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Cliramitug for depletion of cardiac amyloid transthyretin: long-term follow-up of the NI006-101 trial

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In a first-in-human trial (NI006-101), the monoclonal antibody cliramitug, targeting misfolded transthyretin, demonstrated a favorable safety profile and time- and dose-dependent reductions in surrogate markers of cardiac amyloid burden over the course of 12 months in patients with amyloid transthyretin cardiomyopathy (ATTR-CM). Here we evaluate the long-term safety and efficacy of cliramitug in a subgroup of participants of the NI006-101 trial who continued treatment in a second open-label extension (OLE2) and further explore dose- and time-dependent effects on amyloid depletion, cardiac biomarkers and cardiac structure and function. Twenty-three participants (20 receiving background treatment with tafamidis, all male) entered OLE2 and received a median of 10 additional infusions, increasing the maximum total exposure to 24 infusions and extending the median follow-up to 29.3 months. Thirteen participants initially treated with ≤10 mg kg^{-1} were up-titrated to 30 mg kg^{-1} during OLE2. Treatment adherence was high (98%), with no treatment-related serious adverse events or discontinuations. Continued treatment and up-titration in participants with lower prior exposure led to further reductions in cardiac extracellular volume on MRI and tracer uptake on bisphosphonate scintigraphy. Improvements were also observed in NT-proBNP and troponin T levels, left ventricular relaxation, filling pressures and wall thickness. Increases in Kansas City Cardiomyopathy Questionnaire scores suggested potential quality-of-life benefits. Consistent with results from the original trial, cliramitug showed favorable long-term safety and further reductions in cardiac amyloid burden following up-titration to 30 mg kg^{-1}. These time- and dose-dependent improvements across structural, functional and biomarker endpoints support the therapeutic potential of amyloid-depleting therapy with cliramitug in ATTR-CM. ClinicalTrials.gov: NCT04360434.

Amyloid transthyretin amyloidosis (ATTR) is a fatal disease caused by systemic tissue deposition of misfolded transthyretin (TTR) protein forming amyloid fibrils[1,2]. In patients with ATTR cardiomyopathy (ATTR-CM), the progressive deposition of amyloid in the cardiac extracellular space impairs diastolic and systolic function, frequently in combination with conduction system disorders. This causes progressively debilitating symptoms of heart failure and is associated with a high rate of morbidity and mortality, with median survival ranging between 2 and 6 years after diagnosis if left untreated without ATTR-modifying therapy[3–5].

Clinical recognition of ATTR-CM has improved over the last decade due to advances in disease awareness, noninvasive diagnostic tests[6] and availability of more effective treatments for both variant and wild-type ATTR[7]. Tafamidis and acoramidis are small molecules that stabilize the circulating TTR tetramer and have shown to reduce morbidity and mortality in ATTR-CM[8–11]. Similar benefits

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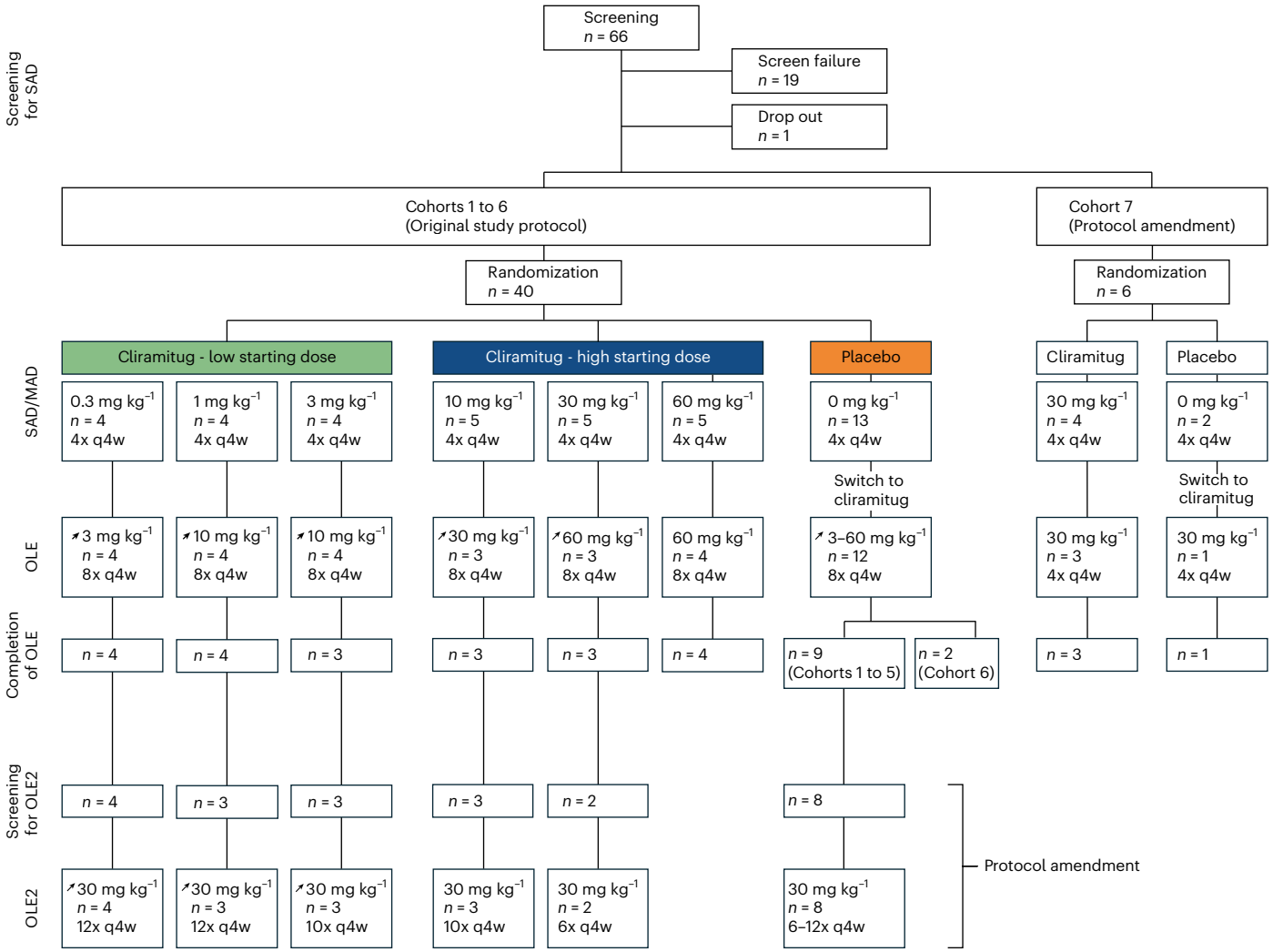

Fig. 1 | CONSORT diagram of the full NI006-101 trial. The original study protocol was amended by adding the expanded OLE (for cohorts 1 and 2), OLE2 (for cohorts 1 to 5) and cohort 7. For the purpose of this manuscript, expanded OLE and OLE2 are summarized together as OLE2. Arrows indicate average up-titration achieved within each cohort during the respective study phase. OLE, open-label extension; q4w, every 4 weeks; SAD/MAD, single ascending dose/multiple ascending dose.

have been shown for vutrisiran, a liver-directed TTR silencer[12]. Cumulative clinical and biomarker data indicate that TTR stabilizing and silencing result in slowing disease progression. However, ATTR deposits in organs are not directly eliminated by these therapies, and persisting amyloid burden and slower but continued disease progression occur, especially in patients in moderate to advanced disease stages.

The recombinant human monoclonal antibody cliramitug, previously known as NI301A, NI006 and ALXN2220, was designed to selectively bind misfolded and aggregated forms of the TTR protein and to trigger the recruitment and activation of phagocytic immune cells[13]. Cliramitug does not bind to the physiological conformation of TTR, thereby fully preserving its biological functions. Primary data from the first-in-human trial, NI006-101 (NCT04360434), indicated that intravenous treatment with cliramitug at doses up to 60 mg kg^{-1} administered every 4 weeks (q4w) for up to 12 months was generally safe and well tolerated in patients with ATTR-CM[14]. Magnetic resonance imaging (MRI) and bisphosphonate scintigraphy surrogate markers of cardiac ATTR, along with cardiac blood biomarkers, indicated a dose- and time-dependent reduction in cardiac amyloid burden among participants treated with cliramitug. In this article, we report the long-term safety, tolerability and exploratory efficacy of prolonged cliramitug treatment in those trial participants who completed 12 months under the original trial protocol and enrolled in an extended open-label phase (OLE2) of the NI006-101 trial. In addition, dose-response analyses across the entire trial population and longitudinal data on high-dose cliramitug are reported.

Results

Trial population and baseline characteristics of OLE2 participants

A total of 46 participants were enrolled in seven dose cohorts in trial NI006-101, including 40 participants under the original protocol (see CONSORT diagram in Fig. 1). Out of the 26 participants who completed 12 months in Cohorts 1 to 5, 23 participants (89%) continued in the OLE2 following an amendment of the trial protocol. There were no clinically relevant differences in baseline characteristics between the participants of the OLE2 compared to the overall population (Table 1). All OLE2 participants were male, with a median (interquartile range (IQR)) age of 70 (67-75) years, predominance of ATTRwt genotype (n = 18, 78%) and baseline therapy with tafamidis (n = 20, 87%). Most participants were in NYHA class II (n = 16, 70%) and in NAC stage I (n = 14, 61%), with baseline median (IQR) NT-proBNP of 1698 ng liter^{-1} (1196 to 3317), troponin T of 39 ng liter^{-1} (25 to 58) and eGFR of 82 ml/min*1.73 m^2 (64-88).

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Table 1 | Baseline characteristics determined at SAD screening of all participants enrolled under the original protocol and in the OLE2

	Original Trial Protocol (*n*=40)[a]	OLE2 (*n*=23)
Age (years)	72.0 (68.0-77.0)	70.0 (67.0-75.0)
Male sex (*n*)	39 (97.5)	23 (100)
TTRwt genotype (*n*)	33 (82.5)	18 (78.3)
Diagnosis method (*n*)		
Endomyocardial biopsy	12 (30.0)	10 (43.5)
Scintigraphy	28 (70.0)	13 (56.5)
Time since diagnosis (months)	15.4 (11.8-36.3)	15.1 (8.3-39.2)
Weight (kg)	83.7 (74.8-91.3)	80.0 (76.5-91.3)
NT-proBNP (ng liter^{-1})	1,685 (1,357-2,921)	1,698 (1,196-3,317)
Troponin T (ng liter^{-1})	42.5 (32.0-68.7)	39.0 (24.5-58.0)
eGFR (ml/min*1.73m^2)	65.0 (49.6-86.0)	82.4 (63.5-88.2)
NAC Stage (1/2/3)	23/15/2	14/9/0
Mayo Stage (1/2/3)	19/15/6	12/7/4
NYHA Class (I/II/III/IV)	6/29/5/0	5/16/2/0
Baseline tafamidis	36 (90)	20 (87.0)
Coexisting conditions		
Atrial fibrillation	27 (67.5)	15 (68.2)
Coronary artery disease	5 (12.5)	3 (13.6)
Hypertension	25 (62.5)	13 (59.1)
Diabetes mellitus	7 (17.5)	0
ECV (%)	58.9 (53.5-65.9) [*n*=16]	58.2 (53.2-61.9) [*n*=14]
HR/WBR (%)	5.0 (4.2 to 7.0) [*n*=24]	4.9 (4.2-7.1) [*n*=9]
Echocardiography		
ED-IVS (mm)	15.0 (15.0-16.0) [*n*=40]	15.0 (14.5-16.0) [*n*=23]
LVEF (%)	62.5 (55.5-72.0) [*n*=40]	63.0 (54.0-71.5) [*n*=23]
Septal e' (cm s^{-1})	4.1 (3.7-5.0) [*n*=34]	3.9 (3.6-4.9) [*n*=20]
E/e'	17.0 (13.9-20.2) [*n*=32]	16.7 (13.7-19.6) [*n*=19]
Randomized to cliramitug	27 (67.5)	15 (65.2)

Numbers represent number of participants (percentage) or median (IQR). [Brackets] indicate the number of participants with available data at screening. Per protocol, participants were followed either by cardiac MRI or bisphosphonate scintigraphy. [a]Full data of patients enrolled under the original protocol and previously published[14]. ECV, extracellular volume; ED-IVS, end-diastolic interventricular septum thickness; eGFR, estimated glomerular filtration rate; HR/WBR, heart retention over whole-body retention ratio; LVEF, left ventricular ejection fraction; NAC, National Amyloidosis Center; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SAD, single ascending dose; TTRwt, wild-type transthyretin genotype

Cardiac ATTR burden was measured longitudinally using either midventricular extracellular volume (ECV) on cardiac MRI (n = 14) or heart over whole-body ratio (HR/WBR) on planar bisphosphonate scintigraphy (n = 9). Baseline values in both parameters were elevated within the expected range for ATTR-CM (Table 1). Consistently, baseline echocardiographic examinations demonstrated an increased left ventricular wall thickness (measured as the basal end-diastolic interventricular septum), reduced left ventricular relaxation as indicated by reduced septal e' and elevated filling pressure reflected by an increased E/e' ratio, with preserved systolic left ventricular function (Table 1).

Treatment and follow-up during OLE2

All participants who did not previously receive doses of 30 mg kg^{-1} (13 of 23 individuals) were up-titrated to 30 mg kg^{-1} during OLE2. Treatment compliance was high, with 98% (225 of 230) of planned infusions being administered, corresponding to a median (IQR) number of 10 (10-12) infusions per participant. The maximum number of infusions across the entire trial was 24 per participant. Due to a temporary pause in treatment between the original trial and OLE2, particularly in the early cohorts, the maximal total follow-up time from first infusion to last on-site assessment was 1,077 days (35.4 months), with a median (IQR) total follow-up time of 29.3 months (26.1-33.3) and a median (IQR) cumulative cliramitug dose of 31.2 g (26.7-34.8) at the end of OLE2 (Extended Data Table 1).

Safety and tolerability during OLE2

Similar to the original trial, cliramitug was generally safe and well tolerated during OLE2 (Table 2). There were no infusion-related reactions reported as cytokine release syndrome. One participant experienced two nonserious, transient infusion-related reactions associated with mild elevation of blood pressure and temperature along with shivers and cold-like feelings after the first and second doses in OLE2. The participant continued to receive eight additional infusions without further events. Also, there were no events of decreased platelet count in OLE2. The frequency of musculoskeletal events described as arthralgia or arthritis observed in OLE2 was comparable to that found in individuals who were enrolled in high starting dose cohorts (10, 30 and 60 mg kg^{-1}) during the original trial (40% versus 39%). Notably, there were no arthralgia-related discontinuations in OLE2.

In total, 7 patients (30%) experienced serious adverse events in OLE2, none of which were considered related to cliramitug by the investigators or the sponsor (Table 2). One 80-year-old participant initially allocated to placebo in cohort 3 (screening NYHA class II, NAC stage 2) experienced multiple serious adverse events associated with progression of the underlying cardiac disease (including worsening events of aortic stenosis, coronary artery disease and low cardiac output syndrome) and was discontinued by the investigator after six OLE2 infusions (cumulative cliramitug dose 12.6 g). This participant died 13 weeks after the last infusion. No other adverse event resulting in trial discontinuation occurred in OLE2. No anti-drug antibodies were detected in any participant.

Surrogate markers of cardiac amyloid burden, structure and function in OLE2

At the end of the OLE in the original trial, dose-dependent reductions in ECV and HR/WBR were observed (Fig. 2), with participants enrolled in the high starting dose cohorts demonstrating larger reductions from baseline compared to participants with low exposure to cliramitug because of enrollment in the low starting dose cohorts (0.3, 1 or 3 mg kg^{-1}) or initial allocation to placebo[14]. Continued treatment and up-titration of participants with previously low exposure in the original trial, resulted in additional reductions of ECV and HR/WBR during the OLE2 (Fig. 2). At the end of the OLE2, 12 of 13 participants (92%) with available cardiac MRI presented reductions in ECV compared to baseline (Extended Data Fig. 1), corresponding to a median (IQR) absolute reduction of −10.5% (−7.2 to −18.9) and median (IQR) relative reduction of −19.5% (−13.8 to −33.5). All 8 participants (100%) with available scintigraphy data at the end of OLE2 presented reductions in cardiac tracer uptake (Extended Data Fig. 1), with a median (IQR) absolute reduction of −2.2% (−1.3 to −2.8) and median (IQR) relative reduction of −36.1% (−25.9 to −45.7) from baseline.

Improvements in cardiac biomarkers were also observed at the end of OLE2, with absolute reductions from baseline observed in 17 of 21 participants (81%) for NT-proBNP and 16 of 22 participants (73%) for troponin T (Extended Data Fig. 1). This corresponded to median (IQR) absolute and relative reductions of −649 ng liter^{-1} (−222 to −1,050) and −47.3% (−24.8 to −64.7) for NT-proBNP and −6.5 ng liter^{-1} (0.2 to −9.9) and −19.7% (−1.0 to −34.0) for troponin T.

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Table 2 | Summary of adverse events across the different trial phases in participants enrolled under the original protocol and in OLE2

	SAD/MAD[a]			OLE[a]	OLE2
	CliramitugLow starting dose (*n*=12)	CliramitugHigh starting dose (*n*=15)	Placebo – (*n*=13)	All cliramitugMixed (*n*=34)	All cliramitug High dose (*n*=23)
At least one AE	11 (91.7) [60]	15 (100) [98]	13 (100) [47]	31 (91.2) [163]	19 (82.6) [155]
Severe (grade III)	3 (25.0) [3]	2 (13.3) [2]	2 (15.4) [2]	6 (17.6) [11]	6 (26.1) [17]
Life-threatening, death (grade IV, V)	0	0	0	2 (5.9) [2]	1 (4.3) [1]
At least one SAE	4 (33.3) [4]	2 (13.3) [4]	3 (23.1) [3]	7 (20.6) [13]	7 (30.4) [23]
At least one related AE	2 (16.7) [3]	4 (26.7) [24]	0	9 (26.5) [25]	10 (43.5) [13]
At least one related SAE	0	0	0	0	0
AE leading to study discontinuation[b]	0	4 (26.7) [4]	0	1 (2.9) [1]	0
Coronavirus disease	0	2 (13.3) [2]	0	1 (2.9) [1]	0
Arthralgia	0	1 (6.7) [1]	0	0	0
Thrombocytopenia	0	1 (6.7) [1]	0	0	0
AEs of interest based on SAD/MAD					
Cardiac disorders (SOC)	9 (75.0) [16]	11 (73.3) [20]	7 (53.8) [12]	19 (55.8) [33]	10 (43.5) [31]
Heart failures (HLGT)	3 (25.0) [3]	4 (26.7) [5]	3 (23.1) [4]	3 (8.8) [7]	2 (8.7) [8]
Coronavirus disease (PT)	0	2 (13.3) [3]	0	7 (20.6) [7]	6 (26.1) [6]
Cytokine release syndrome (PT)	0	3 (20.0) [3]	0	0	0
Arthralgia, arthritis (HLGT)	2 (16.7) [2]	6 (40.0) [20]	2 (15.4) [2]	11 (32.4) [23]	9 (39.1) [19]
Thrombocytopenia (PT)	1 (8.3) [1]	2 (13.3) [5]	0	0	0

Numbers represent number of participants, with (percentage) or [number of events]. [a]Final data of participants enrolled under the original protocol. [b]Deaths are listed separately and not included in AEs leading to discontinuation. AE, adverse event; HLGT, high-level group term; OLE, open-label extension; PT, preferred term; SAE, serious adverse event; SOC, system organ class.

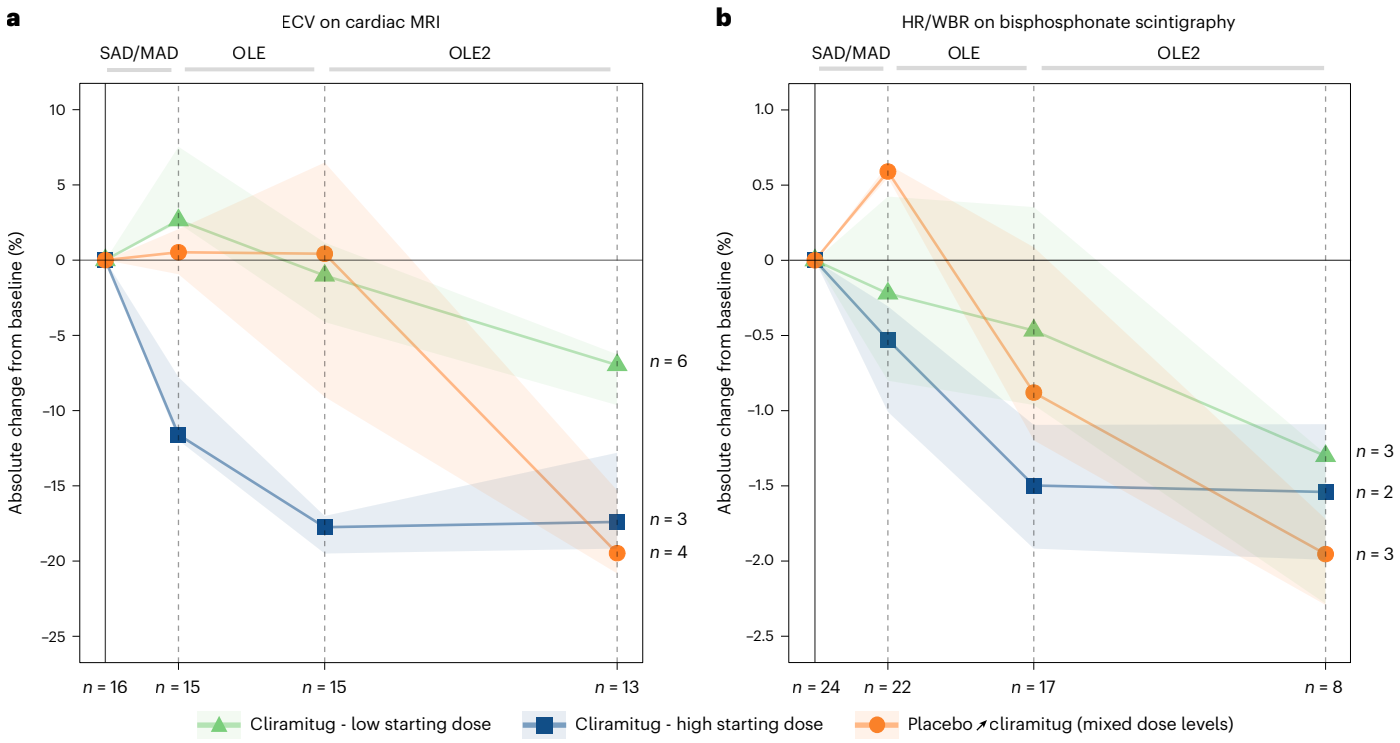

Fig. 2 | Changes in surrogate markers of cardiac ATTR burden over the full trial duration in participants enrolled under the original trial protocol. **a**,**b**, Observed absolute changes from baseline in ECV (**a**) and HR/WBR (**b**) are shown. Lines and shades represent median and IQR, respectively, stratified by initial enrollment in cliramitug low starting dose, cliramitug high starting dose and placebo who switched to cliramitug during the OLE of the initial protocol. HR/WBR, heart retention over whole-body retention ratio.

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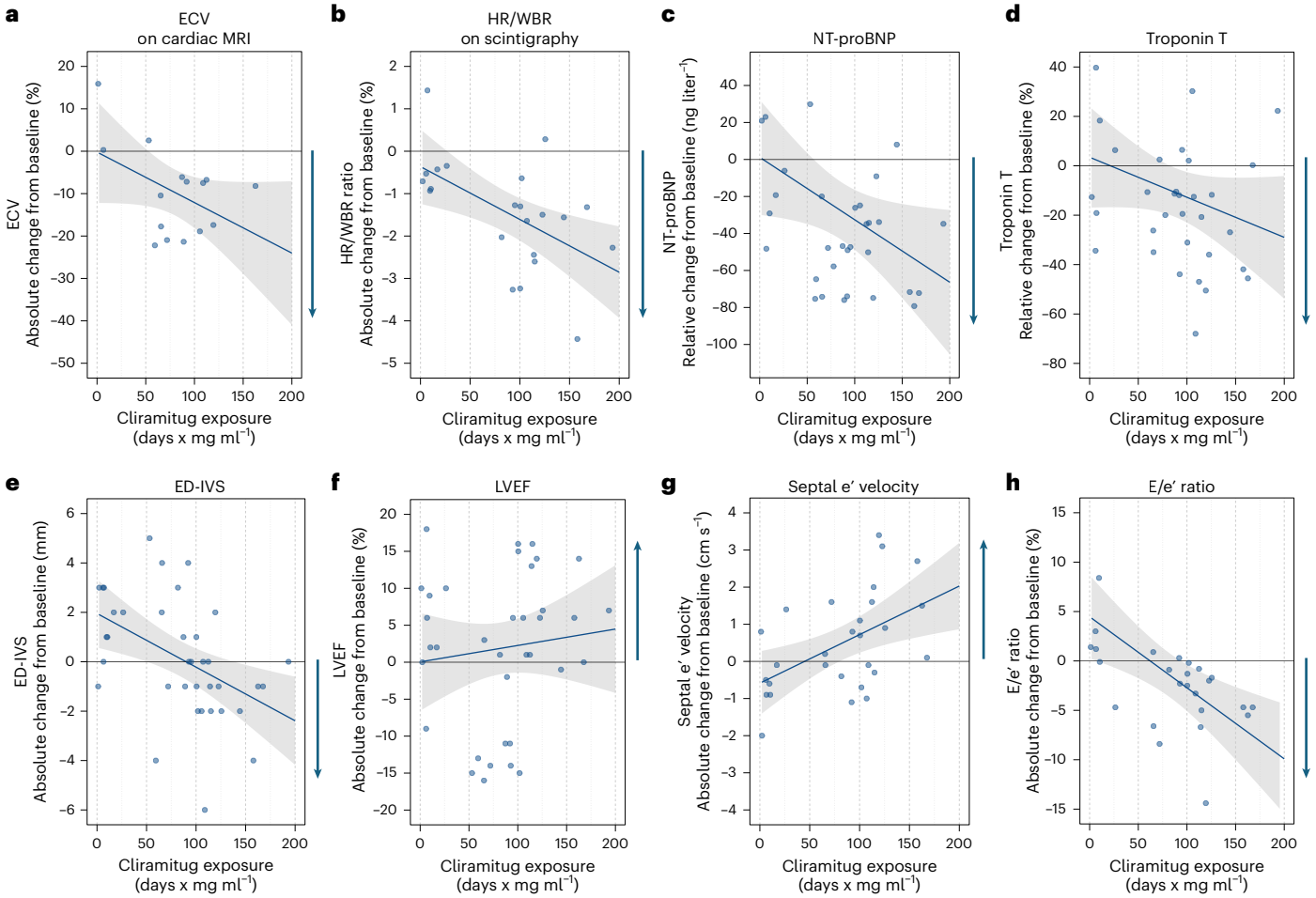

Fig. 3 | Correlations of changes in amyloid burden, cardiac biomarkers and echocardiographic parameters with cumulative cliramitug exposure. **a**–**h**, Changes from baseline to the last observation in trial NI006-101 are presented across cardiac amyloid burden (**a**, **b**), cardiac biomarkers (**c**, **d**) and echocardiographic parameters of cardiac structure and function (**e**–**h**). Dots indicate individual observations. Linear regression lines representing the fitted mean response are shown with unadjusted 95% confidence intervals (gray bands). Arrows indicate direction of improvement. ED-IVSm end-diastolic interventricular septum.

In a majority of OLE2 participants, improvements in left ventricular relaxation were observed by echocardiography: 13 of 15 participants (87%) demonstrated improvements in E/e', and 9 of 15 participants (60%) improvements in septal e' (Extended Data Fig. 2). Median (IQR) change from baseline in left ventricular ejection fraction (LVEF) and left ventricular wall thickness were 1% (−13 to 13) and 0 mm (−1 to 2), respectively.

Exposure-response across the entire trial

Across the entire trial, including data from all trial participants, an exposure-response relationship was observed between the individual cumulative cliramitug exposure and the change from baseline in ECV, HR/WBR, NT-proBNP and troponin T at individual last trial observation (Fig. 3). Greater cumulative exposure to cliramitug was also associated with reduced left ventricular wall thickness, septal e' and reduced E/e', with most pronounced and consistent effects observed in parameters of left ventricular relaxation. In this population with normal LVEF at baseline, there was a trend toward an increase in LVEF with higher doses of cliramitug.

Longitudinal changes in cardiac structure and function at doses of ≥30 mg kg^{-1}

Longitudinal observations at the two highest dose levels (30 and 60 mg kg^{-1}) indicated time-dependent changes in markers of cardiac ATTR and blood biomarkers, with reductions in ECV, HR/WBR and NT-proBNP being observed rapidly after high-dose treatment initiation, while reductions in troponin T occurred with temporal delay (Fig. 4).

Despite larger inter- and intrapatient variability, similar changes were also be observed for echocardiographic parameters of interest, including early improvements in markers of left ventricular relaxation and LVEF, whereas reductions in interventricular septum thickness occurred with temporal delay (Fig. 4). Exemplary echocardiograms recorded at trial baseline and end of OLE2 are presented in Extended Data Fig. 3. Although substantial improvements in left ventricular global longitudinal strain were observed in individual participants, a high rate of atrial fibrillation resulted in missing data, which precluded reliable comparisons of time- and dose-dependent effects of cliramitug on global longitudinal strain.

Changes in quality of life and exercise capacity

Across all dose cohorts, participants demonstrated improved quality of life during the course of the trial as measured by the KCCQ Overall Summary Score and including 17 of 22 patients with available data showing improved KCCQ Overall Summary Score at the end of OLE2 compared to baseline (Extended Data Fig. 4), including 13 patients with improvements above clinically meaningful threshold (≥5 points)[15]. Measurements of 6-min walk test (6-MWT) distance showed considerable variability among patients and across dose cohorts. At the end of the OLE2, half of the participants demonstrated an improvement on

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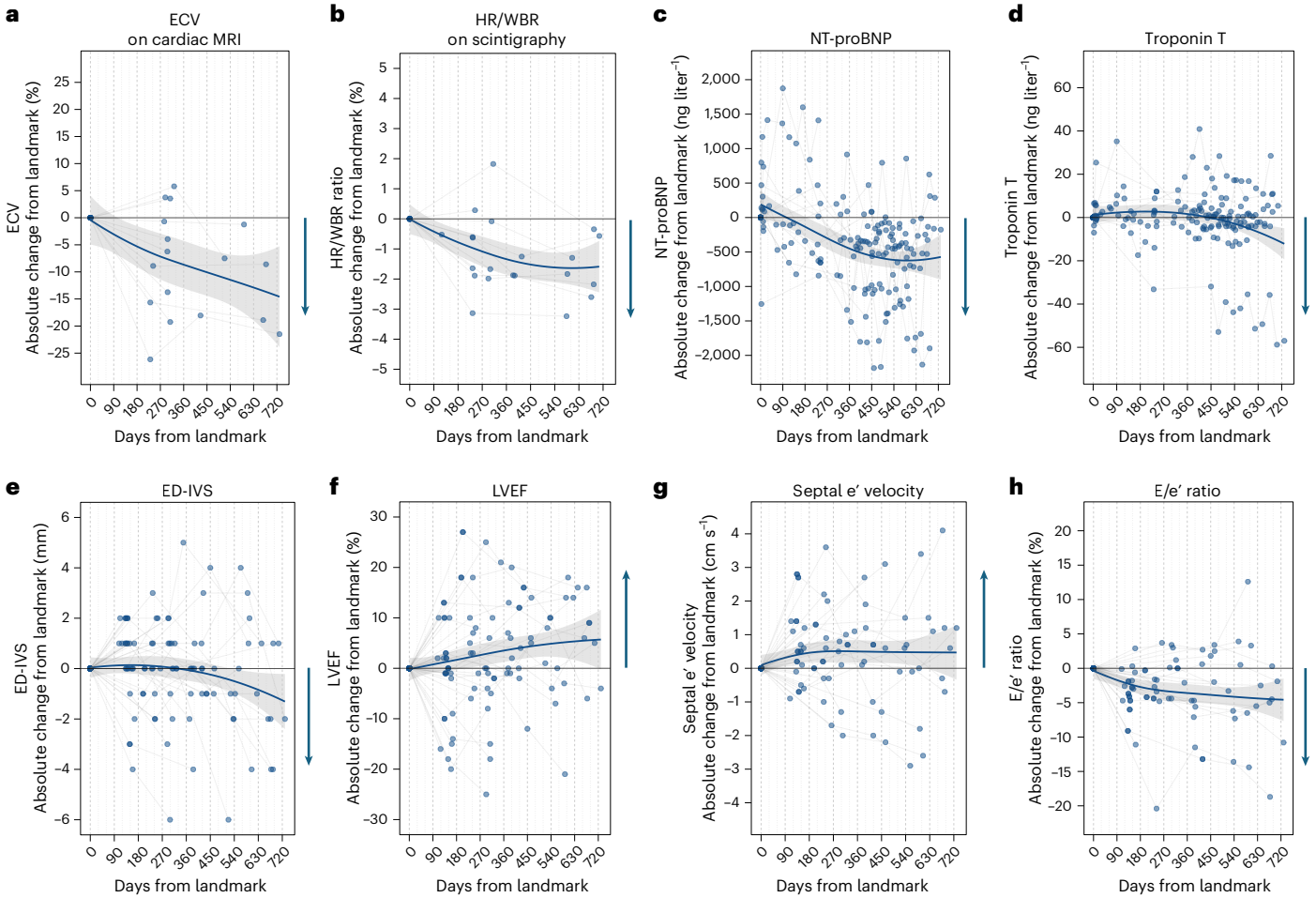

Fig. 4 | Longitudinal changes in amyloid burden, cardiac biomarkers and echocardiographic parameters on high-dose cliramitug. a–**h**, Changes are calculated from last observation prior to the first administration of 30 or 60 mg kg^{-1} and are presented for cardiac amyloid burden (**a**,**b**), cardiac biomarkers (**c**,**d**) and echocardiographic parameters of cardiac structure and function (**e**–**h**). Dots indicate individual observations. LOESS regression lines representing the fitted mean response are shown with unadjusted 95% confidence intervals (gray bands). Arrows indicate direction of improvement. ED-IVS, end-diastolic interventricular septum.

6-MWT distance compared to baseline (median (IQR) change of 13 m (−37 to 51); Extended Data Fig. 4).

Discussion

This trial provides additional insights into the long-term safety, tolerability, and efficacy of cliramitug in patients with ATTR-CM. Our findings demonstrate that long-term administration of cliramitug at high doses is well tolerated and may be associated with clinically meaningful reductions in cardiac ATTR burden and subsequent improvements in blood biomarkers, cardiac structure and function, and quality of life.

Cliramitug's favorable long-term safety profile supports findings from the original trial[14], including a very low frequency of infusion-related reactions, high compliance to treatment and trial procedures. Notably, serious adverse events were infrequent and mainly associated with the progression of the underlying disease rather than the study drug. The lack of anti-drug antibodies demonstrates a favorable immunogenicity profile of cliramitug and supports recurrent administration of the monoclonal antibody for the treatment of ATTR-CM.

The exploratory efficacy data from this OLE2 supports that cliramitug may be able to reduce cardiac ATTR burden and improve disease-related biomarkers and quality of life beyond the 12 months in the original report[14]. Notably, the dose- and time-dependent reductions in ECV and HR/WBR observed across two imaging modalities (cMRI and DPD/HMDP scintigraphy) suggest a direct impact of cliramitug on cardiac ATTR deposits. These reductions are thought to be clinically meaningful, with over 90% of participants showing reductions in ECV by the end of the OLE2. Of note, these results are directionally different from what has been reported for stabilizers and silencers: data from a subgroup of patients treated with acoramidis in the Attribute-CM trial showed a mean absolute ECV increase of 2% after 30 months of therapy[16], whereas stabilization of ECV was documented over 12 months on patisiran (absolute median reduction of <1%)[17] and over 30 months on vutrisiran (absolute mean reduction of 0.1%)[18].

The correlation of cumulative cliramitug exposure and changes in biomarkers further support a dose-response relationship, suggesting that higher doses are associated with greater reductions in cardiac amyloid burden and biomarkers of cardiac stress and damage such as NT-proBNP and troponin T. This finding is substantial, as reductions in these biomarkers have been demonstrated to be linked to improved prognosis and better clinical outcomes in ATTR-CM[19,20].

In addition to its effects on amyloid burden and biomarkers, prolonged administration of cliramitug was associated with beneficial effects on cardiac structure and function. Importantly, improvements across structural and functional parameters were observed compared to pre-treatment baseline, indicating a potential rapid reversal of the disease process rather than a slowing of disease progression. This is in contrast to recently published data for tafamidis from the ATTR-ACT trial[21] and for vutrisiran from the HELIOS-B trial[22], which demonstrated consistent improvements across echocardiographic parameters in the

active arm versus placebo, but not relative to trial baseline after up to 30 months of continuous therapy.

The longitudinal data from this trial further enhance our understanding of the time-dependent nature of the changes associated with cliramitug treatment. Although amyloid burden and left ventricular relaxation may improve rapidly with cliramitug, further functional and structural cardiac changes may require a longer treatment duration to recover the myocardium and to remodel at cellular level. A longer observation time at high-dose cliramitug may be necessary to establish whether there will be further improvement. Together, these findings are first indicators of a putative sequence of events following treatment with cliramitug (Extended Data Fig. 5). All surrogate markers indicate a positive myocardial remodeling after treatment. Notably, there was no indirect evidence for undesirable tissue modification such as fibrosis or myocardial scars.

The improvements observed in quality of life and exercise capacity, as assessed by the KCCQ and the 6-MWT, are promising in consideration of the small sample size and the mild to moderate severity of the disease presentation in this cohort. The findings that 17 of 22 patients showed improved KCCQ scores, including 13 patients with clinically meaningful improvements (>5 points[23]), and 11 of 22 participants had a better 6-MWT performance at the end of the OLE2 compared to baseline suggest that cliramitug could positively affect patient-reported outcomes and functional capacity.

Despite these promising results, this trial was designed and conducted as a hypothesis-generating trial requiring validation and confirmation of its outcomes; hence, there are several limitations that warrant consideration. The open-label design of the OLE2 provides valuable data on long-term treatment effects but is susceptible to biases, including attrition bias. Furthermore, the small sample size and the variability in administered doses increases the heterogeneity of results and limits the ability to draw definitive conclusions regarding the drug's effects over time. It should also be noted that in this trial, consistently with the requirements for a placebo-controlled first-in-human trial, cliramitug was evaluated in a population with a high degree of background therapy with tafamidis and not as monotherapy. Additionally, the follow-up duration, although extended, may still be limited to fully assessing the long-term impact of cliramitug on survival and other critical clinical endpoints. All these limitations are being addressed in the ongoing DepleTTR-CM phase 3 trial (NCT06183931).

In conclusion, the OLE2 of trial NI006-101 provided additional data supporting the development of cliramitug as a treatment option for patients with ATTR-CM that is conceptually different and potentially complementary to existing treatment approaches. Cliramitug exhibited a favorable safety profile and encouraging reduction in surrogate markers of cardiac ATTR, reduction in cardiac biomarkers, improvements in cardiac structure and function and improvements in quality of life. These data and analyses collectively support the phase 3 dosing regimen currently being tested in the ongoing DepleTTR-CM trial, which evaluates whether cardiac amyloid depletion with cliramitug translates into meaningful clinical outcomes such as reduced morbidity and improved survival.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-026-04487-3.

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Methods

Trial oversight

Trial NI006-101 was carried out at six sites across Germany, France, Spain and the Netherlands, in compliance with the Good Clinical Practice guidelines of the International Council for Harmonization and the ethical principles outlined in the Declaration of Helsinki (EudraCT number 2019-001932-80, NCT04360434). The protocol received approval from all pertinent national regulatory authorities (Paul-Ehrlich Institut, Germany; Agence nationale de sécurité du médicament et des produits de santé, France; Agencia Española de Medicamentos y Productos Sanitarios, Spain; and Centrale Commissie Mensgebonden Onderzoek, the Netherlands) and local ethics committees (Ethikkommission der Medizinischen Fakultät Heidelberg, Germany; Comité de protection des personnes Ile de France VII, France; Comité Etico de Investigación Científica - H. Puerta Hierro, Spain; and Medisch Ethische Toetsingscommissie UMCG, the Netherlands). Written informed consent was obtained from all participants. The trial was designed by the authors, who also contributed to the data collection and analysis. The sponsor, Neurimmune, provided cliramitug and placebo and supervised the execution of the trial and statistical analysis.

Trial design

The first-in-human and proof-of-concept trial NI006-101 was designed to investigate the safety and tolerability of intravenous cliramitug at doses up to 60 mg kg^{-1} q4w in patients with confirmed ATTR-CM. An additional focus was on exploring the efficacy of cliramitug. Key eligibility criteria included a left ventricular wall thickness of ≥14 mm, NT-proBNP ≥600 ng $liter^{-1}$ and the ability to walk ≥150 m in the 6-MWT (see Extended Data Table 2 for a full list of eligibility criteria for the SAD). Due to delays in recruitment, largely caused by the COVID-19 pandemic, trial participants enrolled early and at low dose levels could not be up-titrated to the expected efficacious doses as planned[24]. To generate data on the safety and efficacy of cliramitug at a dose level of 30 mg kg^{-1}, the protocol was amended to extend the original 8-month OLE for participants enrolled in cohorts 1 to 5 (0.3 mg kg^{-1}, 1 mg kg^{-1}, 3 mg kg^{-1}, 10 mg kg^{-1} and 30 mg kg^{-1}, respectively; see Extended Data Table 3 for a full list of eligibility criteria for the OLE2). These adaptations, summarized as OLE2 for the purpose of this paper, allowed for 6 to 12 additional administrations of cliramitug depending on the starting dose level, increasing the maximal number of infusions in the entire trial to 24. The full trial protocol is available in the Supplementary Information.

Out of the three participants who did not undergo OLE2 screening, one died during follow-up of the original OLE (previously described (case 1)[14]) and two declined due to the complexity of the trial (eg, monthly visits, advanced age or long travel distance to the site.

Trial intervention

All OLE2 participants received cliramitug in an outpatient setting during the OLE2. Study drug was administered as an intravenous infusion using an infusion bag over approximately 50 to 60 min. In participants with previous exposure to a dose of 30 mg kg^{-1} during the OLE of the original protocol, cliramitug dosing was continued at a level of 30 mg kg^{-1}. In participants with previous exposure below 30 mg kg^{-1}, the first OLE2 dose was 10 mg kg^{-1}, and all subsequent doses were 30 mg kg^{-1}.

Assessment of safety and tolerability

In agreement with the initial trial goals, the primary objective of OLE2 was to further evaluate the safety and tolerability of cliramitug beyond month 12 as determined by the occurrence of treatment-emergent adverse events, changes in laboratory parameters, vital signs and echocardiography parameters. Assessments of all local laboratory results and electrocardiograms were performed by the investigators, and adverse events were recorded. Screening for anti-drug antibodies was performed periodically using a specialized assay.

Assessments of cardiac amyloid burden, structure and function

To characterize the effect of cliramitug on cardiac amyloid burden, all participants underwent either cardiac MRI or planar scintigraphy with DPD (3,3-diphosphono-1,2-propanodicarboxylic acid) or HMDP (hydroxymethylene diphosphonate), depending on local regulations and Investigator decision, to assess changes in the ECV or cardiac tracer uptake (heart over whole-body retention ratio, HR/WBR), respectively. HR/WBR was calculated as the proportion of tracer uptake within the reader-defined cardiac region of interest relative to the total body tracer signal, after exclusion of anatomical areas with confounding high tracer retention (for example, bladder, kidneys or injection site)[25]. Image acquisition was performed using harmonized protocols and image analysis was conducted by two independent readers for each modality at a core laboratory (Biotrial, France). In case of reader disagreement beyond a predefined cut-off, a consensus reading was performed. Changes in cardiac structure and function were assessed using transthoracic echocardiography in all trial participants. Images were acquired by trained sonographers according to a harmonized protocol across all sites. Image analysis was performed centrally by a single reader with documented low intra-reader variability on key echocardiographic parameters (Biotrial). To reduce bias in the assessment of imaging data in this open-label trial, all central readers were blinded to the initial treatment allocation during the placebo-controlled phase of the trial, to the participant ID, and the timepoint of the assessment.

In addition, serum concentrations of disease-relevant cardiac biomarkers NT-proBNP, an indicator of myocardial stretch, and troponin T, an indicator of myocardial damage, were assessed at selected timepoints throughout the trial at a central laboratory (SGS, Germany).

Quality of life and exercise capacity

Changes in quality of life were assessed using the Kansas City Cardiomyopathy Questionnaire. In addition, the 6-MWT was utilized to assess changes in exercise capacity. Both tests complement the objective measures of cardiac status by imaging and blood biomarkers with clinically relevant subjective information, and have been validated as modifiable disease markers in ATTR-CM[19].

Statistical analysis

The results presented here were generated after all participants had completed the full trial and include data from all participants who received at least one dose of study drug. Data were pooled from all sites. Participants assigned to cliramitug were grouped based on starting dose level into high-dose cliramitug (10, 30 or 60 mg kg^{-1}) and low-dose cliramitug cohorts (0.3, 1 or 3 mg kg^{-1}). Participants randomly assigned to receive placebo were pooled from all cohorts. No formal statistical hypotheses were tested, and no imputation of missing data was performed.

As prespecified in the SAP (provided in the Supplementary Information), descriptive statistics are presented for absolute and relative change from baseline to the end of the OLE2 for all participants enrolled (Extended Data Figs. 1 and 2). For participants randomized to placebo, the last assessment prior to OLE is considered as baseline. To describe the continuation of changes among participants included in the initial publication[14], changes are presented for predefined dose groups: low starting dose, high starting dose and placebo (Fig. 2). In an additional post hoc analysis that accounts for missing data, the dose-response relationship between cliramitug and selected exploratory efficacy parameters across all participants in the trial (including patients who did not participate in the OLE2), absolute change from baseline to the last available assessment for each participant was correlated with cumulative cliramitug exposure (area under the curve, AUC, in mg/ml*d) for each individual's last assessment timepoint (Fig. 3). In addition, to explore longitudinal changes in selected exploratory efficacy parameters at the highest dose levels of 30 or 60 mg kg^{-1}, a dose

range currently being investigated in the DepleTTR-CM phase 3 trial (NCT06183931), an additional baseline (landmark) was defined as the most recent assessment prior to the first received dose of 30 or 60 mg kg^{-1}, and absolute change from that landmark was analyzed (Fig. 4). SAS version 9.4 (SAS Institute) and R version 4.4.2 (R Foundation for Statistical Computing) were used for data handling, descriptive statistics and data visualization. Numerical values were formatted for clarity, with decimal precision adjusted based on value magnitude. Linear and LOESS (locally estimated scatterplot smoothing) regression analyses were performed for the correlations of treatment effects with AUC and time, respectively.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The clinical trial datasets generated and/or analyzed during this study are not publicly available because they contain sensitive human participant data and are part of an ongoing clinical development program. De-identified individual participant data underlying the findings reported in this Article, may be made available to qualified researchers upon reasonable request for non-commercial research purposes, subject to sponsor review, applicable regulatory requirements, and execution of a data access agreement. Requests should be directed to the corresponding author. Initial acknowledgment of requests will be provided within 10 business days, and a substantive response can be expected within 8 weeks.

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Author contributions

P.C.K., T.D., A.V.K., C.C.Q., M.F.M., E.H.-K., A.M., J.G., R.M.N., C.H., P.G.-P. and P.v.d.M. designed the trial. P.C.K., F.a.d.S., O.L., E.D., T.D., S.K.-W., E.H.-K., M.T., P.G.-P. and P.v.d.M. contributed to the generation of the data. P.C.K., C.C.Q, M.F.M., S.K.-W., E.H.-K., M.T., A.M., J.G., R.M.N., C.H., P.G.-P. and P.v.d.M oversaw the statistical analysis of the data. P.C.K and P.v.d.M. wrote the first draft of the manuscript. All authors reviewed and approved revisions of the manuscript and affirm the trial's adherence to the protocol and the accuracy and completeness of the data presented.

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Competing interests

T.D. reports consulting fees and/or research grants from Alnylam Pharmaceuticals, Alexion, Akcea, AstraZeneca, Bayer, BridgeBio, Ionis, Pfizer and Neurimmune F.S. reports speaking fees from Pfizer, Ionis Pharmaceuticals, Alnylam Pharmaceuticals, Janssen, Bayer, Alexion and consulting fees from Pfizer, Alnylam Pharmaceuticals and Bayer. P.v.d.M. is supported by a grant from the European research Council (ERC CoG 101045236, DISSECT-HF). The University Medical Center Groningen, which employs P.v.d.M., received consultancy fees and/or grants from Novartis, Pharmacosmos, Vifor Pharma, AstraZeneca, Neurimmune, Pfizer, Pharma Nord, BridgeBio, NovoNordisk and Ionis. O.L. reports speaking/consulting fees from Alnylam, Amicus, AstraZeneca, Bayer, BMS, Pfizer, Sanofi-Genzyme. E.D. reports consulting and speaker fees from AstraZeneca, Pfizer and Alnylam. A.V.K. reports speaking fees from Bayer Vital, Pfizer, NovoNordisk, Attralus, Alexion and Alnylam Pharmaceuticals, and consulting fees from Bayer Vital, Pfizer, Neurimmune, NovoNordisk, Ionis, AstraZeneca and Intellia. M.F.M. and C.C.Q are employed by Alexion, AstraZeneca Rare Disease. J.G., R.M.N. and C.H. are employees and shareholders of Neurimmune AG. E.H.-K., S.K.-W., A.M. and P.C.K. are employees of Neurimmune AG. M.T. is a previous employee of Neurimmune AG. P.G.-P. reports speaking fees from Alnylam Pharmaceuticals, AstraZeneca, Bayer, BridgeBio, Intellia, Ionis Pharmaceuticals, NovoNordisk, and Pfizer, consulting fees from Alexion, Alnylam Pharmaceuticals, AstraZeneca, ATTRalus, Bayer, BridgeBio, Intellia, Ionis Pharmaceuticals, Life Molecular Imaging, Pfizer, Neurimmune, and NovoNordisk, and research/educational support to his institution from Alnylam Pharmaceuticals, AstraZeneca, Bayer, BridgeBio, Intellia, NovoNordisk and Pfizer.

Additional information

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Extended Data Table 1 | Summary of exposure to cliramitug and follow-up duration of participants enrolled under the original protocol and in the OLE2

	SAD/MAD*			OLE*	OLE2
	Cliramitug Low starting dose (n=12)	**Cliramitug High starting dose (n=15)**	**Placebo- (n=13)**	**All cliramitug Mixed (n=34)**	**All cliramitug High dose (n=23)**
Total number of infusions in phase	48	51	50	229	225
Number of infusions at 30 or 60 mg/kg	0	35	0	94	203
Infusions per participant, n	4 (4 to 4)	4 (3 to 4)	4 (4 to 4)	7 (6 to 8)	10 (10 to 12)
Median (IQR) follow-up duration**, months	3.9 (3.9 to 3.9)	4.1 (3.9 to 4.2)	4.0 (3.9 to 4.5)	11.8 (11.5 to 12.0)	29.3 (26.1 to 33.3)
Median (IQR) dose per administration, mg	84 (29 to 213)	2′580 (930 to 5070)	0	831 (222 to 2′706)	2′412 (2′100 to 2′724)
Median (IQR) cumulative dose during phase, mg	319 (122 to 852)	7′839 (3′692 to 14′313)	0	4′751 (2′492 to 18′244)	23′718 (19′113 to 27′478)
Median (IQR) cumulative dose at the end of phase, mg	319 (122 to 852)	7′839 (3′692 to 14′313)	0	5′731 (2′695 to 23′216)	31′205 (26′723 to 34′817)

* Final data of participants enrolled under original protocol. ** Interval from first dose administration in the study to last on-site visit in the respective study phase. IQR = interquartile range; OLE = open-label extension; SAD/MAD = single ascending dose / multiple ascending dose

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Extended Data Table 2 | Eligibility criteria for original protocol (SAD/MAD)

Inclusion criteria for participation in the SAD	
1.	Written informed consent obtained from the subject prior to any trial-related procedure indicating that he/she understands the purpose of, and procedures required for the trial and is willing to participate in it.
2.	Male or female subjects aged ≥18 years (and < 85 years only for cohort 7) at the time of obtaining informed consent and with confirmed availability for the scheduled trial visits.
3.	Confirmed ATTR-CM diagnosis established by: • Polarizing light microscopy of green birefringent material in Congo red-stained tissue specimens and confirmed diagnosis of ATTR amyloidosis by IHC or mass spectrometry **OR** • positive bone scintigraphy using either ^{99m}Tc -3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), ^{99m}Tc-hydroxyl-methylene-diphosphonate (HMDP) or ^{99m}Tc-pyrophosphate (PYP), with cardiac signal intensity indicative of ATTR-CM (early phase imaging: cardiac mediastinum ratio > 1.21; late phase imaging: Perugini Grade 2 or 3) and absence of gammopathy (negative serum and urine immunofixation electrophoresis plus normal free light-chain serum ratio). If a gammopathy is detected, diagnosis must be established based on tissue biopsy as indicated above
4.	Known genotype as follows: a. Known pathogenic TTR mutation for subjects with hereditary ATTR-CM b. Known negative genetic testing for a TTR mutation for subjects with sporadic, WT-ATTR-CM
5.	Chronic Heart Failure with all of the following characteristics: a. LVEF ≥40% b. Left ventricular wall thickness (LVWT) ≥14 mm, measured by echocardiography c. N-terminal pro-B-type natriuretic peptide (NT-proBNP) level ≥600 pg/mL d. Able to walk ≥150 meter in the 6-MWT e. New York Heart Association (NYHA) class III (applicable only for cohort 7) f. No hospitalizations for cardiac disease for at least 30 calendar days prior to screening
6.	General health status acceptable for a participation in a clinical trial with a Karnofsky Performance Status ≥60%
7.	Stable pharmacological treatment of any other chronic condition for at least 30 calendar days prior to screening, with the exclusion of immunomodulatory and immunosuppressive treatments
8.	Absolute neutrophil count (ANC) ≥1000 cells/mm^3, platelet count ≥100,000 cells/mm^3, and hemoglobin ≥10 g/dL
9.	Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at screening and must agree to use highly effective physician-approved contraception from screening to 5 months after ending trial participation
10.	Males must be surgically sterile or must agree to use highly effective physician- approved contraception throughout of the trial participation, and for 5 months after ending trial participation
Exclusion criteria for participation in the SAD	
1.	Amyloid light-chain (AL) amyloidosis or any other non ATTR amyloidosis
2.	Heart failure corresponding to NYHA class IV
3.	Uncontrolled hypertension with systolic pressure ≥180 mmHg or diastolic pressure ≥110 mmHg confirmed by 3 measurements in supine position recorded with 5 minutes break in between the measurements
4.	Hypotension with systolic pressure ≤ 90 mmHg or diastolic pressure ≤ 60 mmHg confirmed by 3 measurements in supine position recorded with 5 minutes break in between the measurements
5.	NT-proBNP ≥6'000 pg/mL (NT-proBNP ≥8'500 pg/mL applicable only for cohort 7)
6.	Heart failure not predominantly caused by ATTR-CM
7.	Any severe uncorrected valve disease
8.	Chronic liver disease with liver function test abnormalities: a. Alanine transaminase (ALT) and aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN) b. Total bilirubin > 2 × ULN
9.	Respiratory insufficiency requiring oxygen therapy
10.	Renal insufficiency with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation
11.	Active malignancy with exception of the following: a. Adequately treated basal cell carcinoma b. Squamous cell carcinoma of the skin c. In situ cervical cancer d. Low risk prostate cancer with Gleason score < 7 and prostate specific antigen < 10 mg/mL e. Any other cancer from which the subject has been disease-free for ≥ 2 years
12.	Uncontrolled infection as per Investigator's judgment
13.	Known human immunodeficiency virus (HIV) infection, seropositivity for HIV, hepatitis B and C as well as active hepatitis A
14.	Autoimmune disease requiring immunosuppressive/modulating treatment in the last 2 years
15.	History of organ transplantation or ventricular assist device (VAD)
16.	Polyneuropathy disability (PND) score > IIIA
17.	Suspected or known intolerance/allergy to proteins or any components of the investigational medicinal product (IMP)[1]

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Extended Data Table 2 (continued) | Eligibility criteria for original protocol (SAD/MAD)

18.	Concomitant immunosuppressant therapy for example, corticosteroids, prednisone, dexamethasone except as indicated in low dose (that is, up to 10 mg prednisone or equivalent daily is allowed) for other medical conditions such as inhaled steroid for asthma
19.	Use of the following drugs acting on TTR or ATTR: tolcapone, diflunisal, patisiran, inotersen, and long-term doxycycline, in the 30 calendar days prior to signing informed consent form (ICF). Tafamidis is permitted if it is given as standard of care in a stable dose for at least 30 calendar days prior to signing the ICF
20.	Participation in another investigational clinical trial or intake of investigational drug within 30 calendar days before signing the ICF
21.	Suspected or known drug or alcohol abuse
22.	Serious psychiatric or any other medical condition (including laboratory abnormalities), which, in the opinion of the Investigator, makes the subject unsuitable for inclusion and puts the subject at an unacceptable risk
23.	Subject is nursing or is considering becoming pregnant during the trial or in the 5 months after ending trial participation
24.	Unwillingness or inability to adhere to the trial requirements
25.	If subject is in any way dependent on Neurimmune AG or the principal Investigator or if the subject is accommodated in an establishment on judicial or administrative order
26.	Employee or immediate family (spouse, parent, child or sibling, whether biological or legally adopted) of an employee of Neurimmune AG, the contract research organization (CRO) or the trial site

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Extended Data Table 3 | Eligibility criteria for OLE2

Inclusion Criteria for participation in the OLE2	
1.	Participation in the OLE in cohorts 1 to 5 with a minimum of one administration of NI006 during OLE
2.	Written informed consent for OLE2 obtained from the subject prior to any OLE2-related procedure indicating that he/she understands the purpose of and procedures required for the trial and is willing to participate in it
3.	Availability for all scheduled visits
4.	WOCBP must have a negative serum pregnancy test at screening and must agree to use highly effective physician-approved contraception from screening to 5 months after ending trial participation
5.	Males must be surgically sterile or must agree to use highly effective physician- approved contraception throughout of the trial participation, and for 5 months after ending trial participation
Exclusion Criteria for participation in the OLE2	
1.	Life-threatening allergic hypersensitivity reactions (Grade 3 or higher) to proteins or any components of the IMP
2.	Heart failure corresponding to NYHA class IV at the time of screening
3.	Occurrence of severe treatment-related adverse reactions to the IMP that led to previous trial discontinuation
4.	Infection with SARS-CoV2 confirmed by reverse transcriptase polymerase change reaction (RT-PCR) in the 30 calendar days prior to signing informed consent form is an exclusion criterion. A negative SARS-CoV2 test is required to enter the trial. Completed SARS-CoV2 vaccination is recommended prior to randomization, but not a requirement
5.	LVEF < 30%
6.	Uncontrolled hypertension with systolic pressure ≥180 mmHg or diastolic pressure ≥110 mmHg confirmed by 3 measurements in supine position recorded with 5 minutes break in between the measurements
7.	Hypotension with systolic pressure ≤ 90 mmHg or diastolic pressure ≤ 60 mmHg confirmed by 3 measurements in supine position recorded with 5 minutes break in between the measurements
8.	Liver disease with liver function test abnormalities: a. ALT and AST > 2.5 × upper limit of normal (ULN) b. Total bilirubin > 2 × ULN
9.	Renal insufficiency with eGFR < 30 mL/min/1.73 m^2 using the CKD-EPI equation for the creatinine clearance
10.	Respiratory insufficiency requiring oxygen therapy
11.	Active malignancy with exception of the following: a. Adequately treated basal cell carcinoma b. Squamous cell carcinoma of the skin c. In situ cervical cancer d. Low risk prostate cancer with Gleason score < 7 and prostate specific antigen < 10 mg/mL e. Any other cancer from which the subject has been disease-free for ≥ 2 years
12.	Uncontrolled infection as per Investigator's judgment
13.	Autoimmune disease requiring immunosuppressive/modulating treatment in the last 2 years
14.	History of organ transplantation or VAD
15.	Concomitant immunosuppressant therapy. Exceptions are low-dose steroids for example, stable dose of prednisone up to 10 mg daily or equivalent, for medical conditions such as gout or chronic obstructive pulmonary disease, or inhaled steroids for asthma
16.	Use of the following drugs acting on TTR or ATTR: tolcapone, diflunisal, patisiran, inotersen, and long-term doxycycline, in the 30 calendar days prior to signing ICF. Tafamidis is permitted if it is given as standard of care
17.	Participation in another investigational clinical trial except NI006-101 or intake of investigational drug since end of participation in the OLE phase of the NI006-101 trial
18.	Suspected or known drug or alcohol abuse
19.	Serious psychiatric or any other medical condition (including laboratory abnormalities), which, in the opinion of the Investigator, makes the subject unsuitable for inclusion and puts the subject at an unacceptable risk
20.	Subject is nursing or is considering becoming pregnant during the trial or in the 5 months after ending trial participation
21.	Unwillingness or inability to adhere to the trial requirements
22.	If subject is in any way dependent on Neurimmune AG or the Principal Investigator or if the subject is accommodated in an establishment on judicial or administrative order
23.	Employee or immediate family (spouse, parent, child or sibling, whether biological or legally adopted) of an employee of Neurimmune AG, the CRO or the trial site

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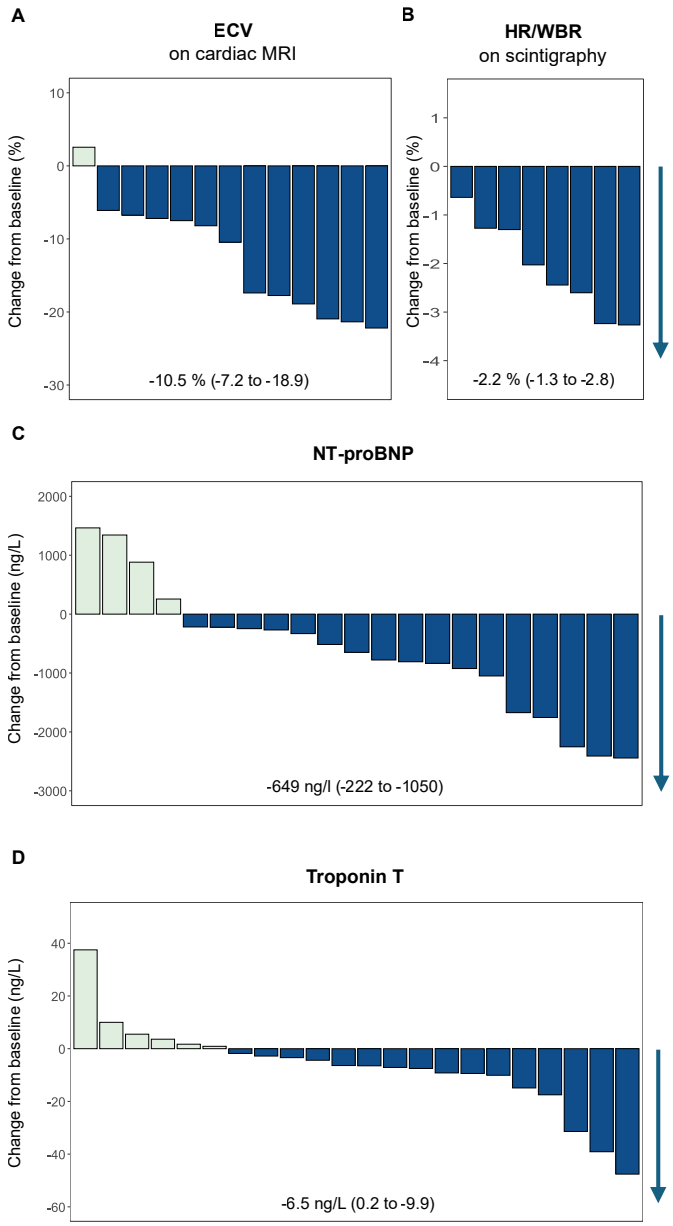

Extended Data Fig. 1 | Waterfall plots of the absolute change from baseline to the end of the OLE2 for measures of cardiac amyloid burden and cardiac blood biomarkers. a-d, Individual changes from baseline to the end of the OLE2 are presented for cardiac amyloid burden (**a**,**b**) and cardiac biomarkers (**c**,**d**). Underneath the waterfall plots, the median (interquartile range) absolute change from baseline is presented for each variable. For participants randomized to placebo, the last assessment prior to OLE is considered as baseline. Blue arrows indicate direction of improvement. HR/WBR = heart over whole-body retention ratio, NT-proBNP = N-terminal pro-B-type natriuretic peptide.

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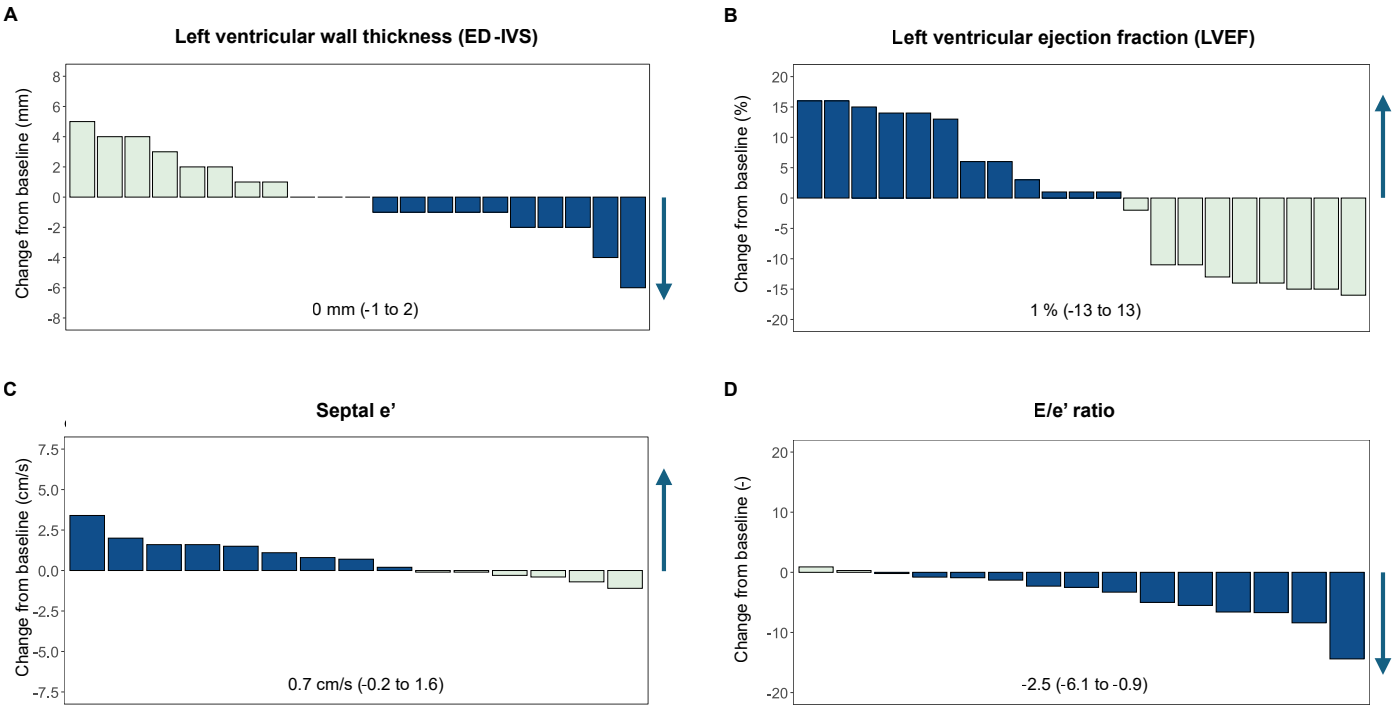
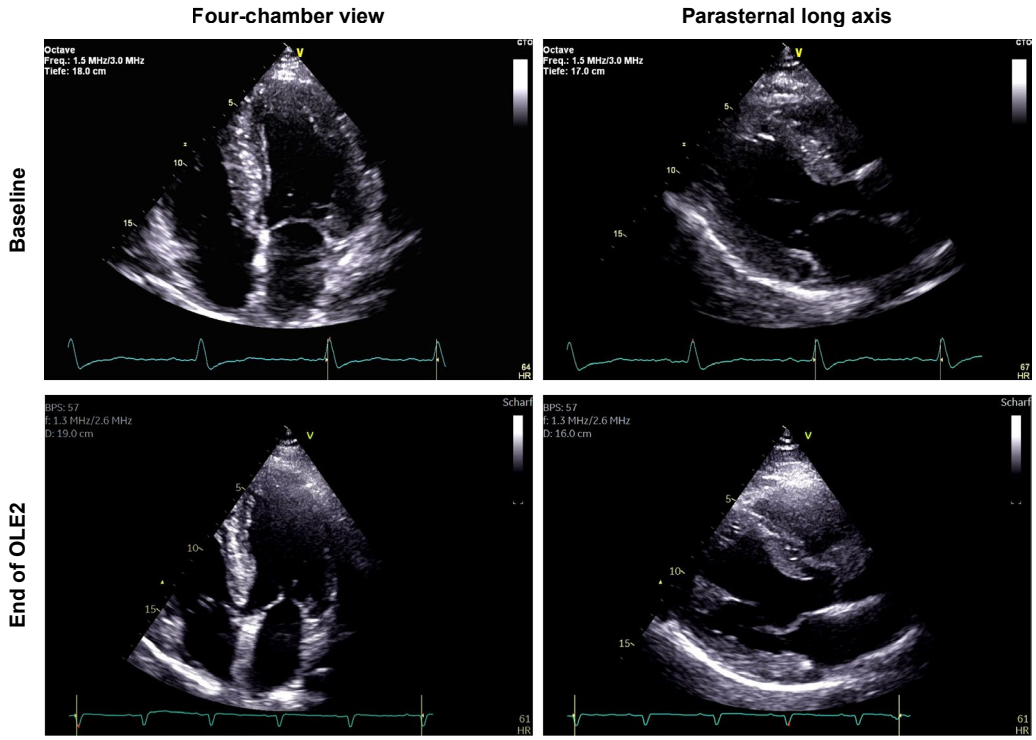


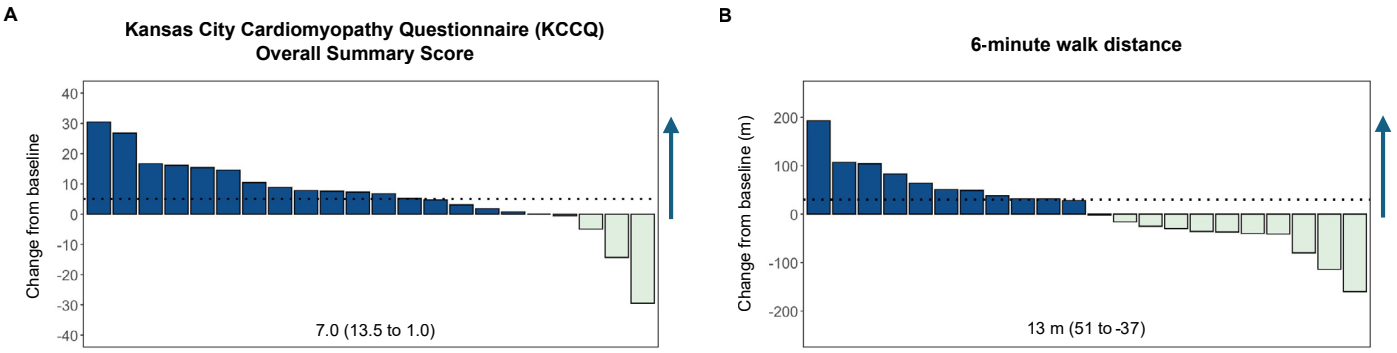
Extended Data Fig. 2 | Waterfall plots of the change from baseline to the end of the OLE2 for key echocardiographic parameters. a-d, Individual changes from baseline to the end of the OLE2 are presented for echocardiographic parameters of cardiac structure and function (**a**-**d**). Underneath the waterfall plots, the median (interquartile range) absolute change from baseline is presented for each variable. For participants randomized to placebo, the last echo prior to OLE is considered as baseline. Blue arrows indicate direction of improvement. ED-IVS = end-diastolic interventricular septum; LVEF = left ventricular ejection fraction.

https://doi.org/10.1038/s41591-026-04487-3



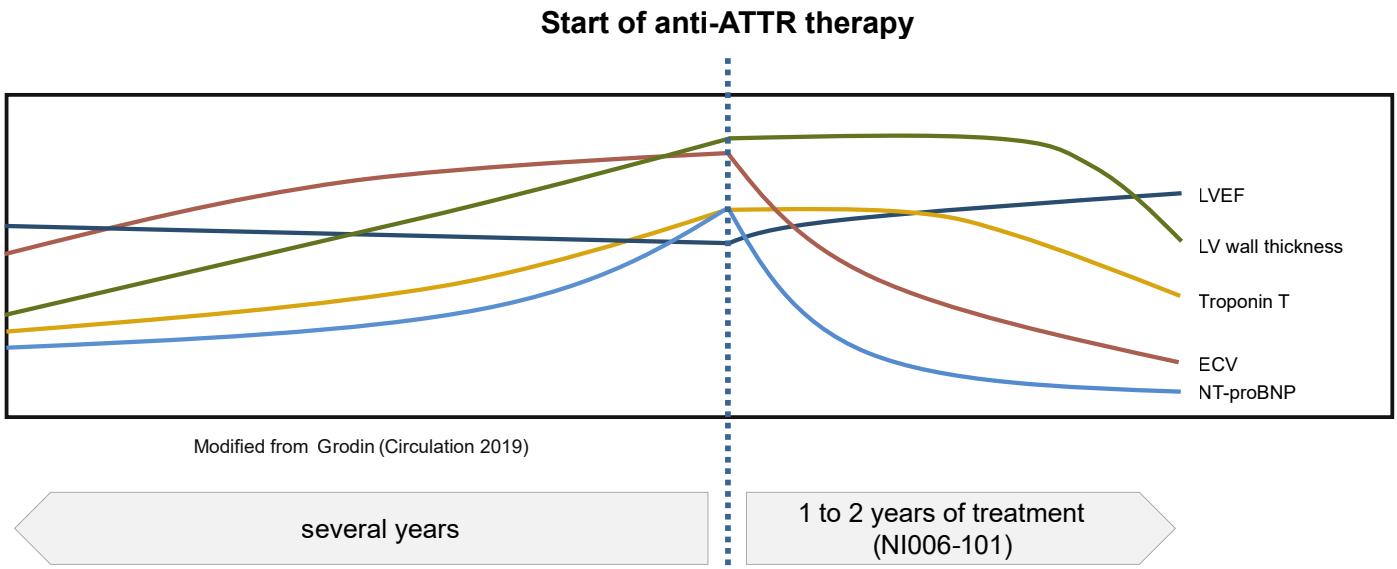
Extended Data Fig. 3 | Example of echocardiographic changes after treatment with cliramitug. Representative case: 69yo male, ATTRwt-CM, NYHA II, NAC 2, on tafamidis at baseline, enrolled in high starting dose cohort (Cohort 5), randomized to cliramitug, received 16×30 mg/kg during study, 19.2 months duration to end of OLE2, total cliramitug exposure 163 days x mg/mL.

https://doi.org/10.1038/s41591-026-04487-3



Extended Data Fig. 4 | Waterfall plots of the absolute change from baseline to the end of the OLE2 for measures of quality of life and overall function. **a**,**b**, Individual changes from baseline to the end of the OLE2 are presented for Kansas City Cardiomyopathy Questionnaire Overall Summary Score (**a**) and 6-minute walk distance (**b**). Underneath the waterfall plots, the median (interquartile range) absolute change from baseline is presented for both variables. For participants randomized to placebo, the last assessment prior to OLE is considered as baseline. Blue arrows indicate direction of improvement. Dotted lines represent accepted thresholds for clinical significance (5 for KCCQ-OSS, 30 m on 6-minute walk test). KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score.

https://doi.org/10.1038/s41591-026-04487-3



Extended Data Fig. 5 | Illustration of changes in plasma biomarkers, cMRI and echocardiography prior and after treatment initiation of an anti-ATTR therapy. The graph represents a model of the time course and sequence of expected changes across relevant markers of ATTR-CM after treatment initiation of high-dose clirametug. The lines are drawn based on based on the LOESS regression lines presented in Fig. 4.

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Reporting Summary

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For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☒	☐ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
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☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	☐ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	SAS version 9.4 for data handling
Data analysis	R version 4.4.2 for data analysis and visualization

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

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All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The clinical trial datasets generated and/or analyzed during this study are not publicly available because they contain sensitive human participant data and are part of an ongoing clinical development program. De-identified individual participant data underlying the findings reported in this Article, may be made available to qualified researchers upon reasonable request for non-commercial research purposes, subject to sponsor review, applicable regulatory requirements, and execution of a data access agreement. Requests should be directed to the corresponding author.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Wildtype ATTR-CM is a disease that primarily affects male patients. While Participant's sex was recorded (self-reported), gender was not determined.
Reporting on race, ethnicity, or other socially relevant groupings	No sex- or gender-based analyses were prespecified. Because of the low sample size (n=1 female participant) no meaningful conclusions can be drawn. Therefore, no post hoc sex- or gender-based analysis was conducted.
Population characteristics	The study population is representative of a contemporary patient population with early to moderate ATTR-CM. Relevant covariate-relevant population characteristics in this study include age, sex, presence of ATTRv genotype, and background disease-modifying therapy.
Recruitment	Recruitment at tertiary referral centers and pre-selection of patients able to comply with the intensive study procedures may have introduced selection bias and may limit generalizability of the results.
Ethics oversight	The study was approved by regulatory authorities and ethics committees in all 4 participating countries under EU directive (EudraCT number 2019-001932-80). The study was registered on CT.gov (NCT04360434) Regulatory authorities: Paul-Ehrlich Institut, Germany; Agence nationale de sécurité du médicament et des produits de santé, France; Agencia Española de Medicamentos y Productos Sanitarios, Spain; and Centrale Commissie Mensgebonden Onderzoek, the Netherlands. Ethics committees: Ethikkommission der Medizinischen Fakultät Heidelberg, Germany; Comité de protection des personnes Ile de France VII, France; Comité Etico de Investigación Científica - H. Puerta Hierro, Spain; and Medisch Ethische Toetsingscommissie UMCG, the Netherlands.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No formal sample size estimation was performed. The study followed a modified 3+3 and 4/2 study design typically used for first-in-human studies. 6 participants (4:2 active:placebo) were enrolled at each of the ascending dose levels. All participants who completed the original OLE in cohorts 1 to 5 were offered to continue treatment in the OLE2.
Data exclusions	No data was excluded from the analysis.
Replication	The present study is the first-in-human study of cliramitug (previously NI006). Based on the results from this study, a Phase 3 study was designed. The Phase 3 study is currently ongoing (NCT06183931)
Randomization	Participants were randomized 4:2 to cliramitug or placebo.
Blinding	The study was blinded, including participants, treating physicians and the sponsor. To reduce bias in image readings, central readers were additionally blinded to the image timepoint and participant ID.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT04360434
Study protocol	The full study protocol is attached to the submission. It is also accessible on the website of NEJM along with the primary results of the study.
Data collection	Trial data was collected using electronic case report forms (eCRF, MediData). Imaging data was transferred from the central imaging laboratory in SDTM format. The time period spanned from February 2020 to July 2023.
Outcomes	The primary objective of the study was to determine the safety and tolerability of cliramitug as assessed by the occurence of treatment emergent adverse events, serious adverse events, as well as changes in clinical laboratory parameters, vital signs, ECG parameters and echocardiogram results. Secondary objective of the study was to determine the PK profile of cliramitug. Relevant exploratory endpoints include the efficacy of cliramitug as assessed by changes in echocardiographic parameters, MRI parameters, heart-over-whole body retention on scintigraphy, and cardiac biomarkers.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*