Results of the Phase 3 VITAL Study of NEOD001 (Birtamimab) Plus Standard of Care in Patients With Light Chain (AL) Amyloidosis Suggest Survival Benefit for Mayo Stage IV Patients

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INTRODUCTION

- AL amyloidosis is a rare, progressive, and typically fatal disease caused by production and extracellular deposition of soluble forms of misfolded immunoglobulin (Ig) light chain proteins[1-4]
- This condition is associated with significant cellular injury, tissue damage, and organ dysfunction that primarily affects the heart, kidneys, and nervous system, leading to high rates of morbidity and mortality[5]
- The mortality risk for newly diagnosed patients can be categorized using the validated Mayo Clinic Staging System, which is based on the level of cardiac biomarkers and plasma cell burden. Mayo Stages range from I to IV, with Stage IV patients having the highest risk for early mortality[6]
  - Median survival following a diagnosis of AL amyloidosis ranges from approximately 6 months to 3 years[2]
  - For patients with Mayo Stage IV disease, median survival from diagnosis is 5.8 months and the 5-year survival rate is 14%,[6] representing a significant unmet need in this population
  - Patients with AL amyloidosis also experience substantial impairment in health-related quality of life (HRQoL)[7]
- Incidence of AL amyloidosis is estimated to be between 3 and 14 cases per million persons per year, which translates to approximately 30,000 to 45,000 patients in the US and EU[2,8]
- There are currently no approved treatments for AL amyloidosis
- NEOD001 is an investigational humanized IgG1 kappa monoclonal antibody designed to neutralize soluble toxic aggregates of misfolded light chains and promote phagocytic clearance of organ-deposited amyloid[9,10]

AIM

- To evaluate the efficacy and safety of NEOD001 + standard of care (SOC) versus placebo + SOC in patients with AL amyloidosis by assessing time to all-cause mortality (ACM) or cardiac hospitalization (CH)

METHODS

- A Phase 3, multicenter, international, randomized, double-blind, placebo-controlled study (VITAL Amyloidosis Study; NCT02312206) was conducted in newly diagnosed, treatment-naive patients with AL amyloidosis and cardiac involvement, defined by all of the following:
  - Past or present clinical signs and symptoms supportive of a diagnosis of heart failure in the absence of an explanation for heart failure other than AL amyloidosis
  - Either an endomyocardial biopsy demonstrating AL amyloidosis or an echocardiogram demonstrating a mean left ventricular wall thickness at diastole >12 mm in the absence of other causes, which would adequately explain the degree of wall thickening
  - N-terminal pro-brain natriuretic peptide (NT-proBNP) ≥650 pg/mL and ≤8500 pg/mL
- Patients were stratified by Mayo Stage, renal stage, and 6-minute walk distance (6MWD) test and randomized in a 1:1 ratio to 24 mg/kg (up to a maximum dose of 2500 mg) intravenous (IV) NEOD001 + SOC or IV placebo + SOC every 28 days
  - Concomitant SOC consisted of a first-line bortezomib-containing chemotherapy regimen, administered subcutaneously (SC) on a weekly basis, with subsequent chemotherapy regimens prescribed as per SOC at the investigator's discretion
- Primary composite endpoint was time to ACM or CH (CH: >90 days after first study drug infusion) as centrally adjudicated by the Clinical Events Committee
- Key secondary endpoints included:
  - Change from baseline to month 9 in the Short Form-36 (SF-36) Version 2 Physical Component Summary (PCS) score
  - Change from baseline to month 9 in 6MWD
- Safety assessments included frequency and severity of adverse events (AEs)
- Statistical considerations
  - Study populations
    - Intent-to-treat (ITT) population: all randomized patients who received any amount of study drug
    - Safety population: all patients who received any amount of study drug
  - Statistical assumptions included an 18-month event rate in the control arm of 60%[6] and an 18-month event rate in the active arm of 42%, corresponding to a hazard ratio (HR) of 0.594
    - The study was designed to have 90% power with 2-sided alpha of 0.05
  - Based on results from the Phase 2b PRONTO study, which did not meet its primary or secondary endpoints, an unplanned futility analysis conducted in April 2018 based on the 103 adjudicated events favored NEOD001 and was not statistically significant for the primary endpoint
    - The study was terminated early by the sponsor due to the futility analysis, and post hoc analyses were subsequently performed
    - Therefore, the initial 12-month study period, which had the least censoring, was the basis of the subsequent modified intent-to-treat (mITT) analyses
    - The mITT efficacy analyses were conducted using a 12-month cutoff, except for SF-36 PCS and 6MWD, which were conducted at month 9

RESULTS

Demographics

- The study enrolled 260 participants (130 in each group) from 79 study sites over approximately 2 years
  - Study arms were well balanced with regard to demographics and baseline clinical characteristics (**Table 1**)
  - Approximately 30% of the patients enrolled in the study had Mayo Stage IV AL amyloidosis (n=77 of 260)

Table 1. Demographics and Clinical Characteristics

	All Patients (n=260)		Mayo Stage IV Patients (n=77)	
	NEOD001 + SOC (n=130)	Placebo + SOC (n=130)	NEOD001 + SOC (n=38)	Placebo + SOC (n=39)
Age, median (Q1, Q3)	64.2 (57.6, 70.9)	62.6 (57.0, 69.3)	63.6 (55.7, 69.8)	63.7 (57.0, 68.4)
Gender (male), n (%)	82 (63)	90 (69)	25 (66)	28 (72)
Gender (female), n (%)	48 (37)	40 (31)	13 (34)	11 (28)
Ethnicity, n (%)				
Hispanic or Latino	2 (1.5)	2 (1.5)	0	0
Not Hispanic or Latino	116 (89.2)	122 (93.8)	34 (89.5)	36 (92.3)
Not provided or unknown	12 (9.2)	6 (4.6)	4 (10.5)	3 (7.7)
Race, n (%)				
White	118 (90.8)	120 (92.3)	36 (94.7)	36 (92.3)
Black or African American	9 (6.9)	3 (2.3)	2 (5.3)	2 (5.1)
Asian	2 (1.5)	2 (1.5)	0	0
Other	1 (0.8)	5 (3.8)	0	1 (2.6)
Age at AL amyloidosis diagnosis (years), median (Q1, Q3)	64.10 (57.51, 70.91)	62.41 (56.83, 69.29)	63.48 (55.61, 69.66)	63.75 (56.83, 68.47)
Duration since AL amyloidosis diagnosis (months), median (Q1, Q3)	1.31 (0.92, 1.87)	1.48 (0.95, 2.17)	1.15 (0.69, 1.58)	1.45 (0.89, 1.81)
Number of derived involved organs at baseline, median (Q1, Q3)	2.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)
Screening NT-proBNP ≥1800 pg/mL, n (%)	95 (73.1)	100 (76.9)	38 (100)	39 (100)
Baseline NT-proBNP (pg/mL), median (Q1, Q3)	3146 (1650, 5173)	3184 (1910, 5551)	5142 (3228, 5939)	5415 (4054, 8073)
Baseline troponin-T (ng/mL)[a], median (Q1, Q3)	0.03 (0.03, 0.06)	0.03 (0.03, 0.08)	0.05 (0.04, 0.09)	0.09 (0.06, 0.13)
Baseline FLC ratio, median (Q1, Q3)	0.10 (0.03, 0.32)	0.11 (0.04, 0.51)	0.05 (0.02, 0.08)	0.05 (0.03, 11.14)
Baseline dFLC[b] (mg/dL), median (Q1, Q3)	26.31 (13.83, 53.05)	38.18 (18.00, 63.06)	44.44 (25.13, 56.17)	57.42 (35.52, 106.28)
Mayo Stage, n (%)				
I	11 (8)	10 (8)	N/A	N/A
II	34 (26)	28 (22)	N/A	N/A
III	47 (36)	53 (41)	N/A	N/A
IV	38 (29)	39 (30)	38 (100)	39 (100)

[a]Mayo Stage criteria for troponin-T levels were modified from a value of 0.025 ng/mL cited in Kumar et al, 2012,[6] to 0.03 ng/mL, the lowest validated determination for the commercially available test.
[b]Baseline dFLC is calculated only for patients with an abnormal baseline FLC ratio (Kappa/Lambda <0.26 or >1.65) and is defined as the difference between involved and uninvolved FLCs.
dFLC, difference between involved minus uninvolved serum free light chains; FLC, free light chain; NT-proBNP, N-terminal pro-brain natriuretic peptide; SOC, standard of care.

Efficacy Endpoints

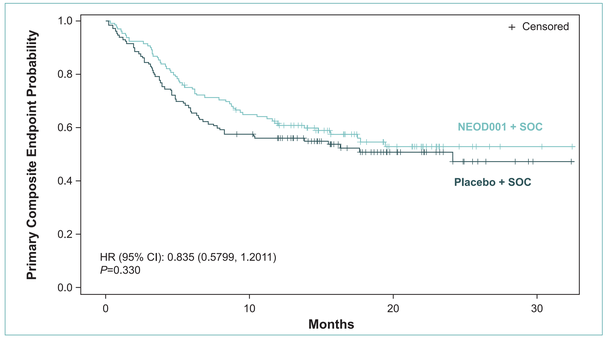
- Consistent with the futility analysis, the final primary endpoint analysis (ITT) showed no statistically significant difference between NEOD001 + SOC and placebo + SOC in the primary composite efficacy endpoint of time to ACM or CH: HR, 0.835; 95% CI, 0.5799–1.2011; *P*=0.330 (**Table 2**; **Figure 1**)
  - Favorability of HR for NEOD001 was largely attributable to time to ACM rather than CH
  - No statistically significant differences were observed for any key secondary endpoint

Table 2. ITT and mITT Results

Mayo Stage	Endpoint[a,b]	N	ITT HR[c] (95% CI) *P*-value[d]	mITT[b] (12 months) HR[c] (95% CI) *P*-value[d]
All	Composite primary endpoint	260	0.835 (0.5799–1.2011) *P*=0.3300	0.784 (0.5341–1.1507) *P*=0.2129
Stage I–III	All-cause mortality	183	1.334 (0.7386–2.4107) *P*=0.3375	1.244 (0.6435–2.4035) *P*=0.5159
Stage IV	All-cause mortality	77	0.544 (0.2738–1.0826) *P*=0.0787	0.498 (0.2404–1.0304) *P*=0.0556

[a]Composite primary endpoint = all-cause mortality or cardiac hospitalization (>90 days). [b]All-cause mortality regardless of cardiac hospitalization. [c]HR <1.0 in favor of NEOD001 + SOC; HR >1.0 in favor of placebo + SOC. [d]All *P*-values other than for the composite primary endpoint for the ITT analysis are descriptive; *P*-value derived from log rank test. [e]mITT = initial 12-month time period.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mITT, modified intent-to-treat.

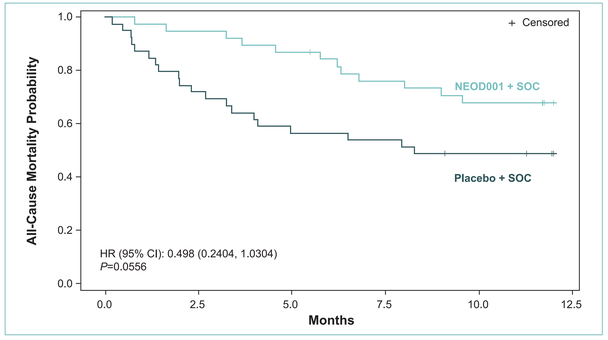
Figure 1. Kaplan-Meier Estimate of Primary Composite Endpoint for All Mayo Stage Disease Groups (N=260)



ACM, all-cause mortality; CH, cardiac hospitalization; HR, hazard ratio; ITT, intent-to-treat; SOC, standard of care.

- Further mITT analyses by prognostic Mayo Staging suggest benefits favoring NEOD001 for both the primary endpoint and ACM (HR=0.498; **Figure 2**) in patients with Mayo Stage IV disease (n=77), who have the highest risk of early mortality
  - Median overall survival in Mayo Stage IV (mITT) was 8.3 months in the placebo + SOC arm and was not reached (>12 months) in the NEOD001 + SOC arm
  - Among Mayo Stage IV patients, most deaths occurred within the first 9 months in the NEOD001 + SOC group versus in the first 3 months for the placebo + SOC group

Figure 2. Kaplan-Meier Estimate of ACM in Patients With Mayo Stage IV Disease (mITT Population: 12 Months)



ACM, all-cause mortality; HR, hazard ratio; mITT, modified intent-to-treat; SOC, standard of care.

- In the mITT analysis, SF-36v2 PCS scores showed significantly less deterioration at 9 months (*P*=0.0258) in the NEOD001 + SOC arm compared with the placebo + SOC arm (**Table 3**)
- Change from baseline in 6MWD was significantly greater at month 9 (*P*=0.0214) in the NEOD001 + SOC group versus the placebo + SOC group in the mITT population (**Table 3**)

Table 3. Change From Baseline in Key Secondary Efficacy Endpoints in Patients With Mayo Stage IV Disease at Month 9 (mITT Population)

Endpoints	NEOD001 + SOC (n=38)	Placebo + SOC (n=39)	*P*-value
SF-36v2 PCS[a], LS mean (SE) 95% CI	3.40 (3.58) -3.62, 10.42	-2.14 (3.47) -8.93, 4.66	0.0258
6MWD[b], rank, mean (SD) Range	44.9 (20.3) 5.5 to 77	33.3 (23.0) 1 to 74	0.0214

[a]Estimates of the LS mean, SE, and 95% CI for each treatment group were estimated using an MMRM methodology including fixed effects for treatment group, categorical time point (all postbaseline visits), treatment group by visit interaction, IWRS stratification factors (Renal Stage: I, II/III; baseline 6MWT distance: <300 meters, ≥300 meters), the associated baseline value as a covariate, and a compound symmetry covariance structure to model the within-subject errors.
[b]Prior to analysis, subjects were ranked from worst to best following the 7-step algorithm.
6MWD, 6-minute walk distance; CI, confidence interval; IWRS, interactive web response system; LS, least squares; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures; SF-36v2 PCS, Short Form-36 Version 2 Physical Component Summary; SE, standard error; SOC, standard of care.

Safety Analysis

- Overall, NEOD011 was generally safe and well tolerated
- 257 patients in the safety population experienced 1 or more treatment-emergent AEs (TEAEs, **Table 4**)
  - The NEOD001 and control arms had similar frequencies of TEAEs (98% and 100%, respectively) and serious TEAEs (69% and 70%, respectively)
  - The most common TEAEs were fatigue, nausea, peripheral edema, constipation, and diarrhea, and were similar in both treatment arms
  - Of the serious TEAEs, 95% were considered not related to NEOD001
- Overall safety results (**Table 4**) were generally similar within and across Mayo Stages (data not shown)

Table 4. Overall Summary of Treatment-Emergent Adverse Events (Safety Population)

	NEOD001 + SOC (n=130)	Placebo + SOC (n=130)
Total number of TEAEs, n	3039	2585
Patients reporting ≥1 TEAE	127 (97.7)	130 (100)
TEAE by maximum CTCAE grade[a]		
Grade 1 – Mild	1 (0.8)	3 (2.3)
Grade 2 – Moderate	29 (22.3)	25 (19.2)
Grade 3 – Severe	59 (45.4)	62 (47.7)
Grade 4 – Life-threatening	19 (14.6)	12 (9.2)
Grade 5 – Fatal	19 (14.6)	28 (21.5)
TEAE CTCAE grade ≥3	97 (74.6)	102 (78.5)
Most commonly reported TEAE by preferred term		
Fatigue	57 (43.8)	52 (40.0)
Nausea	56 (43.1)	44 (33.8)
Peripheral edema	56 (43.1)	56 (43.1)
Constipation	55 (42.3)	55 (42.3)
Diarrhea	52 (40.0)	54 (41.5)

Data reported as n (%) unless otherwise noted.
[a]Patients reporting more than 1 adverse event are counted only once using the closest relationship to study drug, as assessed by the investigator.
CTCAE, Common Terminology Criteria for Adverse Events; SOC, standard of care; TEAE, treatment-emergent adverse events.

CONCLUSIONS

- The VITAL study, as designed, would not have achieved statistical significance for the primary and secondary outcome measures
- However, post hoc analyses suggest a potential survival benefit with NEOD001 in the category of patients at the highest risk for early mortality (Mayo Stage IV)
  - NEOD001 treatment was also associated with significantly less deterioration in quality of life among patients with Mayo Stage IV AL amyloidosis as measured by the Short Form-36 Version 2 Physical Component Summary Score
  - In addition, NEOD001 treatment was associated with a significantly improved functioning among patients with Mayo Stage IV AL amyloidosis as measured by the 6-minute walk distance test
- Overall, the incidence, severity, and seriousness of adverse events were similar in each treatment arm, indicating that NEOD001 was generally safe and well tolerated
- Given that patients with Mayo Stage IV AL amyloidosis are at the highest risk for early mortality and represent a substantial unmet need, additional clinical studies of NEOD001 are warranted

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