ORIGINAL ARTICLE

Phase 1 Trial of Antibody NI006 for Depletion of Cardiac Transthyretin Amyloid

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ABSTRACT

BACKGROUND

Transthyretin amyloid (ATTR) cardiomyopathy is a progressive and fatal disease caused by misfolded transthyretin. Despite advances in slowing disease progression, there is no available treatment that depletes ATTR from the heart for the amelioration of cardiac dysfunction. NI006 is a recombinant human anti-ATTR antibody that was developed for the removal of ATTR by phagocytic immune cells.

METHODS

In this phase 1, double-blind trial, we randomly assigned (in a 2:1 ratio) 40 patients with wild-type or variant ATTR cardiomyopathy and chronic heart failure to receive intravenous infusions of either NI006 or placebo every 4 weeks for 4 months. Patients were sequentially enrolled in six cohorts that received ascending doses (ranging from 0.3 to 60 mg per kilogram of body weight). After four infusions, patients were enrolled in an open-label extension phase in which they received eight infusions of NI006 with stepwise increases in the dose. The safety and pharmacokinetic profiles of NI006 were assessed, and cardiac imaging studies were performed.

RESULTS

The use of NI006 was associated with no apparent drug-related serious adverse events. The pharmacokinetic profile of NI006 was consistent with that of an IgG antibody, and no antidrug antibodies were detected. At doses of at least 10 mg per kilogram, cardiac tracer uptake on scintigraphy and extracellular volume on cardiac magnetic resonance imaging, both of which are imaging-based surrogate markers of cardiac amyloid load, appeared to be reduced over a period of 12 months. The median N-terminal pro–B-type natriuretic peptide and troponin T levels also seemed to be reduced.

CONCLUSIONS

In this phase 1 trial of the recombinant human antibody NI006 for the treatment of patients with ATTR cardiomyopathy and heart failure, the use of NI006 was associated with no apparent drug-related serious adverse events. (Funded by Neurimmune; NI006-101 ClinicalTrials.gov number, NCT04360434.)

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Amyloidosis associated with transthyretin amyloid (ATTR) is a progressive, infiltrative, and fatal disease caused by the misfolding of transthyretin (TTR).[1,2] ATTR amyloidosis may arise as a result of variants in the gene that encodes transthyretin (*TTR*), or it may arise in the presence of wild-type TTR and manifest as a late-onset sporadic disease.[3]

When ATTR amyloidosis leads to cardiomyopathy, ATTR deposits accumulate primarily in the cardiac extracellular space.[4] ATTR deposits stiffen the myocardium and cause diastolic dysfunction; as the disease progresses, conduction abnormalities, arrhythmias, and ultimately impaired systolic function occur.[3,5] The disease has been increasingly recognized as a cause of heart failure owing to increased awareness, advances in cardiac imaging, and the availability of new therapies.[6-9]

In patients with ATTR cardiomyopathy, TTR-stabilization therapy and supportive care are current options for the management of cardiovascular complications, but heart transplantation remains the only approach available for the restoration of cardiac function.[1,10] The oral TTR stabilizer tafamidis is the only approved pharmacologic treatment specifically targeting ATTR cardiomyopathy that has been shown to increase survival and reduce cardiovascular-related hospitalization, but it does not prevent disease progression.[11-13] Additional therapies for TTR stabilization[14] and for TTR gene silencing[15-17] are in late-stage clinical development for the treatment of ATTR cardiomyopathy. However, despite recent advances, there is currently no treatment available that is designed to deplete ATTR from the heart for the reversal of cardiac dysfunction.

NI006 is a recombinant human anti-ATTR monoclonal IgG1 antibody that was generated through comprehensive immune repertoire analyses of memory B-cell complement obtained from healthy older persons.[18] The antibody selectively binds amyloid conformations of both wild-type and variant TTR, but it does not bind to physiologically folded TTR. In preclinical studies, NI006 depleted ATTR by inducing antibody-mediated phagocytosis of ATTR fibrils and removal of ATTR deposits from tissues.[18]

This trial was a first-in-human investigation of NI006. The objective of the trial was to evaluate the safety and side-effect profile of intravenous infusions of NI006 in patients with ATTR cardiomyopathy.

Methods

Trial Design

We conducted the NI006-101 trial, which was a phase 1 (1a–1b), double-blind, placebo-controlled, international, multicenter, combined single-ascending-dose and multiple-ascending-dose, randomized clinical trial with an open-label extension phase. Patients with ATTR cardiomyopathy and chronic heart failure were randomly assigned (in a 2:1 ratio) to receive intravenous infusions of either NI006 or placebo every 4 weeks for 4 months. Patients were sequentially enrolled in six cohorts that received ascending doses (ranging from 0.3 to 60 mg per kilogram of body weight). The 4-month placebo-controlled, ascending-dose phase was followed by an 8-month open-label extension phase in which all participating patients (including those randomly assigned to receive placebo) received NI006 with stepwise increases in the dose. Additional details are provided in Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Trial Oversight

The trial protocol (available at NEJM.org) was approved by local ethics committees and health authorities (EU Clinical Trials Register number, 2019-001932-80). To allow for further safety assessment, the trial protocol was revised to include more time in the open-label extension phase and a dose-expansion cohort; the expanded trial is still ongoing, and those results are not reported here.

The trial was conducted in compliance with the Declaration of Helsinki, and all patients provided written informed consent. The data evaluation committee was responsible for periodic review of blinded safety data and provided recommendations regarding the enrollment of patients in new dose cohorts and phases of the trial. The sponsor (Neurimmune) collaborated with the investigators in the design of the trial and in the collection, analysis, and interpretation of the data. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

The first and penultimate authors wrote the first draft of the manuscript. All the authors participated in manuscript development and made the decision to submit the manuscript for publication. Agreements between the sponsor and the investigators included data confidentiality.

PATIENT POPULATION

From February 2020 through April 2022, patients were recruited at six specialized amyloidosis centers in four European countries. Patients were enrolled in the trial if they met the following inclusion criteria at the time of screening (Table S1): a confirmed diagnosis of ATTR cardiomyopathy[1,2]; a left ventricular wall thickness of at least 14 mm; a left ventricular ejection fraction of at least 40%; a New York Heart Association class of I, II, or III; an estimated glomerular filtration rate of more than 30 ml per minute per 1.73 m^2; and an N-terminal pro–B-type natriuretic peptide (NT-proBNP) level of 600 to 6000 pg per milliliter. Concomitant treatment with tafamidis was allowed, but treatment with other ATTR-specific drugs was not permitted.

SAFETY ASSESSMENTS

The primary objective of the trial was to determine the safety and side-effect profile of NI006. Dose escalation was guided by the assessment of clinically relevant adverse events that occurred during treatment and safety markers, including results of laboratory tests, echocardiography, and electrocardiography (ECG). Blinded safety data were monitored continually by both the investigators and the sponsor and were reviewed by the data evaluation committee. Additional details regarding safety assessments are provided in the Supplementary Appendix.

PHARMACOKINETIC AND IMMUNOGENICITY ASSESSMENTS

Serial serum NI006 concentrations were obtained throughout the trial in all patients with the use of a validated assay. Individual total serum NI006 exposures were calculated as the area under the curve from the simulated pharmacokinetic profiles. Monitoring for antidrug antibodies was performed. Additional information regarding pharmacokinetic and immunogenicity assessments is provided in the Supplementary Appendix.

CARDIAC IMAGING STUDIES

All enrolled patients underwent either serial bisphosphonate scintigraphy or cardiac magnetic resonance imaging (MRI) at 4 and 12 months. The imaging study was selected in accordance with local standards and was performed in accordance with standardized protocols. The results were analyzed at a central laboratory by technicians who were unaware of the trial-group assignments. The effect of NI006 was measured as the change in cardiac tracer uptake (ratio of tracer retention in heart to whole body) on planar scintigraphy or as the change in left ventricular extracellular volume on cardiac MRI, both of which are imaging-based surrogate markers of cardiac amyloid load.

CARDIAC BIOMARKER AND OTHER STUDIES

Changes at 4 and 12 months in the NT-proBNP and troponin T levels were evaluated centrally. In addition, exploratory analyses of overall quality of life, functional capacity, and cardiac structure and function were carried out with assessment of the score on the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS), the 6-minute walk distance, and the results on echocardiography, respectively. KCCQ-OS scores range from 0 to 100, with a score of 0 to 24 indicating very poor to poor quality of life, 25 to 49 poor to fair, 50 to 74 fair to good, and 75 to 100 good to excellent.

STATISTICAL ANALYSIS

The primary results presented here were generated after all patients in the cohort that received the highest dose had completed the placebo-controlled, ascending-dose phase. Results are presented for all patients who received at least one dose of NI006 or placebo (safety population). All available data from the open-label extension phase were included; the data-cutoff date was November 3, 2022. No formal statistical hypotheses were tested, and no imputations for missing data were performed. Patients randomly assigned to receive NI006 were grouped according to the nominal dose cohort assigned at enrollment, whereas patients randomly assigned to receive placebo were pooled from all dose cohorts. Data from the open-label extension phase were aggregated according to the same nominal group-

ing. Prespecified grouping of patients according to whether they received higher doses (≥10 mg per kilogram) or lower doses (≤3 mg per kilogram) was performed to explore the effects of NI006. For cardiac imaging, cardiac biomarker, and other exploratory studies, the absolute or relative change from baseline at 4 and 12 months was calculated. A baseline level was obtained before the open-label extension phase for the calculation of change during the open-label extension phase among patients randomly assigned to receive placebo. SAS software, version 9.4 (SAS Institute), was used for data handling and analysis, and R software, ggplot2 package (R Foundation for Statistical Computing), was used for data visualization.

RESULTS

PATIENT CHARACTERISTICS

A total of 40 patients were enrolled in the trial, of whom 27 were randomly assigned to receive NI006 (at one of six doses ranging from 0.3 to 60 mg per kilogram) and 13 were randomly assigned to receive placebo (Table 1). The median age of the patients was 72 years (range, 28 to 87), and 39 patients were male. In addition, 33 patients had wild-type ATTR cardiomyopathy, and 36 patients were receiving tafamidis, with a median treatment duration of 7 months (interquartile range [IQR], 4 to 16). Patients randomly assigned to receive NI006 appeared to have more advanced disease than patients randomly assigned to receive placebo (Table S2). Adherence to the trial protocol was high: 34 patients received all four scheduled infusions during the placebo-controlled, ascending-dose phase, and 34 of 35 patients who completed this phase were subsequently enrolled in the open-label extension phase (Fig. S2).

SAFETY PROFILE

The use of NI006 was associated with no apparent drug-related serious adverse events (Table 2). During the placebo-controlled, ascending-dose phase, 37 patients had at least one adverse event (Tables S3 and S4). Most of these adverse events were considered to be mild or moderate in intensity; of the 191 total events, 124 were grade 1 events and 60 were grade 2 events (according to the Common Terminology Criteria for Adverse Events, version 5.0). In addition, most events were not dose-dependent. Two deaths that occurred during the open-label extension phase were attributed to progression of amyloidosis; narratives are provided in the Supplementary Appendix.

The most frequently observed adverse events were heart failure and arrhythmias, which are expected complications in this patient population. The frequency and type of adverse events appeared to be similar across NI006 dose cohorts. Three patients (in the 10-mg-per-kilogram or the 30-mg-per-kilogram dose cohort) had cytokine release syndrome with an associated increase in cardiac biomarker levels, which was considered to be a nonserious, grade 1 or 2 adverse event, during the placebo-controlled, ascending-dose phase. All three patients completed treatment through the open-label extension phase without a recurrence; narratives are provided in the Supplementary Appendix.

The number of musculoskeletal events, mainly arthralgias and arthritis, increased with ascending doses of NI006 in the placebo-controlled, ascending-dose phase and increased when patients who had received placebo were switched to NI006 in the open-label extension phase. The majority of these events were mild and were treated with nonsteroidal antiinflammatory drugs or low-dose glucocorticoids, with the course tapered off during continued treatment with NI006. However, 1 patient (in the 10-mg-per-kilogram dose group) withdrew from the trial, and 1 patient (in the 30-mg-per-kilogram dose group) withdrew consent for participation in the open-label extension phase, owing to musculoskeletal events.

Two patients had transient, asymptomatic decreases in the platelet count. One of these patients (in the 60-mg-per-kilogram dose group) withdrew from the trial owing to thrombocytopenia, which was considered to be a nonserious, grade 3 adverse event, after two infusions of NI006. In this patient, thrombocytopenia was considered to be related to NI006 because of the temporal association between the infusion and the decrease in platelet count, as well as the recurrence after rechallenge. No bleeding or other associated adverse events occurred in this patient, and the platelet count normalized within 2 weeks.

At the recommendation of the data evaluation committee, 2 patients were withdrawn from the

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	NI006 (N=27)	Placebo (N=13)
Median age (IQR) — yr	74 (70–77)	68 (67–74)
Sex — no. (%)		
Male	26 (96)	13 (100)
Female	1 (4)	0
Transthyretin genotype — no. (%)		
Variant	4 (15)	3 (23)
Wild-type	23 (85)	10 (77)
Median weight (IQR) — kg	85 (79–92)	75 (71–80)
Race — no. (%)†		
Asian	0	1 (8)
White	14 (52)	7 (54)
Not reported	13 (48)	5 (38)
Median NT-proBNP (IQR) — pg/ml‡	2029 (1433–3674)	1591 (1310–2107)
Median troponin T (IQR) — pg/ml	52 (38–71)	33 (22–43)
Median eGFR (IQR) — ml/min/1.73 m^2§	63 (44–86)	79 (62–86)
NAC stage — no. (%)¶		
Stage 1	12 (44)	11 (85)
Stage 2	13 (48)	2 (15)
Stage 3	2 (7)	0
NYHA class — no. (%)‖		
Class I	3 (11)	3 (23)
Class II	19 (70)	10 (77)
Class III	5 (19)	0
Coexisting condition — no. (%)		
Atrial fibrillation	17 (63)	10 (77)
Hypertension	18 (67)	7 (54)
Coronary artery disease	5 (19)	0
Diabetes mellitus	4 (15)	2 (15)
Country — no. (%)		
France	13 (48)	5 (38)
Germany	9 (33)	4 (31)
Spain	2 (7)	2 (15)
The Netherlands	3 (11)	2 (15)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† Race was reported by the patient. Collection of information regarding race was not permitted at French sites.
‡ The N-terminal pro–B-type natriuretic peptide (NT-proBNP) level was obtained locally at screening.
§ The estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation.
¶ National Amyloidosis Centre (NAC) stage 1 is defined as an NT-proBNP level of ≤3000 pg per milliliter and an eGFR of ≥45 ml per minute per 1.73 m^2, stage II as either an NT-proBNP level of >3000 pg per milliliter and an eGFR of ≥45 ml per minute per 1.73 m^2 or an NT-proBNP level of ≤3000 pg per milliliter and an eGFR of <45 ml per minute per 1.73 m^2, and stage III as an NT-proBNP level of >3000 pg per milliliter and an eGFR of <45 ml per minute per 1.73 m^2.
‖ New York Heart Association (NYHA) class I indicates no symptoms and no limitation in ordinary physical activity, class II mild symptoms and slight limitation in ordinary activity, and class III marked limitation in activity due to symptoms, even during less-than-ordinary activity.

Table 2. Adverse Events during the Placebo-Controlled, Ascending-Dose Phase.*

Adverse Event	NI006, 0.3 mg/kg (N=4)	NI006, 1 mg/kg (N=4)	NI006, 3 mg/kg (N=4)	NI006, 10 mg/kg (N=5)	NI006, 30 mg/kg (N=5)	NI006, 60 mg/kg (N=5)	Placebo (N=13)
Any adverse event							
No. of patients (%)	4 (100)	4 (100)	3 (75)	5 (100)	5 (100)	5 (100)	11 (85)
No. of events	24	14	22	30	37	25	39
Severe adverse event, grade 3							
No. of patients (%)	1 (25)	2 (50)	0	1 (20)	1 (20)	0	2 (15)
No. of events	1	2	0	1	1	0	2
Serious adverse event							
No. of patients (%)	1 (25)	3 (75)	0	1 (20)	1 (20)	0	3 (23)
No. of events	1	3	0	3	1	0	3
Drug-related adverse event							
No. of patients (%)	0	1 (25)	1 (25)	1 (20)	2 (40)	1 (20)	0
No. of events	0	1	2	5	13	4	0
Adverse event leading to temporary discontinuation of NI006 or placebo — no. (%)	0	0	0	0	0	0	1 (8)
Adverse event leading to withdrawal from the trial							
Any — no. (%)	0	0	0	2 (40)	1 (20)	1 (20)	0
Coronavirus disease 2019 — no.	0	0	0	1	1	0	0
Arthralgias — no.	0	0	0	1	0	0	0
Thrombocytopenia — no.	0	0	0	0	0	1	0

* Severity of adverse events was classified according to the Common Terminology Criteria for Adverse Events, version 5.0. No life-threatening adverse events (grade 4 events) or deaths (grade 5 events) and no drug-related serious adverse events occurred.

trial owing to coronavirus disease 2019 (Covid-19) during the placebo-controlled, ascending-dose phase. In the entire trial population, there were no reactions to infusions or apparent clinically important changes from baseline in safety-related laboratory test results, including plasma TTR levels, or in vital signs. Safety-related cardiac monitoring at participating centers included echocardiography and ambulatory ECG, which did not show any apparent evidence of new cardiac dysfunction, pericardial effusion, or an increase in arrhythmias. During the open-label extension phase, 3 patients were withdrawn from the trial prematurely; 1 had Covid-19, and 2 died as described previously.

PHARMACOKINETIC AND IMMUNOGENICITY PROFILE

The NI006 pharmacokinetic profile was consistent with the characteristics of human IgG, with low-to-moderate variability across patients. After the administration of a single intravenous dose, the serum NI006 concentration decreased in a biphasic manner, with the elimination half-life ranging from 15.5 to 19.2 days. Exposure to NI006, which was measured as the maximum concentration and the area under the curve, increased with higher doses in a dose-proportional manner. None of the patients had antidrug antibodies throughout the trial, including the open-label extension phase.

CARDIAC AMYLOID DEPLETION

After 4 months of therapy, high total NI006 exposure appeared to be associated with lower cardiac tracer uptake on scintigraphy and with lower extracellular volume on cardiac MRI than the levels observed at baseline (Fig. 1 and Fig. S3). After continued treatment with NI006 for up to 12 months, cardiac tracer uptake and extracellular volume seemed to be further reduced. By contrast, among patients randomly assigned to receive placebo, there was an apparent increase

in cardiac tracer uptake on scintigraphy and in extracellular volume on cardiac MRI at 4 months. After these patients entered the open-label extension phase and received NI006 for 8 months, these levels seemed to be decreased.

Representative images from patients who received NI006 and those who received placebo are shown in Figure 2. At doses of at least 10 mg per kilogram, there were apparent reductions in the extracellular volume on cardiac MRI (median extracellular volume among 3 patients, 59.4% [IQR, 56.2 to 68.7] at baseline vs. 49.0% [IQR, 48.4 to 57.3] at 4 months and 41.6% [IQR, 39.1 to 49.2] at 12 months) (Table S5) and apparent reductions in cardiac tracer uptake on scintigraphy (median ratio in heart to whole body, 5.7% [IQR, 4.3 to 6.9] at baseline among 12 patients vs. 3.8% [IQR, 3.3 to 6.2] at 4 months among 11 patients and 2.5% [IQR, 2.3 to 3.2] at 12 months among 6 patients) (Table S6).

CARDIAC BIOMARKERS AND OTHER MEASURES

Exposure to higher doses of NI006 appeared to be associated with changes in the NT-proBNP and troponin T levels (Fig. 3). At doses of at least 10 mg per kilogram, the median NT-proBNP level was 2460 pg per milliliter (IQR, 1443 to 4188) at baseline among 15 patients, and the median level de-

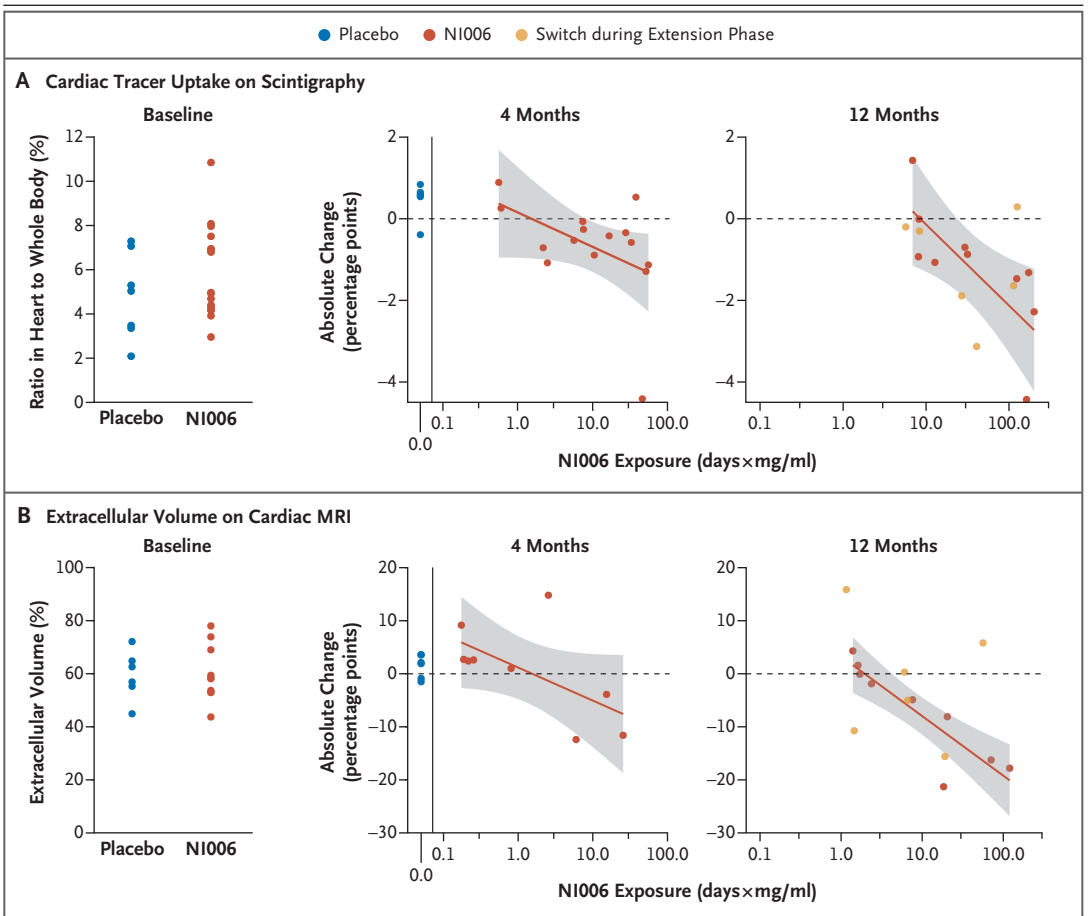
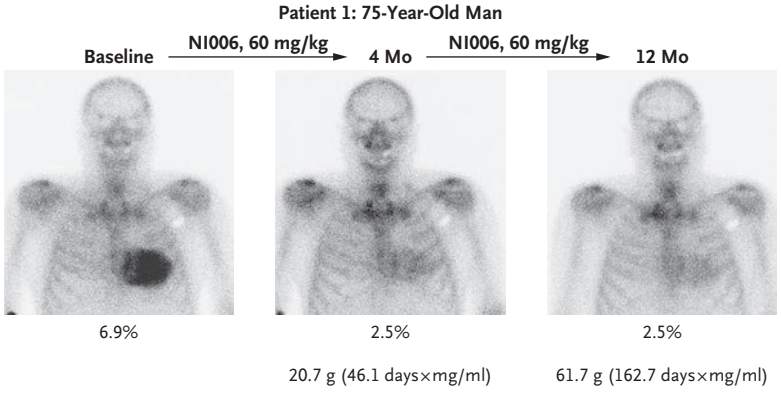


Figure 1. Cardiac Tracer Uptake on Scintigraphy and Extracellular Volume on Cardiac MRI.

Panel A shows the cardiac tracer uptake (ratio in heart to whole body) on scintigraphy at baseline, as well as the absolute change from baseline at 4 months and at 12 months. Panel B shows the extracellular volume on cardiac magnetic resonance imaging (MRI) at baseline, as well as the absolute change from baseline at 4 months and at 12 months. Among patients randomly assigned to the placebo group, placebo was switched to NI006 during the open-label extension phase. Linear regression lines with unadjusted 95% confidence intervals (shaded areas) are shown for patients randomly assigned to receive NI006. The confidence intervals cannot be used to reject or not reject a treatment effect.

A Cardiac Tracer Uptake on Scintigraphy



B Extracellular Volume on Cardiac MRI

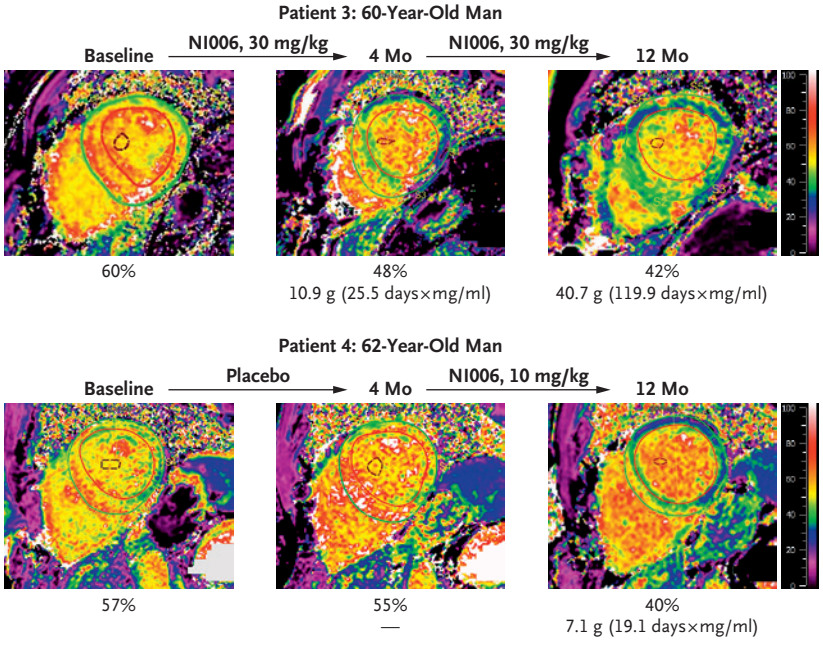


Figure 2 (facing page). Representative Images from Scintigraphy and Cardiac MRI after Treatment with NI006.
Panel A shows images from serial bisphosphonate scintigraphy from one patient randomly assigned to receive NI006 (Patient 1) and one patient randomly assigned to receive placebo (Patient 2). The ratio of cardiac retention in the heart to whole body is reported as a percentage. Panel B shows midventricular extracellular-volume maps from cardiac MRI from one patient randomly assigned to receive NI006 (Patient 3) and one patient randomly assigned to receive placebo (Patient 4). Extracellular volume is reported as a percentage. The images were obtained at baseline, 4 months (after completion of the placebo-controlled, ascending-dose phase), and 12 months (after completion of the open-label extension phase). The individual cumulative administered NI006 dose (reported in grams) and the NI006 exposure (reported as the area under the curve in days times milligrams per milliliter) are provided for the imaging time points after baseline. All the images are from patients with wild-type transthyretin amyloid cardiomyopathy.

creased to 778 pg per milliliter (IQR, 234 to 2416) at 12 months among 9 patients; the median troponin T level was 43 pg per milliliter (IQR, 35 to 72) at baseline among 15 patients, and the median level decreased to 35 pg per milliliter (IQR, 21 to 48) at 12 months among 8 patients (Table S7). In the 30-mg-per-kilogram and 60-mg-per-kilogram dose cohorts, the median NT-proBNP level was 2658 pg per milliliter (IQR, 1403 to 4018) and 1482 pg per milliliter (IQR, 1193 to 2760), respectively, at baseline among 5 patients at each dose level, and the median level decreased to 223 pg per milliliter (IQR, 221 to 1320) and 420 pg per milliliter (IQR, 327 to 599), respectively, at 12 months among 3 patients at each dose level.

The KCCQ-OS score was highly variable across patients. From baseline to 12 months, there was a median increase of 6.8 points among 11 of 12 patients in the lower-dose group and a median increase of 6.0 points among 9 of 15 patients in the higher-dose group (Table S8 and Fig. S3). The changes in the results on echocardiography and the 6-minute walk distance at 12 months are shown in Table S9 and Figures S4 and S5.

DISCUSSION

This phase 1 trial showed the safety and side-effect profile and the pharmacokinetic and pharmacodynamic profile of the human anti-ATTR antibody NI006 in patients with ATTR cardiomyopathy and chronic heart failure. The use of NI006, particularly at doses of at least 10 mg per kilogram given every 4 weeks, was associated with changes in extracellular volume on cardiac MRI and cardiac tracer uptake on scintigraphy, two imaging-based surrogate markers of cardiac amyloid load. These observations were supported by apparent changes in levels of cardiac biomarkers and functional measures.

The safety profile of NI006 and the absence of antidrug antibodies may be related to the human-sourced amino acid sequence of the drug and its selectivity for misfolded TTR, without binding to physiologic TTR.[18] No variation in the plasma TTR level was observed across dose cohorts (Table S10). The type, frequency, and severity of cardiac adverse events in this trial appeared to be similar to those reported in phase 3 trials of tafamidis[11] and patisiran,[16] in which the patient population was larger but patient characteristics were similar. A notable difference in this trial was the occurrence of arthralgias, which might be more common with NI006 and possibly related to its activation of phagocytic immune cells that are aimed at musculoskeletal ATTR deposits.[19,20]

It is currently assumed that the main mechanism of cardiac dysfunction in ATTR cardiomyopathy is mechanical impairment caused by the amyloid deposits, which results in increased ventricular stiffness and diastolic dysfunction.[4] Therefore, reducing the burden of amyloid deposits is a rational therapeutic target for ATTR cardiomyopathy.

Available data from patients with ATTR cardiomyopathy indicate that extracellular volume on cardiac MRI correlates with the amyloid load on histologic analysis, is associated with other markers of ATTR disease status, and predicts mortality.[21-23] Tracer uptake on bisphosphonate scintigraphy has also been associated with the histologic cardiac amyloid load and with outcomes in patients with ATTR cardiomyopathy.[23-26]

Drugs that act as TTR tetramer stabilizers, silencers, and gene-editing therapies have been designed to prevent ATTR accumulation, but these drugs do not directly target amyloid that has already been deposited in the heart.[8,9,27] Although there is some evidence that patients who receive therapies that stabilize or silence TTR might have a lower amyloid load, on the basis of

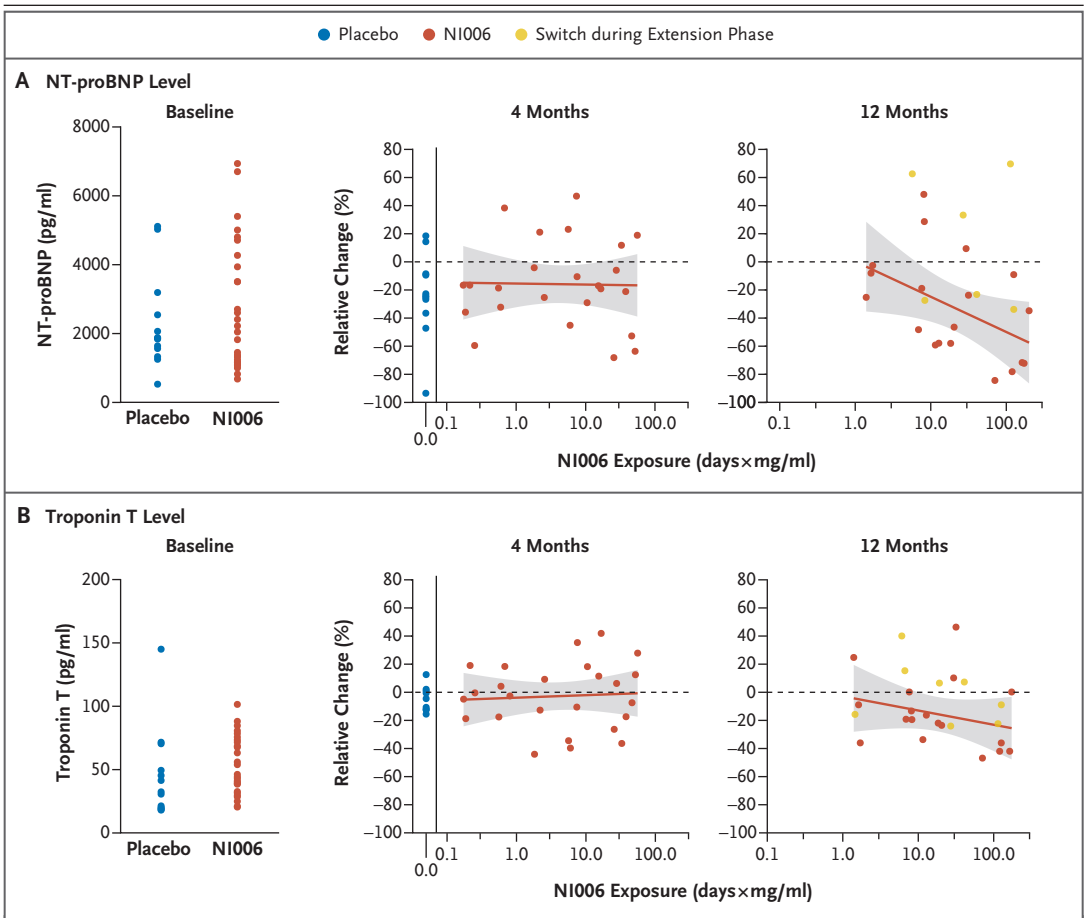


Figure 3. Cardiac Biomarker Levels.

Panel A shows the N-terminal pro–B-type natriuretic peptide (NT-proBNP) level at baseline, as well as the relative change from baseline at 4 months and at 12 months. Panel B shows the troponin T level at baseline, as well as the relative change from baseline at 4 months and at 12 months. Among patients randomly assigned to the placebo group, placebo was switched to NI006 during the open-label extension phase. Linear regression lines with unadjusted 95% confidence intervals (shaded areas) are shown for patients randomly assigned to receive NI006. The confidence intervals cannot be used to reject or not reject a treatment effect.

surrogate markers on scintigraphy and cardiac MRI, than untreated patients,[28-31] substantial reductions are rare.[32] By contrast, patients who received NI006 at doses of at least 10 mg per kilogram seemed to have reductions in cardiac tracer uptake on scintigraphy and in extracellular volume on cardiac MRI after 4 months and 12 months of treatment. These findings may support the proof-of-concept regarding the use of NI006 for the treatment of patients with ATTR cardiomyopathy and appear to be consistent with preclinical data showing activity of NI006 for inducing removal of ATTR.[18]

In patients with ATTR cardiomyopathy, elevated NT-proBNP and troponin T levels are common and associated with a worse prognosis.[33-35] Echocardiographic assessments, functional measures (such as the 6-minute walk distance), and quality-of-life measures (such as the KCCQ-OS score) are also often used to evaluate disease progression.[36] In a recent study, a clinically meaningful increase in the NT-proBNP level (by 500 pg per milliliter from baseline to 12 months) was independently associated with a worse prognosis.[37] Despite the small patient sample in this trial and the variability of results both in individual patients and across patients, the levels of biomarkers (including NT-proBNP and troponin T) and the results of echocardiographic and clinical assessments were suggestive of clinical improve-

ment. However, results were available for only a subset of patients in the trial, and further testing of NI006 is warranted.

This trial has some limitations. The patient sample was small, and the trial had no statistical or inferential power to show a clinical benefit of ATTR depletion in cardiomyopathy. Missing data at 12 months in the open-label extension phase limit interpretation of the results. The use of multiple imaging-based surrogate markers of cardiac amyloid load may limit correlation with the actual ATTR load.[21,22,26] Although the trial population may be representative of a European patient population with predominantly wild-type ATTR cardiomyopathy, the small sample may limit generalizability to younger and female populations (Table S11).

The results of this phase 1 trial show the safety profile of NI006 in patients with ATTR cardiomyopathy and support additional clinical investigation of NI006 for the treatment of patients with ATTR cardiomyopathy.

Supported by Neurimmune.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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