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Safety and Tolerability of CAEL-101 in Combination With Cyclophosphamide-Bortezomib-Dexamethasone and Daratumumab in Patients With AL Amyloidosis

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BACKGROUND

- AL amyloidosis is a rare, progressive disorder caused by plasma cell dyscrasia (PCD), which results in misfolded immunoglobulin light chains that aggregate into amyloid fibrils.[1-4]
- Amyloid fibrils can deposit in tissues and organs such as heart, kidneys, and liver, causing significant mortality and morbidity.[1]
- Current treatment strategies rely on use of anti-PCD therapies to suppress synthesis of amyloidogenic light chain proteins; none directly target the amyloid deposited in tissues and organs.[5]
- CAEL-101 is an immunoglobulin that binds to misfolded light chain fibrils and has been shown to facilitate removal of amyloid deposited in tissues.[6-8]
- Results from the safety observation period of a 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.[9]
- Additional safety results through 4 weeks observed among patients receiving CAEL-101 at 1000 mg/m^2 in combination with CyBorD and daratumumab are presented.

AIM

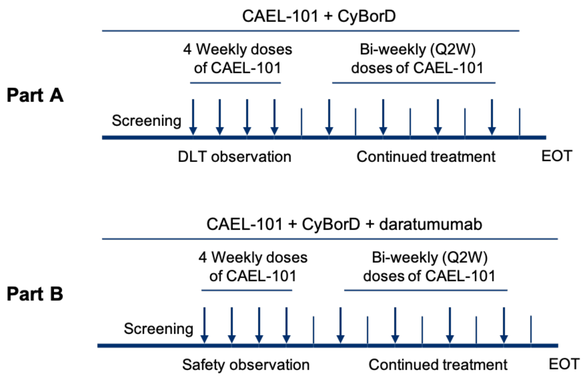
- To define the safety and tolerability through 4 weeks of the dose-limiting toxicity and safety observation period following treatment of patients with CAEL-101 and CyBorD (Part A) and CAEL-101, CyBorD, and daratumumab (Part B) in patients with AL amyloidosis.

METHODS

Study design

- This is an ongoing open-label study for CAEL-101 in 3 US centers in patients with AL amyloidosis (NCT04304144).
  - Patients continue to receive CAEL-101 per protocol until the end of the study or discontinuation.
- Part A consisted of a 3 + 3 dose-escalation design to determine the recommended dose for the phase 3 study in combination with CyBorD. Part B studied 1000 mg/m^2 CAEL-101 + CyBorD + daratumumab **(Figure 1)**.
- Staging was based on the European modification of the 2004 Mayo staging system.[4]
- The study included an initial safety observation period followed by a continued treatment period.

Figure 1. Study Design



CyBorD, cyclophosphamide-bortezomib-dexamethasone; DLT, dose-limiting toxicity; EOT, end of treatment.

Patients

- Adults with a confirmed diagnosis of AL amyloidosis, a minimum life expectancy of 6 months, and measurable hematologic disease were included in 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 other forms of amyloidosis, multiple myeloma, supine systolic blood pressure <90 mm Hg, or symptomatic orthostatic hypotension were excluded.

Treatment

- All patients were treated with 1000 mg/m^2 CAEL-101 plus standard of care CyBorD and daratumumab in Part B.

Endpoint assessments

- Primary: safety assessments included treatment-emergent adverse events (TEAEs), clinical laboratory tests, electrocardiograms, vital signs, and physical examinations through the first 4 weeks of treatment.
- Secondary: pharmacokinetic parameters (C_{max}, trough drug concentration) are summarized with descriptive statistics by cohort.

RESULTS

Patients

- The safety observation period was completed by 13 patients for Part A (CAEL-101 + CyBorD) and 11 patients for Part B (CAEL-101 + CyBorD + daratumumab).
- At baseline, 8/13 (61.5%) in the CAEL-101 + CyBorD group and 10/11 (90.9%) in the CAEL-101 + CyBorD + daratumumab group had cardiac involvement as noted by the investigator.
- For the 24 patients enrolled in the study, baseline demographics are given in **Table 1** and disease characteristics at baseline are given in **Table 2**.

Table 1. Baseline Demographics and Disease Status of Patients

Parameter	CAEL-101 + CyBorD (N = 13)	CAEL-101 + CyBorD + Dara (N = 11)
Age, y		
Mean (SD)	65.2 (10.9)	64.5 (6.7)
Median (min, max)	69.5 (47.6, 79.6)	63.0 (55.9, 77.2)
Sex, n (%)		
Male	10 (76.9)	7 (63.6)
Female	3 (23.1)	4 (36.4)
Race, n (%)		
Black or African American	2 (15.4)	0
White or Caucasian	11 (84.6)	11 (100)

CyBorD, cyclophosphamide-bortezomib-dexamethasone; Dara, daratumumab; PCD, plasma cell dyscrasia; SD, standard deviation.

Table 2. Baseline Disease Characteristics of Patients

Parameter	CAEL-101 + CyBorD (N = 13)	CAEL-101 + CyBorD + Dara (N = 11)
Duration since diagnosis, months		
Mean (SD)	29.3 (42.5)	17.1 (27.7)
Median (min, max)	16.8 (2.7, 163)	3.2 (0.2, 78.5)
Mayo stage at screening, n (%)		
I	1 (7.7)	1 (9.1)
II	9 (69.2)	8 (72.7)
IIIa	3 (23.1)	2 (18.2)
AL amyloidosis in the heart, n (%)*	8 (61.5)	10 (90.9)
Prior anti-PCD treatment, n (%)		
Any anti-PCD treatment	9 (69.2)	8 (72.7)
Bortezomib	8 (61.5)	5 (45.5)
Dexamethasone	8 (61.5)	6 (54.5)
Cyclophosphamide	7 (53.8)	6 (54.5)
Daratumumab	7 (53.8)	3 (27.3)
Melphalan	2 (15.4)	0
Carfilzomib	2 (15.4)	0
Lenalidomide	2 (15.4)	0
Birtamimab	0	2 (18.2)

CyBorD, cyclophosphamide-bortezomib-dexamethasone; PCD, plasma cell dyscrasia; SD, standard deviation.
*As noted by investigator.

Safety

- A summary of safety data is given in **Table 3**.
- The most common TEAEs through the first 4 weeks of treatment were:
  - In the CAEL-101 + CyBorD group: diarrhea (6; 46.2%), nausea (6; 46.2%), fatigue (5; 38.5%), rash (5; 38.5%), and anemia (5; 38.5%).
  - In the CAEL-101 + CyBorD + daratumumab group: nausea, constipation, and insomnia, each experienced by 3 (27.3%) patients.
  - There were 3 discontinuations, including 1 death.
- There was 1 death in the CAEL-101 + CyBorD + daratumumab group due to septic pneumonia; it was considered unrelated to treatment with CAEL-101.

Table 3. Summary of Treatment-emergent Adverse Events through 4 Weeks Experienced by ≥10% of Patients in Either Treatment Group

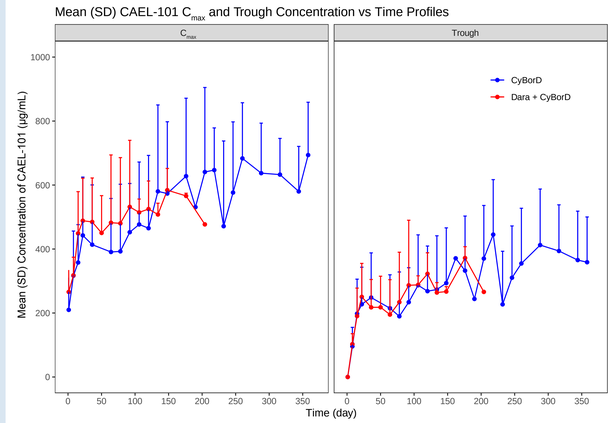
MedDRA Preferred Term	CAEL-101 + CyBorD N = 13	CAEL-101 + CyBorD + Dara N = 11
Patients with ≥1 TEAE	13 (100)	10 (90.9)
Patients with ≥1 possible TEAE related to treatment	6 (46.2)	0
Patients with ≥1 TEAE of Grade ≥3	2 (15.4)	4 (36.4)
Patients with ≥1 SAE	2 (15.4)	2 (18.2)
Discontinuations	1 (7.7)	2 (18.2)
Deaths	0	1 (9.1)
System Organ Class/Preferred Term		
Gastrointestinal disorders	10 (76.9)	5 (45.5)
Abdominal pain	0	2 (18.2)
Constipation	4 (30.8)	3 (27.3)
Diarrhea	6 (46.2)	1 (9.1)
Nausea	6 (46.2)	3 (27.3)
Vomiting	2 (15.4)	1 (9.1)
General disorders and administrative site conditions	8 (61.5)	3 (33.3)
Fatigue	5 (38.5)	2 (18.2)
Skin and subcutaneous tissue disorders	6 (46.2)	4 (36.4)
Rash	5 (38.5)	2 (18.2)
Paresthesia	0	2 (18.2)
Respiratory, thoracic, and mediastinal disorders	7 (53.8)	2 (18.2)
Cough	4 (30.8)	0
Dyspnea	4 (30.8)	0
Pleural effusion	2 (15.4)	0
Metabolism and nutrition disorders	4 (30.8)	3 (27.3)
Hyperkalemia	2 (15.4)	0
Hypokalemia	1 (7.7)	2 (18.2)
Vascular disorders	6 (46.2)	3 (27.3)
Hypertension	3 (23.1)	0
Hypotension	0	2 (18.2)
Blood and lymphatic system disorders	5 (38.5)	1 (9.1)
Anemia	5 (38.5)	0
Eye disorders	3 (23.1)	2 (18.2)
Vision blurred	0	2 (18.2)
Infections and infestations	4 (30.8)	2 (18.2)
Musculoskeletal and connective tissue disorders	3 (23.1)	2 (18.2)
Arthralgia	2 (15.4)	0
Nervous system disorders	4 (30.8)	2 (18.2)
Headache	2 (15.4)	1 (9.1)
Peripheral sensory neuropathy	1 (7.7)	2 (18.2)
Sleep disorders and disturbances	3 (23.1)	3 (27.3)
Insomnia	3 (23.1)	3 (27.3)
Cardiac disorders	2 (15.4)	2 (18.2)
Investigations	2 (15.4)	1 (9.1)

Data presented as number of patients (%).
CyBorD, cyclophosphamide-bortezomib-dexamethasone; Dara, daratumumab; MedDRA, Medical Dictionary for Medical Activities; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Pharmacokinetics

- The pharmacokinetics of CAEL-101 were similar when administered with CyBorD (Part A) or with CyBorD + daratumumab (Part B) **(Figure 2)**.
  - Addition of daratumumab did not alter exposure to CAEL-101.
  - The selected dose of 1000 mg/m^2 for CAEL-101 reached exposure levels to saturate the target.

Figure 2. Pharmacokinetic Profile, (a) C_{max}, (b) Mean Trough Concentration, of CAEL-101 When Administered With CyBorD or With CyBorD + Daratumumab



C_{max}, maximum concentration of drug.
CyBorD, cyclophosphamide-bortezomib-dexamethasone; Dara, daratumumab; SD, standard deviation.

DISCUSSION/CONCLUSIONS

- No new/additional safety signals were observed when CAEL-101 at 1000 mg/m^2 was added to CyBorD + daratumumab treatment, suggesting treatment with this combination is generally well tolerated in the first 4 weeks.
- Pharmacokinetic data demonstrate that adding daratumumab did not alter the exposure to CAEL-101.
- This study is currently ongoing, and longer-term safety data related to the combination of CAEL-101 with CyBord and CyBord + daratumumab will be forthcoming.
- 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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