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Phase 3 Randomized Trial to Evaluate the Impact of Anselamimab on All-Cause Mortality in Kappa Light Chain Amyloidosis

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INTRODUCTION

- Light chain (AL) amyloidosis is a plasma cell dyscrasia (PCD) characterized by kappa (κ) or lambda (λ) light chains aggregate into amyloid fibrils and deposit into organs, most commonly the heart and kidneys.[1] Amyloid fibrils have both mechanical and direct toxic effects on affected organs.[2,3]
- Anselamimab (CAEL-101), is an investigational mAb designed to complement anti-PCD therapy through accelerated removal of amyloid fibrils.
- Preclinical studies showed significant reduction or elimination of λ- and κ-derived amyloidomas, supporting direct amyloid clearance by Anselamimab.[4,5]
- Clinical trials demonstrated favorable tolerability up to 1000 mg/m², including in combination with standard therapies such as cyclophosphamide, bortezomib, dexamethasone (CyBorD) and daratumumab-based regimens, highlighting its potential in AL amyloidosis treatment.[6,7]
- Despite advances with Dara-CyBorD, patients with advanced cardiac AL amyloidosis—particularly Mayo stage IIIB disease—continue to experience poor survival outcomes, highlighting a significant unmet medical need for therapies that directly target amyloid deposits and improve organ function.[8]

OBJECTIVE

- To evaluate the efficacy and safety of anselamimab versus placebo, in addition to anti-PCD therapy, and to assess all-cause mortality, cardiovascular hospitalizations, and safety outcomes in patients with Mayo stage IIIa and IIIb AL amyloidosis enrolled in the CARES (Cardiac Amyloid Reaching for Extended Survival) studies (CAEL-101-302 and CAEL-101-301).

CONCLUSIONS

- Anselamimab is a first-in-class κ light chain–directed, first-line anti-fibril antibody intended to be used alongside anti-PCD therapy.
- While the composite primary endpoint was not met in the overall population, anselamimab improved survival by 62% and reduced the frequency of cardiovascular-related hospitalizations by 71% in patients with κ free light chain (FLC) involvement.
  - Anselamimab binds κ fibrils better than λ fibrils, which may be the reason for these results .
- Anselamimab was generally well tolerated in the overall population, including the κ subgroup. The majority of adverse events were consistent with the underlying medical condition and its treatment with anti-PCD therapy.
- Anselamimab offers a new therapeutic option for patients with newly diagnosed κ AL amyloidosis.

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Poster

Please scan this quick response (QR) code with your smartphone camera or app to access the published manuscript reporting the data presented in this poster.

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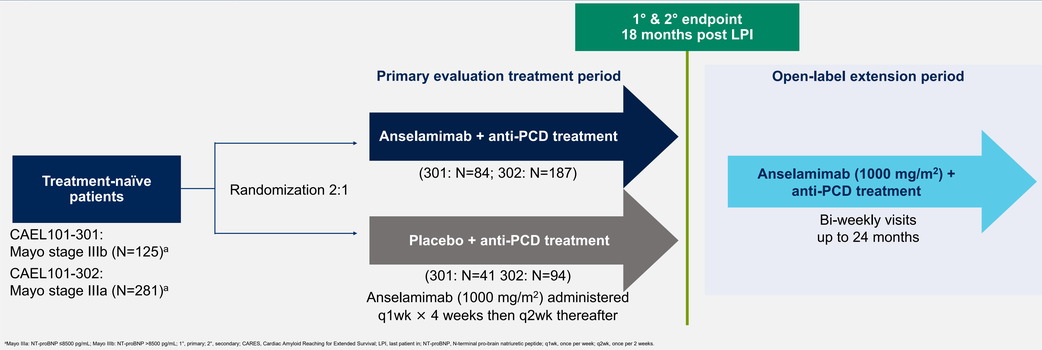
METHODS

Figure 1: CARES studies design



[a]Mayo IIIa: NT-proBNP ≤8500 pg/mL; Mayo IIIb: NT-proBNP >8500 pg/mL; 1°, primary; 2°, secondary; CARES, Cardiac Amyloid Reaching for Extended Survival; LPI, last patient in; NT-proBNP, N-terminal pro-brain natriuretic peptide; q1wk, once per week; q2wk, once per 2 weeks.

- Multicenter, double-blind, randomized, placebo-controlled trials (**Figure 1**).
- All participants received appropriate first-line treatment for PCD.
- First-line anselamimab (CAEL-101) or placebo was added to first-line anti-PCD treatment.

Endpoints and prespecified analyses

Primary endpoint

- Hierarchical composite of time to all-cause mortality (ACM) and frequency of cardiovascular-related hospitalizations (CVH) evaluated using the stratified Finkelstein–Schoenfeld test and win ratio estimation

Key secondary endpoints (change from baseline)

- Time to ACM and frequency of CVH analyzed separately
- Functional capacity based on the 6-minute walk test (6MWT)
- Cardiac function using:
  - Echocardiograph-based global longitudinal strain (GLS%)
  - Cardiac biomarker, NT-proBNP, levels
- Quality of life using
  - The Kansas City Cardiomyopathy Questionnaire–Overall Score
  - Short Form 36 v2–Physical Component Score

Prespecified analysis

- Primary and secondary endpoints based on light chain isotype (kappa or lambda)

RESULTS AND INTERPRETATION

- Baseline demographics and disease-related characteristics are summarized in **Table 1.**
- Treatment with anselamimab did not result in statistically significant improvement in the primary hierarchical composite endpoint of ACM and CVH (**Table 2**).
- Although there was no difference between treatment arms in ACM in the overall population, there was a 62% reduction (nominal P = 0.012) among patients with κ isotype, but no difference among patients with λ isotype (**Figure 2**).
- Reduction in ACM was observed among patients with κ isotype in Mayo stage IIIa (75%) and Mayo stage IIIb (48%) (**Figure 3**).
- Treatment with anselamimab resulted in nominally statistically significant improvement in both ACM (P = 0.012) and CVH (P = 0.028) in patients with κ isotype but not in patients with λ isotype (**Table 3**).
- Improvements were observed among patients with κ isotype Kansas City Cardiomyopathy Questionnaire–Overall Score (KCCQ–OS) and 6-minute walk test (6MWT) at week 50 (**Table 4**).

Table 1: Baseline demographics and disease related characteristics

Characteristic	Overall population		Kappa isotype	
	Anselamimab (N = 271)	Placebo (N = 135)	Anselamimab (N = 48)	Placebo (N = 24)
Median (range) age, y	66 (36–91)	69 (36–90)	68 (44–83)	70 (52–85)
Male, n (%)	183 (67.5)	88 (65.2)	37 (77.1)	18 (75.0)
Involved FLC isotype, n (%)				
Kappa	48 (17.7)	24 (17.8)	48 (100)	24 (100)
Lambda	219 (80.8)	109 (80.7)		
Missing	4 (1.5)	2 (1.5)		
Median (range) dFLC, mg/L	313 (11-10,057)	299 (4-3,651)	385 (11-4,668)	514 (4-3,651)
Median (range) NT-proBNP, ng/L	5458.0 (784-49,896)	5318.6 (742-49,896)	8215.1 (784-49,896)	5456.0 (742-35,418)
KCCQ-OS, mean (SD)	52.2 (22.0)	48.8 (22.6)	52.0 (22.6)	51.5 (22.5)
6MWT, mean (SD), m	295 (129)	276 (131)	307 (111)	276 (96)

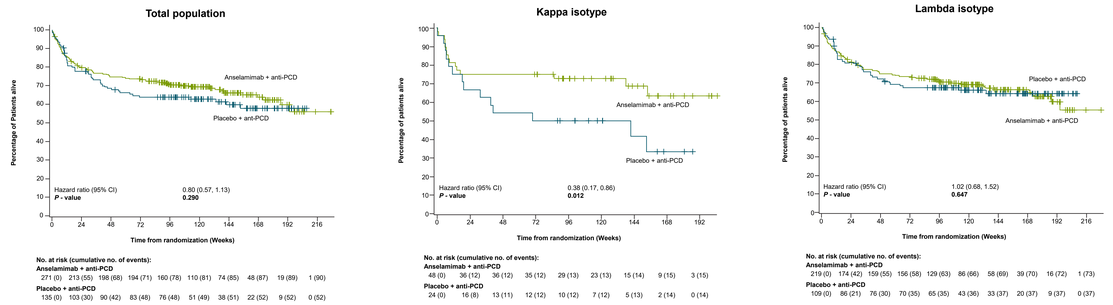
6MWT, 6-minute walk test; dFLC, difference between involved and uninvolved free light chain; FLC, free light chain; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire–Overall Score; NT-proBNP, N-terminal pro-bran natriuretic peptide.

Table 2: Primary efficacy endpoints: overall population

Endpoint		Anselamimab (N = 271)	Placebo (N = 135)	*P* - Value
ACM and CVH win ratio (95% CI)		1.11 (0.83, 1.50)		0.332
ACM	n (%)	90 (33.2)	52 (38.5)	
	Hazard ratio (95% CI)	0.80 (0.57, 1.13)		0.290
CVH	Frequency per year (95% CI)	0.59 (0.42, 0.83)	0.89 (0.55, 1.43)	
	Incidence risk ratio (95% CI)	0.67 (0.39, 1.15)		0.145

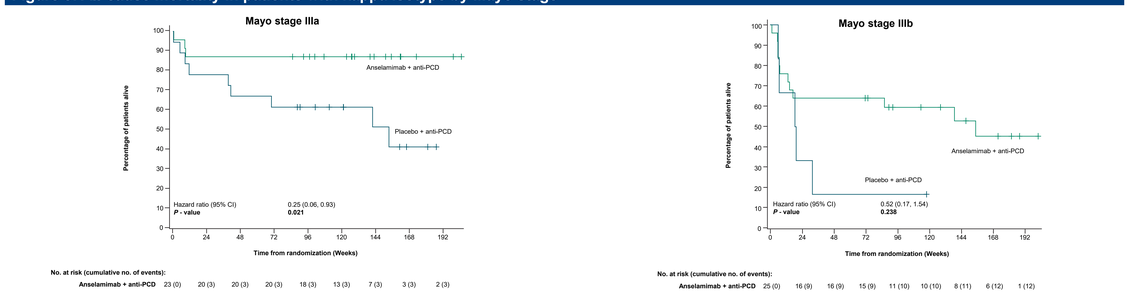
ACM, all-cause mortality; CVH, cardiovascular hospitalization.

Figure 2: All-cause mortality



ACM, all-cause mortality; PCD, plasma cell dyscrasia.

Figure 3: All-cause mortality in patients with kappa isotype by Mayo stage



ACM, all-cause mortality; PCD, plasma cell dyscrasia.

Table 3: Primary endpoints: kappa and lambda isotype

Endpoint		Kappa isotype			Lambda isotype		
		Anselamimab (N = 48)	Placebo (N = 24)	*P* - Value	Anselamimab (N = 219)	Placebo (N = 109)	*P* - Value
ACM and CVH win ratio (95% CI)		2.06 (0.98, 4.31)		0.100	0.90 (0.64, 1.27)		0.848
ACM	n (%)	15 (31.3)	14 (58.3)		73 (33.3)	37 (33.9)	
	Hazard ratio (95% CI)	0.38 (0.17, 0.86)		**0.012**	1.02 (0.68, 1.52)		0.647
CVH	Frequency/year (95% CI)	0.41 (0.20, 0.83)	1.40 (0.58, 3.36)		0.66 (0.44, 0.98)	0.76 (0.43, 1.34)	
	Incidence risk ratio (95% CI)	0.29 (0.10, 0.87)		**0.028**	0.87 (0.46, 1.65)		0.664

ACM, all-cause mortality; CVH, cardiovascular hospitalization.

Table 4: Key secondary endpoints at 50 weeks

Endpoint	Overall population			Kappa isotype		
	Anselamimab (N = 271)	Placebo (N = 135)	*P* - Value	Anselamimab (N = 48)	Placebo (N = 24)	*P* - Value
KCCQ–OS						
Patients evaluated (n)	152	75		28	12	
Mean (SD) change from baseline	13.10 (23.56)	14.02 (23.02)		18.46 (25.92)	9.82 (21.98)	
HLMD from placebo (95% CI)	–2.08 (–8.33, 4.42)		0.979	10.37 (–9.38, 25.56)		0.113
6MWT						
Patients evaluated (n)	158	72		29	11	
Mean (SD) change from baseline	36.38 (139.17)	64.54 (138.95)		41.01 (111.49)	35.11 (116.64)	
HLMD from placebo (95% CI)	–14.00 (–46.50, 16.75)		0.324	18.00 (–71.60, 95.92)		0.145
GLS%, mean (SD)						
Patients evaluated (n)	138	69		25	11	
Mean (SD) change from baseline	0.09 (3.77)	–0.09 (4.15)		–0.52 (3.97)	–1.11 (4.67)	
HLMD from placebo (95% CI)	–0.00 (–1.10, 1.10)		0.597	0.40 (–3.70, 4.30)		0.258

6MWT, 6-minute walk test; GLS, global longitudinal strain; HLMD, Hodges-Lehman median difference; KCCQ–OS, Kansas City Cardiomyopathy Questionnaire–Overall Score.

- Safety data were generally comparable between the anselamimab and placebo groups (**Table 5**).

Table 5: Summary of treatment-emergent adverse events

Description	Anselamimab (N = 271)	Placebo (N = 134)
Any AE	271 (100)	134 (100)
Any SAE	205 (75.6)	101 (75.4)
AEs leading to death	75 (27.7)	41 (30.6)
AEs leading to discontinuation of study intervention	36 (13.3)	14 (10.4)
AEs grade 3 or higher	218 (80.4)	113 (84.3)
Most common AEs in ≥25% of patients		
Diarrhea	107 (39.5)	55 (41.0)
Peripheral edema	103 (38.0)	51 (38.1)
Constipation	92 (33.9)	50 (37.3)
Nausea	91 (33.6)	43 (32.1)
COVID-19	80 (29.5)	32 (23.9)
Hypotension	73 (26.9)	32 (23.9)
Cough	64 (23.6)	34 (25.4)
Fatigue	59 (21.8)	34 (25.4)

AE, adverse event; COVID-19, corona virus disease of 2019; SAE, serious adverse event.