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Safety and Tolerability of CAEL-101 in Patients With AL Amyloidosis In a Phase 2 Study for a Median of 49 Weeks

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BACKGROUND

- AL amyloidosis is a rare, progressive disorder caused by misfolded immunoglobulin light chains that aggregate into amyloid fibrils.
- Amyloid fibrils can deposit in tissues and organs, such as heart, kidneys, and liver, causing significant mortality and morbidity.
- Cardiomyopathy impacts prognosis; hence, cardiac biomarkers are used in the European modification of the 2004 Mayo staging system for AL amyloidosis.[1,2]
- Median overall survival (OS) for patients decreases with higher Mayo Stage **(Table 1)**.[3]

Table 1. Median Overall Survival by the European Modification of the 2004 Mayo Stage System[2]

Stage	Criteria	Median OS (m)
I	TnT ≤0.035 ng/mL; NT-proBNP ≤332 pg/mL	130
II	Either TnT >0.035 ng/mL OR NT-proBNP >332 pg/mL	54
IIIa	TnT >0.035 ng/mL AND NT-proBNP >332 pg/mL, but ≤8500 pg/mL	24
IIIb	TnT >0.035 ng/mL AND NT-proBNP >8500 pg/mL	4

m, months; NT-proBNP, N-terminal pro-brain natriuretic peptide; OS, overall survival; TnT, troponin T.

- Current treatment strategies rely on use of anti-plasma cell dyscrasia (PCD) therapies to suppress synthesis of amyloidogenic light chain proteins; none directly target the amyloid deposited in tissues and organs.
- CAEL-101 is a monoclonal antibody that binds to misfolded light chain fibrils and has been shown to facilitate removal of amyloid deposited in tissues.[4-7]
- Results from the dose-limiting toxicity period (28 days) of this phase 2 study with CAEL-101 in combination with cyclophosphamide-bortezomib-dexamethasone (CyBorD) indicated that CAEL-101 at 1000 mg/m^2 was well tolerated.[8]
- Data for a median treatment of 49 weeks are presented.

AIM

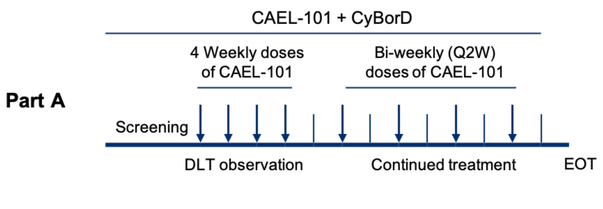
- To define the longer-term safety and tolerability of CAEL-101 + CyBorD in patients with AL amyloidosis during the continued treatment period.

METHODS

Study design

- This is an ongoing multicenter, open-label, sequential cohort, dose-selection study for CAEL-101 being conducted at 3 centers in the US in patients with AL amyloidosis (NCT04304144).
- A 3 + 3 dose-escalation design was used to determine the recommended dose of CAEL-101 for phase 3 studies in combination with a standard regimen of CyBorD, an anti-PCD therapy after which patients entered the continued treatment period **(Figure 1)**.

Figure 1. Study Design



CyBorD, cyclophosphamide-bortezpmib-dexamethasone; DLT, dose-limiting toxiciity; EOT, end of treatment.

Patients

- Adults with a confirmed diagnosis of AL amyloidosis, a minimum life expectancy of 6 months (m), and measurable hematologic disease were eligible for this study.
  - Criteria for hematologic disease were:
    - Difference between involved and uninvolved free light chain (dFLC) >5 mg/dL; OR
    - Free light chain (FLC) >5 mg/dL with abnormal ratio; OR
    - Serum protein electrophoresis (SPEP), showing a monoclonal antibody spike (M-spike) >0.5 g/dL.
- Patients with confirmed AL amyloidosis diagnosis without measurable disease could be enrolled with consultation and approval by the Sponsor Medical Monitor or their designee.
- Patients with other forms of amyloidosis, multiple myeloma, supine systolic blood pressure <90 mm Hg, or symptomatic orthostatic hypotension were excluded.

Treatment

- All patients received weekly intravenous infusions of CAEL-101 for the first 4 infusions, after which they received infusions every other week; all patients received standard of care CyBorD.

Endpoint assessments

- Primary: safety assessments included treatment-emergent adverse events (TEAEs), clinical laboratory tests, electrocardiograms, vital signs, and physical exams.
- Exploratory: cardiac troponin T (cTnT), N-terminal pro-brain natriuretic peptide (NT-proBNP), estimated glomerular filtration rate (eGFR), proteinuria, and alkaline phosphatase (ALP) were measured.

RESULTS

Patients

- This study is ongoing with a current median treatment duration of 49 weeks (range 12-57 weeks), with most patients having had ≥20 infusions of CAEL-101.
  - 11 patients are currently receiving CAEL-101 at 1000 mg/m^2.
  - 1 patient is receiving CAEL-101 at 750 mg/m^2.
  - 1 patient discontinued.
- At baseline, 8 (61.5%) patients had cardiac involvement and 7 (53.8%) had renal involvement, as noted by the investigator.
- For the 13 patients enrolled in the study, baseline demographics are given in **Table 2** and disease characteristics at baseline are given in **Table 3**.

Table 2. Baseline Demographics and Disease Status of Patients

Parameter	Patient Characteristics (N = 13)
Age, y	
Mean (SD)	65.2 (10.9)
Median (min, max)	69.5 (47.6, 79.6)
Sex, n (%)	
Male	10 (76.9)
Female	3 (23.1)
Race, n (%)	
Black or African American	2 (15.4)
White or Caucasian	11 (84.6)

SD, standard deviation.

Table 3. Baseline Disease Characteristics of Patients

Parameter	Patient Characteristics (N = 13)
Duration since diagnosis, months	
Mean (SD)	29.3 (42.5)
Median (min, max)	16.8 (2.7, 163)
Mayo stage at screening, n (%)	
I	1 (7.7)
II	9 (69.2)
IIIa	3 (23.1)
AL amyloidosis in the heart, n (%)*	8 (61.5)
AL amyloidosis in the kidney, n(%)*	7 (53.8)
Prior anti-PCD treatment, n (%)	
Any anti-PCD treatment	9 (69.2)
Bortezomib	8 (61.5)
Dexamethasone	8 (61.5)
Cyclophosphamide	7 (53.8)
Daratumumab	7 (53.8)
Melphalan	2 (15.4)
Carfilzomib	2 (15.4)
Lenalidomide	2 (15.4)

PCD, plasma cell dyscrasia; SD, standard deviation.
*As noted by investigator.

Safety

- A summary of safety data is given in **Table 4**.
- The most-common TEAEs reported by patients were diarrhea (6; 46.2%), nausea (6; 46.2%), fatigue (5 (38.5), rash (5; 38.5%), and anemia (5; 38.5%).
- One patient discontinued due to hematologic disease progression.
- There were no deaths.

Table 4. Summary and Listing of Treatment-emergent Adverse Events (TEAEs) Experienced by ≥10% of Patients at a Median of 49 Weeks Treatment

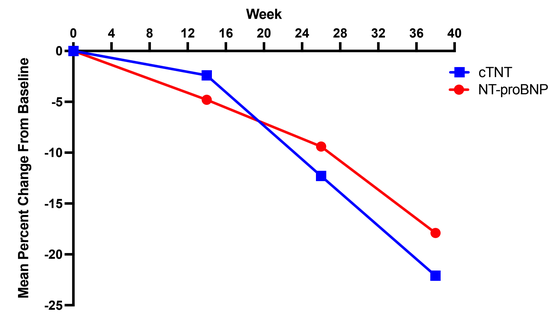
MedDRA Preferred Term	CAEL-101 + CyBorD N = 13
Patients with ≥1 TEAE	13 (100)
Patients with ≥1 TEAE possibly related to treatment	6 (46.2)
Patients with ≥1 TEAE of grade ≥3	2 (15.4)
Patients with ≥1 SAE	2 (15.4)
Discontinuations	1*
Deaths	0
System Organ Class/Preferred Term	
Gastrointestinal disorders	10 (76.9)
Constipation	4 (30.8)
Diarrhea	6 (46.2)
Nausea	6 (46.2)
Vomiting	2 (15.4)
General disorders and administrative site conditions	8 (61.5)
Fatigue	5 (38.5)
Skin and subcutaneous tissue disorders	6 (46.2)
Rash	5 (38.5)
Respiratory, thoracic, and mediastinal disorders	7 (53.8)
Cough	4 (30.8)
Dyspnea	4 (30.8)
Pleural effusion	2 (15.4)
Metabolism and nutrition disorders	4 (30.8)
Hyperkalemia	2 (15.4)
Vascular disorders	6 (46.2)
Hypertension	3 (23.1)
Blood and lymphatic system disorders	5 (38.5)
Anemia	5 (38.5)
Eye disorders	3 (23.1)
Infections and infestations	4 (30.8)
Musculoskeletal and connective tissue disorders	4 (30.8)
Arthralgia	2 (15.4)
Nervous system disorders	4 (30.8)
Headache	2 (15.4)
Sleep disorders and disturbances	3 (23.1)
Insomnia	3 (23.1)
Cardiac disorders	2 (15.4)
Investigations	2 (15.4)

Data presented as number of patients (%). *Patient discontinued due to hematologic disease progression.
CyBorD, cyclophosphamide-bortezomib-dexamethasone; MedDRA, Medical Dictionary for Medical Activities; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Clinical biomarker evaluation

- 8 patients had active cardiac disease at baseline, according to investigators. The median percent changes from baseline for both cTnT and NT-proBNP, surrogate markers for cardiac disease, were lower at each time point, suggesting improvement in cardiac disease **(Figure 2)**.

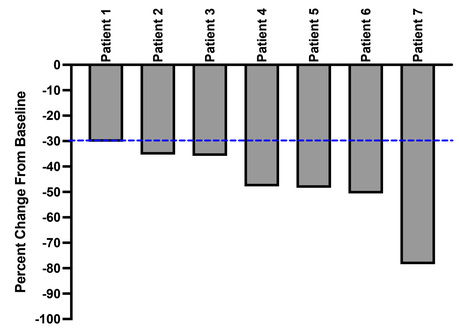
Figure 2. Median Percent Change From Baseline Over Time in cTnT and NT-proBNP for Cardiac Evaluable Patients (n = 8).



cTnT, cardiac troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide.

- Renal response was defined as ≥30% decrease in proteinuria following treatment.[8] All 7 patients who had active renal impairment at baseline showed a decrease of ≥30% in proteinuria from baseline to last measured time point **(Figure 3)**.

Figure 3. Percent Change From Baseline to Most Recent Measurement of Proteinuria in Renally Evaluable Patients



Dashed blue line indicates renal response.

DISCUSSION/CONCLUSIONS

- Data from this ongoing phase 2 study confirm that CAEL-101 in combination with CyBorD in patients with AL amyloidosis was generally well tolerated up to a median of 49 weeks.
  - There were no deaths in this cohort of patients.
- Clinical biomarker evaluations show cardiac disease improvements and renal response among the majority of patients who were diagnosed with cardiac or renal impairment at baseline, respectively.
- Two phase 3 studies (NCT04512235 and NCT04504825) are currently enrolling patients with AL amyloidosis in Mayo Stage IIIa and IIIb to further evaluate the efficacy and safety in these patients.

DISCLOSURES AND ACKNOWLEDGMENTS

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