NEOD001 Demonstrates Organ Biomarker Responses in Patients With Light Chain and Persistent Amyloidosis Organ Dysfunction Independently of Previous Hematologic Responses

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INTRODUCTION

Light chain (AL) amyloidosis is a rare, progressive, and typically fatal disease caused by extracellular deposition of misfolded light chains. Soluble toxic aggregates and deposited fibrils (amyloid) lead to progressive failure of critical organs and systems (eg. heart, kidneys, nervous system), causing significant morbidity and mortality.¹⁻³

- Current treatment approaches reduce LC production by targeting plasma cells, they do not address the amyloid deposited in organs³⁻⁶ and ~75% of patients do not achieve organ responses.⁷⁻¹²
- NEOD001 is a first-in-class investigational antibody that specifically targets disease-causing, misfolded LC aggregates in AL amyloidosis^{13,14}

OBJECTIVES

- To assess safety and tolerability of NEOD001 and determine MTD
- To explore NEOD001 organ responses in AL patients and the relationship with previously achieved hematologic responses or previous PCD therapy

METHODS

Study Design

- Participants were ≥18 years of age, and each had a diagnosis of AL amyloidosis, Eastern Cooperative Oncology Group performance status 0 to 2, evidence of ongoing systemic organ dysfunction, at least partial hematologic response to ≥1 previous systemic therapy (stem cell transplantation allowed), life expectancy of >3 months, no symptoms of multiple myeloma, and no advanced organ dysfunction
- NEOD001 was evaluated in a phase 1/2 study with 2 components (**Figure 1**)

-The dose-escalation phase assessed safety/tolerability in a 3+3 design and determined the maximum tolerated dose (MTD; 24 mg/kg)

-The expansion phase further assessed the safety, preliminary efficacy, and pharmacokinetics of NEOD001 at the MTD in 42 patients in prospectively defined cohorts

Figure 1. NEOD001 phase 1/2 study design (n = 69).

AL, amyloid light chain; IV, intravenous; MTD, maximum tolerated dose; NT-proBNP, N-terminal fragment of probrain natriuretic peptide; PK, pharmacokinetics; TP3D, recommended phase 3 dose. A maximum of 2500 mg per dose permitted – 24 mg/kg selected based on patient body weight. Cardiac and renal best responses were assessed using previously described criteria: cardiac,⁹ >30% and >300 ng/L decrease in patients with baseline NT-proBNP ≥650 ng/L; renal,¹⁵ decrease in proteinuria by ≥30% or below 0.5 g/24 h without renal progression. Neuropathy response was defined as no change, a decrease, or an increase of <2 points from baseline in Neuropathy Impairment Score–Lower

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ACKNOWLEDGMENTS

We thank the patients for their participation in this clinical trial. Medical writing assistance was provided by ApotheCom (San Francisco, CA, USA) and was funded by Prothena Biosciences Inc.

Mechanism of action of NEOD001

The proposed mechanism of action of NEOD001 is to neutralize soluble toxic aggregates and induce clearance of insoluble deposited fibrils through phagocytosis¹³

RESULTS

Safety and Dosing Summary

- The total number of infusions administered was 994 (n = 69 patients), and the mean treatment duration (every 28 days) was 12.8 months (range, 2-35)
- NEOD001 was safe and well tolerated:

No dose-limiting toxicities; No treatment-related discontinuations or serious adverse events (AEs); No persistent antidrug antibodies; One treatment-emergent death, which was not related to NEOD001

Table 2. TEAEs Occurring in ≥10% of Patients, Regardless of Relationship to NEOD001

Most Common TEAEs (preferred terms)	Total Patients N = 69	
	Total AEs, N (%)	Grade ≥3, n (%)
Fatigue	24 (34.8)	1 (1.4)
Nausea	22 (31.9)	0
Upper respiratory tract infection	21 (30.4)	0
Peripheral edema	19 (27.5)	0
Diarrhea	18 (26.1)	0
Anemia	15 (21.7)	1 (1.4)
Increased blood creatinine	13 (18.8)	0
Dizziness	12 (17.4)	0
Cough	11 (15.9)	0
Constipation	10 (14.5)	0
Headache	10 (14.5)	0
Vomiting	10 (14.5)	0
Dyspnea	9 (13.0)	0
Pain in extremity	9 (13.0)	0
Back pain	8 (11.6)	0
Muscle spasms	8 (11.6)	0
Rash	7 (10.1)	0
Urinary tract infection	7 (10.1)	0

AEs, adverse events; TEAEs, treatment-emergent adverse events.

Cardiac Biomarker Responses

- In a best response analysis of the cardiac-evaluable patients (N = 36), 53% (n = 19) met criteria for cardiac response, and the remaining patients met criteria for stable disease (**Figure 2**)
- Median time to initial response was 2 months

Figure 2. Cardiac biomarker best response analysis.

NT-proBNP, N-terminal fragment of probrain natriuretic peptide. Evaluable patients had baseline NT-proBNP ≥650 pg/mL without progressive renal dysfunction. Response: >30% and >300 pg/mL decrease in NT-proBNP. Progression: >30% and >300 pg/mL increase in NT-proBNP. Stable disease: neither response nor progression. Red lines denote response (lower) or progression (upper). ^a30% decline, 453 pg/mL reduction from baseline. ^b42% decline, 271 pg/mL reduction from baseline.

Renal Biomarker Responses

- In a best response analysis of the renal-evaluable patients (N = 36), 64% (n = 23) met criteria for renal response,¹⁵ and the remaining patients met criteria for stable disease (**figure 3**).
- Median time to initial response was 4 months.

Figure 3. Renal biomarker best response analysis.

Evaluable patients had a baseline proteinuria level of ≥5 g/24 hours. Renal response was defined as >30% decrease in proteinuria or a decrease in proteinuria to <0.5 g/24 hours in the absence of renal progression, which was defined as >25% worsening in estimated glomerular filtration rate. Stable disease was defined as neither response nor progression. Red line denotes response threshold.

Cardiac and renal Responses to NEOD001 Were Unrelated to Either Previous HR or Previous PCD Therapy

- Cardiac responses to NEOD001 were not significantly related to time since best or last HR, depth of best or last HR (**Figure 4**), or time since last PCD therapy (**Figure 5**)
- Cardiac responses to NEOD001 were not significantly related to the type of previous PCD therapy
- Renal responses to NEOD001 were not significantly related to time since best or last HR, depth of best or last HR, time since last PCD therapy, or type of last PCD therapy

Figure 4. (A) Time since patients' best or last HR to previous PCD therapy and (B) depth of previous best or last HR did not impact NEOD001 cardiac responses.

Figure 5. Cardiac responses to NEOD001 were similar in patients with durations <6 versus ≥6 months or <12 versus ≥12 months since last PCD therapy.

CONCLUSION

- NEOD001 was safe and well tolerated
- Observed cardiac and renal best response rates were 53% and 64% in evaluable patients, respectively
- NEOD001 Organ responses were relatively short, Median times to NEOD001 organ response were 2 months (cardiac) and 4 months (renal)
- NEOD001 cardiac and renal responses did not appear related to **time** since best or last HR, **depth** of best or last HR, **time** since last PCD therapy, or **type** of last PCD therapy, indicating that responses in this study were likely not due to previous therapies or hematologic responses
- Ongoing studies
- Global phase 2b PRONTO study: previously treated patients with persistent cardiac dysfunction (NCT02632786)
- Global phase 3 VITAL study: treatment-naïve patients with AL amyloidosis and cardiac dysfunction (NCT02312206)