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

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3. STUDY OBJECTIVES3.1. Primary ObjectivesThe primary objectives are:• To determine if CAEL-101 and treatment for PCD improves overall survival in Mayo stage IIIb AL amyloidosis patients who are treatment naïve compared to treatment for PCD alone•...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON51561

Source
ToetsingOnline

Brief title
CAEL101-301

Condition

- Other condition

Synonym
AL amyloidosis, amyloidosis

Health condition

AL amyloidosis

Research involving
Human

Sponsors and support

Primary sponsor: Alexion Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Sponsor funded research

Intervention

Keyword: AL Amyloidosis, bortezomib and dexamethasone (CyBorD), cyclophosphamide, Mayo Stage IIIb, Plasma Cell Dyscrasia

Outcome measures

Primary outcome

10.7.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the time to all-cause mortality and will be assessed from the date of randomization to the date of death (for patients who died) or EOS. Patients living at the end of the study will be censored at their last known date recorded. Patients who prematurely discontinue study treatment or withdraw early from the study will be included in the analysis (even after discontinuation of study treatment or the study) using the date of death or censoring time point (i.e., last known date recorded), as appropriate.

The primary efficacy endpoint will be estimated using a Cox proportional hazard model adjusted by the randomization factor (geographic region). A stratified log-rank test by geographic region will be used to test the treatment effect between the 2 study intervention groups.

Kaplan-Meier curves as well as KM estimates of median survival time will also

be provided.

Secondary outcome

10.7.2. Key Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

• Changes from baseline to Week 50 in the KCCQ-OS

• Changes from baseline to Week 50 in GLS%

• Changes from baseline to Week 50 in the 6MWT distance

• Changes from baseline to Week 50 in the SF-36 v2 PCS

The time slope of each key secondary endpoint will be analyzed using a linear mixed effects model with each parameter (ie, KCCQ-OS, or GLS%, or 6MWT, or SF-36 v2 PCS) as dependent variable and treatment, baseline value for each parameter, time (as a continuous variable), geographic region, and treatment by time interaction as fixed effect and intercept and time as random effects. The parameter of interest is the coefficient for study intervention group and time interaction term, which measures the slope difference between CAEL-101 and placebo over time.

Estimated LS means (+/-SE) for the slope by each study intervention group as well as the difference in LS mean slopes between the 2 study intervention groups along with the p-value of the interaction test between study intervention group and time will be provided.

Study description

Background summary

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). 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.

Study objective

3. STUDY OBJECTIVES
3.1. Primary Objectives
The primary objectives are:
• To determine if CAEL-101 and treatment for PCD improves overall survival in Mayo stage IIIb AL amyloidosis patients who are treatment naïve compared to treatment for PCD alone

• To evaluate the safety and tolerability of CAEL-101 in combination with treatment for PCD

3.2. Key Secondary Objectives

The key secondary objectives in this study are:

• To assess quality of life as measured by the KCCQ-OS
• To assess cardiac improvement as measured GLS%
• To assess functional improvement as measured by the distance walked in the 6MWT
• To assess quality of life as measured by the SF-36v2® PCS

3.3. Exploratory Objectives

Additional objectives in this study include:

• To assess improvement in cardiac amyloidosis as measured by changes 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
• To assess composite cardiac response when both of the following are satisfied:
* a decrease of > 30% in NT-proBNP levels AND a decrease of NT-proBNP > 300 ng/L;
* GLS improvement of >= 2%
• To assess the composite endpoint for cardiac deterioration defined as:
* death (cardiac transplant and left ventricular assist device implantation are treated as death), OR
* > 30% increase in NT-proBNP levels (in the absence of eGFR decline of >= 25%) AND >= 300 ng/L increase in NT-proBNP (in the absence of eGFR decline of >= 25%), OR
* <= 2% improvement in GLS
• 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
• To assess changes in effects on 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
• To assess QoL as measured by the KCCQ domain scores, SF-36v2® scaled domain scores and EQ-5D-5L*
• To assess change in NYHA Functional Classification
• To describe the PK profile based on plasma levels of CAEL-101
• To assess the immunogenicity of CAEL-101

Study design

4. STUDY DESIGN

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. As this is an event-driven study, the study will enroll until at least 101 deaths

have been observed (see Section 10.1).
Approximately 124 patients will be enrolled using a 2:1 randomization ratio and stratification will be based on geographic region across investigator sites. An interim analysis (IA) with stopping rules for early efficacy may be performed when approximately 75% (76/101) of the expected deaths have been observed (see Section 11).
Patients in both study intervention groups will be followed from randomization until death from any cause or until the end of study.
A schematic of the study design is presented in Figure 1 while the Schedule of Assessments is presented in Table 1.

Intervention

6. TREATMENT PLAN
The study is divided into a Screening period, Treatment period, End of Treatment period and Survival Follow-up period.
During the Treatment period, 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 Weeks 1, 10, 26, and 50. Approximately every 12 weeks (starting at Week 14), patients will be assessed for changes in 6MWT and QoL questionnaires. After week 50, the 6MWT and QoL questionnaires are only required every 6 months +/- 30 days. Patients will undergo echocardiography for GLS% and collection of 24-hour urine for assessment of protein, CRP, and assessment of NYHA Functional Classification (Section 8.9) at approximately Weeks 14, 26, and 50 then approximately every 6 months while on study treatment.
During the End of Treatment period, patients who discontinue study drug therapy for reason other than death will be seen in the clinic at approximately every 14 (+/- 1) days following the last dose of study drug twice, then approximately every 28 (+/-1) days for 4 more visits for efficacy and safety assessments.
During the Survival Follow-up period, patients who discontinue study drug therapy for reasons other than death will be contacted approximately every 12 weeks (+/- 7 days) until death or end of the study to assess for survival and PCD therapies received.
Every effort should be made to schedule assessments within the protocol-specified windows. Refer to the Schedule of Assessments in Table 1 for the list and timing of assessments.

6.2.1. Administration of Study Drug
Patients randomized to receive CAEL-101 will receive 1000 mg/m2. 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 6.2.2)
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 6.2.3).
Additional details for study drug administration are included in the Pharmacy Manual.

Study burden and risks

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.
Common side effects (>= 10% of total population) observed in patients who have received any dose of CAEL-101 included nausea, constipation, vomiting, diarrhea, peripheral edema, fatigue, rash, and dyspnea.
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.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

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 2) (Wechalekar 2013, Palladini 2016, Dispenzieri 2004) at the time of Screening
4. Measurable hematologic disease at Screening as defined by at least one of the following:
a. dFLC > 4 mg/dL or
b. iFLC > 4 mg/dL with abnormal Kappa/Lambda ratio or
c. 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:
a. Immunohistochemistry/Immunofluorescence
b. Mass spectrometry
c. 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
b. 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 MRI with gadolinium contrast agent diagnostic of cardiac amyloidosis
7. Planned first-line treatment for plasma cell dyscrasia is a CyBorD-based regimen administered as SoC (Section 6.2.4).
8. Adequate bone marrow reserve and hepatic function as demonstrated by:
a. Absolute neutrophil count >= 1.0 x 109/L
b. Platelet count >= 75 x 109/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. AST <= 3 x ULN
f. ALT <= 3 x ULN
g. ALP <= 5 x ULN (except for patients with hepatomegaly and isozymes specific to liver, rather than bone)
9. WOCBP must have a negative pregnancy test during Screening and must agree to use highly effective contraception (Section 6.9) 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 6.9) 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

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, 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 mol/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:
i. 60% or greater clonal plasma cells on bone marrow examination OR
ii. More than one focal lesion on MRI that is at least 5mm or greater in size
4. Have supine systolic blood pressure < 90 mmHg or symptomatic orthostatic hypotension, defined as a decrease in systolic blood pressure 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. 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 cm2) 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 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.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CAEL-101
Generic name:	CAEL-101

Ethics review

Approved WMO

Date:	10-03-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	14-07-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	05-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	15-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	21-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019□004254□28-NL
ClinicalTrials.gov	NCT04504825
CCMO	NL80408.056.22