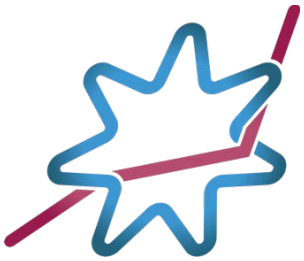


CLINICAL STUDY PROTOCOL

Cardiac Amyloid Reaching for Extended Survival

A Phase 3, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of CAEL-101 and Plasma Cell Dyscrasia Treatment Versus Placebo and Plasma Cell Dyscrasia Treatment in Plasma Cell Dyscrasia Treatment-Naïve Patients with Mayo Stage IIIb AL Amyloidosis

PROTOCOL NUMBER: CAEL-101-301

INVESTIGATIONAL PRODUCT: CAEL-101

SPONSOR:

Alexion Pharmaceuticals, Inc

121 Seaport Boulevard

Boston MA 02210

USA

IND #: 117,316

EudraCT #: 2019-004254-28

CTIS #: 2022-503073-11

Amendment 6.0: 26 Jun 2024

Supersedes: Amendment 5.0 dated 31 Mar 2023

SPONSOR PROTOCOL APPROVAL PAGE

Protocol Title:	A Phase 3, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of CAEL-101 and Plasma Cell Dyscrasia Treatment Versus Placebo and Plasma Cell Dyscrasia Treatment in Plasma Cell Dyscrasia Treatment-Naïve Patients with Mayo Stage IIIb AL Amyloidosis

This document has been e-signed in ARISE (Veeva RIM). Please refer to last page for signature details.

PPD
PPD
Alexion Pharmaceuticals, Inc

Date

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 CAEL-101-301 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 (GCP), 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

Amendment 6.0 (26 Jun 2024)

This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (EU) and in the EU CTR 536/2014 Article 2, 2 (13), and in the US Food and Drug Administration's (FDA) regulation at 21 CFR part 312.30(b), and any applicable local regulations.

The main purpose of this document is to update the primary endpoint from all-cause mortality to a composite endpoint of all-cause mortality and frequency of cardiovascular hospitalizations following discussions with FDA, including the addition of an independent clinical event adjudication committee to adjudicate hospitalization cases; change in exploratory endpoint analysis timepoint from Week 50 to over time; and incorporation of administrative changes from administrative change letter 7.1 (07 Sep 2023). Additional changes include an update to the end of study timing, removal of optional interim analysis, alignment of the text with the current EU CTR regulations and correction of errors.

Changes to Clinical Study Protocol CAEL-101-301 from the Protocol Amendment 5.0 dated 31 Mar 2023 are summarized in the table below.

Overall Rationale for the Amendment

Change	Rationale
Synopsis	Changes made to align with body text.
Section 1.1 Study Schematics Figure 1, footnote Section 4 Study Design Section 4.1 Primary Evaluation Period Section 6.1.2 Primary Evaluation Treatment Period (PETP) Section 6.14 Independent Data Monitoring Committee (IDMC) Section 10.2 Hypothesis Testing and Significance Level Section 11 Interim Analysis (Deleted)	Removal of optional interim analysis.
Section 1.2 Schedule of Assessments Table 2, QoL questionnaires	Addition of QoL questionnaires to be performed at visit 29 during the open label extension period.
Table 2, NT-proBNP and cTnT blood	Addition of NT-proBNP and cTnT blood testing to be performed at EOT visit, which was removed erroneously in Amendment 5.
Table 2, Post-Treatment Follow Up	Updated survival follow up visits to every 4 weeks from every 12 weeks to provide increased oversight of patient safety.

Change	Rationale
Section 6.5 Survival Follow-Up Period (PETP and OLEP) Section 8.1, Overall Survival	
Section 2.2 CAEL-101 and Dose Rationale	Update that Study CAEL101-203 has completed last patient last visit. Addition of maximum established dose of CAEL-101 to align with the pharmacy manual.
Section 2.3 Benefit-Risk Analysis	Text describing previously known common side effects of CAEL-101 was removed due to evolving safety data.
Section 3 Study Objectives and Estimands and/or Endpoints (Table 3) Section 10.2 Hypothesis Testing and Significance Level Section 10.7.1 Primary Efficacy Endpoint	Change of primary endpoint from time to all-cause mortality to a composite endpoint of time to all-cause mortality and frequency of cardiovascular hospitalizations to account for changes to standard of care and increased expected survival of patients with AL-A from the original study design.
Section 3 Study Objectives and Estimands and/or Endpoints (Table 3) Section 10.7.2 Secondary Efficacy Endpoints	Addition of secondary endpoints of time to all-cause mortality, frequency of cardiovascular hospitalizations, NT-proBNP change from baseline to Week 50, and description of the statistical tests to be utilized.
Section 3 Study Objectives and Estimands and/or Endpoints (Table 3) Section 10.7.3 Exploratory Endpoints	Addition of timeframes of analysis from baseline to over time during the PETP to the exploratory endpoint of proportion of patients with composite cardiac response. Clarification of exploratory objective and endpoint from ≤ 2% improvement in GLS percentage to ≥ 2% deterioration in GLS percentage as this was stated in error as improvement in GLS. Addition of timeframes of analysis from baseline to over time during the PETP to the exploratory endpoint of proportion of patients with renal response as the timing of assessments is constrained by the 24h protein test assessment timing. Addition of the exploratory endpoint of time to renal progression to the objective of the assessment of renal response. Addition of the exploratory endpoint of proportion of graded renal response (complete renal response, very good partial renal response, partial renal response) from baseline to over time in PETP.

Change	Rationale
	Addition of the exploratory objective and endpoint of assessment of hepatic response, time to hepatic response, and time to graded hepatic response to the exploratory objectives and endpoints from baseline over time in the PETP to provide organ response data. Added exploratory endpoint of proportion of patients with hepatic complete response, hepatic very good partial response, hepatic partial response, and hepatic non-response from baseline over time in the PETP to provide organ response data. Addition of the exploratory endpoint of proportion of patients with graded cardiac response (with definition), time to cardiac response, and time to graded cardiac response. Change in exploratory endpoint analysis time period from Week 50 to over time. The ANCOVA model was replaced with the MMRM model for the exploratory endpoints of changes from baseline over time as requested by regulatory authorities. Addition of the exploratory endpoint proportion of patients with graded renal response (with definition), time to renal response, and time to graded renal response. Error correction of exploratory endpoint text of immunogenicity parameters of anti-drug antibodies from frequency and count to incidence, response categories, and titers to align with description in Section 10.7.5 Immunogenicity. Removal of the text specifying pretreatment with CAEL-101 during the PETP for assessments of immunogenicity and PK for patients in the OLEP.
Section 3 Study Objectives and Estimands and/or Endpoints (Table 3) Section 11 Open-Label Extension Period (OLEP) Analyses	Removal of the exploratory objectives and endpoints analysis from the OLEP to streamline data analysis.
Section 1.1 Study Schematics Section 1.2 Schedule of Assessments Table 1, footnote ‘a’ Table 1, footnote ‘o’ Section 4 Study Design	Removal of the number of events required to conduct the primary analysis and replacement with the date of the last patient randomized in the study plus 18 months due to study feasibility from the extended survival of patients (which has resulted in a delay in the collection of original event numbers and would prolong the study unnecessarily).

Change	Rationale
Section 4.1 Primary Evaluation Period Section 6.1.2 Primary Evaluation Treatment Period (PETP) Section 6.1.3 End of Treatment Visit During the Primary Evaluation Treatment Period (PETP)	
Section 4.2.2 Open-Label Extension Treatment Period Section 5.3 Continuation and Withdrawal Criteria Section 6.1.3 End of Treatment Visit During the Primary Evaluation Treatment Period (PETP) Section 6.4 End of Open-Label Extension Period (OLEP) Section 6.5 Survival Follow-up Period (PETP and OLEP) Section 8.1 Overall Survival	Alignment of language throughout the protocol that all patients will be followed for survival status until death, heart transplant, left ventricular assist implantation, or study-level end of study to clarify when survival data collection ends for each patient.
Section 5.3 Continuation and Withdrawal Criteria	Addition of patient withdrawal criteria to include patients that undergo cardiac transplant or left ventricular assist device implantation.
Section 6.1.2 Primary Evaluation Treatment Period (PETP)	Clarification of the assessment of safety and immunogenicity measurements at Study Day 1, and every 26 weeks after Week 50.
Section 6.5 Survival Follow-Up Period (PETP and OLEP)	Clarification that subsequent therapies (not specifically PCD) information will be collected and add heart transplant and LVAD implantation information in both treatment groups.
Section 6.6 End of Study	Updated end of study definition to date of last patient, last visit to align with EU-CTR requirements
Section 6.8 Permitted Medications	Clarified that a course of corticosteroids of less than 3 weeks with 20 mg oral prednisone or equivalent for the treatment of musculoskeletal, repository, or dermatological conditions is permitted with consultation with the Medical Monitor.
Section 6.9 Prohibited Medications	Defined immunosuppressive doses of systemic corticosteroids as > 20 mg prednisone or equivalent daily for > 3 weeks.

Change	Rationale
Section 6.12 Blinding	Addition of language to state that if the investigator becomes unblinded for any reason, the patient may need to be withdrawn from the study to protect study integrity.
Section 6.15 Clinical Events Adjudication Committee	Addition of a description of the clinical events adjudication committee for the independent adjudication of cardiovascular related hospitalizations relating to the new endpoint of frequency of cardiovascular hospitalizations.
Section 7 Investigational Product Section 9.2.2 Adverse Event Reporting and Follow-up Section 9.5.2 Medication Error Section 9.5.3 Medication Abuse Section 9.5.4 Medication Misuse Section 13.7 Medication Error, Abuse, and Misuse Section 19.3 Appendix 1	Addition of the identified AxMP drugs (CyBorD) to the protocol to comply with EU CTR requirements.
Section 7.2 CAEL-101 Packaging and Labeling	Addition of 'concentrate' to the description of CAEL-101 to align with the packaging description.
Section 7.5 Accountability and Reconciliation	Addition of statement that the pharmacist or other designated individual will maintain records of other Alexion-supplied medications.
Section 7.7 Treatment of Overdose	Addition of treatment of overdose instructional text and reporting requirements to align with EU CTR requirements.
Section 8.2 Cardiovascular Related Hospitalizations	Addition of description of cardiovascular related hospitalization events and their collection process.
Section 8.4 Quality of Life Questionnaires	Clarification of the description of the five levels of the EQ-5D-5L questionnaire.
Section 9.2.1 Adverse Events Definition	Clarification of the definition of a medication error.
Section 9.2.2 Adverse Event Reporting and Follow-up	Addition of reporting requirements for adverse reactions attributed to non-interventional concomitant medications, included those identified as AxMP to health authorities to align with GVP requirements.
Section 9.2.3 Grading of Adverse Event	Update to the definition of Grade 4: life threatening from disabling to urgent intervention indicated to align with updated safety guidance.

Change	Rationale
Section 9.4 SAE Reporting and Follow-up	Clarification of reporting of SAEs deemed at least possibly related to protocol-specified procedures to align with updated safety guidance. Addition of the requirement that SAEs including deaths considered related to the study intervention captured post-patient discontinuation from the study must be reported to Alexion GPS to align with updated reporting requirements. Addition of the requirement of Investigators to report updates to SAEs to Alexion GPS post-patient discontinuation from the study to align with updated reporting requirements. SAEs to be reported to Sponsor after EOT up through End of Study visit, and clarification that Investigators are encouraged (but are not obligated) to seek AE/SAE data after discontinuation or completion of study, unless they become aware of a SAE considered related to study intervention or of any follow-up information for previously reported SAEs after study participation has concluded, to align with updated safety reporting requirements.
Section 9.4.1 Expedited Reporting of Serious Adverse Events	Addition of SUSAR reporting requirement language in the EU to comply with EU CTR requirements.
Section 9.4.2 Pregnancy	Update of reporting form name to report pregnancies that occur during the study and to clarify the breastfeeding reporting outcome form.
Section 9.4.3 Unexpected Events	Addition of reporting of events other than SAEs that may impact the benefit-risk assessment to align with EU CTR requirements.
Section 9.5 Medication Error, Abuse, and Misuse Section 13.7 Medication Error, Abuse, and Misuse	Update of the language that defines medication error, abuse, misuse, and the timelines for reporting such events to align with EU CTR requirements.
Section 10.1 Statistical Hypotheses	Update of the primary endpoint testing hypothesis to a composite endpoint of a hierarchical combination of time to all-cause mortality and the frequency of cardiovascular hospitalizations and removal of the previously used hazard ratio descriptors.
Section 10.2 Hypothesis Testing and Significance Level	Removal of the hierarchical list of secondary endpoints as these will be tested as specified in the SAP.
Section 10.3 Sample Size Considerations Section 10.4 General Statistical Methods	Removal of text describing event-based efficacy analysis as this has been replaced with analysis of

Change	Rationale
Section 10.7.1 Primary Efficacy Endpoint	the composite endpoint of time to ACM and frequency of CVH. Addition of the Finkelstein Schoenfeld (F-S test) as the test statistic for the hierarchical composite endpoint of time to ACM and frequency of CVH 18 months after the last patient randomized.
Section 10.4 General Statistical Methods	Addition of the covariate of daratumumab usage at baseline to the statistical analysis.
Section 10.4.1 Subgroups	Addition of iFLC/dFLC levels and deep hematologic response subgroup analysis (with definition). Clarification that descriptive subgroup analysis will be provided for the primary and secondary efficacy endpoints, along with other subgroups to be defined in the statistical analysis plan. Additionally, safety summaries will be provided for relevant subgroups. Clarification of the age group 1 subgroup analysis to below, above, or equal to study median age. Removal of Age Group 2 (< 65 years versus ≥ 65 years) as the median patient age is expected to be at least 65 years old. Edits to the subgroup analysis of comparative hematologic response to be based on dFLC: VGPR or better: dFLC < 4 mg/dL versus other response (PR and NR: dFLC≥ 4 mg/dL). Removal of the subgroup analysis of hematological response as this analysis will be performed in the subgroup 'Comparative hematological response based on dFLC'. Addition of the subgroup analyses of the presence or absence of co-existing myeloma.
Section 10.4.2 Analysis Sets	Addition of mITT analysis set defined as all patients who have been randomized and survived for at least 4 weeks from the first dose of study intervention.
Section 10.4.3 Handling of Missing Data	Addition of the date of death as the key data element used for time to ACM determination. As all patients will be followed regardless of study participation, for patients who die, there is no expectation of missing death dates. Clarification that missing data for secondary endpoint analysis only will be described in the SAP.

Change	Rationale
Section 10.7 Efficacy Analysis	Change of primary analysis set from FAS to ITT set to align with regulatory feedback of the SAP.
Section 10.7.1 Primary Efficacy Endpoint Primary Estimand	Update of the primary estimand variable to a hierarchical combination of time to all-cause mortality and the frequency of cardiovascular hospitalization, and the summary measure to the win-ratio of CAEL-101 vs placebo for the hierarchical composite endpoint of time to all-cause mortality and the frequency of cardiovascular hospitalization. Removal of long-rank test and addition of win-ratio analysis of the hierarchical composite endpoint of time to ACM and the frequency of CVH to summary measures. Removal of KM curve and KM estimates of median survival time as this was added in error originally.
Section 10.7.2 Secondary Efficacy Endpoints	The order of secondary endpoints will be tested as described in the SAP and the order is no longer specified in the protocol. Addition of description of testing (Cox proportional hazard model stratified by the randomization factor of geographic region and adjusted by daratumumab usage at baseline) of key the secondary efficacy endpoints of time to ACM. Description of frequency of CVH analysis of negative binomial regression with geographic region, daratumumab use at baseline and an offset term equal to log of each patient's study duration included in the model. Description of the ranked ANCOVA test to include treatment factor, geographic region, daratumumab use at baseline as fixed effects. The ranked baseline value (i.e., baseline 6MWT, baseline KCCQ-OS, baseline SF-36v2 PCS, baseline NT-proBNP, and baseline GLS% as corresponding to each endpoint) will be included as covariates. Removal of least square means and 95% confidence interval testing of each intervention group as these details will be described in the statistical analysis plan.
Section 10.7.3 Exploratory Endpoints	Change in exploratory endpoint analyses will be assessed from baseline over time. The ANCOVA model was replaced with the MMRM model for the

Change	Rationale
	exploratory endpoints of changes from baseline over time. Addition of description of least square mean analysis of exploratory endpoints and removal of description of details of exploratory endpoints as these are described elsewhere. Removal of least square means and 95% confidence interval testing of the exploratory endpoints. Clarification that the exploratory composite endpoint will be based on a hierarchical combination instead of cardiac deterioration alone.
Section 13.3 Data Protection	Update of the description of patients' data protection processes in place during and after the study to align with EU CTR requirements.
Section 14 Ethics	Addition of reporting serious breaches and personal data breach definitions and reporting requirements to align with EU CTR requirements.
Section 14.3 Recruitment Strategy	Addition of language describing the recruitment strategy for the study to align with EU-CTR requirements
Section 15.3 Retention of Records	Update of retention of records time periods to align with EU CTR requirements.
Section 15.4 Handling of Human Biological Samples Section 15.4.1 Chain of Custody Section 15.4.2 Withdrawal of Informed Consent for Donated Biological Samples	Addition of language describing handling of research biological samples, chain of custody, and withdrawal of consent for donated biological samples to align with EU CTR requirements.
Throughout document	Minor administrative changes, corrections, and edits for clarity and consistency. Update of reference list.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

Abbreviation	Definition
6MWT	six-minute walk test
AAS	Anti-drug antibody Analysis Set
ADA	anti-drug antibodies
AE	adverse event
AL	amyloid light chain
AL-A	amyloidosis light chain
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	alkaline phosphatase
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
BP	blood pressure
BSA	body surface area
CarCR	cardiac complete response
CarNR	cardiac no response
CarPR	cardiac partial response
CarVGPR	cardiac very good partial response
CEAC	clinical events adjudication committee
CIOMS	Council for International Organizations of Medical Sciences
CMAD	cardiac mechanical assist device
CRAB	Hypercalcemia, renal failure, anemia, or lytic bone lesions
CRF	case report form
CRP	C-reactive protein
CT	computed tomography
cTnI	cardiac troponin I
cTnT	cardiac troponin T
C_{trough}	lowest exposure levels
CTIS	Clinical Trials Information System
CVH	cardiovascular hospitalizations
CyBorD	cyclophosphamide-bortezomib-dexamethasone

Abbreviation	Definition
DCI	data collection instrument
dFLC	involved/uninvolved free light chain difference
DLT	dose limiting toxicity
DPIA	data protection impact assessment
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOS	End of Study
EOT	End of Treatment
EQ-5D-5L™	European Quality of Life Health 5-Dimension 5-Level questionnaire
EU CTR	European Union Clinical Trials Regulation
FDA	Food and Drug Administration
FLC	free light chain
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLS	global longitudinal strain
GPS	Global Patient Safety
GVP	Good pharmacovigilance practices
hCG	human chorionic gonadotropin
HR	heart rate
hs-cTnT	high sensitivity cardiac troponin T
ICD	implantable cardioverter-defibrillator
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDAC	independent data analysis center
IDMC	independent data monitoring committee
IEC	independent ethics committee
iFLC	involved free light chain
IMP	investigational medicinal product
IQR	interquartile range

Abbreviation	Definition
IRB	institutional review board
IRT	interactive response technology
ITT	Intent-to-Treat
IV	intravenous
IVSd	interventricular septum thickness
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire Overall Score
KM	Kaplan-Meier
LPI	last patient in
LPW	left ventricular posterior wall
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LS	least square
MCS	mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
mg/m^2	milligrams per square meter
mITT	modified intention to treat set
mmHg	millimeters mercury
MMRM	mixed model for repeat measure
MRI	magnetic resonance imaging
NAb	neutralizing antibodies
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NR	no-response
NSAID	non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
OLEP	Open-label Extension Period
OLETP	Open-label Extension Treatment Period
PCD	plasma cell dyscrasia
PET	positron emission tomography
PETP	Primary Evaluation Treatment Period
PK	pharmacokinetic

Abbreviation	Definition
PKAS	Pharmacokinetic Analysis Set
POEMS	plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes
PP	Per Protocol
PR	Partial response
QTcF	QT corrected by Fridericia
QoL	quality of life
RDW	red blood cell distribution width
renVGPR	renal very good partial response
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SF-36v2®	Short Form 36 version 2 Health Survey
SF-36v2® PCS	Short Form 36 version 2 Health Survey Physical Component Score
SmPC	Summary of Product Characteristics
SoC	standard of care
SPEP	serum protein electrophoresis
SS	Safety Analysis Set
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAS	visual analog scale
VGPR	Very Good Partial response
WHO	World Health Organization
WOCBP	women of child-bearing potential
WR	win-ratio

1. SYNOPSIS

Name of Sponsor/Company: Alexion Pharmaceuticals, Inc	
Name of Investigational Product: CAEL-101	
Name of Active Ingredient: CAEL-101 is a chimeric immunoglobulin G1 kappa isotype	
Title of Study: A Phase 3, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of CAEL-101 and Plasma Cell Dyscrasia Treatment Versus Placebo and Plasma Cell Dyscrasia Treatment in Plasma Cell Dyscrasia Treatment-Naïve Patients with Mayo Stage IIIb AL Amyloidosis	
CTIS # 2022-503073-11	
Number of patients: Approximately 124	**Phase of development:** 3
Mapping Objectives to Endpoints/Estimands	
Objective	**Estimand and/or Endpoints**
Primary Evaluation Treatment Period (PETP)	
Primary Efficacy Endpoints	
• To determine if CAEL-101 and treatment for plasma cell dyscrasia (PCD) improves overall survival and/or decreases the frequency of cardiovascular hospitalizations in Mayo stage IIIb amyloid light chain (AL) amyloidosis patients who are treatment naïve compared to treatment for PCD and placebo	• A hierarchical combination of time to all-cause mortality (ACM) and the frequency of cardiovascular hospitalizations (CVH)

• To evaluate the safety and tolerability of CAEL-101 in combination with treatment for PCD and placebo	• Incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs). • Changes from baseline in vital signs, weight, clinical laboratory tests, and 12-lead electrocardiograms (ECGs)
Secondary Efficacy Endpoints	
• To determine if CAEL-101 and treatment for PCD improves survival post-initiation of study treatment in Mayo stage IIIb amyloid light chain (AL) amyloidosis patients who are treatment naïve compared to treatment for PCD and placebo	• Time to ACM in Primary Evaluation Treatment Period (PETP)
• To determine if CAEL-101 and treatment for PCD decreases cardiovascular-related hospitalizations (CVH) post-initiation of study treatment in Mayo stage IIIb amyloid light chain (AL) amyloidosis patients who are treatment naïve compared to treatment for PCD and placebo	• Frequency of CVH in PETP
• To assess quality of life (QoL) as measured by the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS)	• Change from baseline to Week 50 in KCCQ-OS
• To assess improvement in cardiomyopathy as measured by NT-proBNP	• Change from baseline to Week 50 in NT-proBNP

• To assess cardiac improvement as measured by global longitudinal strain (GLS%)	• Change from baseline to Week 50 in GLS%
• To assess functional improvement as measured by the distance walked in the six-minute walk test (6MWT)	• Change from baseline to Week 50 in 6MWT
• To assess quality of life as measured by the Short Form 36 Health Survey Physical Component Score (SF-36v2® PCS)	• Change from baseline to Week 50 in the SF-36v2 PCS
Exploratory Endpoints	
• To assess improvement in cardiac amyloidosis as measured by changes in N-terminal pro B-type natriuretic peptide (NT-proBNP), cardiac troponin T (cTnT), involved/uninvolved free light chain difference (dFLC), and C-reactive protein (CRP)	• Changes from baseline over time in NT-proBNP, cTnT, dFLC, and CRP
• To assess cardiac response, defined as a decrease of > 30% in NT-proBNP levels AND a decrease of NT-proBNP > 300 ng/L	• Proportion of patients with cardiac response from baseline over time until end of PETP (defined as a decrease of > 30% in NT-proBNP levels and decrease of NT-proBNP > 300 ng/L)
• To assess composite cardiac response when both of the following are satisfied: o A decrease of > 30% in NT-proBNP levels AND a decrease of NT-proBNP > 300 ng/L; o GLS improvement of ≥ 2%	• Proportion of patients from baseline over time during the PETP composite cardiac response when both of the following are satisfied: o A decrease of > 30% in NT-proBNP levels and a decrease of NT-proBNP > 300 ng/L o GLS% improvement of ≥ 2%

• To assess CCI CCI	CCI
• To assess graded cardiac response	• Proportion of patients with graded cardiac response, determined using the following definitions: o Cardiac complete response (CarCR) defined as NT-proBNP ≤ 350 pg/ml (≤ 41.39 pmol/L) from baseline o Cardiac very good partial response (CarVGPR) defined as a > 60% reduction in NT-proBNP from baseline level not meeting CarCR o Cardiac partial response (CarPR) defined as a 31–60% reduction in NT-proBNP from baseline level not meeting CarCR o Cardiac no response (CarNR) defined as ≤ 30% reduction in NT-proBNP from baseline level (Muchtar 2023) • Time to cardiac response and time to graded cardiac response

• To assess renal response, defined as 30% decrease in proteinuria or drop of proteinuria below 0.5 g/24 h in the absence of ≥ 25% decrease in eGFR (Palladini 2014). Renal response will be assessed in patients with renal involvement, defined as those with a baseline urinary protein excretion of more than 0.5 g per day	• Proportion of patients with renal response from baseline over time in the PETP (defined as a 30% decrease in proteinuria or drop of proteinuria below 0.5 g/24 h in the absence of ≥ 25% decrease in eGFR). • Time to renal progression

• To assess graded renal response in patients with renal involvement at baseline	• Proportion of patients with graded renal response from baseline (in the absence of renal progression [renal progression defined as greater than/equal to 25% decrease in eGFR]) defined as:
	  • Renal complete response (renCR, 24-h proteinuria ≤ 200 mg/24-h)
	  • Renal very good partial response (renVGPR, > 60% reduction in baseline 24-h proteinuria)
	  • Renal partial response (renPR, 31-60% reduction in baseline 24-h proteinuria)
	  • Renal no response (renNR, 30% or less reduction in baseline 24-h proteinuria) (Muchtar 2021)
	• Time to renal response

• To assess hepatic response in patients with hepatic involvement (defined as alkaline phosphatase [ALP] ≥ 1.5 upper limit of normal [ULN]).	• Proportion of patients with hepatic response from baseline over time (Muchtar 2018), defined as a decrease of ≥ 50% and or normalization of the serum ALP level (Comenzo 2012)
	• Time to hepatic response
	• Time to graded hepatic response defined as:
	  ○ Hepatic complete response (AP ≤ × 2 lower limit of normal
	  ○ Hepatic very good partial response (> 60% reduction from baseline AP level to a nadir above ×2 lower limit of normal)
	  ○ Hepatic partial response (31–60% reduction from baseline AP)
	  ○ Hepatic no response (≤ 30% reduction from baseline AP)

	• Proportion of patients with hepatic progression defined as a decrease of ≥ 50% and/or normalization of the serum ALP level. • Proportion of patients with hepatic complete response, hepatic very good partial response, hepatic partial response, and hepatic non-response from baseline over time (Muchtar 2018)
• To assess changes in effects on liver function including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT)	• Changes from baseline over time in liver function including AST, ALT, ALP, and GGT
• To assess changes in effects on renal function including eGFR, serum creatinine and 24-hour urine protein	• Changes from baseline over time in renal function including eGFR, serum creatinine, and 24-hour urine protein
• To assess QoL as measured by the KCCQ domain scores, SF-36v2® scaled domain scores and European Quality of Life Health 5-Dimension 5-Level questionnaire (EQ-5D-5L™)	• Changes from baseline over time in QoL as measured by the KCCQ domain scores and summary scores, SF-36v2 scaled domain scores and mental component summary (MCS) and EQ-5D-5L Index score and Visual Analog Score (VAS)
• To assess change in New York Heart Association (NYHA) Functional Classification	• Change from baseline in NYHA Functional Classification over time
• To describe the PK profile based on serum levels of CAEL-101	• Descriptive statistics of serum CAEL-101 concentrations include number of patients with nonmissing values, mean, standard deviation, minimum, lower quartile, median, upper quartile, interquartile range (IQR), and maximum at each visit and nominal timepoint
• To assess the immunogenicity of CAEL-101	• Anti-drug antibodies (ADA) incidence, response categories and titers, as well as neutralizing antibodies (NAb) incidence and titers in patients with AL amyloidosis

Open-label Extension Period (OLEP)	
Exploratory (continued)	
• To compare the long-term overall survival in patients with AL amyloidosis enrolled in the Open-label Extension Period (OLEP), who were previously treated with CAEL-101 or placebo during the PETP	• Time to ACM from randomization to the date of death or to the end of the study in patients with AL amyloidosis enrolled in the OLEP, who were previously treated with CAEL-101 or placebo during the PETP
• To compare the long-term overall survival in patients with AL amyloidosis enrolled in the OLEP, who were previously treated with CAEL-101 or placebo, during the PETP, and who received CAEL-101 or placebo for a minimum of 3 months	• Time to ACM from randomization to the date of death or to the end of the study in patients with AL amyloidosis enrolled in the OLEP, who were previously treated with CAEL-101 or placebo, during the PETP, and who received CAEL-101 or placebo for a minimum of 3 months
• To compare the long-term overall survival in patients with AL amyloidosis enrolled in the OLEP, who were previously treated with CAEL- 101 or placebo, during the PETP, and who received CAEL-101 or placebo for a minimum of 6 months	• Time to ACM from randomization to the date of death or to the end of the study in patients with AL amyloidosis enrolled in the OLEP, who were previously treated with CAEL-101 or placebo, during the PETP, and who received CAEL-101 or placebo for a minimum of 6 months
• To assess the long-term efficacy of CAEL-101 in patients with AL amyloidosis who were previously treated with CAEL-101 during the PETP	• Changes from baseline over time in 6MWT, NT-proBNP, KCCQ-QoL, SF-36v2PCS • Assessment of extra-cardiac organ response
• To assess the long-term safety of CAEL-101 in patients with AL amyloidosis	• Incidence of TEAEs and SAEs • Changes from baseline in vital signs, clinical laboratory tests, and 12-lead ECGs
• To assess immunogenicity to CAEL-101 in patients with AL amyloidosis	• Anti-drug antibodies (ADA) incidence, response categories and titers, as well as neutralizing antibodies (NAb) incidence and titers in patients with AL amyloidosis enrolled in the OLEP, who were previously treated with CAEL-101 or placebo for a minimum of 6 months, during the PETP

• To describe the pharmacokinetics (PK) of CAEL-101 in patients with AL amyloidosis	• Descriptive statistics of serum CAEL-101 concentrations include number of patients with non-missing values, mean, standard deviation, minimum, lower quartile, median, upper quartile, interquartile range (IQR), and maximum at each visit and nominal timepoint

Study Design and Duration:

This is a double-blind, randomized, multicenter international Phase 3 study of CAEL-101 combined with standard of care (SoC) plasma cell dyscrasia (PCD) treatment versus placebo combined with SoC PCD treatment in Mayo stage IIIb PCD treatment-naïve amyloid light chain (AL) amyloidosis patients.

Following Screening and randomization, patients will receive blinded treatment of CAEL-101 (1000 mg/m^2) + PCD Treatment OR placebo + PCD Treatment during the Primary Evaluation Treatment Period (PETP). The primary analysis will be conducted 18 months after the last patient is randomized.

All patients will have the option to continue into the Open-label Extension Period (OLEP) which consists of a Transition (Loading Dose) Period and an Open-label Extension Treatment Period (OLETP). During the OLETP, all patients will receive CAEL-101 in addition to any SoC prescribed by the physician. Final study assessments will be performed post-treatment in End of Treatment (EOT) and follow-up visits.

Approximately 124 patients will be enrolled using a 2:1 randomization ratio. Stratification will be based on geographic region across investigator sites.

Patients in both study drug groups will be followed from randomization until death from any cause, heart transplant, left ventricular assist device (LVAD) implantation, or until the study level end of study (EOS).

Investigational Product, Dosage, and Mode of Administration:

CAEL-101 is administered as an intravenous (IV) infusion over approximately 2 hours. Patients will be randomized to either treatment with CAEL-101 or placebo (referred to collectively as "study drug") plus PCD treatment. Patients randomized to receive CAEL-101 will receive 1000 mg/m^2 CAEL-101. Patients will receive study drug every 7 (+/- 1) days for 4 infusions then every 14 (+/- 2) days. The maximum permitted dose of CAEL-101 is 2700 mg.

Study Population:

Key Inclusion Criteria:

- AL amyloidosis stage IIIb based on the European Modification of the 2004 Standard Mayo Clinic Staging (see Table 5) (Wechalekar 2013; Palladini 2016; Dispenzieri 2004) at the time of Screening, which includes
  NT-proBNP > 8,500 ng/L
- Measurable hematologic disease at Screening as defined by at least one of the following:
  - Involved/uninvolved free light chain difference (dFLC) > 4 mg/dL OR
  - Involved free light chain (iFLC) > 4 mg/dL with abnormal Kappa/Lambda ratio OR
  - Serum protein electrophoresis (SPEP) m-spike > 0.5 g/dL
- Histopathological diagnosis of amyloidosis based on polarizing light microscopy of green bi-refringent material in Congo red stained tissue specimens AND confirmation of AL derived amyloid deposits by at least one of the following:
  a. Immunohistochemistry/Immunofluorescence OR
  b. Mass spectrometry OR
  c. Characteristic electron microscopy appearance/Immunoelectron microscopy
- Cardiac involvement as defined by:
  a. Documented clinical signs and symptoms supportive of a diagnosis of heart failure in the setting of a confirmed diagnosis of AL amyloidosis in the absence of an alternative explanation for heart failure

  AND

  b. At least one of the following:
     - Endomyocardial biopsy demonstrating AL cardiac amyloidosis OR
     - Echocardiogram demonstrating a mean left ventricular wall thickness (calculated as [IVSd+LPWd]/2) of > 12 mm at diastole in the absence of other causes (e.g., severe hypertension, aortic stenosis), which would adequately explain the degree of wall thickening OR
     - Cardiac magnetic resonance imaging (MRI) with gadolinium contrast agent diagnostic of cardiac amyloidosis

- Planned first-line treatment for PCD is a cyclophosphamide-bortezomib-dexamethasone (CyBorD)-based regimen administered as SoC
- Women of childbearing potential (WOCBP) must have a negative 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 PCD therapy, whichever is longer
- 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

Key Exclusion Criteria:

- Have any other form of amyloidosis other than AL amyloidosis
- Received prior therapy for AL amyloidosis or multiple myeloma. A maximum exposure of 2 weeks of a CyBorD-based PCD treatment after Screening laboratory samples are obtained and prior to randomization is allowed
- Has POEMS (PCD with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes) syndrome OR multiple myeloma defined as clonal bone marrow plasma cells > 10% from a bone marrow biopsy (performed ≤ 3 months prior to signing the ICF or during Screening) OR biopsy-proven (performed ≤ 3 months prior to signing the ICF or during Screening) bony or extramedullary plasmacytoma AND one or more of the following CRAB features:
    a. Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder (e.g., multiple myeloma and POEMS syndrome), specifically:
        – Hypercalcemia: serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than the upper limit of normal (ULN) or > 2.75 mmol/L (> 11 mg/dL) OR
        – Renal insufficiency: creatinine clearance < 40 mL per minute or serum creatinine > 177 µmol/L (> 2 mg/dL) OR
        – Anemia: hemoglobin value of > 20 g/L below the lowest limit of normal, or a hemoglobin value < 100 g/L OR
        – Bone lesions: one or more osteolytic lesion on imaging tests (performed ≤ 3 months prior to signing the ICF or during Screening): skeletal radiography, computed tomography (CT), or positron emission tomography (PET)/CT, or MRI. If bone marrow has < 10% clonal

plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement

OR

1. Any one of the following biomarkers of malignancy:
    a. 60% or greater clonal plasma cells on bone marrow examination OR
    b. More than one focal lesion on MRI that is at least 5 mm or greater in size
2. Have supine systolic blood pressure (BP) < 90 mmHg or symptomatic orthostatic hypotension, defined as a decrease in systolic BP upon standing of > 30 mmHg despite medical management (e.g., midodrine, fludrocortisones) in the absence of volume depletion

Statistical Methods:

The primary objectives of this study are to determine whether CAEL-101 and treatment for PCD improves overall survival and/or decreases the frequency of cardiovascular hospitalizations compared to placebo and treatment for PCD. The primary statistical hypothesis to be tested is:

- H_0: Neither ACM nor frequency of cardiovascular-related hospitalization is different between CAEL-101 and placebo in patients with Mayo stage IIIb AL amyloidosis.
- H_a: At least one of ACM and frequency of cardiovascular-related hospitalizations are different between CAEL-101 and placebo in patients with Mayo stage IIIb AL amyloidosis.

The effects of CAEL-101 on safety and tolerability, while included as primary objectives, are not to be tested inferentially and thus there is no structured hypothesis for those outcomes.

Efficacy

The primary efficacy endpoint has been revised to a hierarchical combination of time to ACM and the frequency of CVH over a last patient randomized plus 18 months (LPI+18M) treatment duration.

The Finkelstein-Schoenfeld test (FS test) (Finkelstein and Schoenfeld 1999) will be used to test for a treatment effect on the hierarchical composite endpoint. Simulation demonstrates that there is greater than CCI power to reject the null hypothesis that neither ACM nor CVH is different between CAEL-101 and placebo. The simulations were conducted with a 5% two-sided significance level and the assumptions of a CC hazard ratio between CAEL101 and placebo for time to ACM and a CCI rate ratio for CVH.

The hypothesis testing will be performed using the F-S test and the treatment effect estimation using the win-ratio (WR) method (Pocock 2012). Both these methods are based on pairwise comparisons of patient outcomes with the comparisons performed in a hierarchical manner (e.g., first compare patient outcomes based on time to ACM and, if there is no winner due to censoring, then compare based on frequency of CVH).

The F-S test will be stratified by geographic region, and daratumumab usage (versus no use of daratumumab) at baseline (-28 ≤ study day ≤ 1).

To control the Type 1 error, the secondary endpoints will be formally tested sequentially in the order which will be pre-specified in the SAP if the primary endpoint is statistically significant at the 0.05 level.

The time to ACM will be analyzed as follows:

- Testing: a stratified log-rank statistic by geographic region (North America vs rest of the world) and daratumumab usage at baseline (daratumumab use versus no use)
- Estimation: the hazard ratio of CAEL-101 versus placebo based on a Cox proportional hazard model adjusted by geographic region and daratumumab usage at baseline. The 95% confidence interval of hazard ratio will also be reported.

Kaplan-Meier (KM) plots will also be provided by the study intervention groups.

Frequency of CVH will be analyzed using a negative binomial regression model with geographic region, daratumumab use at baseline and an offset term equal to log of each subject's study duration included in the model.

The 5 secondary efficacy endpoints (NTProBNP, KCCQ-OS, GLS%, 6MWT, SF36v2 PCS) based on the changes from baseline to Week 50 will be analyzed using a ranked analysis of covariance (ANCOVA) model. The ranked analysis will account for the patients whose data will be missing due to time to ACM, CVH and other reasons. The outcome for each patient will be ranked based on the order described in the SAP.

The ranked ANCOVA model will include treatment factor, geographic region, daratumumab use at baseline as fixed effects. The ranked baseline value (i.e., baseline 6MWT, baseline KCCQ-OS, baseline SF-36v2 PCS, baseline NT-proBNP, and baseline global longitudinal strain (GLS)% as corresponding to each endpoint) will be included as covariates.

Analyses for the exploratory endpoints will be pre-specified in the SAP.

Safety

All safety analyses will be conducted on the Safety Analysis set (SS). The safety analyses will be descriptive in nature. All safety data will be listed, and data tabulated by study intervention group. Safety data include the following:

- Treatment-emergent Adverse Events (TEAEs)
- Clinical laboratory tests (hematology, chemistry, and urinalysis)
- Immunogenicity laboratory tests (including anti-drug antibodies (ADA), neutralized antibodies (NAb) and other immunogenicity characterization assays)
- Vital signs including respiratory rate, heart rate (HR) and BP
- Physical examination including weight
- Twelve-lead electrocardiogram (ECG) including rate, rate ranges and diagnostic statements

Adverse events (AE) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding. Patient incidence of each System Organ Class and unique Preferred Term will be tabulated, including all TEAEs, at least possibly related TEAEs, TEAEs resulting in discontinuation of study treatment, TEAEs by intensity National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE] grades 1-5) and treatment emergent serious adverse events (SAE).

Treatment-emergent is defined as follows: last study intervention day-first study intervention day + 140 days.

Other safety data presentations will be descriptive in nature and no formal statistical tests will be performed. Analyses of laboratory, vital sign and ECG outcomes will include mean changes from baseline as well as shifts (e.g., normal to abnormal) from baseline and the incidence of potentially clinically significant values. Normal ranges and potentially clinically significant thresholds will be defined in the SAP. Graphics of changes over time in safety parameters will be presented, where appropriate.

Pharmacokinetics

All PK analyses will be performed on the PK Analysis Set. The PK analysis will be descriptive in nature. Individual and mean concentrations versus time data will be tabulated and plotted. Summary statistics of concentration data will be computed for each scheduled sampling time and plotted. In addition, PK and PD data from this study may be combined with data from other studies to conduct additional assessments as per the Sponsor's discretion that are based on the outcome of this trial and future development path.

Ethical Considerations and Benefit-Risk Assessment

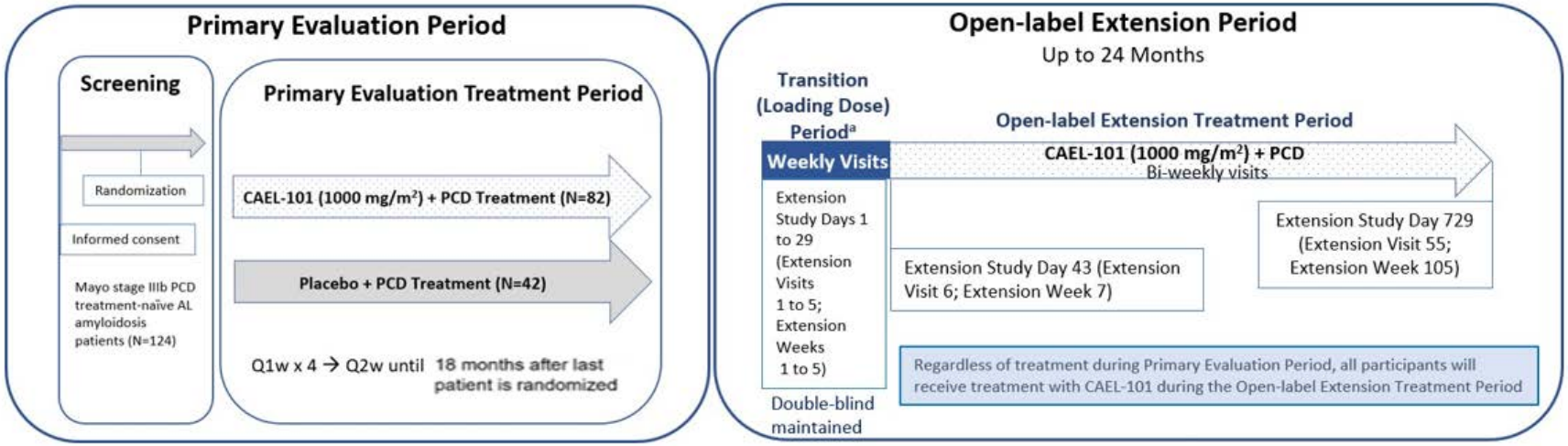
This study will be conducted as specified in this protocol and in accordance with the following:

1. Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2. Applicable ICH Good Clinical Practice (GCP) Guidelines
3. Applicable laws and regulations

A thorough benefit-risk assessment has been performed for CAEL-101 (See CAEL-101 Investigational Brochure for details). Measures will be taken to minimize risk to patients. The potential risks identified in association with CAEL-101 are justified by the anticipated benefits that may be afforded to patients with AL Amyloidosis

1.1. Study Schematics

Figure 1: Study Schema



Note: PETP will be considered complete if patients move into OLEP or if they complete 6 visits during the 140 days EOT.
Note: The PETP will close on the date of the last patient to randomize in the study (globally) plus 18 months.

[a]

	Transition (Loading Dose) Period*				
Treatment Group	Extension Study Day 1**	Extension Study Day 8	Extension Study Day 15	Extension Study Day 22	Extension Study Day 29
Placebo to CAEL-101	Placebo	CAEL-101	CAEL-101	CAEL-101	CAEL-101
CAEL-101 to CAEL-101	CAEL-101	Placebo	CAEL-101	Placebo	CAEL-101

*Double-blind is maintained during the Transition Period

**First dose of study drug for each participant in the Open-label Extension Period

Abbreviations: AL – amyloid light chain; PCD – plasma cell dyscrasia; Q1W – once every week; Q2W – once every two weeks

1.2. Schedule of Assessments

Table 1: Schedule of Assessments: Primary Evaluation Period

	Primary Evaluation Period																															
	Screening	**Primary Evaluation Treatment Period (PETP)**																														Primary Evaluation Period Ends[o]
Visit	V1	V2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	V 12	V 13	V 14	V 15	V 16	V 17	V 18	V 19	V 20	V 21	V 22	V 23	V 24	V 25	V 26	V 27	V 28	V 29			
Week	-4 to 0	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52[a]			
Study Day	≤ 28 prior to V2	1	8	15	22	36	50	64	78	92	106	120	134	148	162	176	190	204	218	232	246	260	274	288	302	316	330	344	358			
		+/- 1 day				+/- 2 days																										
Signed ICF	X																															
Inclusion & exclusion	X																															
Demographics	X																															
AL amyloidosis confirmation[b]	X																															
Medical history & prior meds	X																															
Height & BSA[c]	X																															
Physical exam[d]	X			X		X		X		X		X		X		X		X		X		X		X		X		X				
Pregnancy test[e]	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X				
Vital signs & weight	X[f]	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			
Twelve-lead ECG	X	X[n]	X	X	X											X																
Safety laboratory tests[g]	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X				
NT-proBNP & cTnT	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X				
Serum FLC	X		X	X	X	X		X		X		X		X		X		X		X		X		X		X		X				
Serum and Urine Immunofixation	X		X	X	X	X		X		X		X		X		X		X		X		X		X		X		X				
C-reactive protein (CRP)	X									X						X												X				
24-hour urine protein[h]	X									X						X												X				

Table 1: Schedule of Assessments: Primary Evaluation Period

	Primary Evaluation Period																														
	Screening	**Primary Evaluation Treatment Period (PETP)**																													Primary Evaluation Period Ends[o]
Visit	V1	V2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	V 12	V 13	V 14	V 15	V 16	V 17	V 18	V 19	V 20	V 21	V 22	V 23	V 24	V 25	V 26	V 27	V 28	V 29		
Week	-4 to 0	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52[a]		
Study Day	≤ 28 prior to V2	1	8	15	22	36	50	64	78	92	106	120	134	148	162	176	190	204	218	232	246	260	274	288	302	316	330	344	358		
Echocardiogram[i]	X									X						X												X		
Randomization		X																													
6MWT[j]	X									X						X						X						X		
Study drug infusion[k]		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 Functional Classification		X								X						X												X		
PK samples[l]		X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		
Immunogenicity test		X						X								X												X		
KCCQ, SF-36v2, EQ-5D-5L[m]		X								X						X						X						X		
Survival assessment	X																														
PCD treatment assessment	X																														
Adverse Events	X																														
Concomitant medications	X																														

[a] Once a patient completes V29/Week 52, continue to follow the schedule of assessments repeating V28/Week 50 and V29/Week 52 every two weeks as long as the patient remains on study treatment. In addition, NT-proBNP, cTnT, FLC, PK, physical examinations, safety laboratory tests and pregnancy tests (for WOCBP) are only required every other visit starting with V30/Week 54 (e.g., V30/Week 54, V32/Week 58, V34/Week 62, etc.). The 6MWT, NYHA Functional Classification, Quality of life (QoL) questionnaires, echocardiogram, 24-hour urine protein, CRP samples, immunogenicity tests, are only required every 26 weeks +/- 30 days (e.g., V41/Week 76, V54/Week 102, etc.). The PETP will end on the date of the last patient randomized in the study plus 18 months.

[b] Diagnosis of AL amyloidosis (e.g., biopsy with Congo red staining with typing by immunohistochemistry/immunofluorescence, mass spectrometry, characteristic electron microscopy appearance/ immunoelectron microscopy) and cardiac involvement will be confirmed using historical medical records and historical and current laboratory reports. Mayo staging will be established during Screening based on cTnT and NT-proBNP results.

Table 1: Schedule of Assessments: Primary Evaluation Period

[c] Calculate the patient's BSA in m^2 using the height and weight obtained during Screening. It is not necessary to recalculate the BSA for dosing unless the patient experiences ≥ 20% weight change.

[d] Complete physical required at Screening – general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic & psychiatric. Subsequent physicals may be abbreviated and clinically focused.

[e] For WOCBP, serum human chorionic gonadotropin (hCG) performed by the central laboratory is required at Screening within 14 days of first dose of study drug. Subsequent pregnancy tests may be performed locally using urine dipsticks.

[f] At Screening, measure BP and HR after the patient has rested quietly for at least 5 minutes in a supine position. Then have the patient stand and measure BP and HR right away. Measure the standing BP and HR again after approximately 3 minutes. Subsequent BP and HR measurements after V1 should be taken after the patient has rested quietly for at least 5 minutes in a seated or supine position.

[g] Chemistry – alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), blood urea nitrogen, calcium, chloride, creatinine, estimated glomerular filtration rate (eGFR), gamma-glutamyl transferase (GGT), globulin, glucose, magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, uric acid. Hematology – complete blood count with differential, red blood cell distribution width (RDW), reticulocyte count. Urinalysis – bilirubin, blood, glucose, ketones, leukocytes, pH, protein and specific gravity.

[h] Results of the Screening 24-hour urine protein are for baseline only and are not required to determine eligibility. The Investigator may choose to have the patient collect the urine for Screening after eligibility has been confirmed and a date for first dose has been scheduled as long as the collection is complete prior to administration of study drug. Collection of the 24-hour urine after V1 may be within a +/- 30 day window from the study day. Collection of 24-hour urine samples should not be skipped. If the patient cannot complete a 24-hour urine collection within the assessment window (e.g., the patient is hospitalized), it should be completed as soon as possible. EOT 24-hour urine protein is required ONLY at 14 days following the last dose of study drug (Table 2).

[i] 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. EOT echocardiogram is required ONLY at the 14 days following the last dose of study drug (Table 2).

[j] The 6MWT should only be performed AFTER obtaining samples for cTnT and NT-proBNP. Results of the Screening 6MWT are for baseline only and are not required to determine eligibility. The Investigator may choose to have the patient perform the 6MWT for Screening after eligibility has been confirmed and a date for first dose has been scheduled as long as the test is complete prior to administration of study drug. The 6MWT conducted after V1 may be within a +/- 30 day window from the study day. The 6MWT should not be skipped. If the test cannot be completed within the assessment window (e.g., the patient is hospitalized), it should be completed as soon as possible. The 6MWT may be repeated within the visit window if the test was invalid. EOT 6MWT is required ONLY at 14 days following the last dose of study drug (Table 2).

[k] First dose of CAEL-101 must be administered within 24 hours of randomization. If a dosing event is delayed by ≤ 7 days, administer the study drug "out of window" and obtain associated laboratory assessments for that visit. Resume the patient's pre-determined dosing schedule. If a dosing event is delayed by > 7 day and ≤ 14 days, skip the visit and resume the patient's pre-determined dosing schedule with the next visit. If a dosing event is delayed by > 14 days, contact the Medical Monitor prior to resuming the dosing schedule.

[l] PK sample times – pre-dose will be taken prior to the start of the infusion and post-dose within 30 minutes to 1 hour from the end of infusion. PK samples must be drawn from the opposite arm from the study drug infusion. EOT PK sample is required ONLY at 14 days following the last dose of study drug (Table 2).

[m] Quality of life (QoL) questionnaires must be collected FIRST before all other assessments at visits where required. QoL questionnaires completion after V2 may be within a +/- 30 day window from the study day. QoL questionnaires completion should not be skipped. If the questionnaires cannot be completed within the assessment window (e.g., the patient is hospitalized), they should be completed as soon as possible. EOT QoL questionnaires are required ONLY at 14 days following the last dose of study drug (Table 2).

Table 1: Schedule of Assessments: Primary Evaluation Period

[n] Twelve-lead ECGs will be obtained prior to the first dose then 1 hour (+/- 15 minutes) and 2 hours (+/-15 minutes) following the completion of the first infusion on Study Day 1 only. Subsequent Twelve-lead ECGs will be collected prior to administration of the study drug. EOT ECG is required ONLY at the 14 days following the last dose of study drug (Table 2).

[o] The PETP will end on the date of the last patient randomized in the study plus 18 months. Once the PETP ends, patients will have the option to continue into the OLEP (Table 2). Patients who stop treatment during the PETP or without entering OLEP are to complete Post-Treatment assessments (EOT and Follow-up assessments) (Table 2).

Abbreviations: 6MWT – six-minute walk test, AL – amyloid light chain, BP – blood pressure, BSA – body surface area, cTnT – cardiac troponin T, ECG – electrocardiogram, EQ-5D-5L™ - European Quality of Life Health 5- Dimension 5-Level questionnaire, EOT – end of treatment, FLC – free light chains, HR – heart rate, ICF – informed consent form, KCCQ – Kansas City Cardiomyopathy Questionnaire, NT-proBNP – N-terminal pro b-type natriuretic peptide, NYHA – New York Heart Association, OLEP – Open-label Extension Period, PCD – plasma cell dyscrasia, PETP – Primary Evaluation Treatment Period ; PK – pharmacokinetic, SF-36v2® – Short Form 36 Health Survey version 2, V – visit, WOCBP – women of child bearing potential

Table 2: Schedule of Assessments: Open-label Extension Period (OLEP) (Transition Period to End of Study)

	Open-label Extension Period (OLEP)																													
	Transition (Loading Dose) Period (Double-blind maintained)					**Open-label Extension Treatment Period (OLETP)**																								
Visit	EV1	EV2	EV3	EV4	EV5	EV6	EV7	EV8	EV9	EV10	EV11	EV12	EV13	EV14	EV15	EV16	EV17	EV18	EV19	EV20	EV21	EV22	EV23	EV24	EV25	EV26	EV27	EV28	EV29
Week	E1	E2	E3	E4	E5	E7	E9	E11	E13	E15	E17	E19	E21	E23	E25	E27	E29	E31	E33	E35	E37	E39	E41	E43	E45	E47	E49	E51	E53
Study Day	E1	E8	E15	E22	E29	E43	E57	E71	E85	E99	E113	E127	E141	E155	E169	E183	E197	E211	E225	E239	E253	E267	E281	E295	E309	E323	E337	E351	E365
	+/- 1 day					+/- 2 days																							
Height & BSA[a]	X																												
Physical exam[b]	X			X		X		X		X		X		X		X		X		X			X	X		X			X[c]
Pregnancy test[d]	X	X		X		X		X		X		X		X		X		X		X			X	X		X			X[c]
Vital signs & weight[e]	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[c]
Twelve-lead ECG[f]	X	X	X	X	X											X													X[c]
Safety laboratory tests[g]	X		X		X	X		X		X		X		X		X		X		X		X		X		X		X	X
NT-proBNP & cTnT	X									X						X							X						X[c]
Serum FLC	X									X						X							X						X[c]
Serum and Urine Immunofixation	X									X						X							X						X[c]
C-reactive protein (CRP)	X									X						X													X[c]
24-hour urine protein[h]	X									X						X													X[c]
Echocardiogram[i]	X[j]															X													X[c]
6MWT[k]	X[l]															X													X[c]
Study drug infusion[m]	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[c]

Table 2: Schedule of Assessments: Open-label Extension Period (OLEP) (Transition Period to End of Study)

	Open-label Extension Period (OLEP)																														
	Transition (Loading Dose) Period (Double-blind maintained)					**Open-label Extension Treatment Period (OLETP)**																									
Visit	EV1	EV2	EV3	EV4	EV5	EV6	EV7	EV8	EV9	EV10	EV11	EV12	EV13	EV14	EV15	EV16	EV17	EV18	EV19	EV20	EV21	EV22	EV23	EV24	EV25	EV26	EV27	EV28	EV29
Week	E1	E2	E3	E4	E5	E7	E9	E11	E13	E15	E17	E19	E21	E23	E25	E27	E29	E31	E33	E35	E37	E39	E41	E43	E45	E47	E49	E51	E53
Study Day	E1	E8	E15	E22	E29	E43	E57	E71	E85	E99	E113	E127	E141	E155	E169	E183	E197	E211	E225	E239	E253	E267	E281	E295	E309	E323	E337	E351	E365
NYHA Functional Classification	X															X													X[c]
PK samples[n]	X									X						X							X						X[c]
Immunogenicity test	X									X						X							X						X[c]
KCCQ, SF-36v2, EQ-5D-5L[o]	X															X													X
Survival assessment	X																												
PCD treatment assessment	X																												
Adverse Events	X																												
Concomitant medications	X																												

Table 3: Schedule of Assessments: Open-label Extension Period (OLEP) (Transition Period to End of Study)

	Open-label Extension Period (OLEP)																											Post-Treatment	
	Open-label Extension Treatment Period (OLETP)																												
Visit	EV 30	EV 31	EV 32	EV 33	EV 34	EV 35	EV 36	EV 37	EV 38	EV 39	EV 40	EV 41	EV 42	EV 43	EV 44	EV 45	EV 46	EV 47	EV 48	EV 49	EV 50	EV 51	EV 52	EV 53	EV 54	EV 55	EOT	Follow- up
Week	E 55	E 57	E 59	E 61	E 63	E 65	E 67	E 69	E 71	E 73	E 75	E 77	E 79	E 81	E 83	E 85	E 87	E 89	E 91	E 93	E 95	E 97	E 99	E 101	E 103	E 105		
Study Day	E 379	E 393	E 407	E 421	E 435	E 449	E 463	E 477	E 491	E 505	E 519	E 533	E 547	E 561	E 575	E 589	E 603	E 617	E 631	E 645	E 659	E 673	E 687	E 701	E 715	E 729	14, 28, 56, 84, 112, & 140 days from last dose	every 4 weeks
	+/- 2 days																										+/- 2 days	+/- 7 days
Height & BSA[a]																												
Physical exam[b]		X		X		X		X		X		X		X		X		X		X		X		X		X	X	
Pregnancy test[d]		X		X		X		X		X		X		X		X		X		X		X		X		X	X	
Vital signs & weight[e]	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	
Twelve-lead ECG[f]																X										X	X[f]	
Safety laboratory tests[g]	X		X		X		X		X		X		X		X		X		X		X		X		X	X	X	
NT-proBNP & cTnT							X						X						X								X	
Serum FLC							X						X						X							X		
Serum and Urine Immunofixation							X						X						X							X		
C-reactive protein (CRP)													X													X	X	
24-hour urine protein[h]													X													X	X	
Echocardiogram[i]													X													X	X[i]	
6MWT[k]													X													X	X[k]	
Study drug infusion[m]	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 Functional Classification													X													X	X[p]	
PK samples[n]													X													X	X[n]	
Immunogenicity test													X													X	X	

Table 3: Schedule of Assessments: Open-label Extension Period (OLEP) (Transition Period to End of Study)

	Open-label Extension Period (OLEP)																												
	Open-label Extension Treatment Period (OLETP)																											Post-Treatment	
Visit	EV 30	EV 31	EV 32	EV 33	EV 34	EV 35	EV 36	EV 37	EV 38	EV 39	EV 40	EV 41	EV 42	EV 43	EV 44	EV 45	EV 46	EV 47	EV 48	EV 49	EV 50	EV 51	EV 52	EV 53	EV 54	EV 55	EOT	Follow- up
Week	E 55	E 57	E 59	E 61	E 63	E 65	E 67	E 69	E 71	E 73	E 75	E 77	E 79	E 81	E 83	E 85	E 87	E 89	E 91	E 93	E 95	E 97	E 99	E 101	E 103	E 105		
Study Day	E 379	E 393	E 407	E 421	E 435	E 449	E 463	E 477	E 491	E 505	E 519	E 533	E 547	E 561	E 575	E 589	E 603	E 617	E 631	E 645	E 659	E 673	E 687	E 701	E 715	E 729	14, 28, 56, 84, 112, & 140 days from last dose	every 4 weeks
KCCQ, SF-36v2, EQ-5D-5L[o]													X													X	X[o]	
Survival assessment	X																											
PCD treatment assessment	X																											
Adverse Events	X																											
Concomitant medications	X																											

[a] Calculate the patient's BSA in m^2 using the height and weight obtained during Screening. It is not necessary to recalculate the BSA for dosing unless the patient experiences ≥ 20% weight change.
[b] Complete physical required at Screening – general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic & psychiatric. Subsequent physicals may be abbreviated and clinically focused.
[c] If a patient stops treatment prior to completion of the OLETP, Post-Treatment assessments (EOT and Follow-up) are to be performed
[d] For WOCBP, serum human chorionic gonadotropin (hCG) performed by the central laboratory is required at Screening within 14 days of first dose of study drug. Subsequent pregnancy tests may be performed locally using urine dipsticks.
[e] BP and HR measurements should be taken after the patient has rested quietly for at least 5 minutes in a seated or supine position.
[f] Twelve-lead ECGs will be collected prior to administration of the study drug. EOT ECG is required ONLY at the 14 days following the last dose of study drug.
[g] Chemistry – alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), blood urea nitrogen, calcium, chloride, creatinine, estimated glomerular filtration rate (eGFR), gamma-glutamyl transferase (GGT), globulin, glucose, magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, uric acid. Hematology – complete blood count with differential, red blood cell distribution width (RDW), reticulocyte count. Urinalysis – bilirubin, blood, glucose, ketones, leukocytes, pH, protein and specific gravity.

Table 3: Schedule of Assessments: Open-label Extension Period (OLEP) (Transition Period to End of Study)

[h] Results of the Screening 24-hour urine protein are for baseline only and are not required to determine eligibility. The Investigator may choose to have the patient collect the urine for Screening after eligibility has been confirmed and a date for first dose has been scheduled as long as the collection is complete prior to administration of study drug. Collection of the 24-hour urine after V1 may be within a +/- 30 day window from the study day. Collection of 24-hour urine samples should not be skipped. If the patient cannot complete a 24-hour urine collection within the assessment window (e.g., the patient is hospitalized), it should be completed as soon as possible. EOT 24-hour urine protein is required ONLY at 14 days following the last dose of study drug.

[i] 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. EOT echocardiogram is required ONLY at the 14 days following the last dose of study drug.

[j] If a patient has undergone an echocardiogram assessment within 3 months before the first OLEP visit, the echocardiogram should not be repeated. Subsequent assessments should follow the Schedule of Assessments.

[k] The 6MWT should only be performed AFTER obtaining samples for cTnT and NT-proBNP. The Investigator may choose to have the patient perform the 6MWT for Screening after eligibility has been confirmed and a date for first dose has been scheduled as long as the test is complete prior to administration of study drug. The 6MWT conducted after V1 may be within a +/- 30 day window from the study day. The 6MWT should not be skipped. If the test cannot be completed within the assessment window (e.g., the patient is hospitalized), it should be completed as soon as possible. The 6MWT may be repeated within the visit window if the test was invalid. EOT 6MWT is required ONLY at 14 days following the last dose of study drug.

[l] If a patient has undergone an a 6MWT assessment within 3 months before the first OLEP visit, the 6MWT should not be repeated. Subsequent assessments should follow the Schedule of Assessments.

[m] First dose of CAEL-101 must be administered within 24 hours of randomization. If a dosing event is delayed by ≤ 7 days, administer the study drug "out of window" and obtain associated laboratory assessments for that visit. Resume the patient's pre-determined dosing schedule. If a dosing event is delayed by > 7 day and ≤ 14 days, skip the visit and resume the patient's pre-determined dosing schedule with the next visit. If a dosing event is delayed by > 14 days, contact the Medical Monitor prior to resuming the dosing schedule.

[n] Additional PK sample times will be taken pre-dose, prior to the start of the infusion and post-dose within 30 minutes to 1 hour from the end of infusion. PK samples must be drawn from the opposite arm from the study drug infusion. EOT PK sample is required ONLY at 14 days following the last dose of study drug.

[o] Quality of life (QoL) questionnaires must be collected FIRST before all other assessments at visits where required. QoL questionnaires completion after V2 may be within a +/- 30 day window from the study day. QoL questionnaires completion should not be skipped. If the questionnaires cannot be completed within the assessment window (e.g., the patient is hospitalized), they should be completed as soon as possible. EOT QoL questionnaires are required ONLY at 14 days following the last dose of study drug.

[p] EOT NYHA Functional Classification assessment is required ONLY at the 14 days following the last dose of study drug

Abbreviations: 6MWT – six-minute walk test, BP – blood pressure, BSA – body surface area, cTnT – cardiac troponin T, EQ-5D-5L™ - European Quality of Life Health 5-Dimension 5-Level questionnaire, E – Extension Study, ECG – electrocardiogram, EOT – end of treatment, FLC – free light chains, HR – heart rate, KCCQ – Kansas City Cardiomyopathy Questionnaire, MRI – magnetic resonance imaging, NT-proBNP – N-terminal pro b-type natriuretic peptide, NYHA – New York Heart Association, PCD – plasma cell dyscrasia, PK – pharmacokinetic, SF-36v2® - Short Form 36 Health Survey version 2, V – visit, WOCBP – women of child bearing potential

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 systemically 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 patients 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 2015). The prognosis is very poor, with less than 5% of all patients with AL amyloidosis surviving more than 10 years after diagnosis (Kyle 1986; Palladini 2015; Palladini 2017). 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.

Current treatment regimens are largely derived from anti-myeloma therapies and autologous stem cell transplants. Both therapies seek to reduce abnormal bone marrow-resident plasma cells. Daratumumab, an anti-CD38 antibody which binds to plasma cells, is the only therapy approved by the United States Food and Drug Administration (FDA), under accelerated approval, for the treatment of AL amyloidosis. There are currently no approved treatments for AL amyloidosis that directly target the removal of deposited amyloid fibrils.

2.2. CAEL-101 and Dose Rationale

CAEL-101 is a chimeric immunoglobulin G1 kappa isotype 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 reacts 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 CAEL-101-101, a Phase 1 study, 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 (DLT) were observed in that dose range, including up to the maximum dose of 500 mg/m^2.

All patients in study CAEL-101-203 have completed treatment. The primary objective of Study CAEL-101-203 (Part A) 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) 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. No DLTs 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's 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. In addition to overall exposure levels, dose selection included assessment of target receptor site occupancy for the patient with the lowest exposure levels (Ctrough) (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 Ctrough levels after the second dose.

Therefore, based on safety, tolerability outcomes and PK, the 1000 mg/m^2 dose was selected for use in this study.

Part B of Study CAEL-101-203 studied 1000 mg/m^2 CAEL-101 in combination with CyBorD and daratumumab. This assessment is complete with the combination found to be safe and well tolerated. No DLTs or unexpected treatment emergent adverse events (TEAEs) were observed in any patients.

The maximum permitted dose of CAEL-101 is 2700 mg.

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

2.3. Benefit-Risk Analysis

Treatment options for patients with AL amyloidosis are limited and there are no approved therapies that have the potential to remove or reduce amyloid burden in the organs. CAEL-101 studies to date have provided evidence of the potential for CAEL-101 to have an organ response impact that is additive to hematologic response benefit from current plasma cell dyscrasia (PCD) treatments.

Patients enrolled in this trial have a very poor prognosis and, despite improvements in overall survival over the past 15 years, early mortality in this population represents an unmet medical need.

All patients enrolled in this study will receive standard of care (SoC) PCD treatment and will be randomized in a 2:1 ratio. For every three patients enrolled, two will receive CAEL-101 in addition to their PCD treatment and one will receive placebo in addition to their PCD treatment.

The benefit to risk assessment favors initial and continuing treatment for AL amyloidosis. If new evidence becomes available that would impact this risk assessment, it will be revised and communicated accordingly.

3. STUDY OBJECTIVES AND ESTIMANDS AND/OR ENDPOINTS

Table 4: Mapping Objectives to Endpoints/Estimands

Objective	Estimand and/or Endpoints
Primary Evaluation Treatment Period (PETP)	
Primary Efficacy Endpoints	
• To determine if CAEL-101 and treatment for plasma cell dyscrasia (PCD) improves overall survival and decreases the frequency of cardiovascular hospitalizations in Mayo stage IIIb AL amyloidosis patients who are treatment naïve compared to treatment for PCD and placebo	• A hierarchical combination of time to all-cause mortality (ACM) and the frequency of cardiovascular hospitalizations (CVH)
• To evaluate the safety and tolerability of CAEL-101 in combination with treatment for PCD and placebo	• Incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs). • Changes from baseline in vital signs, weight, clinical laboratory tests, and 12-lead electrocardiograms (ECGs)
Secondary Efficacy Endpoints	
• To determine if CAEL-101 and treatment for PCD improves survival post-initiation of study treatment in Mayo stage IIIb amyloid light chain (AL) amyloidosis patients who are treatment naïve compared to treatment for PCD and placebo	• Time to ACM in Primary Evaluation Treatment Period (PETP)
• To determine if CAEL-101 and treatment for PCD decreases cardiovascular-related hospitalizations (CVH) post-initiation of study treatment in Mayo stage IIIb amyloid light chain (AL) amyloidosis patients who are treatment naïve compared to treatment for PCD and placebo	• Frequency of CVH in PETP
• To assess quality of life (QoL) as measured by the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS)	• Change from baseline to Week 50 in KCCQ-OS
• To assess improvement in cardiomyopathy as measured by NT-proBNP	• Change from baseline to Week 50 in NT-proBNP
• To assess cardiac improvement as measured by global longitudinal strain (GLS%)	• Change from baseline to Week 50 in GLS%
• To assess functional improvement as measured by the distance walked in the six-minute walk test (6MWT)	• Change from baseline to Week 50 in 6MWT
• To assess quality of life as measured by the Short Form 36 Health Survey Physical Component Score (SF-36v2® PCS)	• Change from baseline to Week 50 in the SF-36v2 PCS

Table 4: Mapping Objectives to Endpoints/Estimands

Objective	Estimand and/or Endpoints
Exploratory Endpoints	
• To assess improvement in cardiac amyloidosis as measured by changes in N-terminal pro B-type natriuretic peptide (NT-proBNP), cardiac troponin T (cTnT), involved/uninvolved free light chain difference (dFLC), and C-reactive protein (CRP)	• Changes from baseline over time in NT-proBNP, cTnT, dFLC, and CRP
• To assess cardiac response, defined as a decrease of > 30% in NT- proBNP levels AND a decrease of NT-proBNP > 300 ng/L	• Proportion of patients with cardiac response from baseline over time until end of PETP (defined as a decrease of > 30% in NT-proBNP levels and a decrease of NT-proBNP > 300 ng/L)
• To assess composite cardiac response when both of the following are satisfied: o A decrease of > 30% in NT-proBNP levels AND a decrease of NT-proBNP > 300 ng/L; o GLS improvement of ≥ 2%	• Proportion of patients from baseline over time during the PETP composite cardiac response when both of the following are satisfied: o A decrease of > 30% in NT-proBNP levels and a decrease of NT-proBNP > 300 ng/L o GLS% improvement of ≥ 2%
• To assess CCI CCI	CCI
• To assess graded cardiac response	• Proportion of patients with graded cardiac response, determined using the following definitions: o Cardiac complete response (CarCR) defined as NT-proBNP ≤ 350 pg/ml (≤ 41.39 pmol/L) from baseline o Cardiac very good partial response (CarVGPR) defined as a > 60% reduction in NT-proBNP from baseline level not meeting CarCR o Cardiac partial response (CarPR) defined as a 31–60% reduction in NT-proBNP from baseline level not meeting CarCR

Table 4: Mapping Objectives to Endpoints/Estimands

Objective	Estimand and/or Endpoints
	○ Cardiac no response (CarNR) defined as ≤ 30% reduction in NT-proBNP from baseline level (Muchtar 2023) • Time to cardiac response and time to graded cardiac response.
• To assess renal response, defined as 30% decrease in proteinuria or drop of proteinuria below 0.5 g/24 h in the absence of ≥ 25% decrease in eGFR (Palladini 2014). Renal response will be assessed in patients with renal involvement, defined as those with a baseline urinary protein excretion of more than 0.5 g per day	• Proportion of patients with renal response from baseline over time in the PETP (defined as a 30% decrease in proteinuria or drop of proteinuria below 0.5 g/24 h [in the absence of ≥ 25% decrease in eGFR]). • Time to renal progression
• To assess graded renal response in patients with renal involvement at baseline	• Proportion of patients with graded renal response from baseline (in the absence of renal progression [renal progression defined as greater than/equal to 25% decrease in eGFR]) defined as: • Renal complete response (renCR, 24-h proteinuria ≤ 200 mg/24-h) • Renal very good partial response (renVGPR, > 60% reduction in baseline 24-h proteinuria) • Renal partial response (renPR, 31-60% reduction in baseline 24-h proteinuria) • Renal no response (renNR, 30% or less reduction in baseline 24-h proteinuria) (Muchtar 2021). • Time to renal response
• To assess hepatic response in patients with hepatic involvement (defined as ALP ≥ 1.5 upper limit of normal [ULN]).	• Proportion of patients with hepatic response from baseline over time (Muchtar 2018), defined as a decrease of ≥ 50% and or normalization of the serum ALP level (Comenzo 2012) • Time to hepatic response • Time to graded hepatic response defined as: ○ Hepatic complete response (AP ≤ × 2 lower limit of normal ○ Hepatic very good partial response (> 60% reduction from baseline AP level to a nadir above ×2 lower limit of normal) ○ Hepatic partial response (31–60% reduction from baseline AP)

Table 4: Mapping Objectives to Endpoints/Estimands

Objective	Estimand and/or Endpoints
	○ Hepatic no response (≤ 30% reduction from baseline AP) • Proportion of patients with hepatic progression defined as a decrease of ≥ 50% and/or normalization of the serum ALP level. • Proportion of patients with hepatic complete response, hepatic very good partial response, hepatic partial response, and hepatic non-response from baseline over time (Muchtar 2018)
• To assess changes in effects on liver function including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT)	• Changes from baseline over time in liver function including AST, ALT, ALP, and GGT
• To assess changes in effects on renal function including eGFR, serum creatinine and 24-hour urine protein	• Changes from baseline over time in renal function including eGFR, serum creatinine, and 24-hour urine protein
• To assess QoL as measured by the KCCQ domain scores, SF-36v2® scaled domain scores and European Quality of Life Health 5-Dimension 5-Level questionnaire (EQ-5D-5L™)	• Changes from baseline over time in QoL as measured by the KCCQ domain scores and clinical summary scores, SF-36v2 scaled domain scores and mental component summary (MCS) and EQ-5D-5L Index score and Visual Analog Score (VAS)
• To assess change in New York Heart Association (NYHA) Functional Classification	• Change from baseline in NYHA Functional Classification over time
• To describe the PK profile based on serum levels of CAEL-101	• Descriptive statistics of serum CAEL-101 concentrations include number of patients with nonmissing values, mean, standard deviation, minimum, lower quartile, median, upper quartile, interquartile range (IQR), and maximum at each visit and nominal timepoint
• To assess the immunogenicity of CAEL-101	• Anti-drug antibodies (ADAs) incidence, response categories and titers, as well as neutralizing antibodies (NAb) incidence and titers in patients with AL amyloidosis

Table 4: Mapping Objectives to Endpoints/Estimands

Objective	Estimand and/or Endpoints
Open-label Extension Period (OLEP)	
Exploratory (continued)	
• To compare the long-term overall survival in patients with AL amyloidosis enrolled in the Open-label Extension Period (OLEP), who were previously treated with CAEL-101 or placebo during the PETP	• Time to ACM from randomization to the date of death or to the end of the study in patients with AL amyloidosis enrolled in the OLEP, who were previously treated with CAEL-101 or placebo during the PETP
• To compare the long-term overall survival in patients with AL amyloidosis enrolled in the OLEP, who were previously treated with CAEL-101 or placebo, during the PETP, and who received CAEL-101 or placebo for a minimum of 3 months	• Time to ACM from randomization to the date of death or to the end of the study in patients with AL amyloidosis enrolled in the OLEP, who were previously treated with CAEL-101 or placebo, during the PETP, and who received CAEL-101 or placebo for a minimum of 3 months
• To compare the long-term overall survival in patients with AL amyloidosis enrolled in the OLEP, who were previously treated with CAEL-101 or placebo, during the PETP, and who received CAEL-101 or placebo for a minimum of 6 months	• Time to ACM from randomization to the date of death or to the end of the study in patients with AL amyloidosis enrolled in the OLEP, who were previously treated with CAEL-101 or placebo, during the PETP, and who received CAEL-101 or placebo for a minimum of 6 months
• To assess the long-term efficacy of CAEL-101 in patients with AL amyloidosis who were previously treated with CAEL-101 during the PETP	• Changes from baseline over time in 6MWT, NT-proBNP, KCCQ-QoL, SF-36v2PCS • Assessment of extra-cardiac organ response
• To assess the long-term safety of CAEL-101 in patients with AL amyloidosis	• Incidence of TEAEs and SAEs • Changes from baseline in vital signs, clinical laboratory tests, and 12-lead ECGs
• To assess immunogenicity to CAEL-101 in patients with AL amyloidosis	• Anti-drug antibodies (ADA) incidence, response categories and titers, as well as neutralizing antibodies (NAb) incidence and titers in patients with AL amyloidosis enrolled in the OLEP, who were previously treated with CAEL-101 or placebo for a minimum of 6 months, during the PETP

Table 4: Mapping Objectives to Endpoints/Estimands

Objective	Estimand and/or Endpoints
• To describe the pharmacokinetics (PK) of CAEL-101 in patients with AL amyloidosis	• Descriptive statistics of serum CAEL-101 concentrations include number of patients with non- missing values, mean, standard deviation, minimum, lower quartile, median, upper quartile, interquartile range (IQR), and maximum at each visit and nominal timepoint

4. STUDY DESIGN

A schematic of the study design is presented in Figure 1 while the Schedule of Assessments is presented in Table 1 and Table 2.

This is a double-blind, randomized, multicenter, international Phase 3 study of CAEL-101 combined with SoC PCD treatment versus placebo combined with SoC PCD treatment in Mayo stage IIIb PCD treatment-naïve AL amyloidosis patients. The Primary Evaluation Treatment Period (PETP) part of the study will stop when the last patient is randomized in the PETP plus 18 months (Section 10.3).

Following Screening and randomization, patients will receive blinded treatment of CAEL-101 (1000 mg/m^2) + PCD Treatment or placebo + PCD Treatment during the PETP.

All patients will have the option to continue into the Open-label Extension Period (OLEP) which consists of a Transition (Loading Dose) Period and an Open-label Extension Treatment Period (OLETP). During the OLETP, all patients will receive CAEL-101 in addition to any SoC prescribed by the physician. Final study assessments will be performed post-treatment in End of Treatment (EOT) and Follow-up visits.

Approximately 124 patients will be enrolled using a 2:1 randomization ratio and stratification will be based on geographic region across investigator sites.

Patients may be eligible to receive study intervention until the study intervention is registered (in accordance with country-specific regulations) or for up to 2 years, or the study intervention may be provided via an Alexion early access program or post-trial access program (as allowed by local laws and regulations), whichever occurs first.

4.1. Primary Evaluation Period

The Primary Evaluation Period consists of a Screening Period, randomization, and a Treatment Period (Table 1).

After obtaining informed consent, the patient will be screened for study eligibility through a review of demographic data, medical history, physical examination, and laboratory tests.

Randomization will be carried out using a centralized interactive response technology (IRT) application.

During the PETP (i.e., double-blind treatment period up to last patient randomized in the study plus 18 months (LPI+18M), CAEL-101 (1000 mg/m^2) + PCD Treatment OR placebo + PCD Treatment will be administered through IV infusion per the Schedule of Assessments (Table 1). Regardless of how long a patient has participated in the PETP, the study will end on the date of when the last patient is randomized in the study plus 18 months (Section 10.7.1).

Patients in both study intervention groups will be followed from randomization until death from any cause, heart transplant, left ventricular assist device (LVAD) implantation or until the study-level end of study (EOS).

Patients who stop treatment during the PETP, without entering OLEP, are to complete Post-Treatment assessments (EOT and Follow-up assessments) (Table 2) and will be followed until

death from any cause, heart transplant, LVAD implantation or until the study-level EOS (Section 6.5 and Section 6.6).

4.2. Open-label Extension Period

Patients who complete the PETP will have the opportunity to continue participation in the study in the OLEP (Table 2).

4.2.1. Transition (Loading Dose) Period

The OLEP begins with the Transition (Loading Dose) Period during which patients will transition to open-label treatment with CAEL-101 over the course of 5 weekly visits (Extension Study Visits 1 to 5). Treatment allocation in the previous PETP will remain blinded to avoid unintended unblinding of the study before database lock for the PETP analysis (Figure 1, footnote a).

4.2.2. Open-label Extension Treatment Period

Following completion of the Extension Study Visit 5 (Extension Study Day 29) assessments, patients will enter the OLETP, a 24-month evaluation of the long-term safety and efficacy of CAEL-101.

Upon completion of the OLETP (Extension Visit 55; Extension Study Day 729), Post-Treatment assessments are to be performed according to the Schedule of Assessments (Table 2).

5. SELECTION OF STUDY POPULATION

5.1. Patient Inclusion Criteria

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

1. Be able to and provide written informed consent and be willing and able to comply with all study procedures
2. Adult, 18 years and older
3. AL amyloidosis stage IIIb based on the European Modification of the 2004 Standard Mayo Clinic Staging (see Table 5) (Wechalekar 2013; Palladini 2016; Dispenzieri 2004) at the time of Screening, which includes NT-proBNP > 8,500 ng/L.
4. Measurable hematologic disease at Screening as defined by at least one of the following:
   a. Involved/uninvolved free light chain difference (dFLC) > 4 mg/dL OR
   b. Involved free light chain (iFLC) > 4 mg/dL with abnormal Kappa/Lambda ratio OR
   c. Serum protein electrophoresis (SPEP) m-spike > 0.5 g/dL
5. Histopathological diagnosis of amyloidosis based on polarizing light microscopy of green bi-refringent material in Congo red stained tissue specimens AND confirmation of AL derived amyloid deposits by at least one of the following:
   d. Immunohistochemistry/Immunofluorescence OR
   e. Mass spectrometry OR
   f. Characteristic electron microscopy appearance/Immunoelectron microscopy
6. Cardiac involvement as defined by:
   a. Documented clinical signs and symptoms supportive of a diagnosis of heart failure in the setting of a confirmed diagnosis of AL amyloidosis in the absence of an alternative explanation for heart failure

   AND

   a. At least one of the following:
      i. Endomyocardial biopsy demonstrating AL cardiac amyloidosis OR
      ii. Echocardiogram demonstrating a mean left ventricular wall thickness (calculated as [IVSd+LPWd]/2) of > 12 mm at diastole in the absence of other causes (e.g., severe hypertension, aortic stenosis), which would adequately explain the degree of wall thickening OR
      iii. Cardiac magnetic resonance imaging (MRI) with gadolinium contrast agent diagnostic of cardiac amyloidosis
7. Planned first-line treatment for PCD is a CyBorD-based regimen administered as SoC (Section 6.1.2.4).
8. Adequate bone marrow reserve and hepatic function as demonstrated by:
   a. Absolute neutrophil count $\geq 1.0 \times 10^9$/L
   b. Platelet count $\geq 75 \times 10^9$/L

c. Hemoglobin ≥ 9 g/dL
d. Total bilirubin ≤ 2 times the upper limit of normal (x ULN) unless due to Gilbert's syndrome.
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 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 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. Have any other form of amyloidosis other than AL amyloidosis
2. Received prior therapy for AL amyloidosis or multiple myeloma. A maximum exposure of 2 weeks of a CyBorD-based PCD treatment after Screening laboratory samples are obtained and prior to randomization is allowed.
3. Has POEMS syndrome OR multiple myeloma defined as clonal bone marrow plasma cells > 10% from a bone marrow biopsy (performed ≤ 3 months prior to signing the ICF or during Screening) OR biopsy-proven (performed ≤ 3 months prior to signing the ICF or during Screening) bony or extramedullary plasmacytoma AND any one or more of the following CRAB features:
   a. Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder (e.g., multiple myeloma and POEMS syndrome), specifically:
      i. Hypercalcemia: serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than the ULN or > 2.75 mmol/L (> 11 mg/dL) OR
      ii. Renal insufficiency: creatinine clearance < 40 mL per minute or serum creatinine > 177 µmol/L (> 2 mg/dL) OR
      iii. Anemia: hemoglobin value of > 20 g/L below the lowest limit of normal, or a hemoglobin value < 100 g/L OR
      iv. Bone lesions: one or more osteolytic lesion on imaging tests (performed ≤ 3 months prior to signing the ICF or during Screening): skeletal radiography, CT, or PET/CT, or MRI. If bone marrow has < 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement OR
   b. Any one of the following biomarkers of malignancy:

v. 60% or greater clonal plasma cells on bone marrow examination OR

vi. More than one focal lesion on MRI that is at least 5mm or greater in size

4. Have supine systolic blood pressure (BP) < 90 mmHg or symptomatic orthostatic hypotension, defined as a decrease in systolic BP upon standing of > 30 mmHg despite medical management (e.g., midodrine, fludrocortisones) in the absence of volume depletion
5. Taking prednisone or its equivalent > 10 mg/day
6. Taking doxycycline
7. Receiving dialysis
8. Planned stem cell transplant during the first 6 months of protocol therapy. Stem cell collection during the protocol therapy is permitted.
9. Have had acute coronary syndrome, uncontrolled ventricular arrhythmias within 3 months prior to Screening or percutaneous cardiac intervention with recent stent or coronary artery bypass grafting within 2 months prior to Screening. Exacerbation of chronic condition or new acute condition will require discussion and approval by the Medical Monitor.
10. Left ventricular ejection fraction (LVEF) is < 35% by echocardiogram at Screening per site cardiology interpretation
11. Have severe valvular stenosis (e.g., aortic or mitral stenosis with a valve area < 1.0 cm^2) or severe congenital heart disease
12. Have history of sustained ventricular tachycardia or aborted ventricular fibrillation or a history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker/implantable cardioverter-defibrillator (ICD) is indicated but not placed. (Patients who do have a pacemaker or ICD are allowed in the study.)
13. QT corrected by Fridericia (QTcF) is > 500 msec on Screening electrocardiogram (ECG). Patients with a QTcF of > 500 msec who have a QRS of > 120 msec and confirmed right bundle branch block, left bundle branch block or intraventricular conduction defect may be considered for enrollment in consultation with the Medical Monitor. Patients who have a pacemaker may be included regardless of calculated QTc interval.
14. There is evidence of acute ischemia or active conduction system abnormalities with the exception of any of the following:
    a. First degree atrioventricular block
    b. Second degree atrioventricular block Type 1 (Mobitz Type 1/Wenckebach type)
    c. Right or left bundle branch block (e.g., Left Bundle Branch Block, Right Bundle Branch Block, Left Anterior Fascicular Block, or Left Posterior Fascicular Block)
    d. Atrial fibrillation with a controlled ventricular rate. (An uncontrolled ventricular rate [i.e., > 110 beats per minute] determined by an average of three beats in lead II or representative beats in lead II is not allowed)
    e. Bifascicular block assessed as clinically benign by the Investigator

15. Have had major surgery within 4 weeks of randomization or is planning major surgery during the study. Patients with surgical procedures conducted under local anesthesia may participate
16. There is 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
    d. Other localized and/or low risk malignancies may be permitted with Medical Monitor approval.
17. Have received an investigational drug/device in another clinical investigational study within 60 days before Screening
18. Hypersensitivity to the study drug
19. Have received a live vaccine within 4 weeks prior to first dose of CyBorD
20. Women who are breast feeding
21. Have any other medical, social or psychological factors that could affect the patient's safety or ability to consent personally or comply with study procedures.

5.3. Continuation and Withdrawal Criteria

Patients with progressive disease but with otherwise stable or improved performance and clinical status may continue study treatment if the Investigator determines there is a benefit for treatment beyond progression.

Study drug therapy may be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason
- A medical condition or circumstance occurs that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol
- A serious adverse event (SAE), clinically significant adverse event (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 fails to comply with protocol requirements or study-related procedures
- Termination of the study by the Sponsor or the regulatory authority

- The patient undergoes cardiac transplant or LVAD implantation

Patients will be followed for survival (Section 8.1) status until death, cardiac transplant, or LVAD implantation, or study-level EOS (Section 6.5). If the patient discontinues study drug therapy or withdraws prematurely from the study, the Investigator must promptly notify the Sponsor and ensure every effort is made to complete the full panel of Post-Treatment assessments (EOT + Follow-up assessments) specified in the Schedule of Assessments (Table 2) and perform survival follow-up as specified in Section 6.5.

6. TREATMENT PLAN

The study is divided into a Primary Evaluation Period and the OLEP.

Every effort should be made to schedule assessments within the protocol-specified windows. Refer to the Schedule of Assessments for the list and timing of assessments (Table 1 and Table 2).

6.1. Primary Evaluation Period (PEP)

6.1.1. Screening Period

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 standard of care. Patients will be eligible to enter the Screening period if they have a clinical diagnosis of stage IIIb cardiac AL amyloidosis consistent with the European Modification of the 2004 Standard Mayo Clinic Staging in patients with advanced cardiac involvement (Wechalekar 2013; Dispenzieri 2004) as published by Palladini 2016, described in Table 5, based on laboratory results obtained within 28 days of randomization.

Screening laboratory sample collection needs to be performed before the initiation of PCD treatment.

Table 5: 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: AL - amyloid light chain, cTnI – cardiac troponin I, cTnT – cardiac troponin T, hs-cTnT – high sensitivity cardiac troponin T, NT-proBNP – N-terminal pro b-type natriuretic peptide

The 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).

After signing the ICF, patients will be evaluated for entry criteria during the Screening period (within 28 days before administration of the study drug). Screening assessments with abnormal results or issues with results due to COVID-19, medication, etc may be repeated once at the discretion of the Investigator. Patients may be rescreened at the discretion of the Investigator and in consultation with the Medical Monitor.

6.1.2. Primary Evaluation Treatment Period (PETP)

Patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized as described in Section 6.13 to either treatment with CAEL-101 or placebo (referred to collectively as "study drug").

Patients will be treated until death, unacceptable toxicity, symptomatic deterioration, Investigator decision, patient decision or Sponsor decision to terminate the study, or the date of last patient randomized plus 18 months for the primary endpoint analysis (Section 10.7.1).

Patients will be seen in the clinic every 7 (+/- 1) days for 4 weeks then approximately every 14 (+/- 2) days to receive study drug infusions. Approximately every 28 (+/- 2) days, patients

will be assessed for changes in NT-proBNP, cTnT, FLC, PK, and safety measurements including immunogenicity assessments at Study Day 1, and at Weeks 1, 10, 26, and 50. Approximately every 26 weeks (starting at Week 50), patients will be assessed for changes in 6MWT and QoL questionnaires.

6.1.2.1. Administration of Study Drug

Patients randomized to receive CAEL-101 will receive 1000 mg/m^2. The total dose will be based on the patient's BSA in meters squared which is calculated using the height and weight obtained during the Screening period. See the Pharmacy Manual for instructions on calculation of BSA. It is not necessary to recalculate the BSA for subsequent dosing unless the patient experiences weight change of ≥ 20%. Patients randomized to receive placebo will receive 0.9% normal saline in an equivalent volume to a CAEL-101 infusion (approximately 250 cc). When administered on the same day, the study drug will be administered first before PCD therapy. (Patient may take dexamethasone prior to receiving study drug.) Patients will receive study drug by an IV infusion over approximately 2 hours. Patients will be observed for infusion reactions, injection site reactions and overall well-being in the clinic for approximately 90 minutes, or as long as the Investigator deems appropriate, following the completion of the study drug infusion for the first 4 infusions. (Observations may include vital signs at the Investigator's discretion (Section 6.1.2.2). 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) (Section 6.1.2.3).

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

6.1.2.2. Guidelines for Management of Infusion Reactions

Patients may take diphenhydramine or other similar antihistamine and/or acetaminophen/paracetamol prior to administration of study drug as prophylaxis for infusion reactions or injection site reactions according to investigational site standards of care set for monoclonal antibodies.

If an infusion reaction is observed, the following guidelines for treatment of the patient and dose modifications or delays are provided and may be modified based on investigational site guidelines.

Grade 1 infusion reaction:

A Grade 1 infusion reaction is characterized by mild reaction symptoms where neither intervention nor interruption of the study drug infusion are indicated. For Grade 1 infusion reactions:

- Remain at the bedside and monitor the patient until they recover from symptoms (or return to baseline).
- Premedicate the patient at least 30 minutes prior to subsequent study drug infusions. Recommended medications (The Investigator may choose to follow investigational site standards for premedication):
    - diphenhydramine 50 mg (or equivalent) AND
    - acetaminophen/paracetamol 325 mg to 1000 mg

Grade 2 infusion reaction:

A Grade 2 infusion reaction is characterized by moderate reaction symptoms which require therapy or interruption of the study drug infusion BUT responds promptly to treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs (NSAID), narcotics, corticosteroids, bronchodilators, IV fluids). Prophylactic medications are indicated for ≤ 24 hours. For Grade 2 infusion reactions:

- Stop the study drug infusion and begin an IV infusion of 0.9% sodium chloride.
- Administer diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg.
- Remain at the bedside and monitor the patient until they recover from symptoms (or return to baseline).
- Administer corticosteroid and/or bronchodilator therapy as appropriate.
- When symptoms resolve, restart the study drug infusion at 50% of the original infusion rate. If the patient has no further complications after 30 minutes, the infusion rate may be increase to the original infusion rate.
- Premedicate the patient at least 30 minutes prior to subsequent study drug infusions. Recommended medications (The Investigator may choose to follow investigational site standards for premedication):
    - diphenhydramine 50 mg (or equivalent) AND

- acetaminophen/paracetamol 325 mg to 1000 mg
- corticosteroids (up to 25 mg hydrocortisone or equivalent) may also be given

Grade 3 or Grade 4 infusion reaction:

A Grade 3 or 4 infusion reaction is a severe reaction. A Grade 3 reaction is characterized as prolonged (i.e., not rapidly responsive to treatment and/or brief interruption of the study drug infusion) with recurrence of symptoms following initial improvement. Hospitalization may be indicated for other clinical sequalae (e.g., renal impairment, pulmonary infiltrates). A Grade 4 reaction is life-threatening requiring pressor or ventilatory support. For Grade 3 or 4 infusion reactions:

- Immediately discontinue the study drug infusion and begin an IV infusion of 0.9% sodium chloride.
- Administer bronchodilators, epinephrine subcutaneously or IV and/or diphenhydramine with steroids, as needed.
- Remain at the bedside and monitor the patient until the patient's symptoms have resolved (or returned to baseline) and, in the Investigators judgement, the symptoms will not recur.
- Follow institutional guidelines for treatment of anaphylaxis.
- For Grade 3 infusion reactions, premedicate the patient at least 30 minutes prior to subsequent study drug infusions. Recommended medications (the Investigator may choose to follow investigational site standards for premedication):
  - diphenhydramine 50 mg (or equivalent) AND
  - acetaminophen/paracetamol 325 mg to 1000 mg
  - corticosteroids (up to 25 mg hydrocortisone or equivalent) may also be given
- Study drug should be permanently discontinued after the occurrence of a Grade 4 infusion reaction.

All Grade 3 and Grade 4 infusion reactions that meet the definition of an SAE (Section 9.3) will be reported within 24 hours (Section 9.4).

6.1.2.3. Study Drug Dose Delay or Modification

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 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 g), pregnancy screen (if applicable), and SAE- and AE-specific follow up (if applicable and there are any safety concerns due to residual disease).

Recommended guidelines for missed doses:

- If 1 loading dose or 1 to 2 consecutive maintenance doses are missed, return to regular maintenance dosing
- If ≥ 2 consecutive loading doses or 3 to 4 consecutive maintenance doses are missed, 2 of weekly loading doses are recommended prior to returning to maintenance doses
- If ≥ 5 consecutive maintenance doses are missed, 4 of weekly loading doses are recommended prior to returning to maintenance doses.

6.1.2.4. Concurrent Plasma Cell Dyscrasia Treatment

CAEL-101 or placebo is administered to patients on concurrent treatment for PCD according to institutional SoC.

Patients must have a planned first-line PCD treatment with a CyBorD regimen according to institutional SoC, including dose modifications of each of the individual components as clinically appropriate as per institutional SoC. Institutional SoC may include daratumumab if aligned with local guidelines for AL amyloidosis treatment. The patient's PCD treatment may be initiated during the Screening period and after Screening laboratory samples are obtained. The patient may receive a maximum of 2 weeks of PCD treatment prior to randomization. For patients who receive the first dose of study drug prior to starting their PCD treatment, their PCD treatment must be initiated no later than 7 days after receiving the first dose of study drug.

Refer to the package insert or Summary of Product Characteristics (SmPC) for contraindications, warnings and precautions for anti-PCD medications. For contraceptive requirements, see Section 6.10.

6.1.3. End of Treatment Visit during the Primary Evaluation Treatment Period (PETP)

The end of the PETP visit will be scheduled for the Primary Evaluation Period on the date of the last patient randomized in the study plus 18 months.

Patients who discontinue study treatment during the PETP will be followed for survival status until death, heart transplant, LVAD implantation, or study-level EOS.

The date of end of PETP and reason for end of PETP will be documented in the case report form (CRF).

6.2. Open-label Extension Period (OLEP)

6.2.1. Transition (Loading Dose) Period

Following completion of the study assessments in the Primary Evaluation Period, all patients who continue to the OLEP will be transitioned to open-label treatment during a blinded 5-week Transition (Loading Dose) Period, regardless of treatment during PETP (Figure 1, footnote a).

6.2.2. Open-label Extension Treatment Period (OLETP)

Following completion of the Transition (Loading Dose) Period, patients will receive open-label treatment with CAEL-101 (1000 mg/m^2) from Extension Study Day 43 through Extension Study Day 729.

6.3. End of Treatment Visit (PETP and OLEP)

Patients may choose to discontinue the PETP or the OLEP at any time, for any reason, and without prejudice to further treatment (Section 5.3). Patients who permanently discontinue study drug treatment should complete the End of Treatment (EOT) visits according to the Schedule of Assessments (Table 2).

6.4. End of Open-label Extension Period (OLEP)

End of OLEP visit is defined as the last patient's last visit for patients who participate in the OLEP.

Patients who discontinue the treatment or OLEP for reasons other than death will be followed for survival status until death, heart transplant, LVAD implantation, or study-level EOS. The date of end of OLEP and reason for end of OLEP will be documented in the CRF.

6.5. Survival Follow-up Period (PETP and OLEP)

Patients who discontinue study treatment for reasons other than death will be followed for survival status until death, heart transplant, or LVAD implantation. Follow-up visits may be

conducted via phone, clinic visit, or patient chart review approximately every 4 weeks (+/- 7 days) following the EOT visits or as directed by the Sponsor. If allowed by country regulatory authorities and/or consented to by the patient, study personnel may use public records to check for death for any patient considered lost to follow-up and for patients who withdraw consent for follow-up contact. Data will be collected on subsequent therapies including heart transplant and LVAD implantation in both treatment groups from the time patients discontinue the study treatment. Data will include any systemic chemotherapy or PCD treatment, heart transplant and autologous stem cell transplantation. Cause of death will be collected.

For any toxicity attributed by the Investigator to study drug, the Investigator will assess the patient to determine whether the toxicity is continuing, has resolved, or has worsened.

Follow-up contacts will continue until death, heart transplant, LVAD implantation, withdrawal from the study by the patient, the patient is lost to follow up, or study termination by the Sponsor.

6.6. End of Study

EOS is defined as the date of the last patient's last visit.

6.7. Prior and Concomitant Medications

All medications (prescription and over the counter), vitamin and/or mineral supplements, and/or herbs the patient is taking at Screening or was taking within the 30 days prior to signing the ICF and through the EOT visits will be recorded. Start and stop date, dose and route of administration, dosing frequency and indication will be documented.

6.8. 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 (oral prednisone ≤ 20 mg daily, or equivalent) for treatment of immune-related medical conditions or for prophylaxis of contrast dye allergy is permitted. Use of other doses and durations of corticosteroids are permitted if agreed with the Medical Monitor.

Patients may take diphenhydramine or other similar antihistamine and/or acetaminophen/paracetamol prior to administration of study drug as prophylaxis for infusion reactions or injection site reactions.

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

6.9. Prohibited Medications

- Immunosuppressive agents that are not part of the patient's PCD treatment
- Immunosuppressive doses of systemic corticosteroids (defined as > 20 mg prednisone or equivalent daily for 3 weeks or longer) except those included as part of the patient's PCD treatment and/or as noted in Section 6.8 .
- Non-dihydropyridine calcium channel blockers

- Doxycycline
- Live vaccine within 4 weeks before and while on PCD therapies

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

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 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 1001.

6.12. Blinding

Every effort will be made to maintain the integrity of the blind. The Investigator will have unfettered, primary access to the patient's treatment assignment via the interactive response technology (IRT) system and may break the blind, if needed, to manage serious side effects, AEs or other safety reasons. Instructions to unblind are found in the IRT Site User Guide. The Medical Monitor should be contacted as soon as possible when the blind is broken. If the Investigator becomes unblinded (either intentionally or unintentionally), the patient may need to be withdrawn from the study. Details surrounding the breaking of the blind (e.g., date, time and reason) will be recorded in the patient's study files.

6.13. Method of Randomization

Patients will be randomized in a 2:1 ratio to 1 of the 2 study arms (2 patients to CAEL-101 to every 1 patient to placebo) after confirmation that the patient meets the eligibility criteria. A computer-generated randomization scheme (stratified by geographic region) will be produced by the Sponsor or its designee. Treatment arm will be assigned to patients via the randomization and trial supply management (RTSM) system. The randomization block sizes will not be known to the Investigator.

6.14. Independent Data Monitoring Committee (IDMC)

An IDMC will be established to monitor patient safety data in collaboration with the Independent Data Analysis Center (IDAC). The IDMC Charter includes details regarding meeting frequency, format and membership. The IDMC will meet regularly based on enrollment targets.

The IDMC meetings will include open and closed sessions. Unblinded data will be provided for review in the closed sessions. The IDMC will not review efficacy data, however, overall survival data may be reviewed as part of the safety reviews.

The IDMC may recommend modifications to the protocol or suspension or termination of the study to ensure the safety of the patients. The IDMC will provide the Sponsor a summary of their findings and recommendations for protocol changes following each meeting. Any recommended modifications to the study protocol will be reviewed by the Sponsor. The Sponsor will make the ultimate decision for implementation of any suggested changes.

6.15. Clinical Events Adjudication Committee

A Clinical Events Adjudication Committee (CEAC) comprised of expert cardiologists with no direct relationship to the study, will be appointed by the Sponsor. The CEAC will conduct an independent review and adjudication of hospitalizations during the primary evaluation treatment period to determine whether the primary reason for hospital admission was cardiovascular-related. Hospital admissions which are deemed CV-related will be categorized by the committee as myocardial infarction, heart failure, unstable angina, arrhythmia, stroke or other cardiovascular cause. Committee members will be blinded to the randomized treatment assignment. The adjudication process will be pre-specified in a CEAC charter.

7. INVESTIGATIONAL PRODUCT

CAEL-101 will be supplied to the Investigator by the Sponsor or its designee in an unblinded manner. Refer to the Pharmacy Manual for instructions on masking the study drug prior to administration.

This study has identified CyBorD as auxiliary medicinal products (AxMP). Further details are provided in Section 19.3 .

7.1. Study Interventions Administered

Intervention Label	CAEL-101	Placebo
IMP or AxMP	IMP	IMP
Intervention Name	CAEL-101	Placebo
Intervention Description	CAEL-101 is supplied as a liquid solution of protein plus excipients in a stoppered glass vial (Excipients: 30 mg/mL in 25mM Acetate buffer, 50 mM NaCl, 1% w/v Mannitol, and 0.01% w/v PS80, at pH 5.5)	Commercially available 0.9% Normal Saline
Type	Biologic	Solution
Dose Formulation	Solution	Solution
Unit Dose Strength(s)	Each 10 mL vial contains 300 mg of CAEL-101 at a concentration of 30 mg/mL	250 mL IV of 0.9% Normal Saline
Dosage Level(s)	1000 mg/m^2 weekly (q1w) × 4 → 1000 mg/m^2 biweekly (q2w) (see Section 6 for more details)	Same volume and frequency as CAEL-101
Route of Administration	IV infusion	IV infusion
Use	Experimental	Placebo
Sourcing	Provided centrally by Alexion	Provided by the study site
Packaging and Labeling	Blinded/masked	Blinded/masked

Abbreviations: AxMP – auxiliary medicinal product; IMP – investigational medicinal product; IV – intravenous

7.1.1. CAEL-101

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 CAEL-101 at a concentration of 30 mg/mL CAEL-101 will be diluted with commercially available 0.9% Normal Saline.

7.1.2. Placebo

Sites will use commercially available 0.9% Normal Saline as the placebo.

7.2. CAEL-101 Packaging and Labeling

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

7.3. CAEL-101 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. CAEL-101 Preparation

The instructions for dilution, storage, 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 use.

Only patients enrolled in the study may receive CAEL-101 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.

- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator (institution, the head of the medical institution [where applicable], or authorized site staff) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
    - This responsibility includes the reporting of any temperature excursions and product complaints per Pharmacy Manual instructions. A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product or clinical study material and/or its packaging components after it has been released for distribution to an end customer that affects the performance of such product.

- The pharmacist or other designated individual will maintain records of study intervention and other Alexion-supplied medications delivered to the study site, the inventory at the study site, the distribution to and use by each patient, and the return of materials to the Sponsor for storage or disposal/destruction of materials at the study site. These records should include dates, quantities, batch/serial numbers, expiration dates, in-clinic temperature log, and unique code numbers assigned to the study intervention and study patients.
- The Investigator will maintain records that adequately document that the patients were administered the correct study treatment kits and reconcile the products received from the drug dispensing center. Investigational product will not be returned to the Sponsor or disposed of until accountability has been fully monitored.

- Further guidance regarding preparation, handling, storage, and accountability and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

7.6. CAEL-101 Handling and Disposal

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

7.7. Treatment of Overdose

For this study, any dose of investigational medicinal product (IMP) or Alexion AxMP (CAEL-101 greater than 2700 mg within a 24-hour time period) will be considered an overdose.

In the event of an overdose or suspected overdose, the Investigator should:

- Capture and forward the event, with or without associated AEs, to Alexion Global Patient Safety (GPS) via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Overdose Report Form within 24 hours of awareness.
- Contact the Medical Monitor immediately.
- Evaluate the patient to determine, in consultation with the Medical Monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.

- Obtain a plasma sample for PK analysis within (2) days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration (start and stop dates) of the overdose.

8. ASSESSMENT OF EFFICACY

8.1. Overall Survival

Survival status will be assessed throughout the duration of the study. In the event of patient death, the complete date of death including day, month and year and the cause of death should be obtained.

The Investigator should obtain survival status on all patients who discontinue study treatment, unless the patient withdraws consent to use data, approximately every 4 weeks until the death, heart transplant, or left ventricle implantation of the patient. In the event a patient is lost to follow-up, at least three attempts to contact the patient must be made and documented in the patient's medical record. Attempts to contact the patient should include, at minimum, a letter sent by registered mail. If the patient does not respond to the third attempt within 30 days, the patient may be considered lost to follow-up. In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status.

8.2. Cardiovascular Related Hospitalizations

Cardiovascular-related hospitalization is an efficacy endpoint for this study.

Cardiovascular hospitalization (CVH) events including subcategories, will be reviewed and adjudicated by the CEAC according to definitions and processes specified in the CEAC charter (Section 6.15).

8.3. 6MWT

All patients will complete a 6MWT according to the Schedule of Assessments (Table 1 and Table 2) and following the instructions in the Six Minute Walk Test manual. The 6MWT conducted after V1 may be within a +/- 30 day window from the study day. The 6MWT should not be skipped. If the test cannot be completed within the assessment window (e.g., the patient is hospitalized), it should be completed as soon as possible.

Patients should have had samples for NT-proBNP and cTnT taken before starting the 6MWT. The 6MWT may be repeated within the visit window if the test was invalid. (Refer to the CARES Six Minute Walk Test Manual for test validation instructions.) Results of the Screening 6MWT are for baseline only and are not required to determine eligibility. The Investigator may choose to have the patient complete the 6MWT for Screening after eligibility has been confirmed and a date for the first dose of study treatment has been scheduled so long as the test is complete prior to administration of the study drug.

The 6MWT measures the distance a patient can quickly walk on a flat, hard surface in a period of 6 minutes. It evaluates the global and integrated response of all the systems involved during exercise. This is a self-paced test; patients choose their own intensity of exercise and are allowed to stop and rest during the test (Crapo 2002).

8.4. Quality of Life Questionnaires

All patients will complete the KCCQ, the SF-36 version 2 and the EQ-5D-5L™ according to the Schedule of Assessments (Table 1 and Table 2). QoL questionnaires completion after V2 may be within a +/- 30 day window from the study day. QoL questionnaires completion should not be skipped. If the questionnaires cannot be completed within the assessment window (e.g., the patient is hospitalized), they should be completed as soon as possible.

Patients should complete the QoL questionnaires prior to any other procedures and prior to infusion. If possible, patients should complete the questionnaires in the same setting and same time of day each time.

The KCCQ is a 23-item self-administered questionnaire that quantifies physical function, symptoms, social function, self-efficacy and knowledge and quality of life. It requires an average of 4-6 minutes to complete and uses an ordinal, adjectival (Likert) scale (Green 2000).

The SF-36 questionnaire is a self-administered questionnaire containing 36 items that measures health on functional status, well-being and overall evaluation of health in 8 domains. It requires approximately 5 minutes to complete and uses scaled, ordinal responses (e.g., All of the time, Most of the time, A good bit of the time, etc.) (Brazier 1992).

The EQ-5D-5L™ is a descriptive system assessing mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Patients are asked to indicate the status of each of the dimensions by selecting one of the five levels (no problems [level 1], slight problems [level 2], moderate problems [level 3], severe problems [level 4], and extreme problems [level 5]). The responses are compiled to create a 5-digit number that describe the patient's health state. The EQ-5D-5L™ includes a visual analogue scale (VAS) for the patient to rate their health that reflects the patient's judgement of their own health.

8.5. Echocardiography

Cardiac structure and function will be assessed through echocardiograms according to the Schedule of Assessments (Table 1 and Table 2) and interpreted at a central echocardiography core lab. Image acquisition, storage, and transfer guidelines will be provided in a Study Manual. 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.

8.6. NT-proBNP, cTnT, dFLC, and CRP

Blood samples for NT-proBNP, cTnT, FLC and CRP will be collected according to the Schedule of assessments (Table 1 and Table 2). During visits where the 6MWT is required, the NT-proBNP and cTnT samples must be obtained prior to performing the 6MWT.

8.7. 24-hour Protein

Urine for protein will be collected on all patients over 24 hours according to the Schedule of Assessments (Table 1 and Table 2) following instructions provided in the Laboratory Manual. Results of the Screening 24-hour urine are for baseline only and are not required to determine

eligibility. The Investigator may choose to have the patient collect the urine for Screening after eligibility has been confirmed and a date for the first dose of study treatment has been scheduled so long as the collection is complete prior to administration of the study drug. Collection of the 24-hour urine after V1 may be within a +/- 30 day window from the study day. Collection of

24-hour urine samples should not be skipped. If the patient cannot complete a 24-hour urine collection within the assessment window (e.g., the patient is hospitalized), it should be completed as soon as possible.

8.8. Pharmacokinetic Measurements

Blood samples for PK analyses of CAEL-101 will be collected according to the Schedule of Assessments (Table 1 and Table 2). Post-dose samples should only be obtained from an extremity opposite the administration site.

Where not prohibited by regulatory authorities or IRB/EC, backup aliquots from the PK samples may be stored for future research related to amyloidosis, CAEL-101 or its mechanism of action. No genetic testing will be performed on these samples.

8.9. Immunogenicity Measurements

Samples for immunogenicity testing will be collected according to the Schedule of Assessments (Table 1 and Table 2) and prior to infusion of study drug. Samples that are positive in the anti-drug antibody (ADA) assay will be further characterized in the ADA titer and the NAb assays. Assessment of potential impact of ADA and NAb on PK/PD and clinical safety and efficacy responses may be performed.

8.9.1. ADA Variables

All immunogenicity analyses will be performed on the Anti-drug antibody Analysis Set (AAS).

Immunogenicity variables include ADA status, incidence, response category and titer, as well as NAb status, incidence and titer over the duration of the study. The immunogenicity status and response categories will be provided in the 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
- Treatment-boosted ADA Responses

Patients with a treatment-emergent or treatment-boosted ADA responses will be further categorized as follows:

- Persistent Responses
- Indeterminate Responses

  - Transient Responses

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

8.10. NYHA Functional Classification

Patients will be assessed for the New York Heart Association (NYHA) Functional Classification (Dolgin 1994) according to the Schedule of Assessments (Table 1 and Table 2). The NYHA Functional Classification classifies patients in one of four categories based on their limitations during physical activity; the limitations/symptoms are in regard to normal breathing and varying degrees of shortness of breath and/or angina pain. The classes are as follows:

Class I – No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs etc.

Class II – Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.

Class III – Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20 – 100 meters). Comfortable only at rest.

Class IV – Severe limitation. Experiences symptoms even while at rest. Mostly bedbound patients.

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 and prior to every infusion of study drug. Vital signs include heart rate (HR), respiratory rate, systolic and diastolic BP and temperature. It is preferred that the same arm be used for all BP readings.

At Screening, patients will be screened for orthostatic hypotension. After the patient has rested quietly for at least 5 minutes in a supine position, BP and HR will be measured. The patient will stand and the BP and HR will be obtained right away. The standing BP and HR will be measured again after approximately 3 minutes. Subsequent BP and HR measurements after V1 should be taken after the patient has rested quietly for at least 5 minutes in a seated or supine position.

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 and Table 2). A full physical examination will be performed at Screening and will evaluate general appearance and the following body system/organs: head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic, and psychiatric. If a system is not assessed, the reason should be noted in the source documents. Subsequent physical examinations may be abbreviated to identify changes from baseline or evaluate changes based on the patient's clinical symptoms at the discretion of the Investigator. Weight will be measured at each visit.

Height will be measured one time at Screening.

9.1.4. Twelve-Lead Electrocardiogram

ECGs will be performed on a calibrated Twelve-lead machine according to the Schedule of Assessments (Table 1 and Table 2). The de-identified, native ECG waveform will be sent to a central laboratory for analysis. Details regarding transfer of native data are provided separately in the ECG Acquisition Guide.

Patients with QTcF of > 500 msec on the Screening ECG are not eligible for enrollment. However, patients with a QTcF of > 500 msec who have a QRS of > 120 msec and confirmed right bundle branch block, left bundle branch block or intraventricular conduction defect may be considered for enrollment in consultation with the Medical Monitor.

9.1.5. Clinical Laboratory Tests

Samples for clinical laboratory tests will be obtained according to the Schedule of Assessments (Table 1 and Table 2) and sent to the central laboratory. Results from the central laboratory assessments obtained on dosing days are not required prior to dosing the patient. Investigators may perform selected laboratory assessments locally prior to dosing as part of their routine safety assessment.

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

During Screening and scheduled or unscheduled study visits, sites must obtain and ship samples for Central Lab testing regardless of sample collection for local labs. During Screening and scheduled or unscheduled study visits, Central Lab results prevail over local lab results when both are available.

Delay in Central Lab results beyond the Screening period will make local labs the basis for eligibility determination. In this case, even if the Central Lab result later shows the patient as ineligible, eligibility already determined based on local labs is acceptable.

Local labs without Central Lab results can be used during the study for safety testing, dose modification/withholding, or discontinuation from the study.

Clinical laboratory tests that will be performed for this study are listed in Table 6.

Table 6: 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	• AST • ALT • ALP (ALP isozyme, if applicable) • GGT • Albumin • Globulin • Creatinine • Glucose • Total protein • Total bilirubin • Sodium	• Specific gravity • pH • Glucose • Protein • Bilirubin • Ketones • Leukocytes • Blood
		Pregnancy
		• Serum hCG • Urine pregnancy test
		Special

Table 6: Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis
• MCV • RDW • Reticulocyte count	• Potassium • Chloride • CO_2 • Calcium • Phosphorus • Magnesium • Blood urea nitrogen • eGFR • Uric acid	• Serum FLC • Serum and Urine Immunofixation • iFLC or dFLC or SPEP m-spike • Troponin • NT-proBNP • CRP

Abbreviations: ALP - alkaline phosphatase, ALT - alanine aminotransferase, AST - aspartate aminotransferase, CO_2 – carbon dioxide; CRP - C-reactive protein, dFLC - involved/uninvolved free light chain difference, eGFR - estimated glomerular filtration rate, FLC – free light chain; GGT - gamma-glutamyl transferase, hCG - human chorionic gonadotropin; iFLC - involved free light chain, MCH - mean corpuscular hemoglobin; MCHC - mean corpuscular hemoglobin concentration; MCV - mean corpuscular volume NT-proBNP-N-terminal pro b-type natriuretic peptide, RDW - red blood cell distribution width, SPEP - serum protein electrophoresis

9.1.6. Pregnancy Screen

Serum pregnancy tests will be performed on WOCBP at the Screening visit within 14 days of the first dose of study drug. 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 and Table 2). 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 disease 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).
- A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error.

9.2.2. Adverse Event Reporting and Follow-up

All AEs will be assessed by the Investigator and recorded in the 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 last EOT visit, the final outcome of the ongoing AE will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable.

Additionally, Investigators are encouraged to report any adverse reactions (for which they suspect a causal role of a medicine) attributed to non-interventional concomitant medications, including those identified as AxMP, to the respective marketing authorization holder of the suspected medicinal product and/or the concerned competent authority via a national spontaneous reporting system, as applicable per routine post-marketing safety reporting requirements.

9.2.3. Grading of Adverse Event

The severity of an event and the seriousness are not 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 National Cancer Institute-Common Terminology Criteria for Adverse Events (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; urgent intervention indicated.
- Grade 5: Death

All AEs will be recorded at the highest severity experienced.

9.2.4. 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 or related and possibly related will be considered "related" to the study drug for regulatory reporting requirements.

9.3. Serious Adverse Event Definition

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death (Death is an outcome of an AE, not an AE in itself.) All events leading to death, 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. 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 GPS 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 GPS Email/Fax Cover Sheet signed by the Investigator or Sub-Investigator. The timelines for reporting SAE information to Alexion GPS need to be followed for the initial SAE report and for all follow-up SAE information. SAEs deemed at least 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.

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

An Investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

All SAEs, including those occurring after the EOT visit through the end of study, will be reported to Alexion GPS. Investigators are not obligated to actively seek patient AE or SAE data after conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has discontinued from the study, and they consider the event to be reasonably related to study intervention, or of any additional updates to previously reported SAEs (e.g. resolution, stabilization, condition returns to baseline), the Investigator must promptly notify Alexion GPS.

9.4.1. Expedited Reporting of Serious Adverse Events

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions (SUSARs) in accordance with ICH GCP, FDA and all applicable country and local regulations and 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.

No SAEs are considered expected by the Sponsor for the purpose of expedited reporting of SUSARs.

In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All SUSARs to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.

9.4.2. 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 GPS within 24 hours of Investigator or site staff awareness using the Pregnancy/Breastfeeding Reporting and Outcome Form via email: ClinicalSAE@alexion.com or facsimile: +1-203-439-9347. All paper forms MUST be accompanied by the Alexion GPS 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.

9.4.3. Unexpected Events

Apart from the reporting of SUSARs, there may be other events which are relevant in terms of benefit-risk balance and which should be reported in a timely manner according to regional and national requirements [e.g., European Union Clinical Trials Regulation (EU CTR) 536/2014 (48)].

It is important for patient safety that, in addition to SAEs and reactions, all unexpected events that might materially influence the benefit-risk assessment of the study intervention or that would lead to changes in the administration of the study intervention or in overall conduct of a clinical trial should be reported. Examples of such unexpected events include an increase in the rate of occurrence of expected serious adverse reactions which may be clinically important, a significant hazard to the patient population, such as lack of efficacy of a medicinal product, or a major safety finding from a newly completed animal study (such as, carcinogenicity).

Under the EU CTR 536/2014 (49), where unexpected events require an urgent modification of a clinical trial, it should be possible for Alexion and the Investigator to take urgent safety measures without awaiting prior authorization. If such measures constitute a temporary halt of the clinical trial, Alexion should apply for a substantial modification before restarting the clinical trial.

Under the EU CTR 536/2014, events other than SAEs (e.g., unexpected events) that may impact the benefit-risk balance should be reported.

9.5. Medication Error, Abuse, and Misuse

Medication error, abuse, and misuse will be collected from the date when consent was obtained through the last visit or the last scheduled procedure shown in the Schedule of Activities (Section 1.2).

9.5.1. Timelines

If an event of medication error, drug abuse, or drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate Alexion representatives but no later than 24 hours of when they become aware of it.

The full definitions and examples of medication error, abuse, and misuse can be found in Section 13.7.

9.5.2. Medication Error

Alexion defines a medication error as an unintended failure or mistake in the treatment process for an IMP or Alexion AxMP that either causes harm to the patient or has the potential to cause harm to the patient.

9.5.3. Medication Abuse

Alexion defines medication abuse as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or Alexion AxMP for a perceived reward or desired non-therapeutic effect.

9.5.4. Medication Misuse

Alexion defines medication misuse as the intentional and inappropriate use of IMP or Alexion AxMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or Alexion AxMP, outside the intended use as specified in the protocol, including deliberate administration of the product by the wrong route.

10. STATISTICS

10.1. Statistical Hypotheses

The primary objectives of this study are to determine whether CAEL-101 and treatment for PCD improves overall survival and/or decreases CVH compared to treatment with Placebo and treatment for PCD. The primary statistical hypothesis to be tested is:

- H_0: Neither all-cause mortality (ACM) nor frequency of cardiovascular-related hospitalization is different between CAEL-101 and placebo in patients with Mayo stage IIIb AL amyloidosis.
- H_a: At least one of ACM and frequency of cardiovascular-related hospitalization is different between CAEL-101 and placebo in patients with Mayo stage IIIb AL amyloidosis.

The effects of CAEL-101 on safety and tolerability, while included as primary objectives, are not to be tested inferentially and thus there is no structured hypothesis for those outcomes.

10.2. Hypothesis Testing and Significance Level

All hypothesis testing will be performed using 2-sided tests at the 0.05 level of significance. Hypothesis testing will be conducted in a prespecified hierarchical order to control for overall type I error. First, a 2-sided hypothesis testing will be done for the primary efficacy endpoint. If the p-value is significant then the secondary efficacy endpoints will be tested (at alpha=0.05), in the sequence which will be pre-specified in the SAP.

If any of the p-values are not significant, then the corresponding null hypothesis will not be rejected. Hypothesis testing for all the endpoints specified in the order lower than the one corresponding to the nonsignificant p-value will be suspended. The nominal p-values will be computed for the test statistics based on all these endpoints and summarized for descriptive purpose. All the other efficacy endpoints outside of the hierarchical approach will be tested at the 0.05 level of significance without multiplicity adjustment.

10.3. Sample Size Considerations

This study was originally designed as an event-driven study that was to continue until the number of deaths required has been observed. The power was originally estimated based on the primary endpoint of time to ACM. A sample size of approximately 124 patients in total, randomized in a 2:1 ratio of CAEL-101:placebo, and 101 total deaths was expected to provide at least CCI power to test the hypothesis that hazard ratio = 1 versus hazard ratio ≠ 1 (CAEL-101 versus placebo) using a Cox proportional hazard model with a statistical significance level of 5%, and an assumed hazard ratio through Week 50 of CCI for the stage IIIb patients.

The primary efficacy endpoint has been revised to a hierarchical combination of time to ACM and frequency of CVH over an LPI+18M treatment duration.

The Finkelstein-Schoenfeld test (FS test) (Finkelstein and Schoenfeld 1999) will be used to test for a treatment effect on the hierarchical composite endpoint. Simulation demonstrates that there is greater than CCI power to reject the null hypothesis that neither ACM nor CVH is different between CAEL-101 and placebo. The simulations were conducted with a 5% two-sided

significance level and the assumptions of a [redacted] hazard ratio between CAEL101 and placebo for time to ACM and a [redacted] rate ratio for CVH.

10.4. General Statistical Methods

Data will be tabulated by treatment group using descriptive and inferential statistics, where specified. Statistical analyses for certain efficacy endpoints will be adjusted (wherever appropriate) for two covariates: geographic region and daratumumab usage at baseline.

All data captured on the case report form, clinical laboratory and other electronic databases will be presented in by-domain data listings.

A comprehensive SAP describing the statistical methods for the PETP will be written and approved prior to any database lock and unblinding. This SAP will detail how missing values, windows for study visits and other analysis considerations will be addressed.

Statistical methods describing the OLEP will be presented in a separate SAP.

10.4.1. Subgroups

Analysis of the effects of CAEL-101 on various subgroups will be performed to assess whether there are any intrinsic or extrinsic characteristics that demonstrate clinically meaningful differences or trends. Descriptive analysis of the primary and secondary efficacy endpoints will be provided for the following subgroups, along with other subgroups that will be defined in the SAP. In addition, safety summaries will be provided for relevant subgroups.

- Sex (male and female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Hawaiian or Other Pacific Islander, White or Caucasian, Other)
- Age Group 1 (below study median age, above or equal to study median age)
- Geographic region (North America versus Rest of World)
- FLC subtype (kappa and lambda)
- Baseline dFLC > 18 mg/dL or ≤ 18 mg/dL
- The presence of co-existing myeloma versus absence of co-existing myeloma
- Deep hematologic response defined as either iFLC <2 mg/dL (Muchtar 2019b) or dFLC < 1 mg/dL (Manwani 2019).
- Comparative hematologic response based on dFLC: (VGPR or better: dFLC < 4 mg/dL) versus other response (PR and NR: dFLC ≥ 4 mg/dL)
- Use of daratumumab (versus no use of daratumumab) as first-line background anti-PCD treatment.
    - Use of daratumumab (versus no use of daratumumab) at any time during the study (study day ≥ -28)
- Global longitudinal strain (GLS)% value at baseline
- New York Heart Association (NYHA) Classification (Section 8.9)

This study is not powered to assess treatment outcomes by these subgroups and thus inferential assessments of these endpoints by subgroup are not planned. Rather, trends across the subgroups will be reviewed for any similarities and/or differences.

10.4.2. Analysis Sets

The analysis sets are described in the following table and will include the Screened Set,

Intent-to-Treat (ITT) Analysis Set, Per-Protocol (PP) Analysis Set, PK Analysis Set (PKAS), Safety Analysis Set (SS), Anti-Drug Antibody Analysis Set (AAS), and modified intention to treat set (mITT).

Analysis Set	Description
Screened Set	All consented patients
ITT Analysis Set	All patients who have been randomized.
mITT Analysis Set	All patients who have been randomized and survived for at least 4 weeks from the first dose of study intervention
SS	All patients who received at least 1 dose of study intervention. Patients will be analyzed according to the study intervention they actually received, regardless of the study intervention they were randomized to.
PKAS	All patients who received at least 1 dose of CAEL-101 and have at least 1 measurable serum CAEL-101 concentration.
PP Analysis Set	All patients who meet the definition of ITT (see above) and who are without major protocol deviations that would affect the interpretability of the efficacy outcomes (major protocol deviations will be described in the SAP).
AAS	All patients who received any study intervention and who after the first dose have at least 1 reportable result in the ADA assay. ADA analysis in patients will be conducted based on the actual study intervention they received.

10.4.3. Handling of Missing Data

For the primary efficacy endpoint, missing data will not be imputed. For the time to ACM, the date of death will be the key data element used to determine the outcome. As all patients will be followed regardless of whether they continue study intervention or study participation, it is not expected that there will be any missing death dates (for those patients who die). Patient data will be censored at the last known alive date.

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

10.5. Baseline Characteristics

Baseline characteristics will be tabulated descriptively (e.g., number and percent of patients for each category for categorical parameters and the number, mean, standard deviation and range for continuous parameters).

10.6. Patient Disposition

Patient disposition (including the number and percent of patients who are randomized, who receive randomized treatment, who prematurely discontinue and reasons for discontinuation and who complete the study) will be tabulated by treatment group. The number (%) of patients by exposure duration will be tabulated. Tabulation of the number of patients by region, country and individual study center will be provided.

The exposure duration will be determined from the date of first dose of study drug and the date of last dose of study drug. The number of days exposed will be reported.

10.7. Efficacy Analysis

The primary analysis set for the efficacy analyses will be the ITT.

10.7.1. Primary Efficacy Endpoint

The primary efficacy endpoint is a hierarchical combination of time to ACM and frequency of CVH over an LPI+18M treatment duration.

The hypothesis testing will be performed using the F-S test (Finkelstein and Schoenfeld 1999) and the treatment effect estimation using the win-ratio (WR) method (Pocock 2012). Both these methods are based on pairwise comparisons of patient outcomes with the comparisons performed in a hierarchical manner (e.g., first compare patient outcomes based on time to ACM and, if there is no winner due to censoring, then compare based on frequency of CVH).

The F-S test will be stratified by geographic region, and daratumumab usage (versus no use of daratumumab) at baseline ($-28 \leq$ study day ≤ 1).

Primary Estimand

The primary estimand attributes are as follows:

- **Study intervention:**
  - CAEL-101 plus SoC for PCD
  - Placebo plus SoC for PCD
- **Population**: adults ($\geq$ 18 years of age) with Mayo Stage IIIb AL amyloidosis
- **Variable**: A hierarchical combination of time to ACM and the frequency of CVH
- **Summary measure**: win-ratio of CAEL-101 vs placebo for the hierarchical composite endpoint of ACM and frequency of CVH
- **Intercurrent events**: treatment policy strategy (ICH E9 [R1] Addendum) will be applied to the following intercurrent events:
  1. Study intervention discontinuation
  2. Selected major protocol deviations as described in the SAP

10.7.2. Secondary Efficacy Endpoints

To control the Type 1 error, the secondary endpoints will be formally tested sequentially in the order which will be pre-specified in the SAP if the primary endpoint is statistically significant at the 0.05 level.

The time to ACM will be analyzed as follows:

- Testing: a stratified log-rank statistic by geographic region (North America vs rest of the world) and daratumumab usage at baseline (daratumumab use versus no use)
- Estimation: the hazard ratio of CAEL-101 versus placebo based on a Cox proportional hazard model adjusted by geographic region and daratumumab usage at baseline. The 95% confidence interval of hazard ratio will also be reported.

Kaplan-Meier (KM) plots will also be provided by the study intervention groups.

Frequency of CVH will be analyzed using a negative binomial regression analysis with geographic region, daratumumab use at baseline and an offset term equal to log of each patient's study duration included in the model.

The 5 secondary efficacy endpoints (NTProBNP, KCCQ-OS, GLS%, 6MWT, SF36v2 PCS) based on the changes from baseline to Week 50 will be analyzed using a ranked analysis of covariance (ANCOVA) model. The ranked analysis will account for the patients whose data will be missing due toACM, CVH and other reasons. The outcome for each patient will be ranked based on the order described in the SAP.

The ranked ANCOVA model will include treatment factor, geographic region, daratumumab use at baseline as fixed effects. The ranked baseline value (i.e., baseline 6MWT, baseline KCCQ-OS, baseline NT-proBNP, baseline SF-36v2 PCS, and baseline GLS% as corresponding to each endpoint) will be included as covariates.

Detailed plans for the analyses of the secondary endpoints will be pre-specified in the SAP for the PETP.

10.7.3. Exploratory Endpoints

The exploratory endpoints of changes from baseline over time will be summarized at selected key timepoints over the course of the study. The changes from baseline to Week 50 may be analyzed using MMRM and Ranked ANCOVA as described in Section 10.7.2.

The 95% confidence intervals will be provided for the difference in proportions for the cardiac, renal, and liver related endpoints.

The exploratory composite endpoint based on the hierarchical combination will be analyzed using the Finkelstein-Schoenfeld method (Finkelstein and Schoenfeld 1999).

Other exploratory endpoints and detailed plans for the analyses of the exploratory endpoints will also be pre-specified in the SAP for the PETP.

10.7.4. Safety

All safety analyses will be conducted on the SS. The safety analyses will be descriptive in nature. All safety data will be listed and tabulated by study intervention group. Safety data include the following:

- TEAEs
- Clinical laboratory tests (hematology, chemistry, and urinalysis)
- Vital signs including respiratory rate, HR, and BP
- Physical examination including weight
- Twelve-lead ECG including rate, rate ranges and diagnostic statements

Adverse events will be coded using the MedDRA coding dictionary. Patient incidence of each System Organ Class and unique Preferred Term will be tabulated, including all TEAEs, at least possibly related TEAEs, TEAEs resulting in discontinuation of study treatment, TEAEs by intensity (NCI-CTCAE grades 1-5) and treatment emergent SAEs.

Treatment-emergent is defined as follows: last study intervention day-first study intervention day + 140 days.

Other safety data presentations will be descriptive in nature and no formal statistical tests will be performed. Analyses of laboratory, vital sign and ECG outcomes will include mean changes from baseline as well as shifts (e.g., normal to abnormal) from baseline and the incidence of potentially clinically significant values. Normal ranges and potentially clinically significant thresholds will be defined in the SAP. Graphics of changes over time in safety parameters will be presented, where appropriate.

10.7.5. Immunogenicity

All ADA analyses will be performed on the AAS using the ADA and NAb variables included in Section 8.9.1.

The incidence of ADA response categories will be summarized as absolute occurrence (n) and percent of all patients (%) by treatment group. NAb positive and NAb negative patients will be summarized under treatment-emergent ADA response and treatment-boosted ADA response categories as absolute occurrence (n) and percent of all patients (%) by treatment group.

Additional details will be provided in the SAP.

10.7.6. Pharmacokinetics

All PK analyses will be performed on the PKAS. The PK analysis will be descriptive in nature. Individual and mean concentrations versus time data will be tabulated and plotted. Summary statistics of concentration data will be computed for each scheduled sampling time and plotted. In addition, PK and PD data from this study may be combined with data from other studies to conduct additional assessments as per the Sponsor’s discretion that are based on the outcome of this trial and future development path.

10.8. 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. A focus of the analysis will be new-onset medication (those medications started after the first dose of study medication).

11. OPEN-LABEL EXTENSION PERIOD (OLEP) ANALYSES

Kaplan-Meier graphs and estimates of survival times by intervention group will be provided to assess the long-term overall survival in patients who were previously treated with CAEL-101 or placebo during the PETP.

A stratified log-rank statistic, similar to the one for the secondary endpoint of time to ACM, will be used to compare the long-term overall survival in patients who were previously treated with CAEL-101 or placebo during the PETP.

Descriptive statistics including the number of patients, mean, standard deviation, 95% confidence interval, median, range and interquartile range by visit will be provided for the changes from baseline in 6MWT, NT-proBNP, KCCQ-OS, SF-36v2PCS in the patients who were previously treated with CAEL-101 during the PETP. In addition, mean ± SD graphs over time for changes from baseline in 6MWT, Cardiac response by NT-proBNP, KCCQ-OS,

SF-36v2PCS will be provided by visit.

TEAEs, SAEs as well as changes from baseline in vital signs, weight, clinical laboratory tests, and 12-lead ECGs in the patients who were previously treated with CAEL-101 during the PETP will be analyzed in the same manner as for the PETP.

12. 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

13. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor will implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements. The storage, retention and destruction of data will follow the EU CTR 536/2014 which is 25 years from study archival. The storage, retention and destruction of biological samples is 25 years after the study ends.

13.1. 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.

13.2. Monitoring

In accordance with the Code of Federal Regulations 21 CFR 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.

13.3. Data Protection

- Patients will be assigned a unique identifier by Alexion or designee. Any patient records or datasets that are transferred to Alexion will contain the identifier only; patient names, initials, date of birth, or any information which would make the patient identifiable will not be transferred.
- Patients must be informed about the uses of their personal study-related and coded (pseudonymized) data, who will have access to their personal data, how and how long it will be used, and that it will be used by Alexion in accordance with local data protection law. In addition, multiple local laws require that patients must also be informed of any individuals rights they may have with regard to their personal data.
- Patients will be informed about how their personal study-related data will be disclosed and are provided with the appropriate legal basis for which a controller processes their personal data. The level of disclosure, the security controls used to protect their data, and information regarding any transfer of their personal data outside of their country or region must also be explained to the patient.
- Patients must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, appropriate IRB/IEC members, any third parties acting on behalf of Alexion, and by inspectors from regulatory authorities.

- Alexion and the site as a data controller has implemented privacy and security controls designed to help protect patient personal data, including information security controls, firewalls, incident detection, and secure transfer measures.
- The contract between Alexion and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- The EU GDPR defines pseudonymization as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.
- Appropriate safeguards will be implemented to protect coded data during and after the study that include:
  - Access to the coded data will be limited to specific individuals subject to confidentiality obligations (including the obligation to not attempt to re-identify individuals/decode the clinical data).
  - The coded data will be protected with security measures to avoid data alteration, loss, and unauthorized accesses and further de-identification techniques may be applied.
  - A data protection impact assessment (DPIA), where required, will apply to identify and mitigate privacy risks, if any, associated with each scientific research.
  - The coded data will not be shared for direct marketing purposes or other purposes that are not legal duties or are not considered scientific research according to the applicable data protection legislation. In particular, it will not be used to make decisions about future services available to the patient, such as insurance.
- In addition to having the patients' data and biosamples coded, the data are also protected by high-standard technical security means, such as strong access control and encryption.
- Patients are also protected legally by the following means if the level of disclosure of the coded data includes sharing of the latter with other third parties, as the patient's will be explained in the ICF:
  - The patients' coded data are protected by contractual arrangements, Codes of Conduct, or certifications that set the rules for personal information protection to those available in European countries or other alternatives set forth in the law, as well as any supplementary technical and organizational measures that may results out of conducted transfer impact assessments.

13.4. 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 standard operating procedures 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.

13.5. Dissemination of Clinical Study Data

Study-related information and study results, may be posted on publicly accessible clinical study databases (e.g., the US website www.clinicaltrials.gov or the EU website www.clinicaltrialsregister.eu), as appropriate, and in accordance with national, regional, and local regulations. However, posting of study results per local regulations may be deferred to a later date for one of the following reasons:

Study is still ongoing in other countries or regions

Study is part of an ongoing review for approval by Health Authorities; study result data deferral request can be submitted.

13.6. Study and Site Start

The study start date is the date on which the clinical study will be open for recruitment of patients (i.e., site activation).

13.7. Medication Error, Abuse, and Misuse

Medication Error

Alexion defines a medication error as an unintended failure or mistake in the treatment process for an IMP or Alexion AxMP that either causes harm to the patient or has the potential to cause harm to the patient.

Any events of medication error, with or without associated AEs, are to be captured and forwarded to Alexion GPS via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Medication Error Report Form.

A medication error is not lack of efficacy of the study intervention, but rather a human or process related failure while the intervention is under the control of the study site staff or patient.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the patient received the drug

- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Medication name confusion
- Dispensing error, e.g., medication prepared incorrectly, even if it was not actually given to the patient
- Medication not administered as indicated, e.g., wrong route or wrong site of administration
- Medication not taken as indicated, e.g., tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, e.g., kept in the refrigerator when it should be at room temperature
- Wrong patient received the medication (excluding Interactive Response Technology [IRT]/Randomization and Trial Supply Management [RTSM] errors)
- Wrong drug administered to patient (excluding IRT/RTSM errors)

Examples of events that do not require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed medication dose(s), e.g., forgot to take medication
- Accidental overdose (will be captured as an overdose refer to Section 7.7 for information on overdose)
- Patient failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Medication Abuse

Alexion defines medication abuse as the persistent or sporadic intentional, nontherapeutic excessive use of IMP or Alexion AxMP for a perceived reward or desired nontherapeutic effect.

Any events of medication abuse, with or without associated AEs, are to be captured and forwarded to Alexion GPS via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Drug Misuse or Drug Abuse Report Form. This form should be used both if the medication abuse happened in a study patient or if the medication abuse involves a person not enrolled in the study (such as a relative of the study patient).

Examples of medication abuse include but are not limited to:

- The medication is used with the intent of getting a perceived reward (by the study patient or a person not enrolled in the study)

- The medication in the form of a tablet is crushed and injected or snorted with the intent of getting high

Medication Misuse

Alexion defines medication misuse as the intentional and inappropriate use of IMP or Alexion AxMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or Alexion AxMP, outside the intended use as specified in the protocol, including deliberate administration of the product by the wrong route.

Events of medication misuse, with or without associated AEs, are to be captured and forwarded to Alexion GPS via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Drug Misuse or Drug Abuse Report Form. This form should be used both if the medication misuse happened in a study patient or if the medication misuse involves a person not enrolled in the study (such as a relative of the study patient).

Examples of medication misuse include but are not limited to:

- The medication is used with the intention to cause an effect in another person
- The medication is sold to other people for recreational purposes
- The medication is used to facilitate assault in another person
- The medication is deliberately administered by the wrong route
- The medication is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study patient feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the medication

14. 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, and
- Applicable laws and regulations.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures per local regulations
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, EU CTR 536/2014 for clinical studies, EU MDR 2017/745 for clinical device research, and all other applicable local regulations
  - Promptly notifying Alexion of any (potential) serious breach of the protocol or regulations so that legal and ethical obligations are met. A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated in the clinical study.
- Reporting of serious breaches and personal data breaches:
  - A "serious breach" means a breach likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated in the clinical study.
  - A "personal data breach" means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored or otherwise processed.
  - Alexion will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority (including data protection authorities and, if applicable, affected patients in case of a personal data breach), IRB/IEC, and Investigators. Under EU CTR 536/2014, Alexion is required to enter details of serious breaches into the European Medicines Agency (EMA)) Clinical Trials Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
  - If any (potential) serious breach occurs during the study, Investigators or other site personnel will inform the appropriate Alexion representatives immediately.
- In certain regions/countries, Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.

- The Investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach, including personal data breaches
  - A (potential) serious breach is promptly reported to Alexion or delegated party, through the contacts (email address or telephone number) provided by Alexion.
  - Alexion and the site have taken all necessary steps to avoid personal data breaches and have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (e.g., applying encryption, maintaining and keeping systems and information technology (IT) security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
  - Both Alexion and the study site have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
  - In compliance with applicable laws, the data controller for the processing activity where the personal data breach occurred (Alexion or respectively the study site) will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
  - If patients need to be notified of a personal data breach, the notification is done by the site for the data breaches that occurred within the processing activities for which the site is the data controller. For data breaches that occur within the processing activities of Alexion as the data controller, the notification is done in collaboration with the site and is performed by the site and/or Investigator, acting on behalf of Alexion, so that Alexion has no access to the identifying personal information of the patients. The site and/or Investigator shall conduct the notification by contacting the patients using the information that they gave for communication purposes in clinical research.
  - If a personal data breach occurs in a processor's systems, engaged by Alexion, the processor under contractual obligations with Alexion promptly and in due course after discovering the breach notifies Alexion and provides full cooperation with the investigation. In these cases, to the extent Alexion is the data controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to patients. If the personal data breach needs to be notified to the patients, the notification to patients is done in collaboration with the site and is performed by the site and/or Investigator, acting on behalf of Alexion, so that Alexion has no access to the identifying personal information of the patients.
  - If a personal data breach involving an Alexion’s representative device (e.g., Study Monitor laptop), the Alexion representative will provide Alexion with all of the information needed for notification of the breach, without disclosing data that allows Alexion directly or indirectly to identify the patients. The notification will

be done by Alexion solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of reidentification of the patients. If the data breach must be notified to the data patients, the notification will be done directly by the Study Monitor in collaboration with the site and/or Investigator, acting on behalf of Alexion, so that Alexion has no access to the identifying personal information of the patients. The contract between Alexion and the Study Monitor shall expressly specify these conditions.

- The contract between the study site and Alexion for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and patients, where applicable.

- The Coordinating Investigator will be identified among the enrolling Investigators during the course of the study and will be responsible for reviewing the CSR and confirming that it accurately describes the conduct and results of the study.

14.1. 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 the Sponsor's designee.

14.2. 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.

14.3. Recruitment Strategy

Patients will be identified by qualified research staff. This may be done through a review of medical records, external referrals or using databases. Recruitment strategies may include study posters, referral letters, recruitment brochures, advertisements, social media posts, and websites, where permitted by local regulations. All recruitment materials will be submitted to local IRB/EC as required, for review and approval for use.

15. DATA HANDLING AND RECORDKEEPING

15.1. 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).

15.2. Data Collection Instruments

Various data collection instruments (DCI) such as electronic CRF, electronic clinical outcomes assessments and 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.

15.3. 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 25 years after FDA approval or the approval of a marketing application in an ICH region. No records may be transferred to another location or party without the written approval of the Sponsor. No records may be destroyed during the retention period without the written approval of the Sponsor. Clinical study documents and records required as part of the Trial Master File (TMF) are archived and stored by the Sponsor for at least 30 years. The Investigator/institution will permit the Sponsor or the regulatory authority access to study records and documents for inspection.

15.4. Handling of Human Biological Samples

All research and biological samples, including those for possible future research, are subject to national regulations and will only be conducted in a specified country if approved in that country.

Handling, storage, and shipment of biological samples are detailed in the laboratory manual.

15.4.1. Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each site keeps full traceability of collected biological samples from the patients while in storage at the site until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at the site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

The Sponsor or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the Sponsor-assigned biobanks or other sample archive facilities and will be tracked by the appropriate Sponsor team for the remainder of the sample life cycle.

All appropriately consented samples will be retained for a maximum of 25 years from study completion.

If required, Alexion will ensure that remaining biological samples are destroyed at the end of the retention period.

15.4.2. Withdrawal of Informed Consent for Donated Biological Samples

The Sponsor ensures that biological samples are destroyed at the end of a specified period as described in the informed consent.

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, the Sponsor is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures the patient's withdrawal of informed consent to the use of donated samples is communicated immediately to the Sponsor or delegate.
- Ensures that relevant human biological samples from that patient, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the patient and the Sponsor are informed about the sample disposal.

The Sponsor ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, the action is documented, and study site is notified.

16. 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.

17. 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.

18. REFERENCES

Brazier JE, Harper R, Jones NMB, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ. 1992;305:160-164.

Comenzo RL, Reece D, Palladini G, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. Leukemia. 2012;26(11):2317-2325.

Crapo RO, Enright PL, Zeballos RJ, et al. American Thoracic Society. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111-117.

Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol. 2004;22(18):3751-3757.

Dispenzieri A, Gertz MA, Saenger A, et al. Soluble suppression of tumorigenicity 2 (sST2), but not galactin-3, adds to prognostication in patients with systemic AL amyloidosis independent of NT-proBNP and troponin T. Am J Hematol. 2015;90(6):524-528.

Dolgin M, Fox AC, Gorlin R, et al. The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Little, Brown & Co; 1994.

Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. Stat Med 1999; 18:1341-54.

Green PC, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol. 2000;35(5):1245-1255.

Hemminki K, Li X, Försti A, Sundquist J, Sundquist K. Incidence and survival in non-hereditary amyloidosis in Sweden. BMC Public Health. 2012;12:974.

Kyle RA, Greipp PR, O'Fallon WM. Primary systemic amyloidosis: multivariate analysis for prognostic factors in 168 cases. Blood. 1986;68(1):220-224.

Manwani R, Cohen O, Sharpley F, et al. A prospective observational study of 915 patients with systemic AL amyloidosis treated with upfront bortezomib. Blood. 2019;134(25):2271-2280.

Mikhael JR, Schuster SR, Jimenez-Zepeda VH, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood. 2012;119(19):4391-4394.

Milani P, Merlini G, Palladini G. Light chain amyloidosis. Mediterr J Hematol Infect Dis. 2018;10(1):e2018022.

Muchtar E, Dispenzieri A, Leung N, et al. Depth of organ response in AL amyloidosis is associated with improved survival: grading the organ response criteria. Leukemia. 2018;32(10):2240-2249.

Muchtar E, Kumar SK, Gertz MA, et al. Staging systems use for risk stratification of systemic amyloidosis in the era of high-sensitivity troponin T assay. Blood. 2019;133(7):763-766.

Muchtar E, Wisniowski B, Palladini G, et al. Graded Renal Response Criteria for Light Chain (AL) Amyloidosis. Blood. 2021;138 (Supplement 1):2721-2721.

Muchtar E, Dispenzieri A, Wisniowski B, et al. Graded Cardiac Response Criteria for Patients With Systemic Light Chain Amyloidosis. J Clin Oncol. 2023;41(7):1393-1403.

Muchtar E, Therneau TM, Larson DR, et al. Comparative analysis of staging systems in AL amyloidosis. Leukemia. 2019b;33(3):811-814.

Palladini G, Hegenbart U, Milani P, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood. 2014; 124(15):2325-2332.

Palladini G, Sachchithanantham S, Milani P, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. Blood. 2015;126(5):612-615.

Palladini G, Merlini G. What is new in diagnosis and management of light chain amyloidosis? Blood. 2016;128(2):159-168.

Palladini G, Milani P, Basset M, et al. Severity and reversibility of cardiac dysfunction and residual concentration of amyloidogenic light chain predict overall survival of patients with AL amyloidosis who attain complete response. Amyloid. 2017;24(sup1):54-55.

Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J. 2012;33(2):176-82.

Wechalekar AD, Schonland SO, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Blood. 2013;121(17):3420-3427.

19. APPENDICES

19.1. COVID-19 Risk Assessment

AL amyloidosis can cause irreversible morbidity and even mortality, if untreated. As such, the benefit a patient 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 patients not receiving immunosuppressants. However, there is no specific data to further inform this risk. No patient 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 patient 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 patients 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 patients study discontinuations inadvertently resulting in	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

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

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
	missing data [e.g., for protocol-specified procedures]).	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 the data is missing (e.g., missed study visits or patient study discontinuations due to COVID-19).

19.2. COVID-19 Vaccine Risk Assessment

There is currently no information available evaluating the safety and efficacy of COVID-19 vaccines in patients 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 patient study discontinuations, inadvertently resulting in missing data (e.g., for protocol-specified procedures).	Capture specific information in the eCRF that explains the reason for missing data (e.g., missed study visits due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine).

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

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

19.3. EU Appendix 1

The purpose of this appendix is to provide an explanatory note on the use of AxMPs in this study.

The term AxMP is given to a medicinal product which does not fall within the definition of IMP in CTR No. 536/2014.

List of AxMPs in this Study:

CyBorD

CyBorD is considered SoC for AL-A treatment (Mikhael 2012).

Study CAEL101-301 was designed to include patients concurrently receiving CyBorD as first-line treatment for PCD (Inclusion Criteria #7). All patients must have a planned first-line PCD treatment with a CyBorD regimen according to institutional SoC, including dose modifications of each of the individual components as clinically appropriate. The patient's PCD treatment may have been initiated during the Screening period, after Screening laboratory samples were obtained. The patient may have received a maximum of 2 weeks of PCD treatment prior to randomization. For patients who received the first dose of CAEL-101 prior to starting their PCD treatment, their PCD treatment must have been initiated no later than 7 days after receiving the first dose of CAEL-101.

CyBorD components are used in this study and are listed below by active substance. These authorized AxMPs will either be provided by Alexion or will be sourced by the investigative site, depending upon local availability and regulations.

Active Substances of CyBorD
Cyclophosphamide
Bortezomib
Dexamethasone