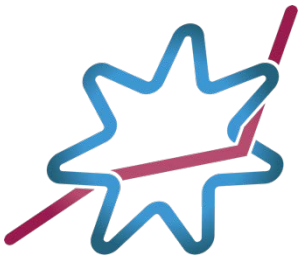

CLINICAL STUDY PROTOCOL

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

INVESTIGATIONAL PRODUCT: CAEL-101

SPONSOR:

Alexion Pharmaceuticals, Inc.
121 Seaport Boulevard
Boston MA 02210
USA

IND #: 117,316

Protocol Amendment 3: 18 July 2022

Supersedes: Protocol Amendment 2 dated December 14, 2021

Original Protocol dated November 4, 2019

SPONSOR PROTOCOL APPROVAL PAGE

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

[redacted]

19-Jul-2022 | 09:25 EDT

Date

[redacted]

Alexion Pharmaceuticals, Inc.

Medical Monitor Name and Contact Information can be found in the Study Contact List.

INVESTIGATOR'S AGREEMENT

By signing below, I agree that:

I have read the CAEL101-203 study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guideline for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 3.0 (18 July 2022)

This amendment is considered to be substantial according to the US Food and Drug Administration's (FDA) regulation at 21 CFR part 312.30(b) and any applicable local regulations.

Overall Rationale for the Amendment

The main purpose of this document is to update the trial sponsorship, extend the End of Treatment period, and change contraception inclusion criteria. Other administrative changes made to the protocol have been incorporated in this amendment. Changes to Clinical Study Protocol CAEL101-203 from the Protocol Amendment 2.0 dated 14 December 2021 are outlined. This amendment is to:

Change	**Rationale**
Title page, Section 9.5 SAE Reporting and Follow-up, Section 9.5.2 Pregnancy, headers, and footers Sponsorship updated	To reflect the change of sponsorship of the study from Caelum Biosciences, Inc to Alexion Pharmaceuticals, Inc
Figures 2 and 3, and throughout document End of Treatment period changed from 14 days to 140 days	To extend the End of Treatment period to 140 days
Figures 2 and 3 Updated	Updated for clarity and readability
Section 1.2 Schedule of Assessments (Table 1) Adverse Event (AE) added to Visit 1 Text added ("Protein") to '24-hour urine collection' row. Text added ('Serum Free Light Chains and') to Serum and Urine Immunofixation row Updated text describing cTnT/cTnI End of Treatment extended to 140 days from last dose Footnotes 'a', 'b', 'c', 'f', 'i', 'j': text updated Footnote 'k' added	End of Treatment extended to 140 days from last dose (eg, Section 6.3 and throughout document) For clarity, added: • Added AE to Visit 1, • Added "protein" to '24-hour urine protein collection' row • Added "and serum and urine' to 'Serum Free Light Chains and serum and urine immunofixation electrophoresis' row • Updated text updated from 'cTnT/cTnI (cardiac patients only)' to 'cTnT/cTnI/hs-cTnT/hs-cTnI (cardiac patients only)' Text updated in:

Change	Rationale
	• Footnote 'a' for consistency with Section 4.1 and Section 6.2 • Footnote 'b' for consistency with Section 9.1.3 • Footnote 'c' for consistency with Section 6.10 • Footnote 'f' to clarify timing of PK and immunogenicity testing • Footnote 'i' to clarify assessments will be completed approximately every 90 days • Footnote 'j' for consistency with End of Treatment extended to 140 days from last dose Added Footnote 'k' to clarify that past 50 weeks, assessments are to be completed every 12 months Cardiovascular magnetic resonance imaging (MRI) removed to be consistent with Section 8.1
Section 3.2 Secondary Objectives Added additional text to secondary objective	To describe that the PK profile of CAEL-101 will be explored when CAEL-101 is given bi-weekly (q2wk) versus once-monthly (q4wk) after the first 50 weeks
Section 4.1 Summary of Study Design Text added Figure 4 added	To provide an alternative maintenance dosing regimen of every four weeks (q4wk). To provide a composite hematologic and organ response model proposed by Sidana et al. (2020). 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 as per the scoring system proposed. Switching could be considered if the score is within the range of 0 to 3.
Section 5.1 Patient Inclusion Criteria Updated verbiage of inclusion criteria #5, #9, #10	#5 Clarify the Kappa/ Lambda ratio for readability #9 Clarify contraception methods for women #10 Clarify contraception methods for men
Section 5.2 Patient Exclusion Criteria Updated verbiage of exclusion criteria #16	#16 Corrected units for prostate-specific antigen from mg to ng

Change	Rationale
Section 6.1 Screening Period Updated Table 2	Revised Table 2 to include the high sensitivity (generation 5) cardiac troponin T (hs-cTnT) threshold value for Mayo Staging of AL amyloidosis
Section 6.2 Treatment Period Text added	To describe the alternative maintenance dosing regimen: 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 should be agreed between the Investigator and the Sponsor Medical Monitor and based on the assessment of the combined hematological and organ responses as per the scoring system proposed by Sidana et al (2020).
Section 6.2.5 Dose Delay Updated text to clarify that Medical Monitor will be notified when there is a study dose delay or modification Added text about delayed dosing events and safety assessments	Clarify that dose delay or modification for safety concerns are permitted at the Investigator's discretion. When not related to safety, decisions regarding dose delay and dose reductions/modifications will be made by the Investigator in consultation with the Medical Monitor To provide guidance to Investigators about delayed dosing events and safety assessments
Section 6.3 End of Treatment Number of days after the last dose of CAEL-101 updated	To extend the End of Treatment period to 140 days
Section 6.4 End of Study Text updated	To update the definition of 'end of study'
Section 6.7 Prohibited Medications Added information about Medical Monitor	To provide guidance to Investigators about consultation with Medical Monitor
Section 6.8 Pharmacokinetic Measurements (previously Section 8.4)	Transposed the section to provide information in a more appropriate section of the protocol since the pharmacokinetic (PK) measurements are not an assessment of efficacy To clarify that CAEL-101 metabolites will not be collected
Section 6.9 Immunogenicity Measurements (previously Section 8.5)	Transposed the section to provide information in more appropriate section as the immunogenicity measurements are not an assessment of efficacy

Change	Rationale
Section 6.9.1 ADA Variables Section added	Added ADA variables to provide better clarity on the expected data and analysis
Section 6.10 Added Contraception Requirements	To clarify contraception requirements
Section 7.3 Study Drug Storage Updated text	For clarification of storage practices
Section 8.1 Echocardiography Cardiovascular MRI removed from section header Revised text describing echocardiography.	To reflect that Cardiovascular MRI is not being performed and is no longer described in this text To provide additional details about echocardiograms
Section 9.1.3 Physical Examination Removed details describing a full physical examination	To be consistent with data captured on the Case Report Form
Section 9.1.5 Clinical Laboratory Tests Table 5 updated	To include complete list of clinical laboratory tests to be performed at local laboratory
Section 9.2.1.1 Adverse Event Reporting and Follow-up Revised text	To clarify timing of AE reporting and to clarify 'pre-treatment AE'
Section 9.5 SAE Reporting and Follow-up Incorporated other administrative text to clarify timing of reporting of SAEs and SAE reporting information of Sponsor	To align with current safety reporting procedures. Update Sponsor contact information for SAE reporting and timing of SAE reporting relative to ICF signing. Clarify that additional records should not be provided unless specifically requested.
Section 9.5.2 Pregnancy Incorporated other administrative text to clarify pregnancy reporting information of Sponsor	To align with current pregnancy reporting procedures. Update Sponsor contact information for pregnancy reporting.
Section 10.1 General Considerations Text added	To describe that the PK profile of CAEL-101 will be explored when CAEL-101 is given q2wk versus q4wk after the first 50 weeks
10.4 Analysis Sets Added ADA Population	To describe the population used in the ADA analysis set
10.5.6 Pharmacokinetics Updated text	To describe that the PK profile of CAEL-101 will be explored when CAEL-101 is given bi-weekly versus once-monthly after the first 50 weeks and these details will be provided in a separate PK SAP.

Change	**Rationale**
Section 10.7 Missing Data Modified text	To clarify that details about handling of missing data will be presented in the Statistical Analysis Plan
Appendix B Organ Involvement and Response Criteria Table updated	To update the title, headers, and response criteria for heart, kidney, and liver
Appendix C Hematologic Response and Progression Criteria Table updated	To update title and description of Complete Response
Appendix E COVID-19 Risk Assessment Added this appendix	To align with regional COVID-19 risk assessment requirements
Appendix F COVID Vaccine Risk Assessment Added this appendix	To align with regional COVID-19 vaccine specific risk assessments
Section 18 References (Previously Section 17)	Relocated reference section to end of document
Minor administrative changes	For improved consistency and clarity

Abbreviations: ADA – antidrug antibody; AE – adverse event; MRI – magnetic resonance imaging; PK – pharmacokinetic; q4wk – every four weeks; SAE – serious adverse event; SAP – Statistical Analysis Plan; V – visit

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ABBREVIATIONS

Abbreviation or Term	Definition
AAS	ADA Analysis Set
ADA	anti-drug antibodies
AE	adverse event
AL	light chain associated, primary amyloidosis
ALECT2	leukocyte chemotactic factor 2
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CRF	case report form
cTnI	cardiac troponin I
cTnT	cardiac troponin T
Ctrough	lowest concentration of drug before the next dose
CyBorD	cyclophosphamide-bortezomib-dexamethasone
dFLC	involved/uninvolved free light chain difference
DLT	dose limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
FLC	free light chain
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
ICD	implantable cardioverter-defibrillator
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IMWG	International Myeloma Working Group
IRB	institutional review board
IV	intravenous
LVEF	left ventricular ejection fraction
mmHg	millimeters mercury

Abbreviation or Term	Definition
MUGA	multigated acquisition scan
NT-proBNP	b-type natriuretic peptide and N-terminal pro b-type natriuretic peptide
PCD	plasma cell dyscrasia
PK	pharmacokinetics
q1wk	every week
q2wk	every two weeks
q4wk	every four weeks
RP3D	recommended phase 3 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SoC	standard of care
SPEP	serum protein electrophoresis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WOCBP	women of child-bearing potential

1. SYNOPSIS

Name of Sponsor/Company: Alexion Pharmaceuticals, Inc.

Name of Investigational Product: CAEL-101

Name of Active Ingredient: CAEL-101 is chimeric fibril-reactive monoclonal antibody 11-1F4

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

Study center(s): Approximately 3 US investigational centers will participate

Number of patients: Approximately 25	**Phase of development:** 2

Objectives:

The *primary objective* is:

- To define the safety and tolerability of CAEL-101 and determine the recommended Phase 3 dose (RP3D) for patients with amyloid light-chain (AL) amyloidosis

Secondary objectives in this study are:

- To define the safety and tolerability of CAEL-101 when administered in combination with standard of care (SoC) cyclophosphamide, bortezomib, dexamethasone (CyBorD)
- To define the safety tolerability of CAEL-101 when administered in combination with SoC CyBorD and daratumumab
- To describe the pharmacokinetic (PK) profile of CAEL-101 and to explore the PK profile of CAEL-101 when given bi-weekly (q2wk) versus once-monthly (q4wk) after the first 50 weeks.

The exploratory objective is:

- To assess the efficacy of CAEL-101 in terms of cardiac, liver, and renal response in patients with AL amyloidosis.

Study Design and Duration

This is a multicenter, open-label, sequential cohort, dose-selection study of CAEL-101 in Mayo Stage I, Stage II and Stage IIIa AL amyloidosis patients. CAEL-101 will be administered in combination with the SoC CyBorD chemotherapy and daratumumab.

The study is divided into two parts:

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

Part A

Part A consists of a Screening period, a safety and tolerability Treatment period and an End of Treatment period. The Treatment period of Part A, the part where the RP3D is determined, is divided into a Dose Limiting Toxicity (DLT) Observation period and a Continued Treatment period. During the DLT Observation period, patients will be seen in the clinic every week (q1wk) for 4 weeks to receive study drug infusions and be assessed for DLTs.

The first CAEL-101 dose to be studied in Part A, 500 mg/m^2, was determined based on the completed study CAEL101-101.

The initial cohort dose assignments in Part A will be: Cohort 1 500 mg/m^2, Cohort 2 750 mg/m^2 and Cohort 3 1000 mg/m^2.

DLT Observation period to determine the RP3D

Part A of the study will employ a 3+3 dose escalation design. At least 3 patients will be enrolled in each dose cohort unless adverse events (AEs) preventing further dosing are observed. Enrollment into a new cohort with a higher dose of CAEL-101 cannot begin until the DLT observation period has completed for the last patient enrolled in the previous cohort.

If 0 out of 3 patients experience a DLT during the DLT observation period, the next dose cohort will be opened. If 1 out of 3 patients experience a DLT during the DLT observation period, the cohort may be expanded to 6 patients. If no further patients in the expanded cohort experience a DLT during the DLT observation period (i.e., 1 out of 6 patients experiences a DLT), increase to the next dose may take place. If 2 or more patients in a cohort experience a DLT during the DLT observation period, further dose increase will cease. New patients will be enrolled at the lower (tolerated) dose level if only 3 patients were previously enrolled in that cohort. The recommended dose will require at least 6 patients treated with CAEL-101 at that dose and ≤ 1 patient having experienced a DLT during the DLT observation period. Based on clinical safety and laboratory data, the safety review team (Sponsor and 1 or more Investigators) may direct that an intermediate dose between the dose demonstrating the DLT and the previously documented safe dose may be explored, or a different dosing regimen starting at a lower dose be explored. Dose increases may be discontinued based on safety or PK findings that may influence the decision about a recommended dose.

The Sponsor and at least one Investigator will jointly decide the following:

- Dose increases in the next cohort and/or dose schedule
- Recommended Phase 3 dose
- Dose reductions based on severity, duration and frequency of toxicities observed at the previous dose level

The Sponsor may choose to evaluate CAEL-101 in additional patients and at other/higher doses and dosing schedules to further assess the PK profile, the benefit/risk profile and/or based on the safety findings from ongoing CAEL-101 clinical trials.

All patients will remain on the dose level assigned to the cohort in which they were originally enrolled until a RP3D is identified. When the RP3D is identified, all patients will be changed to the RP3D. Part B will commence after the RP3D has been identified and enrolled patients have been changed to the RP3D.

Part B

Part B consists of a Screening period, a safety and tolerability Treatment period and an End of Treatment period. The Treatment period of Part B is divided into a Safety Observation period and a Continued Treatment period. During the Part B Safety Observation period, new patients will be seen in the clinic q1wk for 4 weeks to receive study drug infusions and have various safety assessments. A minimum of 6 new patients will receive CAEL-101 administered in combination with SoC CyBorD and daratumumab. Once the newly enrolled patients have completed the Safety Observation period, patients from Part A who are in the Continued Treatment Period and who, in the Investigator's judgment, should have their SoC treatment complemented with daratumumab may do so.

Continued Treatment Period

Patients from both Parts A and B will continue receiving CAEL-101 therapy and SoC. CAEL-101 study drug infusions will continue, with dosing approximately every two weeks (q2wk). 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 as per the scoring system proposed by Sidana et al. (Sidana, 2020). Switching could be considered if the score is within the range of 0 to 3. Approximately every month or every visit as noted in the Schedule of Assessments, patients will be assessed for changes in free light chains (FLC), 24-hour urine protein, PK and immunogenicity tests. Approximately every 90 days from the first dose of study drug, all patients will be assessed for safety and changes in B-type natriuretic peptide and N-terminal pro b-type natriuretic peptide (NT-proBNP). Patients with cardiac AL amyloidosis will be assessed for changes in cardiac troponin T (cTnT)/cardiac troponin I (cTnI).

Patients will be treated until death, unacceptable toxicity, symptomatic deterioration, Investigator decision, patient decision or Sponsor decision to terminate the study.

End of Treatment Period

Patients from both Part A and Part B who discontinue from the study should have the End of Treatment assessments completed as indicated in the Schedule of Assessments.

Investigational product, dosage and mode of administration:

CAEL-101 is administered as an intravenous (IV) infusion over approximately 2 hours.

Study Population:

Eligible patients for both Part A and Part B will meet the same inclusion and exclusion criteria, except as noted.

Key Inclusion Criteria:

1. AL amyloidosis Mayo stage I, II or IIIa
2. For Part A only, measurable hematologic disease defined by at least one of the following:
   a. involved/uninvolved free light chain difference (dFLC) > 5mg/dL or
   b. free light chain (FLC) > 5mg/dL with abnormal Kappa/Lambda ratio or
   c. serum protein electrophoresis (SPEP) m- spike > 0.5 g/dL

   Patients with confirmed AL amyloid diagnosis without measurable disease may be enrolled with consultation and approval by the Sponsor Medical Monitor or their designee.
3. a. For Part A, currently on and continuing OR planned to start concurrent chemotherapy with CyBorD administered weekly as SoC.

   b. For Part B, currently on and continuing OR planned to start concurrent chemotherapy with CyBorD and daratumumab administered as SoC.

Key Exclusion Criteria:

1. Any form of secondary, hereditary, senile, localized, dialysis related or ALECT2 amyloidosis
2. Meets the International Myeloma Working Group (IMWG) definition of multiple myeloma. Patients with signs and/or symptoms attributable ONLY to amyloidosis and who do NOT meet IMWG definition of smoldering myeloma may be enrolled upon approval of the medical monitor.
3. Supine systolic blood pressure < 90 millimeter of mercury (mmHg), or symptomatic orthostatic hypotension, defined as a decrease in systolic blood pressure upon standing of > 20 mmHg despite medical management (e.g., midodrine, fludrocortisones) in the absence of volume depletion
4. Receiving dialysis

5. Myocardial infarction, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or percutaneous cardiac intervention with recent stent, coronary artery bypass grafting or major cerebrovascular accident within 6 months prior to screening
6. Left ventricular ejection fraction (LVEF) < 45% by echocardiogram or multigated acquisition scan (MUGA)

Statistical methods:
Safety

Safety assessments will include AEs, clinical laboratory tests, vital signs, physical examinations and electrocardiograms (ECGs). The incidence of DLTs will be evaluated for each dose escalation cohort. All treatment-emergent adverse events (TEAEs) will be summarized by system organ class and preferred term for each dose cohort. All TEAEs will be summarized by incidence, severity and potential causality to study drug.

Clinical laboratory tests and vital signs will be summarized descriptively for each dose cohort. All abnormal findings in clinical laboratory test results, vital signs, physical examinations and ECGs will be listed.

Pharmacokinetics

PK parameters will be tabulated and summarized with descriptive statistics by cohort and/or study part. Patients in Part A who discontinue for non-safety reasons may be replaced.

Efficacy

Efficacy endpoints, including NT-proBNP, cTnT/cTnI, proteinuria, will be assessed for absolute changes (and percent changes) over time. Patients with organ involvement (eg, cardiac, renal) will be identified at baseline through minimum thresholds for each relevant biomarker and defined as being Cardiac Evaluable, Renal Evaluable, etc, accordingly. These specific analysis populations will then be assessed for changes over time in the organ-specific biomarkers. Patients may be classified as responders (by organ) according to varying definitions of response, eg, for NT-proBNP, a decrease of 30% may be defined as one type of cardiac responder. As this analysis is exploratory, various definitions may be used to allow for a thorough understanding of the treatment benefit over time.

Organ-specific outcomes for renal, hepatic, and cardiac biomarker response from pre-CAEL-101 treatment will be collected retrospectively and prospectively. The retrospective collection may include a review of the patient record at the site. Further, prospective collection of these data has been added to collect future organ response outcomes. The combination of retrospective and prospective data collection will allow for a more robust determination of the effects of CAEL-101 on efficacy in these patients.

1.1. Study Schematics

Figure 1: CAEL101-203 Part A Dose Selection Schema

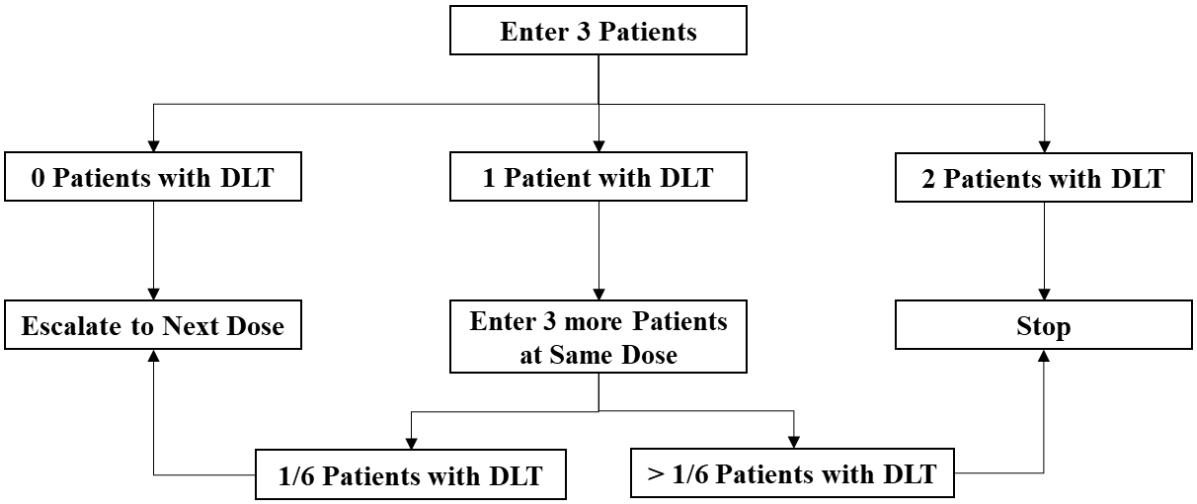
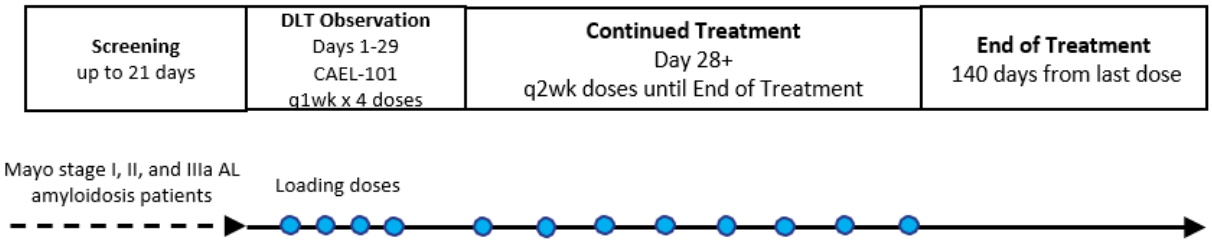
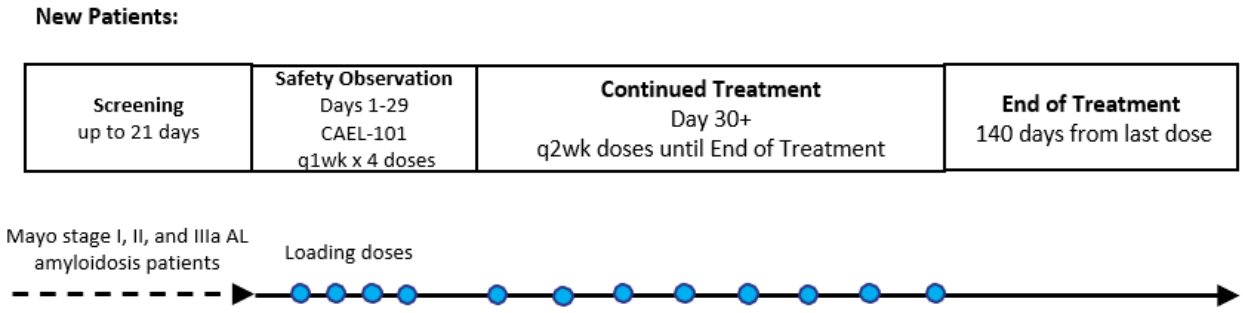


Figure 2: CAEL101-203 Part A Cohort Schema Dose Selection



Note: There are 3 cohorts in Part A: 500, 750 and 1000 mg/m^2
Abbreviations: DLT – dose limiting toxicity; q1wk – every week; q2wk – every two weeks

Figure 3: CAEL101-203 Part B Schema



Abbreviations: q1wk – every week; q2wk – every two weeks

1.2. Schedule of Assessments

Table 1: CAEL101-203 Schedule of Assessments (Parts A and B)

	Screening	**DLT/Safety Observation Period**					**Continued Treatment Period**																							**EOT**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29[a]**	**140 d from last dose**
Week	-3 to 0	1	2	3	4	5	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50[a]	
Day	≤ 21 days prior to V2	1	8	15	22	29	36	50	64	78	92	106	120	134	148	162	176	190	204	218	232	246	260	274	288	302	316	330	344	14, 28, 56, 84, 112, & 140 days from last dose
Procedure Window			+/- 1 day				+/- 2 days																							+/- 1 day
Signed informed consent	X																													
Inclusion & exclusion	X																													
Demographics	X																													
AL amyloidosis confirmation	X																													
Medical history	X																													
Physical examination[b]	X	X	X	X	X						X						X						X						X	X
Height	X																													
Pregnancy test[c]	X	X									X						X						X						X	X
Vital signs & weight	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NYHA classification[h]		X					X		X		X		X		X		X		X		X		X						X	X
Twelve-lead electrocardiogram	X	X				X					X						X						X						X	X
Safety laboratory tests[d]	X	X	X	X	X	X	X[e]	X[e]			X						X						X						X	X
24-hour urine protein collection[h,j]		X									X						X						X						X	X
Serum Free Light Chains and serum and urine immunofixation electrophoresis[h]		X					X		X		X		X		X		X		X		X		X		X		X		X	X
Echocardiogram[h,j]		X																											X[k]	

NT-proBNP[h]		X					X		X		X		X		X		X		X		X		X		X		X		X[i]	X
cTnT/cTnI/hs-cTnT/hs-cTnI (cardiac patients only)		X									X						X						X						X	X
Immunogenicity tests[f]		X	X	X	X		X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X	X
Study drug infusion		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK samples [f, g]		X	X	X	X		X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X	X
DLT (Part A only)		X	X	X	X	X																								
Adverse Events	X	X																												X
Concomitant medications	X	X																												X

Table 1: CAEL101-203 Schedule of Assessments (Parts A and B)

a. Once a patient completes V29/Week 50, continue to follow the schedule of assessments repeating the procedures at V24-V29/Weeks 40-50 for as long as the patient remains on study treatment. 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 as per the scoring system proposed by Sidana et al. (Sidana, 2020), switching could be considered if the score is within the range of 0 to 3 (Figure 4).

b. The Investigator or a licensed team member, per local regulations, will perform physical examinations.

c. For women of childbearing potential only, serum human chorionic gonadotropin (hCG) required at screening. Subsequent pregnancy tests may be performed using urine dipstick. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient

d. Chemistry – ALT, albumin, ALP, AST, BUN, eGFR, calcium, chloride, creatinine, GGT, globulin, glucose, phosphorus, potassium, sodium, total bilirubin, total protein, uric acid. Hematology – CBC with differential, RDW, reticulocyte count. Urinalysis -- bilirubin, blood, glucose, ketones, leukocytes, pH, protein and specific gravity. Patients in Part B beginning treatment with daratumumab after the Safety Observation period will have weekly CBC with differential tests for at least 8 weeks.

e. For Patients in Part B, only CBC with differential test required on V7 and V8. Patients should also have a CBC with differential test performed on Week 7/Day 43.

f. Collect PK and immunogenicity tests (pre-dose within 1 hour of the start of the infusion) every other visit (i.e., every 28 days +/- 2d) from V15 through V29. After V29/Week 50, samples collected approximately every 182 days and at end of treatment.

g. PK sample times – pre-dose within 1 hour of the start of the infusion and post-dose between 30 minutes and 1 hour from the end of the infusion. PK samples must be drawn from the opposite arm from the CAEL-101 infusion, unless approved by the Sponsor.

h. Ensure that all available assessments have been recorded in the CRF for each visit (detailed above) during the study. Any additional measurements, if already collected at time points other than the pre-defined visits, shall be recorded in the CRF.

i. Past 50 weeks, assessments will be completed approximately every 90 days.

j. Evaluations obtained after Screening may be within a +/-30 day window from the study day. Evaluations should not be skipped. If the patient cannot undergo an evaluation within the assessment window (e.g., the patient is hospitalized), it should be completed as soon as possible. EOT evaluation is required ONLY at 140 days following the last dose of study drug.

k. Past 50 weeks, assessment will be completed every 12 months

2. INTRODUCTION

2.1. Background

Amyloidosis is a rare and serious heterogeneous group of diseases characterized by fibrillar protein deposits and amyloids localized in a single organ or systematically in many organs (Hemminki, 2012). Amyloid light-chain (AL) amyloidosis is the most common form of systemic amyloid disease, accounting for approximately 70% of all subjects suffering from the disease (Milani, 2018). All organs, except for the brain, can be affected in AL amyloidosis leading to irreversible organ dysfunction and death if unrecognized or treated ineffectively (Milani, 2018). The disease is inevitably progressive and accumulating amyloid protein deposits interfere with the tissue or organ's healthy function causing clinical symptoms, organ failure and death. Thirty to 40% of patients die within 12 months of diagnosis (Dispenzieri, 2015a). The prognosis is very poor, with less than 5% of all subjects with AL amyloidosis surviving more than 10 years after diagnosis (Kyle, 1986; Palladini, 2017; Palladini, 2015). The prognosis of patients with AL amyloidosis depends on the burden of the amyloid in the tissues, especially the heart, and the size of the plasma cell clone and its biology, which predict the ability to achieve a hematologic response.

Treatment of AL amyloidosis is largely based on chemotherapy and/or autologous stem cell transplants and are targeted to eradicate the pathologic plasma cells and stop the production of new amyloid and the resulting fibrils. There are no approved treatments for organ-deposits of AL amyloidosis, and the only available options for patients is to be treated with experimental treatments, most often in clinical trials (Dispenzieri, 2015a; Palladini, 2018). Subjects suffering from AL amyloidosis are at high risk of death and are extremely susceptible to treatment toxicity in the first few months after diagnosis. Whereas, if they survive this initial treatment, they enjoy a better long-term outcome (Dispenzieri, 2013). There is a high unmet need for a therapeutic treatment that removes existing amyloid deposits to limit and reverse organ dysfunction.

2.2. CAEL-101

CAEL-101 (Ch11-1F4, NSC-711516), is a chimeric immunoglobulin G1 kappa isotype version of m11-1F4, the parent murine monoclonal antibody of CAEL-101, which binds to a cryptic epitope at the N-terminal of both κ and λ light chain proteins that adopt a non-native structure. CAEL-101 was found to react with specificity in a conformation-dependent manner with light chain components in amyloid fibrils, but not with free non-amyloid light chains.

The first in human experience with CAEL-101 was study protocol CAEL101-101, in which doses from 0.5 mg/m^2 up to 500 mg/m^2 were tested for safety and tolerability in both single-dose and multi-dose regimens. No dose-limiting toxicities (DLTs) were observed in that dose range, including up to the maximum dose of 500 mg/m^2.

The primary objective of this study was to describe the safety and tolerability of CAEL-101 in combination with cyclophosphamide-bortezomib-dexamethasone (CyBorD) and to determine the recommended Phase 3 dose during an initial 14-day (Cohort 1) or 27-day (Cohorts 2 and 3) treatment and follow-up period (referred to as the Dose-Limiting Toxicity, ie, DLT, Observation period).

This assessment has been completed, with all three tested dose levels of CAEL-101 (500, 750, and 1000 mg/m^2), when administered with concurrent CyBorD, found to be safe and well-tolerated by the patients enrolled. No dose-limiting toxicities were observed in any patients at any of these dose levels during the DLT Observation period. Based on these safety and tolerability data, and protocol guidance, the final cohort review by the study site Principal Investigator and the Sponsor Medical Monitor concluded that the 1000 mg/m^2 dose is recommended for the Phase 3 studies.

The pharmacokinetic (PK) review of the three CAEL-101 dose levels showed that PK exposure increases in a generally linear manner with increasing dose over the studied dose range. In addition to overall exposure levels, dose selection included assessment of target receptor site occupancy for the patient with the lowest exposure levels (C_{trough}) (with a minimum of 90% receptor site occupancy desired). To support the broadest range of patients and to account for patient exposure variability, the 1000 mg/m^2 dose fulfills these requirements and achieves the desired C_{trough} levels after the second dose.

Therefore, based on safety, tolerability outcomes and pharmacokinetics, the 1000 mg/m^2 dose was selected for use in the Phase 3 studies, CAEL101-301 and CAEL101-302, as well as in Part B of this study.

Refer to the CAEL-101 Investigator's Brochure for detailed preclinical and clinical study data.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective in this study is to define the safety and tolerability of CAEL-101 and determine the recommended Phase 3 dose (RP3D) for patients with AL amyloidosis.

3.2. Secondary Objectives

The secondary objectives in this study are to:

- define the safety and tolerability of CAEL-101 when administered in combination with standard of care (SoC) CyBorD
- define the safety and tolerability of CAEL-101 when administered in combination with SoC CyBorD and daratumumab
- describe the PK profile of CAEL-101 and to explore the PK profile of CAEL-101 when given bi-weekly (q2wk) versus once-monthly (q4wk) after the first 50 weeks.

3.3. Exploratory Objective

The exploratory objective in this study is to assess the efficacy of CAEL-101 in terms of cardiac, liver, and renal response in patients with AL amyloidosis.

4. STUDY DESIGN

4.1. Summary of Study Design

This is a multicenter, open-label, sequential cohort, dose-selection study of CAEL-101 in Mayo Stage I, Stage II and Stage IIIa AL amyloidosis patients. CAEL-101 will be administered in combination with SoC CyBorD chemotherapy and daratumumab.

The study is divided into two parts:

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

Part A

Part A consists of a Screening period, a safety and tolerability Treatment period and an End of Treatment period. The Treatment period of Part A, the part where the RP3D is determined, is divided into a DLT Observation period and a Continued Treatment period. During the DLT Observation period, patients will be seen in the clinic every week (q1wk) for 4 weeks to receive study drug infusions and be assessed for DLTs.

Part A of the study will employ a 3+3 dose escalation design. At least 3 patients will be enrolled in each dose cohort unless adverse events (AEs) preventing further dosing are observed. Enrollment into a new cohort with a higher dose of CAEL-101 cannot begin until the DLT observation period has completed for the last patient enrolled in the previous cohort.

The recommended dose will require at least 6 patients treated with CAEL-101 at that dose and ≤ 1 patient having experienced a DLT during the DLT observation period. Dose increases may be discontinued based on safety or PK findings that may influence the decision about a recommended dose.

All patients will remain on the dose level assigned to the cohort in which they were originally enrolled until an RP3D is identified. When the RP3D is identified, all patients will be changed to the RP3D. Part B will commence after the RP3D has been identified and enrolled patients have been changed to the RP3D.

Part B

Part B consists of a Screening period, a safety and tolerability Treatment period and an End of Treatment period. The Treatment period of Part B is divided into a Safety Observation period and a Continued Treatment period. During the Part B Safety Observation period, new patients will be seen in the clinic q1wk for 4 weeks to receive study drug infusions and have various safety assessments. A minimum of 6 new patients will receive CAEL-101 administered in combination with SoC CyBorD and daratumumab.

Continued Treatment Period

Patients from both Parts A and B will continue receiving CAEL-101 therapy and SoC. CAEL-101 study drug infusions will continue, with dosing approximately every two weeks (q2wk).

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 as per the scoring system proposed by Sidana et al. (Sidana, 2020). Switching could be considered if the score is within the range of 0 to 3 (Figure 4).

Figure 4: Composite Hematologic and Organ Response Model (Sidana, 2020)

	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

End of Treatment Period

Patients from both Part A and Part B who discontinue from the study should have the End of Treatment assessments completed as indicated in the Schedule of Assessments.

Schematics of the study design are presented in Figure 1, Figure 2, and Figure 3 while the Schedule of Assessments is presented in Table 1.

4.2. Number of Patients

Approximately 25 patients will be enrolled in the study. Part A enrolled approximately 13 patients.

For Part B, a minimum of 6 newly enrolled patients are expected to receive CAEL-101 administered in combination with SoC CyBorD and daratumumab. Once the newly enrolled patients have completed the Safety Observation period, patients from Part A who are in the Continued Treatment Period and who, in the Investigator's judgment, should have their SoC treatment complemented with daratumumab may do so.

5. SELECTION OF STUDY POPULATION

5.1. Patient Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study.

1. Provide written informed consent and be willing and able to comply with all study procedures
2. Adult, 18 years and older
3. Minimum life expectancy of 6 months
4. AL amyloidosis Mayo stage I, II, or IIIa at the time of Screening
5. For Part A only, measurable hematologic disease defined by at least one of the following:
   a. dFLC > 5mg/dL or
   b. FLC > 5mg/dL with abnormal Kappa/Lambda ratio or
   c. SPEP m- spike > 0.5 g/dL

   Patients with confirmed AL amyloid diagnosis without measurable disease may be enrolled with consultation and approval by the Sponsor Medical Monitor or their designee.
6. Histopathological diagnosis of amyloidosis based on detection by immunohistochemistry and polarizing light microscopy of green bi-refringent material in Congo red stained tissue specimens (in an organ other than bone marrow) or characteristic electron microscopy appearance
7. a. For Part A, currently on and continuing OR planned to start concurrent chemotherapy with CyBorD administered weekly as SoC. Mayo stage IIIa patients will not have received CyBorD for more than 3 months at the time of first dose of CAEL-101.

   b. For Part B, currently on and continuing OR planned to start concurrent chemotherapy with CyBorD and daratumumab administered as SoC. Mayo stage IIIa patients will not have received CyBorD for more than 3 months at the time of first dose of CAEL-101.
8. Adequate bone marrow reserve and hepatic function as demonstrated by:
   a. Absolute neutrophil count ≥ 1.5 x10^9/L
   b. Platelet count ≥ 75 x 10^9/L
   c. Hemoglobin ≥ 9 g/dL
   d. Total bilirubin ≤ 2 times the upper limit of normal (x ULN)
   e. Aspartate aminotransferase (AST) ≤ 3 x ULN
   f. Alanine aminotransferase (ALT) ≤ 3 x ULN
   g. Alkaline phosphatase (ALP) ≤ 5 x ULN (except for patients with hepatomegaly and isozymes specific to liver, rather than bone)
9. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test during Screening and must agree to use highly effective contraception (Section 6.10) from Screening to at least 5 months following the last study drug administration or 12 months following the last dose of her plasma cell dyscrasia (PCD) therapy, whichever is longer

10. Men must be surgically sterile or must agree to use highly effective contraception (Section 6.10) and refrain from donating sperm from Screening to at least 5 months following the last study drug administration or 12 months following the last dose of their PCD therapy, whichever is longer

5.2. Patient Exclusion Criteria

Patients who meet any of the following criteria will not be permitted entry to the study.

1. Any form of secondary, hereditary, senile, localized, dialysis-related or leukocyte chemotactic factor 2-related (ALECT2) amyloidosis
2. Meets the International Myeloma Working Group (IMWG) definition of multiple myeloma (Appendix A). Patients with signs and/or symptoms attributable ONLY to amyloidosis and who do NOT meet IMWG definition of smoldering myeloma may be enrolled upon approval of the medical monitor.
3. Supine systolic blood pressure < 90 mmHg or symptomatic orthostatic hypotension, defined as a decrease in systolic blood pressure upon standing of > 20 mmHg despite medical management (e.g., midodrine, fludrocortisones) in the absence of volume depletion
4. Taking prednisone or its equivalent > 10 mg/day
5. Receiving dialysis
6. Planned stem cell transplant during the first 6 months of protocol therapy. Stem cell collection during the protocol therapy is permitted
7. Myocardial infarction, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or percutaneous cardiac intervention with recent stent, coronary artery bypass grafting or major cerebrovascular accident within 6 months prior to screening
8. Left ventricular ejection fraction (LVEF) < 45% by echocardiogram or multigated acquisition scan (MUGA) within the last 6 months
9. Severe valvular stenosis (e.g. aortic or mitral stenosis with a valve area <1.0 cm^2) or severe congenital heart disease
10. History of sustained ventricular tachycardia or aborted ventricular fibrillation or with a history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker/implantable cardioverter-defibrillators (ICD) is indicated but not placed (participants who do have a pacemaker/ICD are allowed on study)
11. QTcF > 500 msec. Participants who have a pacemaker may be included regardless of calculated QTc interval.
12. Evidence of acute ischemia or active conduction system abnormalities with the exception of any of the following:
    a. First degree AV-block
    b. Second degree AV-block Type 1 (Mobitz Type 1/Wenckebach type)
    c. Right or left bundle branch block

d. Atrial fibrillation with a controlled ventricular rate (uncontrolled [i.e., >110 bpm] ventricular rate is not allowed [determined by an average of three beats in Lead II or representative beats if Lead II is not representative of the overall electrocardiogram {ECG}])

13. Major surgery within 4 weeks of first dose or planned major surgery during the study. Patients with surgical procedures conducted under local anesthesia may participate.
14. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein [M-protein] and skin changes) (Appendix A)
15. Active malignancy (including lymphoma) with the exception of any of the following:
    a. Adequately treated basal cell carcinoma, squamous cell carcinoma, or in situ cervical cancer
    b. Adequately treated Stage I cancer from which the patient is currently in remission and has been in remission for > 2 years
    c. Low-risk prostate cancer with Gleason score < 7 and prostate-specific antigen < 10 ng/mL
16. Patients receiving an investigational drug/device in another clinical investigational study within 60 days before Screening.
17. Nursing mothers will not be permitted entry into the study.

5.3. Continuation and Withdrawal Criteria

Any patient receiving clinical benefit from the administration of CAEL-101 (as determined by the Investigator) in the absence of unacceptable toxicity will be allowed to remain on the study and should continue to receive CAEL-101 per protocol.

Patient participation in this clinical study may be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol
- Any serious adverse event (SAE), clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation in the study is not in the best interest of the patient
- Pregnancy
- Requirement of a prohibited concomitant medication
- Patient failure to comply with protocol requirements or study-related procedures
- Termination of the study by the Sponsor or the regulatory authority

If the patient withdraws prematurely from the study, the Investigator will promptly notify the Sponsor and ensure every effort is made to complete the full panel of End of Treatment (EOT) assessments specified in the Schedule of Assessments (see Table 1).

In the event a patient is lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical record.

6. TREATMENT PLAN

The study is divided into two parts:

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

Part A consists of a Screening period, a Treatment period and an End of Treatment period. The Treatment period of Part A, the part where the RP3D is determined, is divided into a DLT Observation period and a Continued Treatment period. During the DLT Observation period, patients will be seen in the clinic q1wk for 4 weeks to receive study drug infusions and be assessed for DLTs.

Part B consists of a Screening period, a Treatment period and an End of Treatment period. The Treatment period of Part B is divided into a Safety Observation period and a Continued Treatment period. During the Safety Observation period, new patients will be seen in the clinic q1wk for 4 weeks to receive study drug infusions and have various safety assessments. A minimum of 6 new patients will receive CAEL-101 administered in combination with SoC CyBorD and daratumumab. Once the newly enrolled patients have completed the Safety Observation period, patients from Part A who are in the Continued Treatment Period and who, in the Investigator's judgment, should have their SoC treatment complemented with daratumumab may do so.

During the Continued Treatment period for Part A and Part B, patients will receive study drug infusions approximately q2wk. Approximately every month or every visit as noted in the Schedule of Assessments, patients will be assessed for changes in FLC, 24-hour urine protein, PK and immunogenicity tests. Approximately every 90 days from the first dose of study drug, all patients will be assessed for safety and changes in B-type natriuretic peptide and N-terminal pro b-type natriuretic peptide (NT-proBNP). Patients with cardiac AL amyloidosis will be assessed for changes in cardiac troponin T (cTnT)/cardiac troponin I (cTnI).

Every effort should be made to schedule visits within the protocol-specified windows. Refer to the Schedule of Assessments in Table 1 for the list and timing of assessments.

6.1. Screening Period

The Screening Period is the same for Part A and for new patients enrolling in Part B. Patients will provide written informed consent to participate in this study before completing any protocol-specified procedures or evaluations not considered to be part of the patient's SoC. Patients will be eligible to enter the Screening period if they have a clinical diagnosis of Stage I, II or IIIa AL amyloidosis consistent with the 2013 modifications to the 2004 Mayo staging criteria (Table 2) at the time of Screening. One Stage I patient will be permitted to enroll per cohort in Part A and a maximum of two Stage I patients will be permitted to enroll in Part B.

Table 2: Staging of AL Amyloidosis with Advanced Cardiac Involvement for CARES Studies based on the European Modification of the 2004 Mayo Staging (Palladini, 2016), adapted with (Muchtar, 2019)*

Stage I	Stage II	Stage IIIa	Stage IIIb
Zero markers above threshold: • NT-proBNP < 332 ng/L AND one 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 one 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 ≤ 8,500 ng/L AND one 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 > 8,500 ng/L AND one of the following: • hs-cTnT ≥ 50 pg/mL (0.05 ng/mL) • cTnT ≥ 0.035 ng/mL • cTnI ≥ 0.1 ng/mL

* 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, high sensitivity cardiac troponin (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: cTnI – cardiac troponin I, cTnT – cardiac troponin T, hs-cTnT – high sensitivity cardiac troponin T, NT-proBNP – N-terminal pro b-type natriuretic peptide

After signing the informed consent form (ICF), patients will be evaluated for entry criteria during the Screening period (within 21 days before administration of the study drug). Screening assessments with abnormal results may be repeated at the discretion of the Investigator.

6.2. Treatment Period

Patients in both Part A and Part B of the study, who meet all of the inclusion criteria and none of the exclusion criteria will be treated with CAEL-101 plus CyBorD chemotherapy (and daratumumab in Part B) until death, unacceptable toxicity, symptomatic deterioration, Investigator decision (see Section 6.2.2 for allowed changes to CyBorD regimen), patient decision or Sponsor decision to terminate the study. All patients in Parts A and B will receive CAEL-101 q1wk (+/-1d) for the first 4 infusions. During the Continued Treatment period, patients will receive CAEL-101 q2wk (+/-2d). 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 should be agreed between the Investigator and the Sponsor Medical Monitor and based on the assessment of the combined hematological and organ responses as per the scoring system proposed by Sidana et al. (Sidana, 2020) Switching could be considered if the score is within the range of 0 to 3 (Figure 4).

6.2.1. Administration of Study Drug

In Part A, each patient's CAEL-101 dose will be determined by the CAEL101-203 Dose Assignment scheme (see Table 3) and the patient's body surface area in meters squared.
In Part B, patients will receive the RP3D. When administered on the same day, CAEL-101 will be administered first before CyBorD chemotherapy or daratumumab. Patients will receive CAEL-101 by an IV infusion over approximately 2 hours q1wk (+/-1d) for 4 infusions then q2wk (+/-2d) thereafter. Patients will be observed in the clinic for 90 minutes, or as long as the Investigator deems appropriate, following the completion of the study drug infusion for the first 4 infusions for infusion reactions, injection site reactions and overall well-being of the patient (may include vital signs at the Investigator's discretion).

Every effort should be made to assure the patient receives CAEL-101 according to the Schedule of Assessments (see Table 1). All doses of study drug should be administered on schedule based on the first dose received. For example, if dose 2 (V3) is administered on study day 8, dose 3 (V4) should still be administered on study day 14 (+/-1d). If the patient misses a dose entirely, the Investigator must contact the Medical Monitor before resuming dosing. All patients will remain on the dose level assigned to the cohort in which they were originally enrolled (Table 3) until the RP3D is identified. When the RP3D is identified, all patients will be changed to the RP3D.

Additional details for study drug administration are included in the Pharmacy Manual.

6.2.2. Concurrent Chemotherapy

In addition to CAEL-101, all patients in Part A will receive concurrent chemotherapy with CyBorD according to institutional SoC. Patients may initiate their chemotherapy regimen within 7 days of the receiving the first dose of CAEL-101 or may be on CyBorD at the time they enroll in the study. Patients with Mayo Stage IIIa AL amyloidosis will not have received CyBorD for more than 3 months at the time of their first dose of CAEL-101. Patients will receive concurrent CyBorD chemotherapy in combination with CAEL-101 throughout the DLT Observation period. Once the DLT Observation period is complete and if the patient is not benefiting from or tolerating CyBorD in the Investigator's judgement, the Investigator may change the CyBorD regimen or stop it.

New patients enrolled in Part B will receive concurrent chemotherapy with CyBorD plus daratumumab according to institutional SoC along with CAEL-101. Patients may initiate their concurrent regimen within 7 days of the receiving the first dose of CAEL-101 or may be on CyBorD plus daratumumab at the time they enroll in the study. Patients with Mayo Stage IIIa AL amyloidosis will not have received CyBorD for more than 3 months at the time of their first dose of CAEL-101. Patients will receive concurrent CyBorD chemotherapy and daratumumab in combination with CAEL-101 throughout the Safety Observation period. It is the intent of this protocol that patients will receive CyBorD plus daratumumab per institution SoC in the study, as long as they are tolerating it. However, after two cycles of CyBorD, if the patient is not benefiting from or tolerating CyBorD or daratumumab in the Investigator's judgment, the Investigator may change the regimen or stop it.

Once the newly enrolled patients in Part B complete the Safety Observation period, daratumumab may be added to the SoC treatment regimen for patients in Part A at the

Investigator's discretion. At the start of daratumumab treatment, patients will have additional complete blood count (CBC) with differential tests performed for at least 8 weeks to assess any changes in blood cell counts.

Patients in Part A and Part B may be considered for other plasma cell dyscrasia (PCD)-directed therapies after consultation with the sponsor Medical Monitor or designee.

6.2.3. Recommended Phase 3 Dose Selection

Part A of the study will employ a 3+3 dose escalation design. Initial cohort dose assignments are described in Table 3 and movement between cohorts will be carried out as listed in Table 4.

The first CAEL-101 dose to be studied 500 mg/m^2 was determined based on the completed study CAEL101-101.

The Sponsor and at least one Investigator will jointly decide the following:

- Dose increases in the next cohort and/or dose schedule
- Recommended Phase 3 dose
- Dose reductions based on severity, duration and frequency of toxicities observed at the previous dose level

Table 3: CAEL101-203 Cohort Dose Assignment (Part A)

Cohort	CAEL-101
1	500 mg/m^2
2	750 mg/m^2
3	1000 mg/m^2

Table 4: CAEL101-203 Cohort Dose Increase Guide

Number of Patients with DLT at a Given Dose Level	Cohort Dose Increase Decision Guide
0 out of 3	Enter 3 patients at the next higher dose level.
1 out of 3	Enter at least 3 more patients at the current dose level. If 0 of the additional patients experience a DLT, proceed to the next dose level. If 1 or more of the additional patients experience a DLT, stop the dose escalation. Enter 3 additional patients at the lower dose level if only 3 patients were treated previously at that dose.
≥ 2	Stop dose increases. Enter 3 additional patients at the lower dose level if only 3 patients were treated previously at that dose.
≤ 1 out of 6 at highest dose level given	This is the RP3D.

Abbreviations: DLT = dose limiting toxicity; RP3D = recommended Phase 3 dose

The 500 mg/m^2 dose was studied in the CAEL101-101 study. CAEL-101 was well tolerated and there were no DLTs observed in that study. Further, the preclinical data does not point to safety concerns which would require an extended DLT observation period for this dose level.

Therefore, the DLT observation period for the first cohort will be 14 days. For subsequent cohorts, the DLT observation period will be 27 days following the first dose of CAEL-101.

At least 3 patients will be enrolled in each dose cohort unless AEs preventing further dosing are observed. Enrollment into a new cohort with a higher dose of CAEL-101 cannot begin until the DLT observation period has completed for the last patient enrolled in the previous cohort.

Definition and instructions for assessment of DLT is presented in Section 6.2.4. If 0 out of 3 patients experience a DLT during the DLT observation period, the next dose cohort will be opened. If 1 out of 3 patients experience a DLT during the DLT observation period, the cohort may be expanded to 6 patients. If no further patients in the expanded cohort experience a DLT during the DLT observation period (i.e., 1 out of 6 patients experiences a DLT), increase to the next dose may take place. If 2 or more patients in a cohort experience a DLT during the DLT observation period, further dose increase will cease. New patients will be enrolled at the lower (tolerated) dose level if only 3 patients were previously enrolled in that cohort. The recommended dose will require at least 6 patients treated with CAEL-101 at that dose and ≤ 1 patient having experienced a DLT during the DLT observation period. Based on clinical safety and laboratory data, the safety review team (Sponsor and 1 or more Investigators may direct that an intermediate dose between the dose demonstrating the DLT and the previously documented safe dose may be explored, or a different dosing regimen starting at a lower dose be explored. Dose increases may be discontinued based on safety or PK findings that may influence the decision about a recommended dose.

The Sponsor may choose to evaluate CAEL-101 in additional patients and at other/higher doses and dosing schedules to further assess the PK profile, the benefit/risk profile and/or based on the safety findings from ongoing CAEL-101 clinical trials.

6.2.4. Dose Limiting Toxicity

For Part A of this study, a DLT is defined as any Grade 3 or greater study drug-related AE that is clinically significant.

DLTs will be assessed during the DLT observation period for each cohort in Part A (See Section 6.2.3). DLTs that occur after the DLT observation period will not be used to determine dose increases or the RP3D dose but will be collected and evaluated by the Investigators and the Medical Monitor on an ongoing basis.

6.2.5. Dose Delay

Dose delay or modification for safety concerns are permitted based on the Investigator's discretion. When not related to safety, decisions regarding dose delay and dose reductions/modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient. Patients will receive study drug every 7 (+/-1) days for 4 infusions then every 14 (+/-2) days. Doses may be delayed due to patient care requirements (e.g., hospitalization, side effects).

The study drug infusion may be delayed, or the dose reduced for infusion reactions. If the study drug infusion is delayed and in the absence of chemotherapy-related toxicities that would warrant PCD treatment delay, the patient may continue to receive their concurrent PCD treatment.

Guidelines for study drug dose reduction or delay:

- Grade 1 or 2 reactions: No requirement for dose delay or dose reduction. If the reaction persists at Grade 2 following completion of 4 doses of CAEL-101, a dose delay or dose reduction may be implemented at the discretion of the Investigator.
- Grade 3 reactions: Study drug may be withheld if an infusion reaction cannot be managed by adequate medical intervention. Study drug dosing may resume at the same dose and infusion rate or at the lower dose level (750 mg/m^2) when an infusion reaction resolves to Grade 1 or symptoms return to baseline, except for instances where the potential recurrence of the even poses an undue risk for the patient (e.g., Grade 3 reaction that is deemed to be related to the study drug in the Investigator's judgement).
- Grade 4 reactions: Study drug should be stopped, and the study treatment withheld. Study drug should be permanently discontinued after the occurrence of a Grade 4 infusion reaction.

If a dosing event is delayed by > 14 days, the patient can be resumed with the investigational product after a safety assessment. The local lab testing is acceptable to confirm the patient's eligibility to continue receiving the study drug. The safety assessments are determined by the primary investigator, however, the following are recommended: vital signs, medical history, physical exam, ECG, safety laboratory tests (detailed in Table 1, footnote d), pregnancy screen (if applicable), and SAE- and AE-specific follow up (if applicable and there are any safety concerns due to residual disease).

6.3. End of Treatment

Patients may choose to discontinue the trial at any time, for any reason, and without prejudice to further treatment. (See Section 5.3) Patients who permanently discontinue CAEL-101 treatment should complete the EOT visits according to the Schedule of Assessments (Table 1) within 140 days after the last dose of CAEL-101.

6.4. End of Study

End of study is defined as when the Sponsor decides to terminate the study.

6.5. Prior and Concomitant Medications

All prior medications for AL amyloidosis that the patient has ever taken will be recorded. All medications (prescription and over the counter), vitamin and/or mineral supplements, and/or herbs the patient is taking at screening will also be recorded. Start and stop date, dose and route of administration, dosing frequency and indication will be documented.

6.6. Permitted Medications

Patients may take topical, ocular, intra-articular, intranasal, and inhalational corticosteroids with minimal systemic absorption. A brief course of less than 3 weeks of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-immune conditions is permitted with consultations with the medical monitor. Patients may take up to 10 mg of corticosteroids for other conditions.

Concomitant palliative and supportive care, including diuretics, for disease related symptoms is allowed.

6.7. Prohibited Medications

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as noted in Section 6.6)
- Any chemotherapy other than CyBorD during the DLT observation period (Part A)

Please consult the Medical Monitor for any questions regarding immunosuppressive agents or live vaccine.

6.8. Pharmacokinetic Measurements

Blood samples for PK analyses of CAEL-101 will be collected according to the Schedule of Assessments (Table 1). Post-dose samples should only be obtained from an extremity opposite the administration site, unless approved by the Sponsor.

6.9. Immunogenicity Measurements

Samples for immunogenicity tests for CAEL-101 will be collected according to the Schedule of Assessments (Table 1). Samples will be analyzed by screening assays to determine the presence of anti-drug antibodies (ADAs) for all patients at all time points. Based on the presence of antibodies, additional characterization will be done (confirming positivity, dissecting specificity, neutralizing assays, and assays for assessing cell mediated immune responses) and assessment of correlation to clinical responses.

6.9.1. ADA Variables

ADA variables include ADA response category incidence and titer over the duration of the study as follows. ADA response category definitions and titer thresholds will be provided in the Statistical Analysis Plan (SAP).

ADA response categories

- ADA Negative
- ADA Positive

Patients who are ADA positive will be categorized as follows:

- Pre-existing Immunoreactivity
- Treatment-emergent ADA Responses

  Patients with a treatment-emergent ADA response will be further categorized as follows:

  - Persistent Treatment-emergent Responses
  - Indeterminate Treatment-emergent Responses
  - Transient Treatment-emergent Reponses

- Treatment-boosted ADA Responses
- NAb Positive or Negative

ADA Maximum Titer Value Categories:

- Lower Titer
- Moderate Titer
- High Titer

6.10. Contraception Requirements

A woman is considered a WOCBP following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Female patients of childbearing potential are eligible to participate in this trial (Section 5.1) if they agree to use a highly effective method of contraception consistently and correctly from Screening until at least 5 months following the last study drug administration or 12 months following the last dose of her PCD therapy, whichever is longer.

Birth control methods which may be considered as highly effective can achieve a failure rate of less than 1% a year when used consistently and correctly and include:

- Combined (estrogen and progestogen containing): oral, intravaginal or transdermal hormonal contraception associated with inhibition of ovulation
- Progestogen-only oral, injectable or implantable hormonal contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner: a vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP patient and that the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence: sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Fertile male patients are eligible to participate in this trial (Section 5.1) if they agree to use condoms during heterosexual intercourse with WOCBP from Screening until at least 5 months following the last study drug administration or 12 months following the last dose of his PCD therapy, whichever is longer.

Non-pregnant WOCBP partners of fertile male patients should also use highly effective methods of contraception during the male patient's treatment and until at least 5 months following the last study drug administration or 12 months following the last dose of the male patient's PCD therapy, whichever is longer.

Patients should be permitted to seek advice about donation and cryopreservation of germ cells prior to starting treatment with study drug or PCD therapy, if possible and as their need to start treatment allows.

Refer to the package insert or Summary of Product Characteristics (SmPC) for PCD medications for additional guidance on contraceptive use requirements.

6.11. Assigning Patient Numbers

Each patient will be assigned a unique patient number after signing the ICF. The patient number will be used on all of the patient's study information. Patient numbers will not be reassigned. The first 4 digits will be the site number (XXXX) followed by a 4-digit patient ID (YYYY) that together will be the patient number (XXXX-YYYY). The second set of 4 digits (YYYY) will be sequential within sites, starting with 0001.

7. INVESTIGATIONAL PRODUCT

CAEL-101 will be supplied to the Investigator by the Sponsor or its designee. Commercially available CyBorD chemotherapy drugs and daratumumab may be locally procured.

7.1. Study Drug

The investigational product, CAEL-101, is formulated as a sterile, liquid solution of protein plus excipients for dilution in a single-use, stoppered, glass vial. Each 10 mL vial contains 300 mg of chimeric fibril-reactive monoclonal antibody 11-1F4 at a concentration of 30 mg/mL. CAEL-101 will be diluted with commercially available 0.9% Normal Saline.

7.2. Study Drug Packaging and Labeling

CAEL-101 will be packaged and labeled as per country regulations. CAEL-101 solution for infusion is packaged in cartons containing 10 mL vials.

7.3. Study Drug Storage

CAEL-101 investigational product should be refrigerated at 2°C to 8°C (36°F to 46°F). CAEL-101 should not be frozen. The vials should be stored in the original package until time of use. Vials do not contain preservative and are intended for single use only. Vials should be discarded after use and product reconciliation.

7.4. Study Drug Preparation

The instructions for dilution and administration of CAEL-101 are described in the Pharmacy Manual.

7.5. Accountability and Reconciliation

CAEL-101 will be supplied to the Investigator by the Sponsor or its designee.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received and that any discrepancies are reported and resolved before dosing a patient.

Only participants enrolled in the study may receive study drugs and only authorized site staff may prepare, supply or administer the drug. All study drug must be stored in a secure, environmentally controlled and monitored area in accordance with the labeled storage conditions. Access to study drug will be limited to the Investigator and authorized site staff.

The Investigator is responsible for study drug accountability, reconciliation and record maintenance.

7.6. Study Drug Handling and Disposal

Sponsor may authorize sites to destroy unused and partially used study drug per site specific procedures. If site does not have adequate procedures in place, study drug may be returned to the Sponsor for destruction.

8. ASSESSMENT OF EFFICACY

Efficacy will be assessed through the evaluation of cardiac, renal, hepatic, and hematologic response (see Appendix B and Appendix C).

Organ-specific outcomes for renal, hepatic, and cardiac biomarker response will be assessed using both retrospective and prospective data. The retrospective collection may include a review of the patient record at the site. Further, prospective collection has been added to collect future organ response outcomes. The combination of retrospective and prospective data collection will allow for a more robust determination of the effects of CAEL-101 on efficacy in patients with AL amyloidosis.

8.1. Echocardiography

Cardiac structure and function will be assessed through echocardiograms according to the Schedule of Assessments (Table 1). Echocardiograms obtained after screening may be within a +/- 30 day window from the study day. Echocardiograms should not be skipped. If the patient cannot undergo an echocardiogram within the assessment window (e.g., the patient is hospitalized), it should be completed as soon as possible.

8.2. NT-proBNP, cTnT/cTnI, dFLC

Blood samples for NT-proBNP, cTnT/cTnI, and FLC will be collected according to the Schedule of assessments (Table 1). Investigators may continue to collect samples for NT-proBNP, cTnT/cTnI, and FLC for local analysis and patient care per the local SoC. Such analyses will not be considered part of the study and will not be recorded in the electronic case report form (eCRF).

8.3. 24-hour Urine Protein

Urine for protein will be collected from all patients over 24 hours according to the Schedule of Assessments (Table 1).

9. ASSESSMENT OF SAFETY AND ADVERSE AND SERIOUS ADVERSE EVENTS

9.1. Safety Parameters

9.1.1. Medical History

Relevant and significant medical history and concurrent illnesses will be collected for all patients and noted as to whether the condition is active at the first visit of the Screening period.

9.1.2. Vital Signs

Vital signs measurements will be recorded at every visit. Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure and oral temperature. It is preferred that the same arm be used for all blood pressure readings. Pulse and blood pressure measurements will be taken after the subject has been resting quietly for at least 5 minutes.

9.1.3. Physical Examination

The Investigator or a licensed team member, per local regulations, will perform physical examinations according to the Schedule of Assessments (Table 1).

9.1.4. Twelve-Lead Electrocardiogram

Electrocardiograms will be performed on a calibrated Twelve-lead machine according to the Schedule of Assessments (Table 1). Patients must be resting quietly in a supine position for at least 5 minutes before the Twelve-lead ECG.

9.1.5. Clinical Laboratory Tests

Clinical laboratory tests will be performed according to the Schedule of Assessments in Table 1. Clinical laboratory tests will be performed by the site's local laboratory. Results of laboratory tests will be recorded in the eCRF.

The Investigator or qualified sub-Investigator should review and evaluate out of range laboratory results. Any clinically significant abnormal laboratory value should be immediately re-checked whenever possible and documented as an AE as applicable.

Clinical laboratory tests that will be performed for this study are listed in Table 5.

Table 5: CAEL101-203 Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis
• Hematocrit • Hemoglobin • Red blood cells • White blood cells • Platelet count • Neutrophils (absolute) • Lymphocytes (absolute) • Monocytes (absolute) • Eosinophils (absolute) • Basophils (absolute) • MCH • MCHC • MCV • MPV • RDW • Reticulocyte count	• AST • ALT • ALP (ALP isozyme, if applicable) • GGT • Albumin • Globulin • Creatinine • Glucose • Total protein • Total bilirubin • Sodium • Potassium • Chloride • CO_2 or Bicarbonate • Calcium • Phosphorus • Blood urea nitrogen • eGFR • Uric acid	• Specific gravity • pH • Glucose • Protein • Bilirubin • Ketones • Leukocytes • Blood **Pregnancy** • Serum hCG • Urine pregnancy test **Special** • Serum Free Light Chains and serum and urine immunofixation electrophoresis • dFLC or SPEP m-spike • Troponin • NT-proBNP

9.1.6. Pregnancy Screen

Serum pregnancy tests will be performed on WOCBP at the screening visit. WOCBP must have a negative pregnancy screening in order to continue in the study. Additional urine pregnancy tests will be provided by the Sponsor and will be performed at the site according to the Schedule of Assessments (Table 1). A negative pregnancy test result must be obtained before the administration of the study drug.

A pregnancy test does not need to be performed on women who are postmenopausal for at least 1 year or surgically sterile prior to signing the ICF.

9.2. Adverse and Serious Adverse Events

9.2.1. Adverse Events Definition

An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product, at any dose, that is not necessarily related to the treatment.

An AE can therefore be any unfavorable and/or unintended sign, symptom or disease temporally associated with the use of a medicinal product, regardless of whether it is considered related to the medicinal product. An AE can also arise from any use of the drug and from any route of administration, formulation or dose. This definition includes intercurrent illnesses or injuries and exacerbation of preexisting conditions as well as events attributed to protocol-mandated

procedures. A clinical laboratory abnormality will only be reported as an AE if it is deemed clinically significant by the Investigator and/or is associated with signs and symptoms, requires treatment or requires follow-up.

An AE does not include the following:

- A medical or surgical procedure (e.g. surgery, endoscopy, tooth extraction or transfusion); an AE is the underlying condition that leads to the procedure
- Pre-existing diseases or conditions present or detected before the start of study drug administration that do not worsen or increase in severity or frequency after the administration of study drug
- Situations where an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery for a condition that has not worsened on study, social and/or convenience admissions to grant families respite in caring for a patient).

9.2.1.1. Adverse Event Reporting and Follow-up

All AEs will be assessed by the Investigator and recorded in the case report form (CRF). Data to be entered includes but is not limited to the following: the event term, the date of onset and resolution, seriousness, severity, relationship to study drug, outcome, treatment of the event and action taken with the study drug. AEs will be reported starting from the date of signing of the ICF until day 140 (5 months) after the last dose of study drug.

An AE occurring after the patient has provided written informed consent and before the first dose of study treatment will be collected as a pre-treatment AE.

Example 1:

> Thrombophlebitis associated with a blood draw for assessments required prior to dosing per protocol is an event that is related to protocol-mandated procedures. In this scenario, the event of "thrombophlebitis" will be captured as an AE and it will be documented as being "unrelated" to the study drug.

Example 2:

> An ankle sprain following an unexpected fall from a flight of stairs while at home, after the patient has provided informed consent, but before the first dose of study drug, is clearly unrelated to any protocol-mandated procedures and would also be captured as an AE.

All ongoing AEs will be followed to resolution or for 140 days after the patient's last dose of study drug, whichever is earlier. In case the AE has not completely resolved by the end of treatment visit, the final outcome of the ongoing AE will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable. Any new AEs occurring after the end of treatment visit will not be captured unless related to the study drug.

9.2.1.2. Grading of Adverse Event

The severity of an event and the seriousness are not to be considered synonymous. The severity is grading the intensity of an event. The seriousness of an event is based on the patient/event outcome or action. All AEs will be assessed for severity using NCI-CTCAE version 5 by the

Investigator. If a particular AE is not listed in the NCI-CTCAE, the following criteria will be used:

- Grade 1 (Mild): the event results in mild or transient discomfort, not requiring or needing only minimal intervention or treatment; does not limit or interfere with daily activities (e.g., insomnia, mild headache).
- Grade 2 (Moderate): the event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (e.g., fever requiring antipyretic medication).
- Grade 3 (Severe): the event results in significant symptoms that prevent normal daily activities; may require hospitalization or invasive intervention.
- Grade 4: Life threatening or disabling.
- Grade 5: Death

9.2.1.3. Causality Relationship of Adverse Event

The relationship of each AE to the study drug as applicable will be evaluated by the Investigator using the following definitions:

- Not related: The AE is clearly not related to the study drug. The AE can be explained to be likely related to other factors such as concomitant medications or the patient's clinical state.
- Possibly related: The AE may be related to the study drug. A plausible temporal sequence exists between the time of administration of the study drug and the development of the AE, and it follows a known response pattern to the study drug. The reaction may have been produced by the patient's clinical state or other concomitant therapies or interventions.
- Related: The AE is clearly related to the study drug. A plausible temporal sequence exists between the time of administration of the study drug and the development of the AE, and it follows a known response pattern to the study drug. The occurrence of the AE can be confirmed with a positive re-challenge test or supporting laboratory data.

The causality criteria of related and possibly related will be considered "related" to the study drug for regulatory reporting requirements.

9.3. Serious Adverse Event Definition

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death
    - Death is an outcome of an AE and not an AE in itself.
    - All events leading to death (except natural disease progress), regardless of causality, must be reported.

- Is life threatening, i.e., in the opinion of the Investigator, the AE places the patient at immediate risk of death from the event as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization for medical reasons for any length of time, or prolongation of an existing hospitalization that occurs during the course of a patient's participation in a clinical study, except for those due to the following:
    - A surgery or procedure that was planned before the patient entered the study and which is part of the planned study procedure is not an SAE
    - Nonmedical reasons, in the absence of an AE, are not considered SAEs
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed above.

9.4. Disease Progression – Not Reportable as an AE

It is anticipated that during this study a proportion of patients will experience progression of their AL amyloidosis resulting in hospitalization or death prior to study discontinuation. Such events leading to hospitalization or death of a study patient are typically considered "serious", requiring submission of an SAE report. However, reporting the term "disease progression" as either an AE or SAE in this study is not necessary.

9.5. SAE Reporting and Follow-up

All SAEs regardless of causality attribution will be reported from the date of signing of the ICF through 140 days following the patient's last dose of study drug. Any SAEs occurring after ICF signature but before the first dose of treatment are captured as pre-treatment SAEs. All SAEs will be reported to Alexion Global Drug Safety (GDS) within 24 hours of the Investigator or site staff awareness using the paper Safety Report Form via email: ClinicalSAE@alexion.com or facsimile: +1-203-439-9347. All paper forms MUST be accompanied by the Alexion GDS Email/Fax Cover Sheet signed by the Investigator or Sub-Investigator. The timelines for reporting SAE information to Alexion GDS need to be followed for the initial SAE report and for all follow-up SAE information. SAEs deemed possibly related to protocol-specified procedures occurring after the patient signed the ICF will also be reported to the Sponsor drug safety representative within 24 hours of when the site becomes aware of the event. In addition, if, in the opinion of the Investigator, an SAE occurring outside the specified time window occurs and is deemed to be related to study drug, the event will be reported to the Sponsor drug safety representative within 24 hours of when the site becomes aware of it.

Any additional records (such as hospital records, consultant reports and autopsy findings) are to be provided upon Sponsor request.

The Investigator must complete the SAE form, assess the causality relationship to the study drug as applicable, record any medication or therapeutic measures taken to treat the event and send the completed form to the Sponsor drug safety representative.

Reporting of SAEs to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be done in accordance with the procedures and policies of the IRB/IEC. Documentation must be provided to the sponsor, showing that the IRB/IEC was properly notified. SAEs will be reported by the Sponsor or designee to the regulatory authorities per local regulations.

All SAEs will be followed until resolution, stabilization of condition, return to baseline, 30 days from the end of the study or until follow-up is no longer possible.

9.5.1. Expedited Reporting of Serious Adverse Events

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions (SUSARs) in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP), Food and Drug Administration (FDA) and all applicable regulatory guidelines. The Sponsor will also inform all Investigators as required. When required due to local regulations, the Investigator will provide expedited reports to the IRB/IEC.

9.5.2. Pregnancy

The Sponsor will be notified within 24 hours of the initial report and any follow-up reports of a female patient or a male patient's female partner becoming pregnant during the course of the study and for 5 months after the last dose of the study drug or 12 months after the last dose of PCD treatment, whichever is longest.

If a female patient becomes pregnant, administration of the study drug must be discontinued immediately.

A pregnancy notification form is provided by the Sponsor drug safety representative.

Cases of pregnancy that occur during maternal or paternal exposure to study drug will be reported to Alexion GDS within 24 hours of Investigator or site staff awareness using the Pregnancy Report Form via email: ClinicalSAE@alexion.com or facsimile: +1-203-439-9347. All paper forms MUST be accompanied by the Global Drug Safety Email/Fax Cover Sheet signed by the Investigator or Sub-Investigator.

Pregnancy, although reportable, is not considered an AE/SAE unless a female patient or a male patient's female partner experiences signs or symptoms of pregnancy complications. Female patients who become pregnant and female partners of male patients will be followed until the outcome of the pregnancy is known. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth and the presence or absence of any congenital abnormalities or birth defects of the offspring.

10. STATISTICS

10.1. General Considerations

The primary objective in this study is to define the safety and tolerability of CAEL-101 and determine the recommended Phase 3 dose. Secondary objectives include describing the pharmacokinetic profile of CAEL-101 and exploring the PK profile of CAEL-101 when given q2wk versus q4wk after the first 50 weeks, and assessing the safety and tolerability of CAEL-101 when administered with CyBorD, and with the combination of CyBorD and daratumumab. The statistical methods are consistent with these objectives. Specifically, the use of descriptive statistics is the primary method for presentation of data outcomes; descriptive statistics (and by-patient 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 3 patients, that the interpretation of descriptive statistics is limited. All data will be listed by cohort and patient, with the primary determination of safety/tolerability outcomes based on review of these data listings. Figures/graphics of by-patient data will be presented where these will enable optimal review of outcomes across dose levels and over time.

Consistent with the study objectives for Part A vs Part B (as well as due to the number of cohorts in this study), Part A data may be tabulated separately from Part B data. This will allow for review of data in the context of the objectives for each study part. Further, analysis populations and other analysis considerations may be performed separately for Part A from Part B, where appropriate.

10.2. Determination of Sample Size

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

The total study sample size will be data-driven and dependent upon how many doses are tested and safety and tolerability outcomes from that testing.

10.3. Replacement of Patients

For Part A, patients who discontinue for non-safety reasons prior to the DLT period having elapsed may be replaced.

10.4. Analysis Sets

Several populations will be identified for purposes of analysis.

- Safety Population: All subjects treated with at least one dose of CAEL-101 (the study treatment) will be included in the Safety Population.
- PK Population: The PK Population will include all subjects who have sufficient PK concentrations to be included in the PK analysis. The study pharmacokineticist will determine which patients have sufficient data to be included in the PK population and will document instances where a patient is excluded.
- ADA Population: The ADA Analysis Set (AAS) includes all study participants who received any study drug and who after the first dose have at least one reportable result in the ADA assay. ADA analysis in study participants will be conducted based on the actual treatment they receive.

For Part A, this study will include cohort safety reviews after the DLT observation periods. Analyses for these reviews may include data listings, tabulations and graphs.

For Part A, an analysis will be performed for the completed cohorts (dosing levels) and an abbreviated CSR will be generated to document the findings and conclusions for the selected dose to be carried forward into the subsequent study. This report will be limited to the data collected to inform the dose selection decision.

After study completion, a final ICH-compliant clinical study report will be written that will include both study parts.

10.5. Planned Analyses

10.5.1. Demographics and Baseline Characteristics

Baseline characteristics (including age, gender, race, disease Stage, and other disease-specific characteristics) will be tabulated descriptively (e.g., number and percent of subjects for each category for categorical parameters, and the number, mean, standard deviation, and range for continuous parameters).

Additionally, NYHA status (see Appendix D) and organ involvement will be summarized.

10.5.2. Subject Disposition

Subject completion status and reasons for early termination will be tabulated descriptively. Exposure characteristics will be tabulated (i.e., number of patients treated with each dose level, and number of doses of CAEL-101 received). Total dose given will be tabulated by cohort.

10.5.3. Safety

Safety assessments will include AEs, clinical laboratory tests, vital signs, physical examinations and ECGs. In Part A, the incidence of DLTs will be evaluated for each dose escalation cohort.

All treatment-emergent adverse events (TEAEs) will be summarized by system organ class and preferred term for each dose cohort. All TEAEs will be summarized by incidence, severity and potential causality to study drug.

Clinical laboratory tests and vital signs will be summarized descriptively for each dose cohort and/or study part. All abnormal findings in clinical laboratory test results, vital signs, physical examinations and ECGs will be listed.

Adverse events will be coded using the MedDRA coding dictionary; subject incidence of each system organ class and unique term 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.

Adverse events starting after the first dose of treatment will be considered treatment-emergent AEs and will be reported as occurring during the treatment phase and will be associated with the most recent treatment (dose level) given.

10.5.4. Efficacy

Summary statistics (mean, standard deviation, standard error of mean < minimum, maximum, 95% confidence interval) will be presented for the following efficacy endpoint. No hypothesis testing will be performed.

- Cardiac:
  - NT-proBNP
  - cTnT/cTnI
  - Global Longitudinal Strain
- Renal:
  - 24-hour urine protein
- Hepatic:
  - Alkaline phosphatase

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

10.5.5. Immunogenicity

Immunogenicity assessments will be listed and tabulated as provided in the SAP.

10.5.6. Pharmacokinetics

While PK parameters will be tabulated and summarized with descriptive statistics by cohort and/or study part, the primary assessment of PK concentrations will be via by-patient data assessment (including listings and figures of PK data over time). In addition, the PK profile of CAEL-101 when given bi-weekly (q2wk) versus once-monthly (q4wk) after the first 50 weeks will be assessed via population PK modeling. Details will be provided in a separate population PK SAP.

10.6. Concomitant Medications

Prior and concomitant medications will be reviewed and coded using the WHO Drug Dictionary and tabulated by treatment. Concomitant medications will be reported in a fashion similar to that of AEs.

10.7. Missing Data

For the primary, secondary, and exploratory endpoints, handling of missing data will be described in the SAP.

11. STUDY TERMINATION

The Sponsor may discontinue the study at any time. Reasons for discontinuation may include, but are not limited to, any of the following:

- Safety concerns that preclude continuation of the study
- A request from a regulatory authority to discontinue the study
- Insufficient enrollment
- Issues with the manufacture and/or supply of CAEL-101
- Business or financial factors that preclude continuation of the study

12. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor will implement and maintain quality control and quality assurance procedures with written SOPs to ensure the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements.

12.1. Changes to the Protocol

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB/IEC except when necessary to eliminate immediate hazards to the patient. Protocol deviations may result in the requirement to withdraw the patient from the study and may render their data not evaluable.

12.2. Monitoring

In accordance with the Code of Federal Regulations 21CFR 312 Subpart D, ICH GCP and local regulations, the study monitor will assess the adequacy of Investigator site research facilities and evaluate the progress of the study. The monitor will verify the accuracy and completeness of the CRF; ensure that all protocol requirements are being met, that Investigator responsibilities are being fulfilled and provide aid and support to ensure any inconsistencies in study records are satisfactorily resolved.

12.3. Data Protection

Each patient will be assigned a unique identifier after signing the ICF. Patient numbers will not be reassigned. Any patient records or datasets transferred to the Sponsor must contain only the unique identifier and must not include patient names or any information which would make the patient identifiable. Patients will be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection laws and that their medical records may be examined by representatives of the Sponsor, IRB/IEC members and by inspectors from regulatory authorities. Study monitors will inspect all documents and records that are required to be maintained by the Investigator for this study.

12.4. Audits and Inspections

The Sponsor or designee may conduct monitoring and auditing activities at the Investigator site at any time during study conduct or after completion of the study. The Investigator will be informed if an audit is to take place and advised as to its scope. Inspections and audits will typically be carried out during the clinical and reporting phases of the study to ensure that the study is conducted, and data are generated, documented and reported in compliance with the protocol, ICH GCP, written SOPs and applicable regulations and laws.

Representatives of the FDA or other regulatory agencies and IRB/IEC representatives may also conduct an audit of the study. If informed of such an inspection, the Investigator should notify the Sponsor immediately. The Investigator will ensure that the auditors have access to the clinical supplies and study site facilities and that all data, including original source records and study files are available upon request.

13. ETHICS

This study will be conducted in accordance with the protocol and with:

- the consensus international ethical principles that have their origin in the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines, and
- applicable ICH GCP guidelines, and
- applicable laws and regulations.

13.1. IRB/IEC Approval

Before enrollment of patients into the study as required by applicable regulations and ICH GCP, the current protocol, ICF, advertisements and any written information for patients will be reviewed and approved by an appropriate IRB or IEC. A letter documenting the IRB/IEC approval must be received by the Sponsor or designee before the initiation of the study at the Investigator's site. Amendments to the protocol will be subject to the same requirements as the original protocol.

The Investigator will submit a progress report at least once yearly to the IRB/IEC or more frequently as required. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB/IEC per their requirements and in compliance with applicable regulations and ICH GCP.

The Investigator, the Sponsor or designee shall promptly notify the IRB/IEC of any SAEs, or any other information that may affect the safe use of the study drug during the course of the study.

No study drug will be released to the Investigator's site until IRB/IEC authorization has been received by the Sponsor, or Sponsor's designee.

13.2. Written Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/IEC prior to its use. The ICF must be in compliance with all ICH GCP and applicable regulatory and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation. The Investigator must ensure that each patient has been informed of his/her rights to privacy. The patients must be notified that they are free to discontinue from the study at any time and should be given the opportunity to ask questions and allowed time to consider the information provided. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and will document in the source records that consent was obtained prior to the patient's enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by the Sponsor, their representatives, auditors, the IRB/IEC and regulatory authorities. A copy of the signed and dated ICF will be given to each patient.

14. DATA HANDLING AND RECORDKEEPING

14.1. Study Records

During the study, the Investigator will provide evidence of the existence of the patient and substantiate the integrity of the data collected. Source documents filed at the investigator site include records of potential study patients screened, medical records, and records detailing the progress of the study for each enrolled patient, laboratory reports, CRF, signed ICF, drug accountability records, correspondence with the IRB/IEC and regulatory agencies, AE reports and information regarding patient discontinuation. The Investigator will ensure the accuracy, completeness, legibility and timeliness of data reported to the Sponsor in the CRF and in all required reports. Changes to source data should be traceable, should not obscure the original entry and should be explained when necessary (e.g. via an audit trail).

14.2. Data Collection Instruments

Various data collection instruments (DCIs) such as the electronic CRF and/or paper forms will be used in this study. These instruments transmit the information collected during the conduct of the study to the Sponsor, the Sponsor's designee and regulatory authorities. The Investigator retains full responsibility for the appropriateness and accuracy of all data collected. S/he will review all DCIs and will approve all data, including any changes made.

14.3. Retention of Records

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 2 years after FDA approval or the approval of a marketing application in an ICH region, or for a at least 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without the written approval of the Sponsor. The Investigator/institution will permit the Sponsor or the regulatory authority access to study records and documents for inspection.

15. FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

16. PUBLICATION POLICY

All data are the property of the Sponsor. Each Investigator is obliged to keep data pertaining to the study confidential. However, it is intended that the results of the study will be published and/or presented at scientific meetings. Formal presentation of data from this study will be considered for joint publication by the Investigator(s) and appropriate Sponsor personnel. Authorship will be determined by mutual agreement.

The Investigator may be required to sign the clinical study report if it is to be used in a registration submission to the health authorities of some countries.

17. APPENDICES

APPENDIX A INTERNATIONAL MYELOMA WORKING GROUP (IMWG) CRITERIA FOR THE DIAGNOSIS OF MULTIPLE MYELOMA

The new definition of active multiple myeloma is:

Clonal bone marrow plasma cells >10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following CRAB features and myeloma-defining events:

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcemia: serum calcium > 0.25 mmol/L (> 1mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (> 11mg/dL)
    - Renal insufficiency: creatinine clearance < 40 mL per minute or serum creatinine > 177mol/L (> 2mg/dL)
    - Anemia: hemoglobin value of > 20g/L below the lowest limit of normal, or a hemoglobin value < 100g/L
    - Bone lesions: one or more osteolytic lesion on skeletal radiography, CT, or PET/CT. If bone marrow has < 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement
- Any one or more of the following biomarkers of malignancy (MDEs):
    - 60% or greater clonal plasma cells on bone marrow examination
    - Serum involved / uninvolved free light chain ratio of 100 or greater, provided the absolute level of the involved light chain is at least 100mg/L (a patient's involved free light chain either kappa or lambda is the one that is above the normal reference range; the uninvolved free light chain is the one that is typically in, or below, the normal range)
    - More than one focal lesion on MRI that is at least 5mm or greater in size.

Table 6: IMWG Plasma Cell Disorders

Plasma Cell Disorder	Definition
Smoldering Multiple Myeloma	Both criteria must be met: Serum monoclonal protein (IgG or IgA) >30g/L or urinary monoclonal protein >500mg per 24h and/or clonal bone marrow plasma cells 10-60% Absence of myeloma-defining events or amyloidosis

Table 6: IMWG Plasma Cell Disorders

Plasma Cell Disorder	Definition
Non-IgM monoclonal gammopathy of undetermined significance (MGUS)	Serum monoclonal protein < 30g/L Clonal bone marrow plasma cells < 10% Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder
IgM MGUS	Serum IgM monoclonal protein < 30g/L No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly, or other end-organ damage that can be attributed to the plasma cell proliferative disorder
Light chain MGUS	Abnormal FLC ratio (< 0.26 or > 1.65) Increased level of the appropriate free light chain (increased FLC in patients with ratio > 1.65 and increased FLC in patients with ratio < 0.26) No immunoglobulin heavy chain expression on immunofixation Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder Clonal bone marrow plasma cells < 0% Urinary monoclonal protein < 500mg/24h
Solitary plasmacytoma	Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Normal bone marrow with no evidence of clonal plasma cells Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder
Solitary plasmacytoma with minimal marrow involvement	Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Clonal bone marrow plasma cells < 10% Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder

Table 6: IMWG Plasma Cell Disorders

Plasma Cell Disorder	Definition
POEMS syndrome	Polyneuropathy Monoclonal plasma cell proliferative disorder Any one of the 3 other major criteria: sclerotic bone lesions, Castleman's disease, elevated levels of VEGFA Any one of the following 6 minor criteria: Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) Extravascular volume overload (edema, pleural effusion, or ascites) Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails) Papilledema Thrombocytosis/polycythemia
Systemic AL amyloidosis	Presence of an amyloid-related systemic syndrome (e.g., renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement) Positive amyloid staining by Congo red in any tissue (e.g., fat aspirate, bone marrow, or organ biopsy) Evidence that amyloid is light-chain-related established by direct examination of the amyloid using mass spectrometry-based proteomic analysis or immunoelectron microscopy Evidence of a monoclonal plasma cell proliferative disorder (serum monoclonal protein, abnormal free light chain ratio, or clonal plasma cells in the bone marrow)

Source: International Myeloma Working Group

APPENDIX B ORGAN INVOLVEMENT AND RESPONSE CRITERIA

Organ	Organ Involvement	Response	Progression	No Response/Stability
Cardiac	NT-proBNP > ng/L (0.33 mg/mL or 39.2 pmol/L)	Decrease of > 30% in NT-proBNP levels AND a decrease of NT-proBNP > 300 ng/L in patients with a baseline NT-proBNP of ≥ 650 ng/L[a]	Increase of > 30% in NT-proBNP levels (in the absence of eGFR decline of ≥ 25%) and ≥ 300 ng/L increase in NT-proBNP (in the absence of eGFR decline of ≥ 25%)	Neither response nor progression
Renal	24-hr urine protein > 0.5 g/day predominantly albumin	Decrease of ≥ 30% in proteinuria or drop of proteinuria below 0.5 g/24 h in the absence of ≥ 25% decrease in eGFR	Worsening of ≥ 25% in eGFR	Neither response nor progression
Liver	ALP > 1.5 times institutional upper limit of normal	Decrease of ≥ 50% and/or normalization of serum ALP level	Increase of ≥ 50% in the serum ALP level	Neither response nor progression

Abbreviations: ALP – alkaline phosphatase, eGFR – estimated glomerular filtration rate; hr – hour; NT-proBNP – N-terminus pro-brain natriuretic peptide.
[a]Patients with baseline NT-proBNP < 650 ng/L are not considered to have cardiac involvement.
Source: (Dispenzieri, 2015b; Palladini, 2014)

APPENDIX C HEMATOLOGIC RESPONSE AND RESPONSE CRITERIA

Response	Criteria
Complete response (CR)	Complete response (CR) (both criteria must be met): • Absence of amyloidogenic light chains (either free and/or as part of a complete immunoglobulin) defined by negative immunofixation electrophoresis of both serum and urine • Either a FLC ratio within the reference range or the uninvolved FLC concentration is greater than involved FLC concentration with or without an abnormal FLC ratio
Very good partial response (VGPR)	dFLC < 4 mg/dL
Partial response (PR)	dFLC decrease ≥ 50% from baseline
No response (NR)	Less than a partial response

Abbreviations: dFLC – involved/uninvolved free light chain difference; FLC – free light chain.
Sources: (Dispenzieri, 2015b); University of Rochester Medical Center

APPENDIX D NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

NYHA Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Abbreviation: NYHA – New York Heart Association.
Source: Adapted from Dolgin 1994

APPENDIX E COVID-19 RISK ASSESSMENT

AL amyloidosis can cause irreversible morbidity and even mortality, if untreated. As such, the benefit a participant may receive from treatment with CAEL-101 is potentially significant.

Given that treatment for AL amyloidosis does involve immunosuppression, there is a theoretical concern that the risk for infection may be higher than in participants not receiving immunosuppressants. However, there is no specific data to further inform this risk. No participant should be discontinued or excluded from the study due to COVID-19 infection. The site Investigator will therefore balance the risk/benefit considerations in the study participant taking these factors into account.

The potential operational risks identified and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 7.

Table 7: Potential Operational Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Healthcare institution availability for non-COVID-19 related activities	COVID-19 pandemic may impact the workload of healthcare institutions globally and may reduce staff availability to perform non-urgent activities and non-COVID-19 related activities.	During the time that the COVID-19 pandemic is active, Alexion will not open study sites or enroll new participants at sites unless the sites have the resourcing and capabilities to implement the study per protocol.
Data quality and integrity	Lack of availability of site personnel to perform study assessments and capture study specific data in a timely manner and to maintain adequate quality standards. Lack of availability of site personnel to ensure adequate and continuous chain of custody, storage conditions, and monitoring for investigational product and biological samples. Inability of study monitors and quality personnel to conduct in-person visits to exercise adequate oversight of study execution at investigational sites. Missing data (COVID-19 pandemic may impact study visit schedules, and increase missed visits and/or participant study discontinuations inadvertently resulting in missing data [eg, for protocol-specified procedures]).	During the time that the COVID-19 pandemic is active, Alexion will only open study sites that report enough personnel capacity to sufficiently conduct clinical study-related activities. During this timeframe, site capacity will be reviewed by the site Investigator and the study Medical Monitor prior to Screening. Each site is also evaluated for the capacity to perform remote monitoring visits and remote source data verification. During the time that the COVID-19 pandemic is active, it will be important to capture specific information in the eCRF that explains the reason

Table 7: Potential Operational Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
		the data is missing (eg, missed study visits or participant study discontinuations due to COVID-19).

Abbreviations: COVID-19 – coronavirus disease 2019; eCRF – electronic case report form.

APPENDIX F COVID VACCINE RISK ASSESSMENT

There is currently no information available evaluating the safety and efficacy of COVID-19 vaccines in participants treated with CAEL-101. It is unlikely that the immune response to a COVID-19 vaccine (and therefore the efficacy of the vaccination) would be diminished by CAEL-101 administration, based on CAEL-101 mechanism of action. It is also unlikely that COVID-19 vaccination would impact CAEL-101 mechanism of action.

Local and national guidelines should be consulted for recommendations related to COVID-19 vaccination.

The potential operational risks identified and mitigation measures put in place in light of the COVID-19 vaccination rollout are provided in Table 8.

Table 8: Potential Operational Risks and Mitigation Measures due to COVID-19 Vaccine

Risks Category	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential risks		
Data quality and integrity	Missing data due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine may impact study visit schedules, and increase missed visits and/or participant study discontinuations, inadvertently resulting in missing data (eg, for protocol-specified procedures).	Capture specific information in the eCRF that explains the reason for missing data (eg, missed study visits due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine).

Abbreviations: COVID-19 – coronavirus disease 2019; eCRF – electronic case report form.

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