STATISTICAL ANALYSIS PLAN

Version Number: 2.0

Protocol Title: A Phase 2, Open-label, Multicenter, Dose Selection Study to Evaluate the Safety and Tolerability of CAEL-101 in Patients With AL Amyloidosis

Protocol Number: CAEL101-203 Protocol Amendment 3

Compound: CAEL-101

Short Title: A Phase 2 Study of CAEL-101 to Evaluate the Safety and Tolerability in Patients With AL Amyloidosis

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VERSION HISTORY

This statistical analysis plan (SAP) for Study CAEL101-203 is based on Protocol Amendment 3, dated 18 Jul 2022.

SAP Version	Version Date	Change	Rationale
1.0	20 March 2023	Original	Final version
2.0	25 April 2024	Additional Analyses added	• Added the following analyses: 1. Graded renal response 2. Graded cardiac response 3. Deep Hematologic response 4. Summary of subsequent lines of anti-PCD therapy 5. Cardiac, renal, and liver (hepatic) response by hematologic response 6. Time to first organ response, time to graded first response 7. Adverse events by SMQ 8. Summaries of liver enzymes and eDISH plot • Added visit windowing for End of Treatment visits • Added clarity for the definition of concomitant medication • Updated the cohort being presented for the CSR • Added the equation to be used for eGFR calculation • Added spaghetti plots for all biomarkers

APPROVAL SIGNATURES

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Date

1. INTRODUCTION

This is a Phase 2 study that was designed sequentially and was amended dynamically to allow for identification of the optimal dose to carry forward into Phase 3, as well as to assess the safety and tolerability of the said dose in combination with multiple plasma cell dyscrasia concomitant medications. The study itself has 2 parts as follows:

- Part A: designed to determine the recommended Phase 3 dose (RP3D) and define the safety and tolerability of CAEL-101 in combination with standard-of-care cyclophosphamide, bortezomib, and dexamethasone (CyBorD). The outcomes from the first 4 weeks of treatment (i.e., the dose-limiting toxicity [DLT] Observation Period) formed the basis for the determination of the dosing regimen for the Phase 3 study.
- Part B: designed to determine the safety and tolerability of CAEL-101 in combination with standard-of-care CyBorD and daratumumab to allow for use of daratumumab in the Phase 3 study. Part B commenced after the RP3D was determined from Part A. The outcomes from the first 4 weeks of treatment (i.e., the Safety Observation Period) formed the basis for allowing the use of daratumumab in the Phase 3 program.

Part A consists of a Screening period, a safety and tolerability Treatment Period, and an EOT Period. The Treatment Period of Part A is divided into a DLT Observation Period and a Continued Treatment Period. A clinical study report has been written that described the outcomes from Part A DLT Observation Period through 31 Jul 2020, with the primary focus on the determination of the RP3D. Part B consists of a Screening Period, a safety and tolerability Treatment Period, and an EOT Period. The Treatment Period of Part B is divided into a Safety Observation Period and a Continued Treatment Period. The Continued Treatment Period for both Parts A and B is designed to follow the long-term safety and tolerability of CAEL-101, with dose titration up to the Phase 3 dose. Last participant last visit was completed on 14 November 2023. Although this study is open label and unrandomized, select efficacy outcomes (e.g., biomarkers for cardiac, hepatic, and renal organ response) may be assessed.

This statistical analysis plan (SAP), in general, describes the statistical methods for analyzing data for the protocol titled “A Phase 2, Open-label, Multicenter, Dose Selection Study to Evaluate the Safety and Tolerability of CAEL-101 in Patients with AL Amyloidosis.” The current SAP includes Parts A and B of the study design described in the protocol.

Standard data presentation instructions, along with the table, figure, and listing specifications, are contained in the data presentation plan in a separate document. Analyses related to safety and tolerability objectives of the study are specified in this SAP.

1.1. Objectives and Endpoints

The objectives and endpoints for this study are as follows:

Objectives	Endpoints
Primary	
• To define the safety and tolerability of CAEL101 for participants with amyloid light chain (AL) amyloidosis in Parts A and B of the study	• Safety parameters to be assessed: treatment-emergent serious adverse events (SAEs) and adverse events (AEs), AEs leading to treatment discontinuation, abnormal laboratory tests of clinical significance, abnormal physical examination, abnormal vital signs, and abnormal electrocardiogram (ECG) parameters of clinical relevance
• To determine the RP3D for patients with AL amyloidosis in Part A of the study	• DLTs during the DLT Observation Period in Part A of the study
Secondary	
Part A • To define the safety and tolerability of CAEL-101 when administered in combination with standard-of-care CyBorD Part B • To define the safety and tolerability of CAEL-101 when administered in combination with standard-of-care CyBorD and daratumumab For both Parts A and B: • To describe the pharmacokinetic (PK) profile of CAEL-101 and to explore the PK profile of CAEL-101 when given biweekly (q2wk) versus once monthly (q4wk) after the first 50 weeks	• Safety parameters to be assessed separately for Parts A and B: treatment-emergent SAEs and AEs, AEs leading to treatment discontinuation, abnormal physical examination findings, abnormal vital signs, abnormal ECG parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern • PK parameters (eg, maximum concentration, minimum concentration, and area under the concentration-time curve)
Exploratory	
• To assess the efficacy of CAEL-101 in terms of cardiac, hepatic, and renal response in participants with AL amyloidosis	The following parameters will be assessed: • Cardiac: N-terminal pro b-type natriuretic peptide (NT-proBNP), cardiac Troponin T (cTnT), cardiac Troponin I (cTnI), global longitudinal strain (GLS)% • Renal: 24-hr urine protein and eGFR • Hepatic: Alkaline phosphatase

1.2. Study Design

This section summarizes the planned study design. This study is ongoing, with participants from both Parts A and B participating in the Continued Treatment Period. Therefore, although the core objectives of Part A (DLT Observation Period) and Part B (Safety Observation Period) have been completed, they are described below to put the study into perspective.

This is a multicenter, open-label, sequential cohort, dose-selection study of CAEL-101 in Mayo Stage I, II, and IIIa AL amyloidosis participants. The study is divided into 2 parts:

- Part A defines the safety and tolerability of CAEL-101 in combination with standard-of-care CyBorD and determines the RP3D
- Part B evaluates the safety and tolerability of CAEL-101 in combination with standard-of-care CyBorD and daratumumab

Part A

Part A consists of a Screening Period, a safety and tolerability treatment period, and an EOT Period. The treatment period of Part A is divided into a DLT Observation Period and a Continued Treatment Period. Part A employed a 3 + 3 dose escalation design. 3 participants were enrolled in each dose cohort unless AEs preventing further dosing were observed. Enrollment into a new cohort with a higher dose of CAEL-101 did not begin until the DLT Observation Period was complete for the last participant enrolled in the previous cohort.

The recommended dose required at least 6 participants to be treated with CAEL-101 at that dose and ≤ 1 participant having experienced a DLT during the DLT Observation Period. A DLT was defined as any Grade 3 or greater study intervention-related AE. Dose increases were discontinued based on safety or PK findings that may influence the decision about a recommended dose.

All participants remained on the dose level assigned to the cohort in which they were originally enrolled until an RP3D was identified. When the RP3D was identified, all participants changed to the RP3D. Part B commenced after the RP3D had been identified.

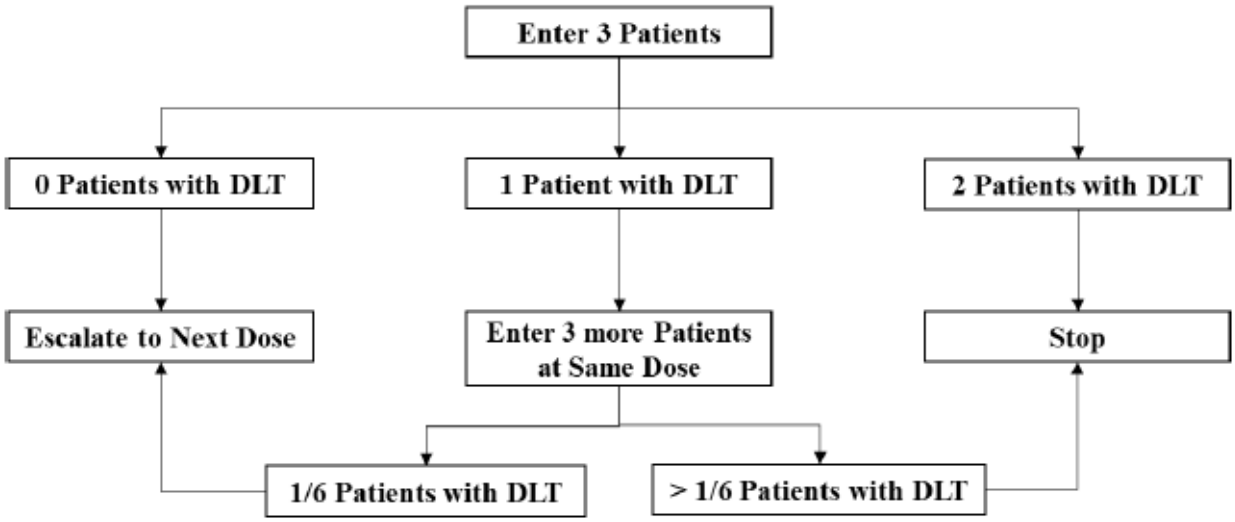
The assessment for RP3D has been completed. No DLTs were observed in any participants at any of the dose levels (500, 750, and 1000 mg/m^2) when administered with concurrent CyBorD during the DLT Observation Period. Based on the safety and tolerability data, and protocol guidance, the final cohort review by the study site Principal Investigator and the Caelum Biosciences, Inc. Medical Monitor concluded that the 1000 mg/m^2 dose is recommended for the Phase 3 studies and Part B of this study. For detailed discussion on the determination of RP3D, refer to Section 8 of the Abbreviated Summary Report for CAEL101-203 Safety Summary for Recommended Phase 3 Dose Selection Period by Caelum Biosciences, Inc. on 07 Aug 2020.

Part B

Part B consists of a Screening Period, a safety and tolerability treatment period, and an EOT Period. The treatment period of Part B is divided into a Safety Observation Period and a Continued Treatment Period. Although the original design indicated a minimum of 6 participants to receive CAEL101, 12 participants have received CAEL-101 in combination with standard-of-care CyBorD and daratumumab.

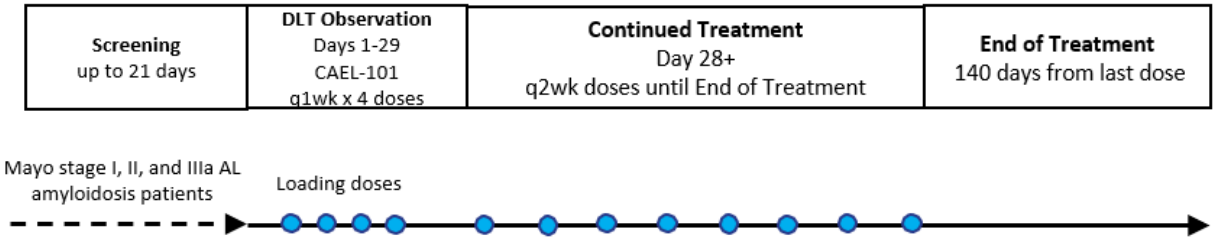
Schematics of the study design are presented in Figure 1, Figure 2, and Figure 3.

Figure 1: CAEL101-203 Part A Dose-Selection Schema



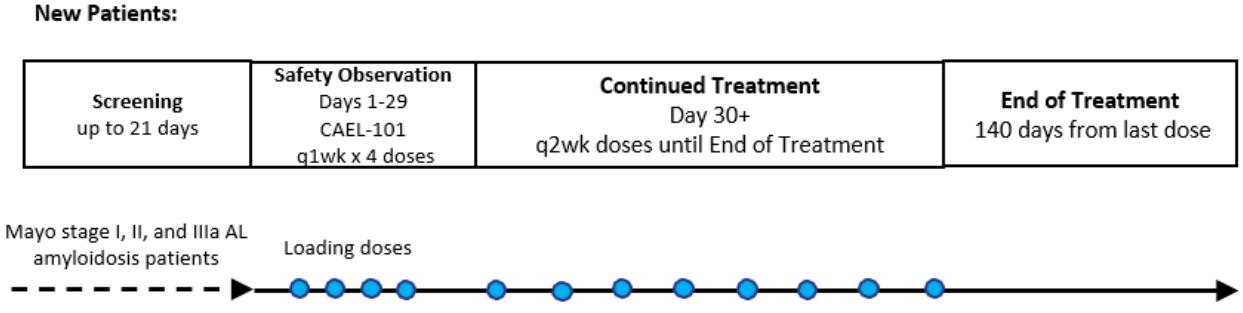
Abbreviation: DLT = dose-limiting toxicity

Figure 2: CAEL101-203 Part A Cohort Dose-Selection Schema



Note: There are 3 cohorts in Part A: CAEL-101 500, 750, and 1000 mg/m^2
All participants in Part A will receive CyBorD
Abbreviations: DLT = dose-limiting toxicity; q1wk = every week; q2wk – every two weeks

Figure 3: CAEL101-203 Part B Schema



Note: All participants enrolled in part B will receive Daratumumab in addition to CAEL-101 and CyBorD.
Abbreviations: q1wk = every week; q2wk – every two weeks

After completing approximately 50 weeks of treatment, participants may switch to an alternative maintenance dosing regimen of every four weeks (q4wk), and then start following the assessment pattern of V29-V25-V27-V29-V25 and so on. The option of treatment switching

from bi-weekly (q2wk) to once every 4 weeks (q4wk) should be agreed between the Investigator and the Sponsor Medical Monitor and based on the assessment of the combined hematological and organ responses per the scoring system proposed by Sidana et al (2020). Switching could be considered if the score is within the range of 0 through 3 (Figure 4).

Figure 4: Composite Hematologic and Organ Response Model

	RESPONSE	SCORE
Hematologic Response	Complete response	0
	Very good partial response	1
	Partial response	2
	No response/Progression	3
	Non-evaluable: Complete response	0
	Non-evaluable: No response	1
Organ Response	All organ response	0
	Mixed organ response	1
	No organ response	2

All organ response (AOR)	Response in all involved major organs (heart, kidney, liver)
Mixed organ response (MOR)	Response in some of the involved major organs
No organ response (NOR)	No response in any involved major organ

2. STATISTICAL HYPOTHESES

This is a Phase 2, open-label, dose-selection study in which safety and tolerability outcomes were used to determine the dosing regimen to carry into Phase 3. No formal statistical hypotheses were defined as part of the design, and no formal inferential testing will be performed.

3. SAMPLE SIZE DETERMINATION

The Part A sample size was based on similar studies in which a safe dose was selected for use in future larger efficacy/safety clinical studies (thus, the sample size was not selected based on a specific testable study hypothesis). A sample size of N = 3 participants for a given dose level without a DLT was judged to be clinically sufficient to allow for escalation to the next higher dose level. For both Parts A and B, a sample size of N = 6 participants for a given CAEL-101/standard of care treatment regimen was judged to be sufficient to allow for determination of tolerability in expectation that the CAEL-101/standard of care regimen may be used in the subsequent Phase 3 programs.

The total study sample size was data driven and dependent on how many doses were tested and on safety and tolerability outcomes from that testing.

25 participants were enrolled in the study at 3 Investigator sites. Part A enrolled 13 participants. For Part B, 12 participants have received CAEL-101 administered in combination with standard of care CyBorD and daratumumab. Once the newly enrolled participants had completed the Safety Observation Period, participants from Part A who were in the Continued Treatment Period and who, in the Investigator's judgment, could have their standard of care treatment complemented with daratumumab were allowed to do so. One participant from Part A was therefore enrolled into Part B.

4. ANALYSIS SETS

Three populations have been identified for purposes of analysis.

Analysis Set	Description
Safety Set (SS)	All participants treated with at least 1 dose of CAEL-101 (the study treatment) will be included in the SS.
PK Analysis Set (PKS)	The PKS will include all participants who have at least 1 measurable plasma concentration.
Antidrug Antibody Analysis Set (AAS)	The AAS includes all study participants who received any study intervention and who, after the first dose, have at least 1 reportable result in the antidrug antibody (ADA) assay. An ADA analysis will be conducted based on the actual treatment the participants have received.

5. STATISTICAL ANALYSES

5.1. General Considerations

All assessments will use descriptive statistics, and no inferential analysis will be performed. Descriptive statistics (and by-participant listings of data) will form the basis from which conclusions regarding study objectives will be made. There are no plans to generate inferential (e.g., p-values) statistics, as the sample size is generally insufficient to allow for use of such methods.

In general, data will be tabulated by cohort to allow for comparison of key outcomes by dose level, recognizing that, if a given cohort has only N = 2 or N = 3 participants, the interpretation of descriptive statistics is limited. A within-cohort t-test on changes from Baseline may be performed to evaluate if the change from Baseline is significant or not, but no formal inference from this result will be derived. All data will be listed by cohort, participant, and visit, with the primary determination of safety and tolerability outcomes based on review of these data listings. Figures/graphics of by-participant data will be presented where these will enable optimal review of outcomes across dose levels and over time. For clarity, the following are the definitions of the 4 cohorts in this study:

- Part A Cohort 1: participants treated with CAEL-101 500 mg/m^2 + CyBorD
- Part A Cohort 2: participants treated with CAEL-101 750 mg/m^2 + CyBorD
- Part A Cohort 3: participants treated with CAEL-101 1000 mg/m^2 + CyBorD
- Part B: participants treated with CAEL-101 1000 mg/m^2 + CyBorD + Dara

For the DLT observation period, tables for Part A will be structured with cohorts presented left to right (by ascending dose) and referred to in the tables (as well as other statistical outputs) as Cohort 1, 2, or 3.

For the Clinical study report, the 2 study parts will be presented together, tables (as well as other statistical outputs) will be structured with cohorts presented from left to right as follows:

- Part A
- Part B

Part A will include cohorts 1, 2 and 3.

All study data will be listed by (part A and B), participant, and visit (as applicable). No preliminary rounding will be performed; rounding will only occur after analysis.

Categorical variables will be summarized by cohort and visit using frequency counts and percentages. Continuous variables will be summarized by cohort and visit using descriptive statistics (number of participants (N), number of participants with available data (n), mean, SD, median, minimum, and maximum values). Minimum and maximum will be presented to the same number of decimal places as the raw data. Mean and median will be presented to 1 more decimal place than the raw data, and SD will be presented to 2 more decimal places than the raw data.

In general, the baseline value is the last non-missing value prior to the first study intervention. If the Day 1 assessment is missing, then last Screening assessment will be used as the Baseline assessment.

All data and all outcomes derived from the data will be presented in detailed data listings or summary tabulations. Figures/graphics of by-patient data will be presented where these will enable optimal review of outcomes across dose levels and over time.

All analyses will be performed using Statistical Analysis Software® (SAS®; Version 9.4 or higher; SAS Institute, Inc, Cary, NC, USA) release or other validated statistical software.

Medical history information and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; Version 25.0 or higher).

Medications will be mapped to a generic term using the World Health Organization Drug Dictionary (WHO-DD) of 15 Mar 2018 or later.

The analysis visit windows are defined in Table 1 to 7.

Table 1: Analysis Visit Windows for Physical Examination

Visit	Scheduled Study Day	Window Study Day	
		Lower Limit	Upper Limit
Week 1 (Baseline)	-21 to 1	-21	1
Week 2	8	2	12
Week 3	15	13	19
Week 4	22	20	57
Week 14	92	58	134
Week x (x = 26, 38, 50[a])	[((x - 1) * 7) + 1]	[((x - 1) * 7) - 40]	[((x - 1) * 7) + 43]
End of Treatment + Day 14	EOT +14	EOT + 1	EOT + 21
End of Treatment + Day 28	EOT + 28	EOT + 22	EOT + 42
End of Treatment + Day 56	EOT + 56	EOT + 43	EOT + 70
End of Treatment + Day 84	EOT + 84	EOT + 71	EOT + 98
End of Treatment + Day 112	EOT +112	EOT + 99	EOT + 126
End of Treatment + Day 140	EOT + 140	EOT + 127	EOT + 154

[a] Since the End of Study is defined as no more than 3 years after the last participant received the first dose of CAEL-101 or the Sponsor's decision to terminate the study, whichever comes first, some participants will be treated beyond 50 weeks. Data collection may be longer than what is specified in SoA. The scheduled study day and window study day for visits beyond Week 50 will follow the formula used for Week 50. Analysis will be performed using all data through the time at which the participant remains on study treatment or until the End of Study, whichever comes first.

Abbreviation: SoA = Schedule of Assessments; EOT = End of Treatment

Table 2: Analysis Visit Windows for Vital Signs and Weight

Visit	Scheduled Study Day	Window Study Day	
		Lower Limit	Upper Limit
Week 1 (Baseline)	-21 to 1	-21	1
Week 2	8	2	12
Week 3	15	13	19
Week 4	22	20	29
Week 6	36	30	43
Week x (x = 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50[a])	[((x - 1) * 7) + 1]	[((x - 1) * 7) - 5]	[((x - 1) * 7) + 8]
End of Treatment + Day 14	EOT +14	EOT + 1	EOT + 21
End of Treatment + Day 28	EOT + 28	EOT + 22	EOT + 42
End of Treatment + Day 56	EOT + 56	EOT + 43	EOT + 70
End of Treatment + Day 84	EOT + 84	EOT + 71	EOT + 98
End of Treatment + Day 112	EOT +112	EOT + 99	EOT + 126
End of Treatment + Day 140	EOT + 140	EOT + 127	EOT + 154

[a] Since the End of Study is defined as no more than 3 years after the last participant received the first dose of CAEL-101 or the Sponsor's decision to terminate the study, whichever comes first, some participants will be treated beyond 50 weeks. Data collection may be longer than what is specified in SoA. The scheduled study day and window study day for visits beyond Week 50 will follow the formula used for Week 50. Analysis will be performed using all data through the time at which the participant remains on study treatment or until the End of Study, whichever comes first.

Abbreviation: SoA = Schedule of Assessments; EOT = End of Treatment

Table 3: Analysis Visit Windows for 12-Lead Electrocardiogram

Visit	Scheduled Study Day	Window Study Day	
		Lower Limit	Upper Limit
Week 1 (Baseline)	-21 to 1	-21	1
Week 5	29	2	61
Week 14	92	62	134
Week x (x = 26, 38, 50[a])	[((x - 1) * 7) + 1]	[((x - 1) * 7) - 40]	[((x - 1) * 7) + 43]
End of Treatment + Day 14	EOT +14	EOT + 1	EOT + 21
End of Treatment + Day 28	EOT + 28	EOT + 22	EOT + 42
End of Treatment + Day 56	EOT + 56	EOT + 43	EOT + 70
End of Treatment + Day 84	EOT + 84	EOT + 71	EOT + 98
End of Treatment + Day 112	EOT +112	EOT + 99	EOT + 126
End of Treatment Day + 140	EOT + 140	EOT + 127	EOT + 154

[a] Since the End of Study is defined as no more than 3 years after the last participant received the first dose of CAEL-101 or the Sponsor's decision to terminate the study, whichever comes first, some participants will be treated beyond 50 weeks. Data collection may be longer than what is specified in SoA. The scheduled study day and window study day for visits beyond Week 50 will follow the formula used for Week 50. Analysis will be performed using all data through the time at which the participant remains on study treatment or until End of Study, whichever comes first.

Abbreviation: SoA = Schedule of Assessments; EOT = End of Treatment

Table 4: Analysis Visit Windows for Safety Laboratory Tests

Visit	Scheduled Study Day	Window Study Day	
		Lower Limit	Upper Limit
Week 1 (Baseline)	-21 to 1	-21	1
Week 2	8	2	12
Week 3	15	13	19
Week 4	22	20	26
Week 5	29	27	33
Week 6	36	34	43
Week 8	50	44	71
Week 14	92	72	134
Week x (x = 26, 38, 50[a])	[((x - 1) * 7) + 1]	[((x - 1) * 7) - 40]	[((x - 1) * 7) + 43]
End of Treatment + Day 14	EOT +14	EOT + 1	EOT + 21
End of Treatment + Day 28	EOT + 28	EOT + 22	EOT + 42
End of Treatment + Day 56	EOT + 56	EOT + 43	EOT + 70
End of Treatment + Day 84	EOT + 84	EOT + 71	EOT + 98
End of Treatment + Day 112	EOT +112	EOT + 99	EOT + 126
End of Treatment + Day 140	EOT + 140	EOT + 127	EOT + 154

[a] Since the End of Study is defined as no more than 3 years after the last participant received the first dose of CAEL-101 or the Sponsor's decision to terminate the study, whichever comes first, some participants will be treated beyond 50 weeks. Data collection may be longer than what is specified in SoA. The scheduled study day and window study day for visits beyond 50 weeks will follow the formula used for Week 50. Analysis will be performed using all data through the time at which the participant remains on study treatment or until End of Study, whichever comes first.

Abbreviation: SoA = Schedule of Assessments; EOT = End of Treatment

Table 5: Analysis Visit Windows for CTnT/cTnI and 24-Hr Urine Protein

Visit	Scheduled Study Day	Window Study Day	
		Lower Limit	Upper Limit
Week 1 (Baseline)	1	1	1
Week 14	92	2	134
Week x (x = 26, 38, 50[a])	[((x - 1) * 7) + 1]	[((x - 1) * 7) - 68]	[((x - 1) * 7) + 15]
End of Treatment + Day 14	EOT +14	EOT + 1	EOT + 21
End of Treatment + Day 28	EOT + 28	EOT + 22	EOT + 42
End of Treatment + Day 56	EOT + 56	EOT + 43	EOT + 70
End of Treatment + Day 84	EOT + 84	EOT + 71	EOT + 98
End of Treatment + Day 112	EOT +112	EOT + 99	EOT + 126
End of Treatment + Day 140	EOT + 140	EOT + 127	EOT + 154

[a] Since the End of Study is defined as no more than 3 years after the last participant received the first dose of CAEL-101 or the Sponsor's decision to terminate the study, whichever comes first, some participants will be treated beyond 50 weeks. Data collection may be longer than what is specified in SoA. The scheduled study day and window study day for visits beyond Week 50 will follow the formula used for Week 50. Analysis will be performed using all data through the time at which the participant remains on study treatment or until End of Study, whichever comes first.

Abbreviations: CTnI = cardiac Troponin I; CTnT = cardiac Troponin T; SoA = Schedule of Assessments; EOT = End of Treatment

Table 6: Analysis Visit Windows for NT-proBNP, Serum FLC, and Serum and Urine Immunofixation Electrophoresis

Visit	Scheduled Study Day	Window Study Day	
		Lower Limit	Upper Limit
Week 1 (Baseline)	1	1	1
Week 6	[((x - 1) * 7) + 1]	2	43
Week 10		44	71
Week 14		72	106
Week x (x = 18, 22, 26, 30, 34, 38, 42, 46, 50[a])		[((x - 1) * 7) - 12]	[((x - 1) * 7) + 15]
End of Treatment + Day 14	EOT +14	EOT + 1	EOT + 21
End of Treatment + Day 28	EOT + 28	EOT + 22	EOT + 42
End of Treatment + Day 56	EOT + 56	EOT + 43	EOT + 70
End of Treatment + Day 84	EOT + 84	EOT + 71	EOT + 98
End of Treatment + Day 112	EOT +112	EOT + 99	EOT + 126
End of Treatment + Day 140	EOT + 140	EOT + 127	EOT + 154

[a] Since the End of Study is defined as no more than 3 years after the last participant received the first dose of CAEL-101 or the Sponsor's decision to terminate the study, whichever comes first, some participants will be treated beyond 50 weeks. Data collection may be longer than what is specified in SoA. The scheduled study day and window study day for visits beyond Week 50 will follow the formula used for Week 50. Analysis will be performed using all data through the time at which the participant remains on study treatment or until End of Study, whichever comes first.

Abbreviations: FLC = free light chain; NT-proBNP = N-terminal pro b-type natriuretic peptide; SoA = Schedule of Assessments; EOT = End of Treatment

Table 7: Analysis Visit Windows for Immunogenicity Tests and PK Samples

Visit	Scheduled Study Day	Window Study Day	
		Lower Limit	Upper Limit
Week 1 (Baseline)	1	1	1
Week 2	8	2	12
Week 3	15	13	19
Week 4	22	20	29
Week x (x = 6, 8, 10, 12, 14, 16, 18, 20)	[((x - 1) * 7) + 1]	[((x - 1) * 7) - 5]	[((x - 1) * 7) + 8]
Week 22		142	162
Week x (x = 26, 30, 34, 38, 42, 46, 50[a])		[((x - 1) * 7) - 12]	[((x - 1) * 7) + 15]
End of Treatment + Day 14	EOT +14	EOT + 1	EOT + 21
End of Treatment + Day 28	EOT + 28	EOT + 22	EOT + 42
End of Treatment + Day 56	EOT + 56	EOT + 43	EOT + 70
End of Treatment + Day 84	EOT + 84	EOT + 71	EOT + 98
End of Treatment + Day 112	EOT +112	EOT + 99	EOT + 126
End of Treatment + Day 140	EOT + 140	EOT + 127	EOT + 154

[a] Since the End of Study is defined as no more than 3 years after the last participant received the first dose of CAEL-101 or the Sponsor's decision to terminate the study, whichever comes first, some participants will be treated beyond 50 weeks. Data collection may be longer than what is specified in SoA. The scheduled study day and window study day for visits beyond Week 50 will follow the formula used for Week 50. Analysis will be performed using all data through the time at which the participant remains on study treatment or until End of Study, whichever comes first.

Abbreviations: PK = pharmacokinetic; SoA = Schedule of Assessments; EOT = End of Treatment

Table 8: Analysis Visit Windows for NYHA Class Assessment

Visit	Scheduled Study Day	Window Study Day	
		Lower Limit	Upper Limit
Week 1	1	1	1
Week 6	36	2	36
Week 10	64	37	78
Week x (x = 14, 18, 22, 26, 30, 34)	[((x - 1) * 7) + 1]	[((x - 1) * 7) - 12]	[((x - 1) * 7) + 15]
Week 38		247	302
Week 50[a]		[((x - 1) * 7) - 40]	[((x - 1) * 7) + 43]
End of Treatment + Day 14	EOT +14	EOT + 1	EOT + 21
End of Treatment + Day 28	EOT + 28	EOT + 22	EOT + 42
End of Treatment + Day 56	EOT + 56	EOT + 43	EOT + 70
End of Treatment + Day 84	EOT + 84	EOT + 71	EOT + 98
End of Treatment + Day 112	EOT +112	EOT + 99	EOT + 126
End of Treatment + Day 140	EOT + 140	EOT + 127	EOT + 154

[a] Since the End of Study is defined as no more than 3 years after the last participant received the first dose of CAEL-101 or the Sponsor's decision to terminate the study, whichever comes first, some participants will be treated beyond 50 weeks. Data collection may be longer than what is specified in SoA. The scheduled study day and window study day for visits beyond Week 50 will follow the formula used for Week 50. Analysis will be performed using all data through the time at which the participant remains on study treatment or until End of Study, whichever comes first.

Abbreviations: NYHA = New York Heart Association; SoA = Schedule of Assessments; EOT = End of Treatment

No analysis windowing is used for echocardiograms as most of the data is being collected and retrospectively. Echocardiogram data is not being used for any analysis, it will just be presented in a listing.

5.2. Study Participants

The number and percentage of participants in the following disposition categories will be summarized using the SS:

- Participants in each analysis set
- Participants who completed study intervention
- Participants who discontinued study intervention along with the reasons for discontinuation
- Participants who completed the study
- Participants who discontinued from the study along with the reasons for discontinuation

A listing of participants will be provided for the following:

- Participants who failed the screening

- Participants included or excluded in the given analysis sets along with the reasons for exclusion from the respective analysis sets
- Participants who discontinued study intervention
- Participants who discontinued study

5.3. Primary Endpoints Analysis

The primary analysis set for the primary endpoints will be the Safety Set.

5.3.1. Endpoints

Safety assessments will include the following endpoints:

- Treatment-emergent SAEs.
- AEs.
- AEs leading to treatment discontinuation.
- Abnormal laboratory tests of clinical relevance.
- Abnormal vital signs.
- Abnormal ECG parameters of clinical relevance.
- Evaluation of DLTs for each dose escalation cohort for Part A only. A DLT was defined as any Grade 3 or greater study intervention-related AE.

5.3.2. Main Analytical Approach

For Part A only, a table on the incidence of DLTs per cohort during the DLT Observation Period was derived. The RP3D was determined as the dose level with at least 6 participants treated with CAEL-101 at that dose and ≤ 1 participant having experienced a DLT during the DLT Observation Period. The assessment of RP3D was completed in which no incidence of DLTs has been observed at any dose level, and thus, the RP3D was concluded to be the 1000 mg/m^2 dose.

Safety assessments will include AEs, clinical laboratory tests, vital signs, and ECGs.

Clinical laboratory tests and vital signs will be summarized descriptively for part A and B and overall. All abnormal findings in clinical laboratory test results, vital signs, and ECGs will be listed.

5.3.2.1. Adverse Events

AEs will be coded using MedDRA (Version 25.0 or higher); AEs will be reported starting from the date of signing of the informed consent form (ICF) until Day 140 (5 months) after the last dose of study intervention. Participant incidence of each System Organ Class (SOC) and Preferred Term (PT) will be tabulated. AE incidence will also be tabulated according to relationship to study medication and severity. Serious AEs and AEs resulting in premature discontinuation will be tabulated.

AEs starting after the first dose of treatment and before the last dose of study drug +140 days will be considered treatment-emergent AEs (TEAEs), will be reported as occurring during the treatment phase, and will be associated with the most recent treatment (dose level) given.

AEs occurring after the participant has provided written informed consent and before the first dose of study treatment will be considered as pretreatment AEs.

All TEAEs will be summarized by SOC and PT for part A and B and overall. All TEAEs will be summarized by incidence, severity, and potential causality to study intervention.

5.3.2.1.1. Across Cohorts

A summary of AEs and SAEs across part A and B and overall will be presented. The number of events (E) and the number and percentage of participants with events (n, %) will be shown by the relationship of events to study intervention (i.e., not related or related).

The AEs resulting in study intervention withdrawal and the severity grades of the AEs (Grade 1 through Grade 5) will be summarized similarly.

These statistics will be prepared separately for all AEs and SAEs. In addition, the number and percentage of participants who died during the study will be presented.

5.3.2.1.2. Adverse Events and Serious Adverse Events by System Organ Class and Preferred Term

The number of AEs and the number and percentage of participants with events will be presented by SOC and PT. Participants are counted once in each SOC and PT. Percentages will be based on the total number of participants in the SS. SOCs will be listed in alphabetical order, and PT will be listed in order of frequency of occurrence within the SOC.

Additional summary tables stratifying AEs by age, gender, and race will also be provided. SAEs will be summarized similarly.

5.3.2.1.3. Adverse Events and Serious Adverse Events by System Organ Class, Preferred Term, and Relationship

The number of AEs and the number and percentage of participants with events will be presented by SOC and PT as described above by relationship (related versus not related). If a participant has > 1 occurrence of an AE, the strongest relationship to study intervention will be used in the summary table.

The causality criteria of related and possibly related will be considered “related” to the study intervention.

SAEs will be summarized similarly.

5.3.2.1.4. Adverse Events and Serious Adverse Events by System Organ Class, Preferred Term, and Severity Grade

The number of AEs and the number and percentage of participants with events will be presented by SOC and PT as described above by severity grade (Grades 1 through 5). If a participant has > 1 occurrence of an AE, the highest grade will be used in the summary table.

SAEs will be summarized similarly.

5.3.2.1.5. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

AEs leading to death, AEs leading to withdrawal of study intervention, and AEs resulting in the modification of the study intervention, including interruption and reduction, will also be presented by SOC and PT as described above.

Listings for the SAEs and deaths will be produced.

5.3.2.1.6. Adverse Events of Special Interest

The following adverse event categories will be analyzed by part A and B and overall:

- Narrow SMQ for 'Hypersensitivity' or 'Anaphylactic reaction'
    - Narrow SMQ for 'Hypersensitivity' or 'Anaphylactic reaction' that occurred within 24 hours of drug administration.
- Narrow SMQ for 'Hypersensitivity' or 'Anaphylactic reaction' excluding High Level Term (HLT) of 'Infusion site reactions and administration site reactions NEC'
    - Narrow SMQ for 'Hypersensitivity' or 'Anaphylactic reaction' excluding High Level Term (HLT) of 'Infusion site reactions and administration site reactions NEC' that occurred within 24 hours of drug administration.
- HLT of Infusion site reactions and administration site reactions NEC
    - HLT of 'Infusion site reactions and administration site reactions NEC' that occurred within 24 hours of drug administration.

For time period calculation (within 24 hours), if AE start time is missing or infusion time is missing then Infusion start date $\leq$ AE Start Date $\leq$ (Infusion Start Date + 1) per subject, infusion start date.

Overall summaries, summaries by SOC and PT, Serious adverse events, summaries by relationship and by severity will be provided for the above categories.

5.3.2.2. Clinical Laboratory Assessments

Descriptive statistics by time of assessment will be presented for each laboratory parameter. Changes from Baseline, as well as shift tables, will be presented. All laboratory values will be classified as normal, below normal, or above normal based on the normal ranges supplied by the local laboratory. Frequencies of abnormal values will be presented in tabular form, as appropriate. For purposes of analyses, laboratory results based on standardized units will be used. For consistency, the Estimated Glomerular Filtration Rate will be calculated using the CKD- EPI Creatinine equation (2021) (without race). A listing of each laboratory parameter will be presented by participant, visit, and part A and B. In addition, a listing of serum free light chains (FLCs; kappa and lambda), their changes from Baseline, and their ratio of kappa/lambda will be listed by cohort, participant, and visit. A listing that shows the Mayo staging and European staging will also be produced by participant, visit, and part A and B for cardiac-evaluable participants.

Evaluation of Drug Induced Serious Hepatotoxicity

A Hy's law case refers to an increase in aminotransferase >3 X the reference upper limit of normal (ULN), with bilirubin >2 X ULN. Possibly Hy's law cases can be visualized with use of evaluation of drug- induced serious hepatotoxicity (eDISH) plots, a log-log scatter plot where the x-axis is the peak post- baseline ALT as a multiple of ULN, and the y-axis is the peak post-baseline Bilirubin as a multiple of ULN. An eDISH plot by quadrant will be presented for each part A and B.

Summaries of liver enzymes will be provided in a separate table as well.

5.3.2.3. Vital Signs

Observed values and changes from Baseline in vital signs (systolic and diastolic blood pressure, pulse rate, oral temperature and respiratory rate) at each visit will be summarized descriptively. A listing of vital signs will be presented by participant, visit, and part A and B and overall.

5.3.2.4. 12-Lead ECG

The number and percentage of participants with abnormal 12-lead ECG findings will be summarized by visit and part A and B and overall. A listing will also be created.

5.3.2.5. Physical Examinations

A listing will be created to present the visits when physical examination was conducted.

5.4. Secondary Endpoints Analysis

The secondary endpoint analysis will evaluate PK parameters. The analysis set for the PK profile analysis is the PKS.

5.4.1. Key Secondary Endpoints

The plasma concentrations will be determined from the blood samples collected at the following time points: Weeks 1 to 4, Weeks 6 to 22, and then at every other 2-week study visit after Week 22. After Week 50, samples will be collected approximately every 182 days and at the EOT. The PK profile of CAEL-101 when given bi-weekly (q2wk) versus once-monthly (q4wk) after the first 50 weeks will also be explored.

5.4.1.1. Main Analytical Approach

For PK concentration summaries, values below the limit of quantification will be set to 0. Missing values will not be imputed.

PK concentration data will be summarized using the following descriptive statistics: number of participants (N), number of participants with available data (n), arithmetic mean, SD, median, minimum, and maximum. The following conventions will be applied to PK presentations and summaries:

- For continuous variables, all mean and median values are formatted to 1 more decimal place than the raw data. SD values are formatted to 2 more decimal places

than the raw data. Minimum and maximum values are presented with the same number of decimal places as the raw data.

- Date variables are formatted as DDMMMYYYY for presentation. Time is formatted in military time as HH:MM for presentation.

Plasma concentrations versus time data will be presented in a data listing by participant. Plasma concentration data will be summarized separately by analyte, visit (week), nominal study day, and time point using descriptive statistics. In addition, plasma concentrations will be plotted to allow for visual comparison of concentrations between cohorts and over time.

5.5. Exploratory Endpoints Analysis

The analysis set for the exploratory endpoints will be the SS.

5.5.1. Exploratory Endpoints

The organ-specific outcomes for cardiac, renal, and hepatic biomarker response will be assessed using both retrospective and prospective data. The following parameters will be evaluated.

- Cardiac:
  - NT-proBNP
  - cTnT, cTnI
  - GLS%
- Renal:
  - 24-hr urine protein
- Liver (Hepatic):
  - Alkaline phosphatase
- Hematologic response:
  - Involved - uninvolved FLC difference (dFLC)

5.5.2. Main Analytical Approach

Summary statistics (mean, SD, SEM, minimum, maximum) will be computed and displayed for each efficacy endpoint. For GLS%, only a listing will be presented.

Efficacy endpoints will also be assessed for absolute changes (and percent changes) over time. Participants with organ involvement (e.g., cardiac and renal, liver (hepatic)) will be identified at Baseline through minimum thresholds for each relevant biomarker and defined as being cardiac evaluable, renal evaluable, and hepatic evaluable, accordingly. These specific analysis populations will then be assessed for changes over time in the organ-specific biomarkers. Participants may be classified as responders, progressors, and stable (by organ) according to varying definitions of response.

The criteria in Table 9 will be used for organ involvement and response status. Missing values will not be imputed.

By-visit summaries of response status by organ will be presented for evaluable participants. Most recent response status (by organ) will also be tabulated for the evaluable participants.

Biomarker values and change from Baseline values for NT-proBNP (for cardiac evaluable participants), urine protein and estimated glomerular filtration rate (eGFR) (for renal evaluable participants), and alkaline phosphatase (for liver (hepatic) evaluable participants) will be plotted by visit by participant. The timepoint at which the participant progressed to Q4 dosing will be marked.

A waterfall plot of percent change from Baseline in NT-proBNP for the last assessment will be plotted for each cardiac evaluable participant. Similarly, a waterfall plot for percent change from Baseline in 24-hr urine protein and eGFR will be plotted for renal evaluable participants and percent change from Baseline for alkaline phosphatase for liver (hepatic) evaluable participants.

A spaghetti plot will be presented for percent change from Baseline in NT-proBNP by visit for cardiac evaluable participants.

For renal evaluable participants, a side-by-side spaghetti plot of percent change from Baseline for 24-hr urine protein and eGFR by visit will be presented for renal evaluable participants.

Similarly, for hepatic evaluable participants, a spaghetti plot for percent change from Baseline in Alkaline Phosphatase by visit will be presented.

In addition, a spaghetti plot for NT-proBNP values for cardiac evaluable participants, 24-hr urine protein and eGFR for renal evaluable participants and Alkaline phosphatase for hepatic evaluable participants for will also be presented by visit.

Table 9: Organ Involvement and Response Criteria

Organ	Organ Involvement	Response	Progression	No Response / Stability
Cardiac	NT-proBNP ≥ 332ng/L (39.2 pmol/L)	A decrease of > 30% in NT-proBNP levels and a decrease of NT-proBNP > 300 ng/L in participants with a baseline NT-proBNP of ≥ 650 ng/L[a]	An increase of > 30% in NT-proBNP levels (in the absence of eGFR decline of ≥ 25%) and an increase of ≥ 300 ng/L in NT-proBNP (in the absence of eGFR decline of ≥ 25%)	Neither response nor progression
Renal	24-hr urine protein > 0.5 g/day	A decrease of ≥ 30% in urine protein or decrease of urine protein to < 0.5 g/24 hr in the absence of an eGFR decrease of ≥ 25%	Worsening of ≥ 25% in eGFR	Neither response nor progression
Liver (Hepatic)	ALP > 1.5 times institutional upper limit of normal	A decrease of ≥ 50% and/or normalization of the serum ALP level	An increase of ≥ 50% in the serum ALP level	Neither response nor progression

Dispenzieri et al (2015) and Palladini (2014)

[a] Abbreviations: ALP = alkaline phosphatase; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminus pro-brain natriuretic peptide

eGFR calculated using the CKD- EPI Creatinine equation (2021) (without race) will be used to derive the response status.

CKD-EPI Creatinine Equation (2021)

$$eGFRcr = 142 * \min\left(\frac{Scr}{K}, 1\right)^{\alpha} * \max\left(\frac{Scr}{K}, 1\right)^{-1.200} * 0.9938^{Age} * 1.012(if\ female)$$

Where:

Scr = standardized serum creatinine in mg/dL

K = 0.7 (females) or 0.9 (males)

α = -0.241 (female) or -0.302 (males)

min (Scr/K,1) is the minimum of Scr/K or 1.0

max (Scr/K,1) is the maximum of Scr/K or 1.0

Age (years)

In addition to the above criteria, graded cardiac response and graded renal response will also be presented by visit.

- Graded cardiac response, determined using the following definitions, will be assessed in participants with cardiac involvement:
  - Cardiac complete response (CarCR) defined as NT-proBNP ≤ 350 ng/L (≤ 41.39 pmol/L)
  - Cardiac very good partial response (CarVGPR) defined as a >60% reduction in NT-proBNP from baseline level not meeting CarCR
  - Cardiac partial response (CarPR) defined as a 31–60% reduction in NT-proBNP from baseline level not meeting CarCR
  - Cardiac no response (CarNR) defined as ≤ 30% reduction in NT-proBNP from baseline level
- Graded renal response, determined using the following criteria, will be assessed in participants with renal involvement:
  - Renal complete response (RenCR, 24-hr urine protein ≤200 mg/24 h, in the absence of ≥ 25% decrease in eGFR)
  - Renal very good partial response (RenVGPR, > 60% reduction in baseline 24-hr urine protein and not meeting RenCR, in the absence of ≥ 25% decrease in eGFR)
  - Renal partial response (RenPR, 31-60% reduction in baseline 24-hr urine protein, in the absence of ≥ 25% decrease in eGFR)
  - Renal no response (RenNR, 30% or less reduction in baseline 24-hr urine protein)
  - Renal progression (≥ 25% decrease in eGFR)

The following endpoints will be assessed by part A and B and overall:

- Time to first cardiac response
- Time to first graded cardiac response, defined as the first of any responses (CarCR, CarVGPR or CarPR)
- Time to first CarCR
- Time to first CarVGPR
- Time to first CarPR
- Best Cardiac Response, defined as the best cardiac response (by NT-proBNP) of a participant among all assessed timepoints, best being a responder and worst being a progressor.
- Time to first renal response
- Time to first graded renal response, defined as the first of any responses (RenCR, RenVGPR, RenPR), best being a responder and worst being a progressor.
- Time to first RenCR
- Time to first RenVGPR

- Time to first RenPR
- Best Renal Response, defined as the best renal response (by 24-hr urinary protein) of a participant among all assessed timepoints.
- Time to first liver (hepatic) response

The organ-specific outcomes for cardiac, renal, and hepatic biomarker response will be assessed using both retrospective and prospective data. The retrospective collection may include a review of the participant record at the site. The combination of retrospective and prospective data collection will allow for a more robust determination of the effects of CAEL-101 on efficacy in participants with AL amyloidosis.

Hematological Response:

Hematologic response will be evaluated using the below criteria

Proportion of participants in the following categories will be presented by treatment group at each visit:

- Very good partial response or better (dFLC < 4 mg/dL)
- Partial response or no response (dFLC ≥ 4 mg/dL)

Proportion of participants who achieved

- Deep hematologic response by dFLC < 1mg/dL
- Deep hematologic response by iFLC < 2mg/dL

Deep hematologic response by dFLC < 1mg/dL or iFLC < 2mg/dL

Hematologic response by visit will also be presented in a listing for each participant.

Immunoglobulin results for both serum and urine sample will be presented by visit in a listing.

Organ (Cardiac, renal, and liver(hepatic)) responses will also be presented by hematologic response by visit. For example, for cardiac involvement participants having cardiac response, they will be further categorized by hematologic response categories:

1. VGPR or Better

2. Partial response or no response for each visit and cohort.

5.5.3. Biomarker Evaluation

AL amyloidosis-related biomarkers (NT-proBNP, cTnT, cTnI, hs-cTnT, hs-cTnI, and serum FLCs) are collected and will be assessed by part A and B and overall and visit via descriptive statistics, as well as observed and change from Baseline values over time. These will also be presented in the listings.

5.6. Other Safety Analyses

5.6.1. Extent of Exposure

The SS will be used to summarize study treatment duration, study intervention exposure, and treatment compliance.

The duration (month) of exposure to study intervention will be calculated as [(date of last exposure to treatment – date of first dose) + 1]/30.4375, regardless of dose interruptions or dose reductions. Non-integer values will be rounded to 1 decimal place. Exposure will be summarized by descriptive statistics and by categories of < 3 months, 3 to < 6 months, 6 to < 9 months, 9 to < 12 months, 12 to < 15 months, 15 to < 18 months, and ≥ 18 months.

The number (%) of participants by exposure duration will be tabulated. Tabulation of the number of participants by individual study center will be provided.

Participants will receive the dose based on the cohort to which they belong. The planned total dose will be based on the participant's body surface area (BSA) in square meters, which is calculated using the height and weight obtained during the Screening Period.

The treatment compliance of CAEL-101 is defined as the actual total doses administered (where doses are expected every 2 weeks) divided by the planned total doses over treatment period.

$$Overall\ compliance\ (\%) = \frac{Actual\ total\ doses\ administered}{Planned\ total\ doses} \times 100$$

The planned dose for a missed visit is the planned dose based on the participant's BSA from the previous non-missing visit, and the actual dose administered is 0.

Treatment compliance will be summarized by descriptive statistics and as frequency counts and percentages for the following categories: < 80% versus ≥ 80%. Participants will be grouped into 3 columns corresponding to 500/750/1000 mg/m^2 CAEL-101 + CyBorD (Part A), 1000 mg/m^2 CAEL-101 + CyBorD + Dara (Part B), and Total (both Parts A and B) in the tables. Participants being treated with a lower dose will be identified in the listings but pooled with all participants in the tables.

5.6.2. Pregnancy Test

Serum or urine pregnancy test will be listed and tabulated as the data warrant.

5.6.3. Background Plasma Cell Dyscrasia Treatments

Background plasma cell dyscrasia treatments will be listed and tabulated.

5.7. Other Analyses

5.7.1. Immunogenicity Assessment

ADA and neutralizing antibody (NAb) response and associated categorical variables will be collected according to the Schedule of Assessments.

Samples for immunogenicity testing will be collected according to the Schedule of Assessments and prior to infusion of study intervention. Samples collected at designated time points will be analyzed using validated ADA assays in all participants included in the AAS. Samples positive in the ADA assay will be further characterized in the ADA titer and the NAb assays (when the NAb assay is available). The impact of ADA on PK analysis will be described as part of the population PK SAP and thus is not included in this current SAP.

All immunogenicity assessments will be performed on the AAS using the following ADA variables:

- ADA negative: defined as a negative signal in the ADA assay at all timepoints collected for the AAS
- ADA positive: defined as a positive signal in the ADA assay at any timepoint collected for the AAS

  ADA-positive participants will be further categorized for ADA response as follows:

  – Pre-existing immunoreactivity: defined as either an ADA-positive response at Baseline in the ADA assay with all post-first dose ADA results negative OR a positive response at Baseline with all post-first dose ADA responses < 4-fold over baseline titer levels

  – Treatment-boosted ADA responses: defined as a positive response in the ADA assay post-first dose that is ≥ 4-fold over baseline titer levels, when baseline results are positive

  – Treatment-emergent ADA responses: defined as a positive response in the ADA assay post-first dose when baseline results are negative or missing

  Participants with a treatment-emergent or treatment-boosted responses will be further categorized based on the duration of the response as follows:

  – Persistent response: defined as an ADA-positive response with 2 or more consecutive ADA-positive sampling timepoints separated by at least a 16-week period, with no ADA negative samples in between, irrespective of missing samples

  – Indeterminate response: defined as an ADA-positive sample only at the last collected sample

  – Transient response: defined as an ADA response that is neither a persistent nor an indeterminate response

ADA-positive samples will be further characterized for neutralizing activity in the NAb assay. NAb status categories for a participant are defined as follows:

- NAb negative: defined as a negative signal in the NAb assay for the participant at all timepoints
- NAb positive: defined as a positive signal in the NAb assay for the participant at any timepoint

The incidence of ADA response categories will be summarized as absolute occurrence (n) and percentage (%) of all participants by part A and B and overall. Maximum ADA titer levels will be listed and summarized for ADA-positive participants by part A and B and overall. NAb-positive and NAb-negative participants will be summarized as absolute occurrence (n) and percentage (%) of all participants by part A and B and overall.

Associations between ADA response categories and systemic exposure to CAEL-101 may be explored for CAEL-101-treated participants.

For analyses of the association of immunogenicity with impact on safety:

- Associations between ADA response categories and SAEs and severe AEs, including SAEs such as systemic hypersensitivity, anaphylaxis, (injection/infusion) site reactions lasting > 24 hours, and other immune-related SAEs, may be explored.

For analyses of the association of immunogenicity with impact on efficacy:

- Associations between ADA response categories and key efficacy endpoints or variables may be explored for CAEL-101-treated participants. Plots of key efficacy endpoints may be analyzed for potential impact of immunogenicity on drug efficacy.

5.7.2. Demographics and Baseline Characteristics

Baseline characteristics (including age, gender, race, disease stage, and other disease-specific characteristics) will be tabulated descriptively (e.g., the number and percentage of participants for each category for categorical parameters and the number of participants, mean, SD, and range for continuous parameters).

Additionally, New York Heart Association (NYHA) class (see Appendix D of the protocol) and organ involvement will be summarized.

5.7.3. Participant Disposition

Participant completion status and reasons for early termination will be tabulated descriptively. Exposure characteristics will be tabulated (i.e., treatment duration and the number of doses of CAEL-101 received). Total dose given will be tabulated by part A and B.

5.7.4. Medical History

Relevant and significant medical history and concurrent illnesses will be presented in data listings for all participants and noted as to whether the condition is active at the first visit of the Screening Period. Any AEs occurring after the participant has provided written informed consent and before the first dose of treatment will be included in the medical history.

5.7.5. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO-DD and tabulated by cohort. Concomitant medications will be reported in a manner similar to that of AEs. The number and percentage of participants who take concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC Level 3) drug class and PT, across all cohorts and by cohort, and presented in a by-participant listing. Prior and concurrent plasma cell dyscrasia (PCD) treatments will be summarized separately. Proportion of participants who received subsequent lines of anti-PCD treatments will be presented. For Part A - Any participant who proceeded to a non-CyBorD regimen would be defined as requiring subsequent line of therapy (and daratumumab would be included as subsequent line of therapy). Similarly for part B - Any participant who proceeded to a non-CyBorD + daratumumab would be defined as requiring a subsequent line of therapy.

Medications will be classified as follows:

- **Prior medications**: prior medications are those that have a start date/time and end date/time prior to the start of the first treatment administration.

- **Concomitant medications**: medications will be considered as concomitant if the medication either started prior to first dose of study medication and was continuing at the time of first dose of study medication; or started on or after the date of the first dose of study medication.
- **New-onset concomitant medications**: medications starting on or after the start of the first dose of study medication.

If a missing medication start date cannot be definitively determined as having started after the first dose, the medication will be considered as started prior to the first dose; similarly, if a missing medication stop date/time cannot be determined as having stopped prior to the first dose, the medication will be considered concomitant (taken after the first dose).

However, for medications that are clearly prior medications (e.g., the stop year is 2018, while this study is being run in 2020), imputation of the date will be performed to properly allocate the medication to the correct table. When this is done, if the year and month are present but the day is missing, the first day of the month will be used as the imputed value.

5.7.6. Overall Survival Assessment

The overall survival will be produced for exploratory evaluation through Kaplan-Meier plots by part A and B. In addition, Kaplan-Meier plots stratified by baseline Mayo stage will be produced.

5.7.7. Missing Data

Missing data will not be replaced or imputed except for missing dates as stated in Section 6.1.

5.8. Interim Analyses

This is an open-label study in which analyses will be performed for safety reporting, publication, and internal scientific exploratory purposes. Thus, although there is no planned “formal” interim analysis for this study, analysis of data during the course of the study will be performed for the afore-mentioned purposes.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: Technical Specifications for Derived Variables

The following derived data will be calculated prior to the analysis.

6.1.1. Age

Age at enrollment will be presented as the number of years between the date of birth and the date of signing ICF.

In cases where only the month and year are provided for a date, the day for the date will be imputed as 15. A missing month will be imputed as June. In cases where the day is observed but the month is missing, the date will be imputed as 15 Jun.

6.1.2. Adverse Events

The analysis of AEs is described in detail in Section 5.3.2.1.

TEAEs are events with start dates and start times on or after the date and time of the first study intervention dose and before the last dose +140days. If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE do not indicate that it occurred prior to the first dose, then the AE is considered as treatment emergent if:

- The start year is after the year of the first study intervention dose.
- The start year is the same as the year of the first study intervention dose:
  - The start month is missing.
  - The start month is present and is the same or after the month of the first study intervention dose.
- The start date is completely missing.

An AE occurring after the participant has provided written informed consent and before the first dose of study treatment is considered a pretreatment AE.

Percentages are based on the total number of participants in the SS.

To be able to calculate time from the first dose to AE, the following are the imputation rules for AE start dates:

Imputation Rules for Partial Dates (D = day, M = month, Y = year)			
Parameter	**Missing**	**Additional Conditions**	**Imputation**
Start date for AEs	D	M and Y same as M and Y of the first dose of study intervention	Date of the first dose of study intervention
		M and/or Y not same as the date of the first dose of study intervention	First day of the month
	D and M	Y same as Y of the first dose of study intervention	Date of the first dose of study intervention
		Y is after Y of the first dose	Set to 01 Jan
	D, M, and Y	None; date is completely missing	Date of the first dose of study intervention

AE duration (days) = date of stop of AE – date of start of AE + 1

Duration will be set to "missing" if the stop date of AE is incomplete or if the AE is ongoing.

6.1.3. Medical History

To be able to calculate the amount of time since diagnosis of a medical condition, the imputation rules for missing start date of medical history are as follows:

Imputation Rules for Partial Dates (D = day, M = month, Y = year)		
Parameter	**Missing**	**Imputation**
Start date for medical history	D	First day of the month
	D and M	Set to 01 Jan
	D, M, and Y	Informed consent date

Time (months) since diagnosis of a condition = (informed consent date – start date for medical history + 1)/365.25

6.1.4. Estimated Glomerular Filtration Rate (eGFR)

eGFR will be calculated using the CKD- EPI Creatinine equation (2021) (without race) using the below formula.

CKD-EPI Creatinine Equation (2021)

$$eGFRcr = 142 * \min\left(\frac{Scr}{K}, 1\right)^{\alpha} * \max\left(\frac{Scr}{K}, 1\right)^{-1.200} * 0.9938^{Age} * 1.012(if\ female)$$

Where:

Scr = standardized serum creatinine in mg/dL

K = 0.7 (females) or 0.9 (males)

α = -0.241 (female) or -0.302 (males)

min (Scr/K,1) is the minimum of Scr/K or 1.0

max (Scr/K,1) is the maximum of Scr/K or 1.0

Age (years)

6.2. Appendix 2: Study and Participant Characteristics

6.2.1. Protocol Deviations

Protocol deviations will be presented in a listing, including severity, protocol deviation category, and the action taken, if any. The decision whether a protocol deviation is a major or minor deviation will be made on a case-by-case basis. The possible reasons of major protocol deviations include, but are not limited to, the following:

- Failure to obtain informed consent.
- Violation of inclusion/exclusion criteria.

- SAE (pregnancy) reporting requirement not followed.
- Any known study medication administration error.
- Any study-specific related procedure done before the signature of the informed consent.
- Noncompliance with study intervention. A participant is defined as noncompliant if the participant took < 80% of the planned doses during the time the participant was enrolled in the study. Participants whose dose has been adjusted (reduced) due to tolerability will be considered to have been fully compliant for purposes of this assessment.
- Intake of prohibited medication.
- Source document/data missing.

Major protocol deviations will be summarized by part A and B and overall based on the SS. All participants with protocol deviations including those specified above will be listed. Protocol deviations from monitoring reports and other relevant sources will also be reviewed, and any important deviations will be included in the list that is summarized and reported. Coronavirus disease 2019 (COVID-19)-related major protocol deviations will also be summarized by part A and B and overall.

6.2.2. Demographics, Disease Characteristics, and History

All demographic and baseline characteristics information will be summarized and listed using the SS.

Descriptive statistics (number of participants (N), number of participants with available data (n), mean, SD, median, minimum, and maximum) will be provided for all continuous variables. Frequency counts and percentages of participants in each category will be provided for all categorical variables.

6.2.2.1. Demographics

The following demographic and baseline characteristic variables will be summarized:

- Gender (male or female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, not reported, or unknown)
- Race (American Indian or Alaska Native, Asian, Black or African American, Hawaiian or other Pacific Islander, White Caucasian, or other)
- Age (years) at Baseline (continuous)
- Age (years) at Baseline (categorical; < 65 or ≥ 65)
- Height at Baseline (centimeters)
- Weight at Baseline (kilograms)
- BSA (m^2)

6.2.2.2. Disease Characteristics

The following disease characteristics at Baseline will be summarized descriptively:

- Mayo stage (I, II, and IIIa) as reported by the Investigator at Screening
- AL amyloidosis in the heart (yes and no)
- NT-proBNP
- cTnT, cTnI, hs-cTnT, and hs-cTnI
- FLC subtype (kappa and lambda)
- FLC ratio
- Time since diagnosis of AL amyloidosis (years)
- NYHA class (I, II, or III)
- Cardiac evaluable (yes and no)
- Renal evaluable (yes and no)
- Liver evaluable (yes and no)

Time since diagnosis of the disease will be presented as the number of years between the date of the first dose and the date of diagnosis (i.e., time since diagnosis of the disease = [date of the first dose – date of diagnosis + 1]/365.25, rounded up to 1 decimal place).

Participants Staging (Mayo Staging 2012 and European Modification of 2004 Mayo Staging) will be provided by presented in a listing.

Mayo 2012 Staging: Patients were assigned a score of 1 for each of FLC-diff ≥ 18 mg/dL, cTnT ≥ 0.025 ng/mL, and NT-ProBNP ≥ 1,800 pg/mL, creating stages I to IV with scores of 0 to 3 points, respectively.

Table 10: Staging of AL Amyloidosis With Advanced Cardiac Involvement for CARES Studies Based on the European Modification of the 2004 Mayo Staging

Stage I	Stage II	Stage IIIa	Stage IIIb
Zero markers above threshold: • NT-proBNP < 332 ng/L AND 1 of the following: • hs-cTnT < 50 pg/mL (0.05 ng/mL) • cTnT ≤ 0.035 ng/mL • cTnI ≤ 0.1 ng/mL	One marker above threshold: • NT-proBNP ≥ 332 ng/L OR 1 of the following • hs-cTnT ≥ 50 pg/mL (0.05 ng/mL) • cTnT ≥ 0.035 ng/mL • cTnI ≥ 0.1 ng/mL	Two markers above threshold: • 332 ng/L ≤ NT-proBNP ≤ 8500 ng/L AND 1 of the following: • hs-cTnT ≥ 50 pg/mL (0.05 ng/mL) • cTnT ≥ 0.035 ng/mL • cTnI ≥ 0.1 ng/mL	Two markers above threshold: • NT-proBNP > 8500 ng/L AND 1 of the following: • hs-cTnT ≥ 50 pg/mL (0.05 ng/mL) • cTnT ≥ 0.035 ng/mL • cTnI ≥ 0.1 ng/mL

Palladini and Merlini (2014), adapted with Muchtar et al (2019)

[a] The 2013 European Modification of the 2004 Standard Mayo Clinic Staging in patients with advanced cardiac involvement is based on the conventional (generation 4) cTnT assay. However, hs-cTnT, or generation 5 assay, is becoming more widely available and is used more commonly in clinical practice. It is established that a cTnT value of > 0.035 ng/mL can be extrapolated to a hs-cTnT value of ≥ 50 pg/mL (0.05 ng/mL) for the determination of Mayo stage (Muchtar, 2019).

Abbreviations: AL = amyloid light chain; cTnI = cardiac Troponin I; cTnT = cardiac troponin T; hs-cTnT = high-sensitivity cardiac Troponin T; NT-proBNP = N-terminal pro b-type natriuretic peptide

6.2.2.3. Medical/Surgical History and Baseline Physical Examination

Medical history information will be coded to primary SOC and PT using MedDRA (Version 25.0 or higher). Medical history will be summarized by SOC and PT. Summaries will be presented as prior disease and concomitant disease, with the prior and concomitant status determined by whether the condition was active at the time of Screening. Participant listings will be presented including medical history condition, start and end dates, and status as ongoing.

6.2.3. Prior and Concomitant Medications/Therapies

Medications will be mapped to a generic term using the WHO-DD of 15 Mar 2018 or later.

The following steps will be implemented to categorize the medications:

Algorithm for Categorization of Medications (Prior or Concomitant)			
Parameter	**Value**	**Additional Conditions**	**Medication Category/Action**
Ongoing flag	Yes	Not applicable	Concomitant
	No	Medication end date is partial or missing	Perform the imputation on medication end date and then assign the medication category
		Medication end date is before the first dose of study intervention	Prior
		Medication end date is on or after the first dose of study intervention	Concomitant

Imputation Rules for Partial Dates (D = day, M = month, Y = year)			
Parameter	**Missing**	**Additional Conditions**	**Imputation**
Start date of medication	D	M and Y same as M and Y of the first dose of study intervention	Day of the earlier of (date of the first dose of study intervention, end date of medication)
		M and/or Y not same as the date of the first dose of study intervention	First day of the month
	D and M	Y same as Y of the first dose of study intervention	Day and month of the earlier of (date of the first dose of study intervention, end date of medication)
		Y is after Y of the first dose	Day and month of the end date of medication
	D, M, and Y	None; date is completely missing	Earlier of (date of the first dose of study intervention, end date of medication)

Imputation Rules for Partial Dates (D = day, M = month, Y = year)			
Parameter	**Missing**	**Additional Conditions**	**Imputation**
End date of medication	D	M and Y same as M and Y of the first dose of study intervention	Day of the later of (date of the first dose of study intervention, start date of medication)
		M and/or Y not same as the date of the first dose of study intervention	Last day of the month
	D and M	Y same as Y of the first dose of study intervention	Day and month of the later of (date of the first dose of study intervention/start date of medication)
		Y is after Y of the first dose	Day and month of the start date of medication
	D, M, and Y	None - date is completely missing	Later of (date of the first dose of study intervention, start date of medication)

Summaries of prior and concomitant medications will be presented separately. Summaries of prior and concomitant background plasma cell dyscrasia treatment will also be presented separately. The number and percentage of participants who took concomitant medications will be summarized by ATC drug class and PT, overall and by part A and B, and presented in a by-participant listing. The data listing will include start and end dates (or indication of ongoing), dose, unit, frequency, route, indication, and a flag of whether the medication usage is prior or concomitant. A separate listing will be created for background plasma cell dyscrasia treatments and prohibited medications.

Nonpharmacologic therapies and procedures will be coded using MedDRA (Version 25.0 or higher). All data will be listed, including the start and end dates (or indication of ongoing) of the procedure, procedure (including SOC, PT, and reported term), indication, results for diagnostic tests, and whether the procedure was performed prior to the first dose of study intervention (prior/concomitant).

6.3. Appendix 3: Instrument Scoring Details

Not applicable.

6.4. Appendix 4: Additional Details on Statistical Methods

6.4.1. Analysis Considerations Related to COVID-19

On 11 Mar 2020, COVID-19 was declared a pandemic by the WHO (Cucinotta, 2020). This section summarizes additional analysis considerations to assess the potential impact of COVID-19 (Meyer, 2020). The following additional sensitivity and supplementary analyses will be included to assess the impact of the pandemic disruption on the study and to address pandemic-related missing data.

1. The summary of participant disposition will include COVID-19-related discontinuations and withdrawals.
2. A summary of known COVID-19 exposure or diagnosis will be provided using the SS.
3. A summary of COVID-19-related important protocol deviations will be provided. A by-participant listing of all protocol deviations will be provided.

6.5. Appendix 5: Changes to Protocol-Planned Analyses

The following additional analyses will be done that were not planned in the protocol:

- Graded cardiac response
- Graded renal response
- Deep hematologic response

The following analyses that were planned in the protocol, but will not being conducted:

- Analyses of GLS% - Since GLS% was added as an exploratory analysis in a protocol amendment, the baseline data for most subjects was not available. Only a listing will be provided for the same.
- Physical Examination – Though physical examinations were done as per the schedule of assessments; the data for abnormality was not collected by body system. Only a listing will be provided.

6.6. Appendix 6: List of Abbreviations

Abbreviation	Definition
AAS	Antidrug Antibody Analysis Set
ADA	antidrug antibody
AE	adverse event
AL	amyloid light chain
ATC	Anatomical Therapeutic Chemical
BSA	body surface area
COVID-19	coronavirus disease 2019
cTnI	cardiac Troponin I
cTnT	cardiac Troponin T
CyBorD	cyclophosphamide, bortezomib, and dexamethasone
DLT	dose-limiting toxicity
dFLC	Involved-uninvolved free light-chain difference
iFLC	Involved free light-chain difference
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EOT	End of Treatment
FLC	free light chain
GLS	global longitudinal strain
hs-cTnT	high-sensitivity cardiac Troponin T
hs-cTnI	high-sensitivity cardiac Troponin I
ICF	informed consent form
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibody
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
PCD	Plasma cell dyscrasia
PK	pharmacokinetic
PKS	Pharmacokinetic Analysis Set
PT	Preferred Term
q2wk	biweekly
q4wk	once monthly
RP3D	recommended Phase 3 dose
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	Statistical Analysis Software®
SOC	System Organ Class

Abbreviation	Definition
SS	Safety Set
TEAE	treatment-emergent adverse event
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

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