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The PRONTO Amyloidosis Study: A Randomized, Double-Blind, Placebo-Controlled, Global, Phase 2b Study of NEOD001 in Previously Treated Patients With Light Chain Amyloidosis and Persistent Cardiac Dysfunction

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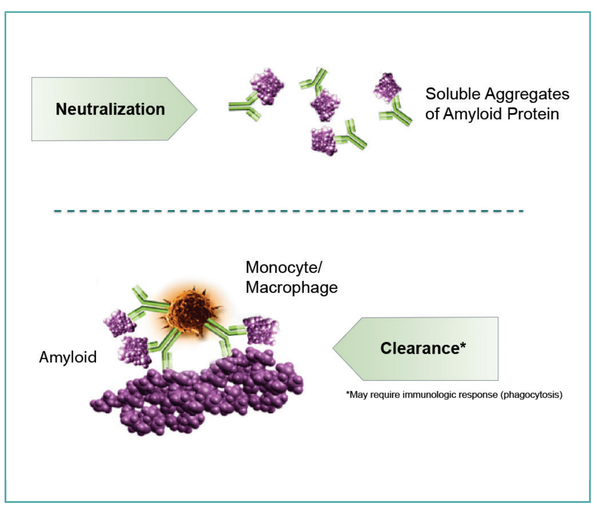
INTRODUCTION

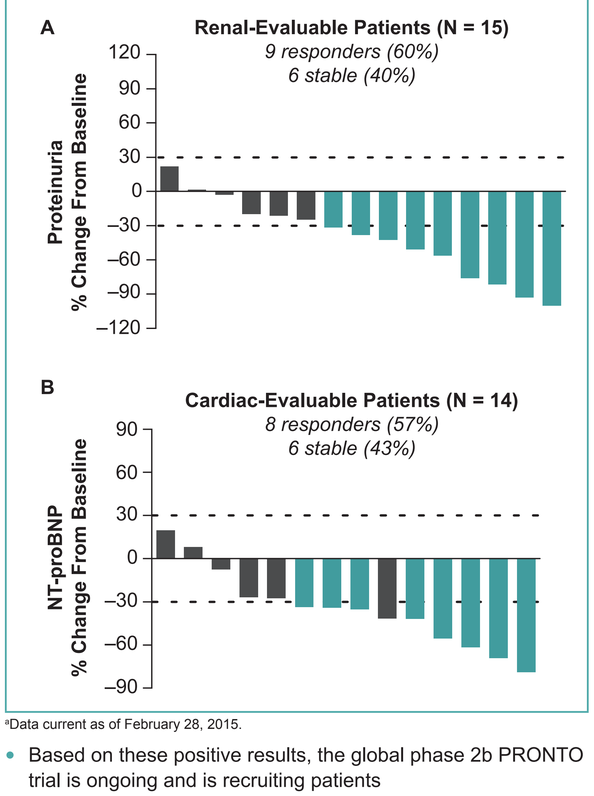
- In amyloid light chain (AL) amyloidosis, misfolded immunoglobulin light chain (LC) protein, produced by clonal plasma cells, deposits in organs and progressively affects their function[1,2]
- Multiple organs can be impacted, including the heart (70%), kidneys (70%), peripheral and autonomic nervous systems (15%-20%), liver (17%), and soft tissue (17%)[3-6]
- Diagnosis is often delayed; in a survey of 533 patients, 37% received the diagnosis ≥1 year after symptom onset, and a majority saw ≥3 different types of physicians before receiving the correct diagnosis[7]
- Approximately two-thirds of patients with AL amyloidosis present with 1 or 2 major organ systems involved, and one-third of patients present with >2 organ systems involved[8]
- Most deaths are attributed to cardiac involvement; the survival rate is poor if cardiac involvement is significant[1,2,9]
- No treatments have been approved for AL amyloidosis; the current standard of care is aimed at reducing or eliminating the underlying plasma cell dyscrasia
- Treatment options include high-dose chemotherapy with stem cell transplantation, alkylating agents, steroids, proteasome inhibitors, and immunomodulatory drugs[2,4,10,11]
  - These do not directly address the amyloid protein already accumulated in organs, and they are associated with significant toxicity
  - Many patients have persistent and progressive organ dysfunction despite hematologic response with plasma cell–directed therapy
- Organ response has the highest correlation with survival; safe and effective therapy that specifically improves organ dysfunction is urgently needed
- In patients with cardiac dysfunction, changes in N-terminal probrain natriuretic peptide (NT-proBNP) predict cardiac prognosis and survival[8]
- NEOD001 is an investigational antibody directed against a cryptic epitope on amyloid fibrils
  - NEOD001 specifically targets misfolded LC
  - NEOD001 may directly neutralize soluble LC aggregates and mark insoluble amyloid deposits for phagocytic clearance from organs and tissue (**Figure 1**)
  - Amyloid removal may contribute to clinical benefit

Figure 1. A mechanism of action of NEOD001.



- Interim results of an ongoing phase 1/2 study (NCT02613182) in 27 patients with AL amyloidosis and persistent organ dysfunction show monthly NEOD001 infusions were well tolerated, with no reported hypersensitivity reactions. In a best response analysis of patients with measurable organ involvement, 60% met renal (**Figure 2A**) and 57% met cardiac (**Figure 2B**) response criteria[12]

Figure 2. (A, B) Organ response to NEOD001.[a]



[a]Data current as of February 28, 2015.

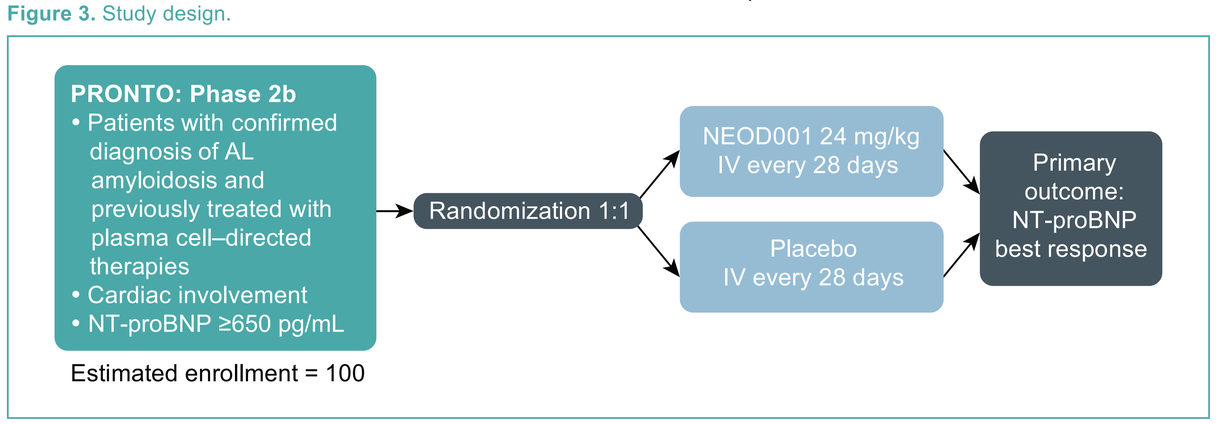
- Based on these positive results, the global phase 2b PRONTO trial is ongoing and is recruiting patients

METHODS

Study Design

- PRONTO is an international, multicenter, randomized, double-blind, placebo-controlled, phase 2b clinical trial of NEOD001 compared with placebo in patients with AL amyloidosis who achieved hematologic response to previous systemic treatment but have persistent cardiac dysfunction (NCT02632786) (**Figure 3**)
- 100 patients with AL amyloidosis will be randomly assigned in a 1:1 ratio to receive 24 mg/kg NEOD001 (established as the maximum tolerated dose in the phase 1/2 study) or placebo (normal saline) intravenously every 28 days
- Patients will be stratified based on 2 factors
  - Response to first-line therapy: complete (CR) or very good partial response (VGPR) vs partial response (PR)
  - NT-proBNP <1800 pg/mL vs NT-proBNP ≥1800 pg/mL
- Study duration for each subject will be ≤13 months (1-month screening phase followed by 12-month treatment phase)

Figure 3. Study design.



IV, intravenously; NT-proBNP, N-terminal probrain natriuretic peptide.

Key Patient Eligibility Criteria

- Inclusion and exclusion criteria will be reviewed to assess eligibility (**Table 1**)

Table 1. Key Patient Eligibility Criteria

Inclusion	Exclusion
• ≥18 years old • Diagnosis of AL amyloidosis confirmed by — Histochemical diagnosis (Congo red) OR electron microscopy AND — Immunohistochemistry OR mass spectrometry • ≥1 previous plasma cell–directed therapy with at least hematologic PR • Cardiac involvement — Stable NT-proBNP ≥650 pg/mL without renal failure • eGFR ≥30 mL/min/1.73 m^2 as estimated by the CKD-EPI equation	• Non-AL amyloidosis • Diagnosis of multiple myeloma according to the International Myeloma Working Group definition • NT-proBNP >5000 pg/mL • Plasma cell–directed chemotherapy within 6 months before enrollment • Autologous stem cell transplantation within 12 months before enrollment

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal probrain natriuretic peptide; PR, partial response.

Study End Points

- Primary and secondary end points of this study are shown in **Table 2**

Table 2. Primary and Secondary End Points

Primary
• Cardiac best response as measured by NT-proBNP over 12 months (**Table 3**)
Key secondary
• Change in SF-36 PCS from baseline to 12 months • Change in 6MWT distance from baseline to 12 months • For renal-evaluable subjects, renal best response as measured by proteinuria over 12 months (**Table 4**) • For patients with neuropathy, change in NIS-LL over 12 months • Change in KCCQ from baseline to 12 months • Progression-free survival over 12 months • Safety of NEOD001 evaluated through vital signs, ECG, laboratory tests, and AEs over 12 months

AEs, adverse events; ECG, electrocardiography; KCCQ, Kansas City Cardiomyopathy Questionnaire; NIS-LL, Neuropathy Impairment Score-Lower Limb; NT-proBNP, N-terminal probrain natriuretic peptide; PCS, Physical Component Summary; SF-36, 36-Item Short-Form Health Survey; 6MWT, Six-Minute Walk Test.

Table 3. Cardiac Response and Progression Criteria[8]

Response	Progression
NT-proBNP response • >30% and >300 ng/L decrease in patients with baseline NT-proBNP ≥650 ng/L OR NYHA class response • ≥2 class decrease in patients with baseline NYHA class 3 or 4	NT-proBNP progression • >30% and >300 ng/L increase[a]

NT-proBNP, N-terminal probrain natriuretic peptide; NYHA, New York Heart Association.
[a]Patients with progressively worsening renal function cannot be scored for NT-proBNP progression.

Table 4. Renal Response and Progression Criteria[5]

Response	Progression
≥30% decrease in proteinuria or decrease in proteinuria below 0.5 g/24 hours in the absence of renal progression	≥25% decrease in eGFR

eGFR, estimated glomerular filtration rate.

Efficacy

- End points will be analyzed in the modified intention-to-treat population (all patients who received ≥1 dose of study drug)
- For the primary analysis, NT-proBNP best response will be compared across both study arms using the 2-sided Mantel-Haenszel test (α = 0.05)
- If the outcome of the primary analysis is significant, key secondary end points will be analyzed

Safety

- All safety analyses will be based on the safety population (all subjects who receive the study drug)

SUMMARY

- There is a substantial need for a safe and effective therapy that specifically attenuates organ dysfunction in patients with AL amyloidosis
- NEOD001 is an investigational antibody designed to target misfolded LCs. It is part of an emerging class of potential treatments that may improve organ function
- Interim data show that NEOD001 was safe and well tolerated in an ongoing phase 1/2 study in 27 patients with AL amyloidosis who achieved hematologic response to chemotherapy but who had persistent organ dysfunction. Monthly infusions produced encouraging organ response rates, and expansion phase data are anticipated in Q3 2016
- The global phase 2b PRONTO Amyloidosis Study of NEOD001 in previously treated patients with diagnosed AL amyloidosis and persistent cardiac dysfunction is ongoing and is enrolling patients
- NEOD001 is also being evaluated in an ongoing global phase 3 VITAL Amyloidosis Study in treatment-naive patients with newly diagnosed, confirmed AL amyloidosis with cardiac involvement

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http://1.usa.gov/1t1VRyE

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