might arise during its shelf life, the same batch of CSL312 SFP 200mg (PFS) was also tested after storage for 34 months at (b) (4). Among the identified leachables, only the level of (b) (4) was above the QT of (b) (4) µg/day. An assessment indicated that the level of (b) (4) does not pose a toxicological concern.

Levels of elemental (metal) leachables were also determined to pose no safety concerns.

In conclusion, the levels of leachables from the primary container closure system of CSL312 SFP 200mg do not appear to pose any safety concerns. The assessment was not ideal as only 1 batch was evaluated.

1.3.2 Nonclinical Comments to Sponsor

None.

2 Drug Information

2.1 Drug

CAS Registry Number:

2162134-62-3

Generic Name

Garadacimab

Code Names:

CSL312

Chemical Name

Human IgG4 monoclonal antibody that binds to activated human coagulation factor XII (FXIIa)

Molecular Formula/Molecular Weight

Human monoclonal Ab/ 148.2 kDa

Structure or Biochemical Description

CSL312 is a fully human IgG4 monoclonal antibody comprised of two heavy and two light chains, joined by disulfide bonds. CSL312 binds to activated human coagulation factor XII (FXIIa) and inhibits its catalytic activity.

Table 1. Amino acid sequence of CSL312 heavy and light chains

a) *CSL312 heavy chain amino acid sequence*

1	(b) (4)	50
51		100
101		150
151		200
201		250
251		300
301		350
351		400
401		450
451		456

b) *CSL312 lambda light chain amino acid sequence*

1	<u>QSVLTQPPSASGTPGQRVTISCSGSSSNIGRNYVYWYQQLPGTAPKLLIY</u>	50
51	<u>SNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDASLRGVF</u>	100
101	<u>GGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVA</u>	150
151	<u>WKADSSPVKAGVETTTPSKQSNKYAASSYLSLTPEQWKSHRSYSCQVTH</u>	200
201	EGSTVEKTVAPTECS	

(a) CSL312 heavy chain amino acid sequence. **Red:** heavy chain variable region sequence; **Black:** heavy chain constant region. (b) (4) of the heavy chain is underlined/bold.

(b) CSL312 lambda light chain amino acid sequence. **Blue:** lambda light chain variable region sequence; **Grey:** lambda light chain constant region.

(Excerpted from Sponsor submission)

Pharmacologic Class

FXIIa ligand inhibitor (proposed)

2.2 Relevant IND

Application #	Division	Indication	Current Status (Date)
IND 139936	DPACC	Prevention of hereditary angioedema (HAE) attacks in adult patients with HAE	Active (07/14/2018)

2.3 Drug Formulation

CSL312 SFP (Semi-Finished Product, to be combined with injection device as the final drug product) 200mg is presented as a sterile liquid solution. The composition of the ingredients for CSL312 SFP 200mg is listed below.

Table 2. Composition of CSL312 SFP 200mg

Name of ingredient	(b) (4)	Nominal concentration	Function	Compliance
CSL312 API	204 mg	170 mg/mL	(b) (4)	See Section 3.2.S.4.1
L-Histidine	3.7 mg	20 mM	(b) (4)	Ph. Eur., USP, JP
(b) (4) Arginine monohydrochloride	37.9 mg	150 mM	(b) (4)	Ph. Eur., USP, JP
L-Proline	19.3 mg	140 mM	(b) (4)	Ph. Eur., USP
Polysorbate 80	0.24 mg	0.02% w/w	(b) (4)	Ph. Eur., USP/NF, JP
Water for Injection (WFI)	(b) (4)	(b) (4)	(b) (4)	Ph. Eur., USP

API: Active pharmaceutical ingredient

^a Related to a nominal volume of 1.2 mL. The setpoint for the filling volume is (b) (4) mL to ensure that the claimed volume is administered

(Excerpted from Sponsor submission)

The container closure system for CSL312 SFP 200mg is (b) (4)

[Redacted]

Table 3. Container closure system for CSL312 SFP 200mg

Table 3.2.P.7-1 Container Closure System for CSL312 SFP 200mg

(b) (4)



a Not in contact with the liquid

(Excerpted from Sponsor submission)

The PFS is housed inside an Auto-Injector (AI).

2.4 Comments on Impurities/Degradants of Concern

The CSL312 SFP 200 mg was studied for extractables and leachables. An extractable study was performed on (b) (4) rubber plunger stopper with (b) (4). Leachable profiling studies were performed on CSL312 SFP 200mg at an initial timepoint, and after storage of the SFP for 34 months at (b) (4).

The safety assessment of extractables and leachables from the primary container is described in Section 11.

Table 4. Schematic Representation of the Device Assembly Process with the CSL312 SFP 200 mg to Manufacture CSL312 DP 200 mg NSD or CSL312 DP 200 mg AI



SFP= Semi-Finished Product, AI = autoinjector; DP = drug product; NSD = Needle Safety Device.
(Excerpted from Sponsor submission)

2.5 Proposed Clinical Population and Dosing Regimen

The recommended dose of Garadacimab (CSL312) is an initial loading dose of 400 mg administered subcutaneously as two 200 mg injections on the first day of treatment followed by a monthly dose of 200 mg to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients (aged 12 years and older).

2.6 Regulatory Background

BLA 761367 was submitted to the FDA on October 13, 2023. Upon reviewing the extractable and leachable information, one information request was sent to the Sponsor on March 25, 2024. The responses from the Sponsor were included in the current review.

1. IR dated 03/25/2024

We are reviewing your October 13, 2023, submission, and have the following request for information.

In Section 3.2.P.5.5 of your submission, Characterization of Impurities, results of extractable and leachable studies were summarized.

1. This included an extractable study summary (Section 3.2.P.5.5-1, Document ES-505-01). However, original study reports are needed for our review (Study ID 3790041 and 4945673). Provide original study reports of extractable studies or if they were submitted, direct us to their location in the application.
2. For each identified extractable and leachable, provide information of maximum patient exposure on a $\mu\text{g}/\text{day}$ or $\mu\text{g}/\text{dose}$ basis.

In order to facilitate the review of your submission, submit the requested information to your BLA no later than April 3, 2024.

3 Studies Submitted

3.1 Studies Reviewed

The Sponsor's summaries as well as laboratory reports of the extractables and leachables studies with the primary container system were reviewed to conduct safety assessments of the levels of extractables and leachables.

3.2 Previous Reviews Referenced

None.

11 Integrated Summary and Safety Evaluation

CSL312 drug substance contains CSL312 monoclonal antibody (active ingredient) in a buffer containing 20 mM Histidine, 150 mM Arginine, 140 mM Proline and 0.02% w/v Polysorbate 80, pH 6.1.

The container-closure system for CSL312 SFP 200mg is (b) (4). During storage of CSL312 SFP 200mg, the liquid solution has (b) (4) contact with the (b) (4) container closure system including (b) (4).

(b) (4). The presence of Polysorbate 80, a non-ionic detergent, in the CSL312 SFP liquid formulation, may increase the potential for materials to leach from materials in contact with the liquid.

A standalone extraction study was conducted with plunger stopper as this was considered the primary source of extractables and leachable. To assess leachables in CSL312 SFP 200mg resulting from the manufacturing process and/or storage, leachable profiling studies were performed on CSL312 SFP 200mg at an initial timepoint, and after storage of the SFP for 34 months at (b) (4).

Per PQRI (Product Quality Research Institute) guidelines, an Analytical Evaluation Threshold (AET) for organic extractables and leachables in the CSL312 SFP 200mg was calculated to be (b) (4) $\mu\text{g}/\text{mL}$ using the Safety Concern Threshold (SCT) of (b) (4).

µg/day based on the following equation and worst-case assumptions: 1 labeled dose per container, 2 containers per day (i.e., for the loading dose of 400 mg, two containers are used), and 1.2 mL per container.

Estimated AET = [REDACTED] (b) (4)

Extractables

An extractables study (Study # 3790041) was performed on [REDACTED] (b) (4) rubber stopper with [REDACTED] (b) (4). The extraction conditions were: 1) static extraction (PBS buffer at pH 2.5 and pH 9.5, and 50% aqueous ethanol solution (v/v) at 50°C for 24 hours), analyzed by headspace gas chromatography with mass spectrometry (HS-GC-MS); 2) thermal extraction at 80°C for 1 hour, analyzed by gas chromatography with flame ionization detection and mass spectrometry (GC-FID/MS), gas chromatography with flame ionization detection (GCFID) ([REDACTED] (b) (4)), high-performance liquid chromatography with diode array detector and mass spectrometry (HPLC-DAD/MS), mass spectrometry with inductively coupled plasma (ICP-MS); and 3) Soxhlet extraction performed with methanol, analyzed by gas chromatography with thermal energy analysis (GC-TEA) ([REDACTED] (b) (4)).

The Analytical Threshold (AT) reference solution was set to [REDACTED] (b) (4) µg/mL. The AT is acceptable, as it is lower than AET of [REDACTED] (b) (4) µg/mL and therefore is sensitive enough. To reach the final AT concentration in the samples for analysis, 10 pieces of rubber stopper were extracted with 150 ml of solvent. Eleven extractables were identified and presented in the table below.

Table 5. Identified extractables in the extractable study (Study # 3790041)

Identified Substances	Amount [µg/g]	CAS #	Detection Method
(b) (4)			HS-GC-MS
			HS-GC-MS
			HS-GC-MS
			HS-GC-MS
			HS-GC-MS
			GC-FID/MS
			GC-FID/MS
			GC-FID/MS
			GC-FID/MS
			GC-FID (b) (4)
			GC-FID (b) (4)

(Excerpted from Sponsor submission)

For (b) (4) (in Study # 4945673), five glass vials filled with water for injection (WFI, 6 ml) and closed with a (b) (4) rubber stopper were extracted sequentially with Toluene. Subsequently, the Toluene extract was analyzed by THGA - AAS (Transversely Heated Graphite Atomizer Atomic Absorption Spectroscopy) to determine (b) (4).

Table 6. Identified substances in the (b) (4) extractable study (Study # 4945673)

Identified Substances	Amount [µg/vial]
(b) (4)	

(Excerpted from Sponsor submission)

For calculation of maximum patient exposure (µg/dose), the amounts of identified extractable substances (in µg/g) were converted by multiplying by 0.8 g (2 stoppers for 2 doses; each syringe stopper weights 0.4 g).

Table 7. Extractable substance and calculation of maximum patient exposure (µg/dose)

Extractable substance	Amount [µg/g]	Calculation of maximum patient exposure [µg/dose]
(b) (4)		

1 Determination of (b) (4) was performed with vials closed with stoppers with a weight of 1.8g/stopper. The reported value of (b) (4) µg/vial (per vial one stopper) was converted to µg/g.

(Excerpted from Sponsor submission)

Eleven substances were identified at detectable levels, as well as (b) (4). Compared to the QT of (b) (4) µg/day, only the maximum patient exposure to (b) (4) exceeded this level. However, in both the initial and long-term leachable studies, (b) (4) was not identified to be greater than AET.

Leachables

To assess potential leachables in CSL312 SFP 200mg (PFS), a leachable profiling study was performed on one batch (batch P100172586) shortly after its production (Study # 5366678). To monitor leachables that might arise during its shelf life, the same batch of CSL312 SFP 200mg (PFS) was also tested after storage for 34 months at (b) (4) (Study # 6379671).

In the initial profiling study (Study # 5366678) and end of shelf life study (Study #6379671), semi-volatile organic compounds were profiled by gas chromatography with flame ionization detection and mass spectrometry (GC-FID/MS), while non-volatile substances were profiled by high performance liquid chromatography with diode array detector and mass spectrometry (HPLC-DAD/MS). In addition, (b) (4) content was profiled by transversely heated graphite atomizer – atomic adsorption spectroscopy (THGA-AAS). Elemental impurities were profiled using inductively coupled plasma mass spectrometric detection (see below). The analytical threshold (AT) for identification of leachables was set to (b) (4) µg/mL. The (b) (4) content detected with THGA-AAS corresponds to (b) (4) µg/mL. The AT is acceptable, as it is lower than AET of (b) (4) µg/mL and therefore is sensitive enough. In the end of shelf life/long-term storage study (Study # 6379671), the AT remained to be (b) (4) µg/mL, which is acceptable.

The table below shows the compounds identified in CSL312 SFP 200mg with amounts at or above the AT as a comparison for both time points (i.e., initial study vs. long-term storage). The amount values were used to calculate maximum patient exposures.

Table 8. Results for GC-FID/MS and HPLC-DAD/MS with Amounts ≥ AT Level of (b) (4) µg/mL

Substance	Identified Substances (CAS#)	Amount (µg/mL) initial study	Amount (µg/mL) long-term storage	Analytical Method
(b) (4)			(b) (4)	GC-FID/MS
				HPLC-DAD/MS
				GC-FID/MS
				HPLC-DAD/MS
				HPLC-DAD/MS
				HPLC-DAD/MS

- a Identification was possible in long-term study, reported as “unknown” in initial study
- b Results from both studies were compared by RRT (MBR-VAL-000552453 “6379671: Leachables Screening CSL312 syringes end of shelf life”). Peak association was only possible by chromatogram peak shape, as no mass peaks could be associated with the signals in the initial study (MBR-VAL-000523520 “5366678: Leachables Profiling CSL312)

(Excerpted from Sponsor submission)

For calculation of maximum patient exposure (µg/dose), leachables study results were reported in µg substance per mL product and were converted to µg substance per maximum patient dose (2.4 mL corresponding to two syringes for the loading dose of 400 mg, see the table below). Among the leachables identified, only one ((b) (4)) was above the QT of (b) (4) µg/day, and required a risk assessment which is provided in paragraphs below. The rest of the observed leachables were judged to pose no safety concerns.

Table 9. Leachable substance and calculation of maximum patient exposure [µg/dose]

Leachable substance	Amount [µg/mL]	Calculation of maximum patient exposure [µg/dose]
(b) (4)		

(Excerpted from Sponsor submission)

Toxicological Risk Assessment: (b) (4)

(b) (4)

(b) (4)

For CSL312 SFP 200mg, the maximum patient exposure is (b) (4) µg of (b) (4)

(b) (4)
as a leachable does not pose a toxicological concern.

Table 10. Structure of (b) (4)A large rectangular area of the document is completely redacted with a solid grey fill. The redaction covers the entire content of Table 10.

(Excerpted from Sponsor submission)

Toxicological Risk Assessment: (b) (4)

The maximum patient exposures of (b) (4) were (b) (4) and (b) (4) µg, from extractable and leachable studies, respectively. Both values were lower than the QT of (b) (4) µg/day, and a risk assessment was not needed.

The summary formula of (b) (4) (see figure below).

Table 11. (b) (4)A large rectangular area of the document is completely redacted with a solid grey fill. The redaction covers the entire content of Table 11.

(Excerpted from Sponsor submission)

Elemental Impurities

Elemental Impurities were profiled using inductively coupled plasma mass spectrometric detection (ICP-MS) in the long-term storage study (Study # 6379671). The results are summarized in the table below. All detectable elemental impurities remain below limits defined in ICH Q3D(R2), and therefore pose no safety concerns.

Table 12. Results for ICP-MS after Long-term Storage with Amounts $\geq$ LOQ Level

Compound	CAS #	Amount ($\mu\text{g/mL}$)	LOQ ($\mu\text{g/mL}$)
(b) (4)			

(Excerpted from Sponsor submission)

Overall Conclusion

In conclusion, it was concluded that the observed levels of leachables from the primary container closure of CSL312 SFP 200mg do not appear to pose any safety concerns. The assessment limited to 1 batch was not considered ideal.

Reference

(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YU-CHEN TSAI
06/05/2024 04:07:48 PM

TIMOTHY W ROBISON
06/05/2024 05:02:16 PM
I concur