L'immunothérapie
Pour l'amylose TTR sauvage et héréditaire

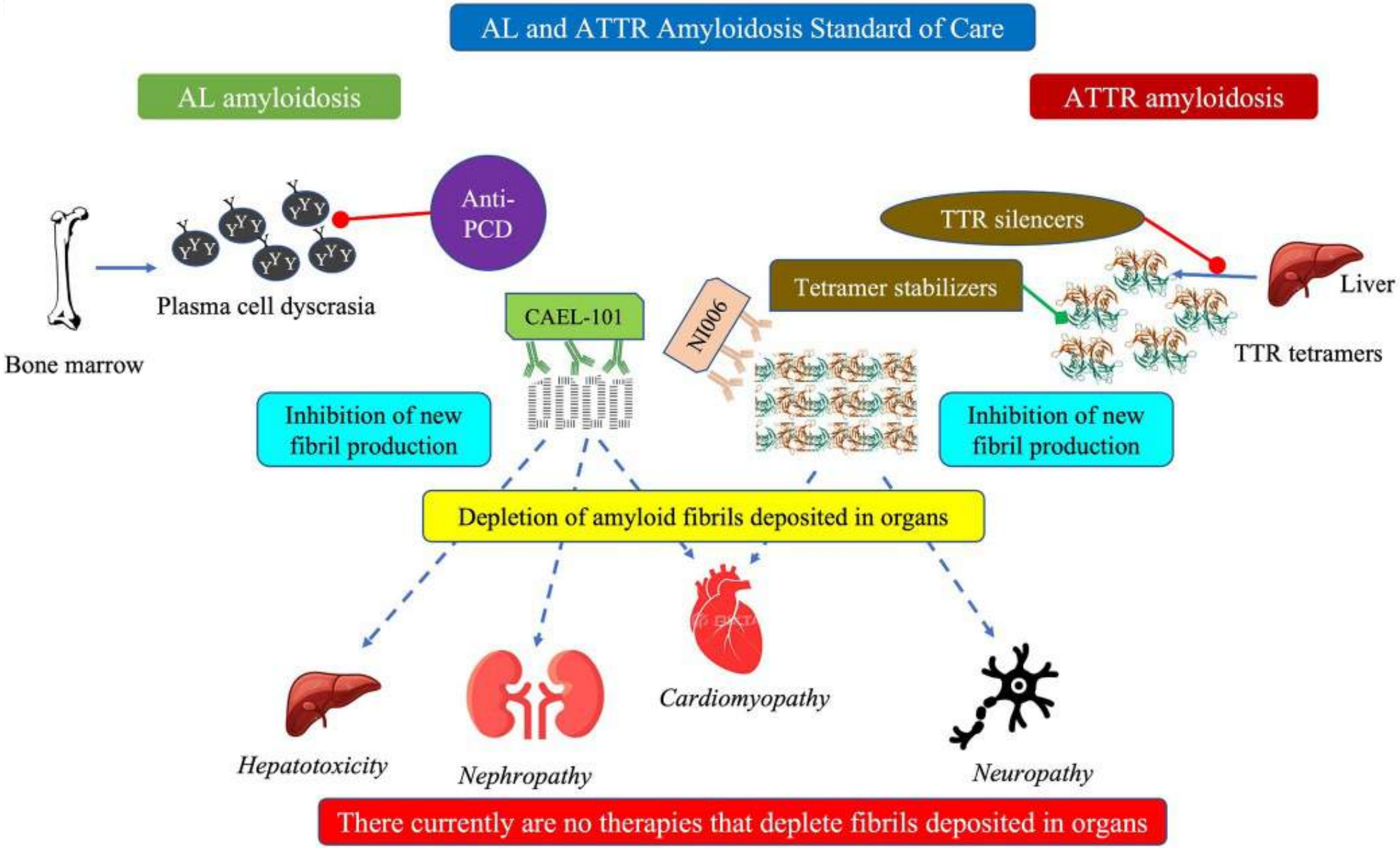
Pr DONAL Erwan

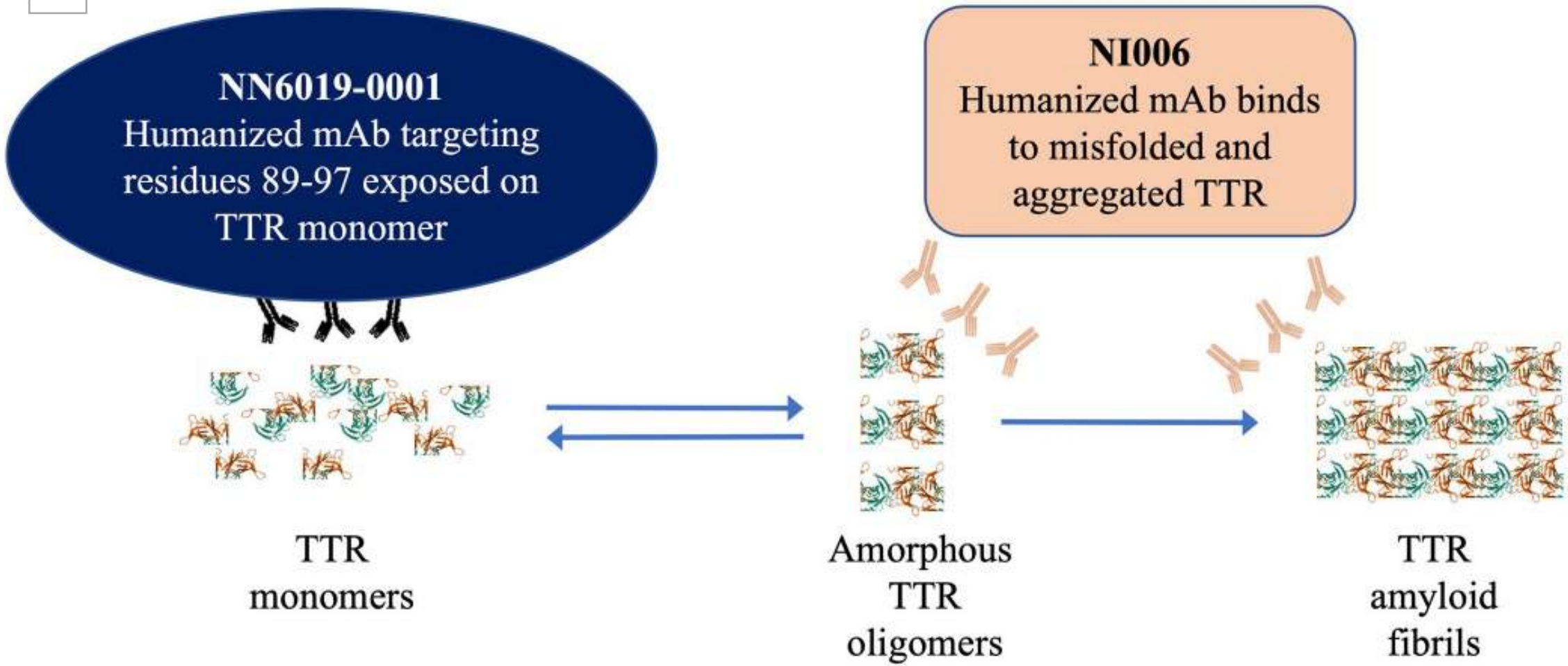
Rennes University Hospital and LTSI, INSERM1099

RENNES, France

erwan.donal@chu-rennes.fr

@DonalErwan


AL and ATTR Amyloidosis Standard of Care
AL amyloidosis
ATTR amyloidosis
Anti-PCD
Plasma cell dyscrasia
Bone marrow
TTR silencers
Tetramer stabilizers
Liver
TTR tetramers
CAEL-101
NI006
Inhibition of new fibril production
Inhibition of new fibril production
Depletion of amyloid fibrils deposited in organs
Hepatotoxicity
Nephropathy
Cardiomyopathy
Neuropathy
There currently are no therapies that deplete fibrils deposited in organs


NN6019-0001
Humanized mAb targeting residues 89-97 exposed on TTR monomer
NI006
Humanized mAb binds to misfolded and aggregated TTR
TTR monomers
Amorphous TTR oligomers
TTR amyloid fibrils

Recombinant human anti-ATTR immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that was generated based on a comprehensive immune repertoire analysis of memory B-cell complements of healthy elderly human subjects

- **The primary mode of action of the treatment is to induce an antibody-mediated phagocytosis of ATTR fibrils by phagocytic immune cells such as macrophages, resulting in the clearance of ATTR deposits from tissues**.

  By activating the elimination of ATTR deposits in patients suffering from ATTR amyloidosis, the objective:

  to restore organ function and structure, and specifically,

  by decreasing cardiac muscle stiffness and improving heart contractility and elasticity and possibly improve peripheral neurological functions.

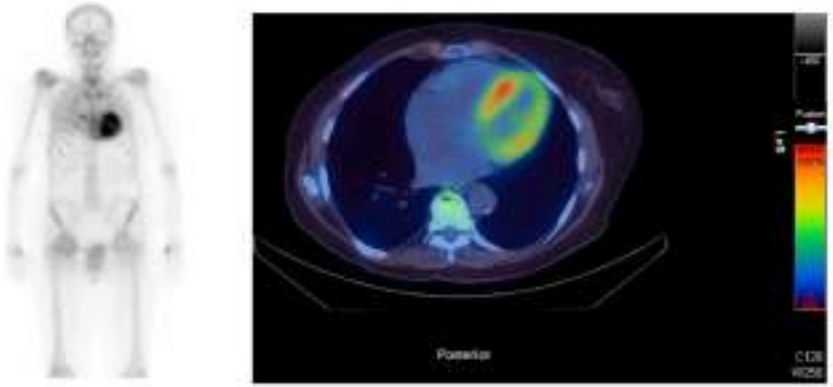
  This effect is expected to result in symptom stabilization or regression and to improve organ function and survival.

L’immunothérapie

Primary results of the Phase Ib proof-of-concept study of NI006, a recombinant human antibody to deplete amyloid deposits in ATTR-cardiomyopathy

Background & Rationale

ATTR cardiac amyloidosis in (SPECT)-CT ^{99m}Tc-DPD scan [1]

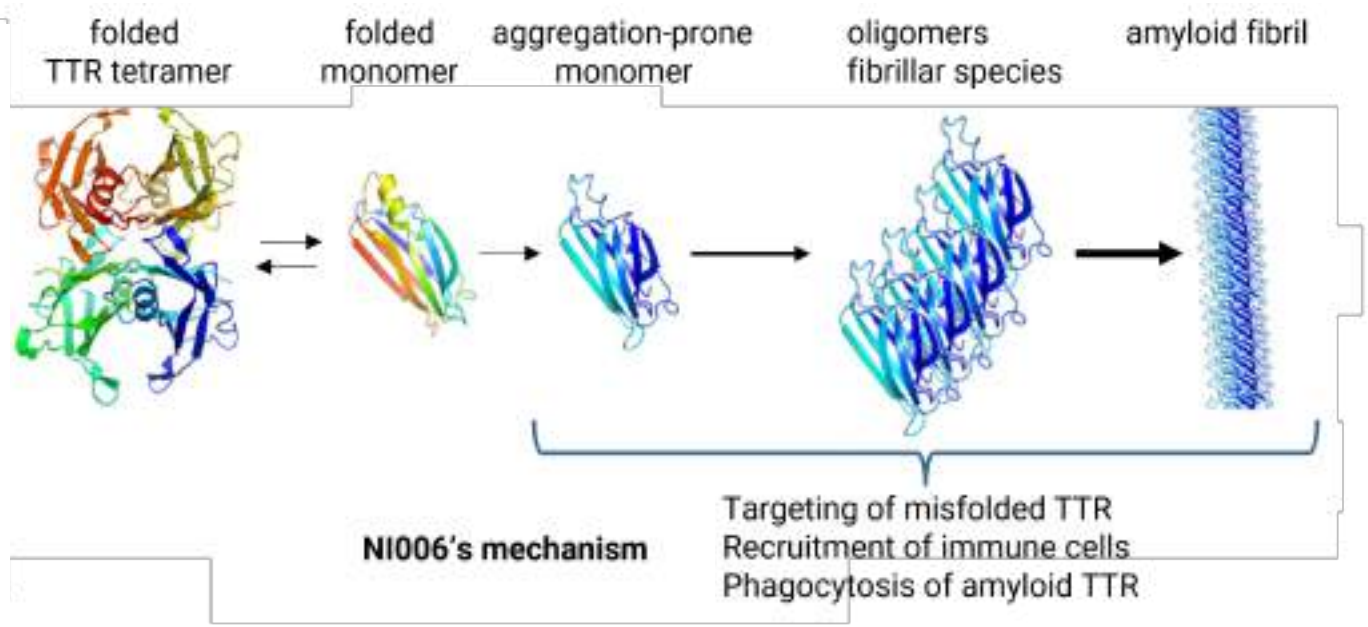


Transthyretin amyloidosis with cardiomyopathy

- Progressive, infiltrative and fatal disease with heart failure
- Sporadic (ATTRwt) or genetic cause (ATTRv)
- Cardiac deposition of transthyretin amyloid (ATTR)
- Increased cardiac muscle thickness and stiffness
- No treatment available to directly eliminate ATTR

NI006

- Investigational human anti-ATTR antibody
- Discovered from human B-cell memory repertoires
- Selective for misfolded transthyretin
- Designed to deplete ATTR amyloid
- Effective in preclinical models [2]



[1] Sabharwal NK et al., *Heart* 2017; [2] Michalon et al., *Nature Communications* 2021
Figure adopted from: Azevedo E, et al., *Amyloidosis* 2013

Design of NI006 Phase Ib proof-of-concept study in ATTR cardiomyopathy

Key In-/Exclusion Criteria

- Confirmed diagnosis of ATTR-CM
- LV-wall thickness ≥ 14 mm
- NT-proBNP 600 – 6000 pg/mL
- Tafamidis allowed

Primary Objective

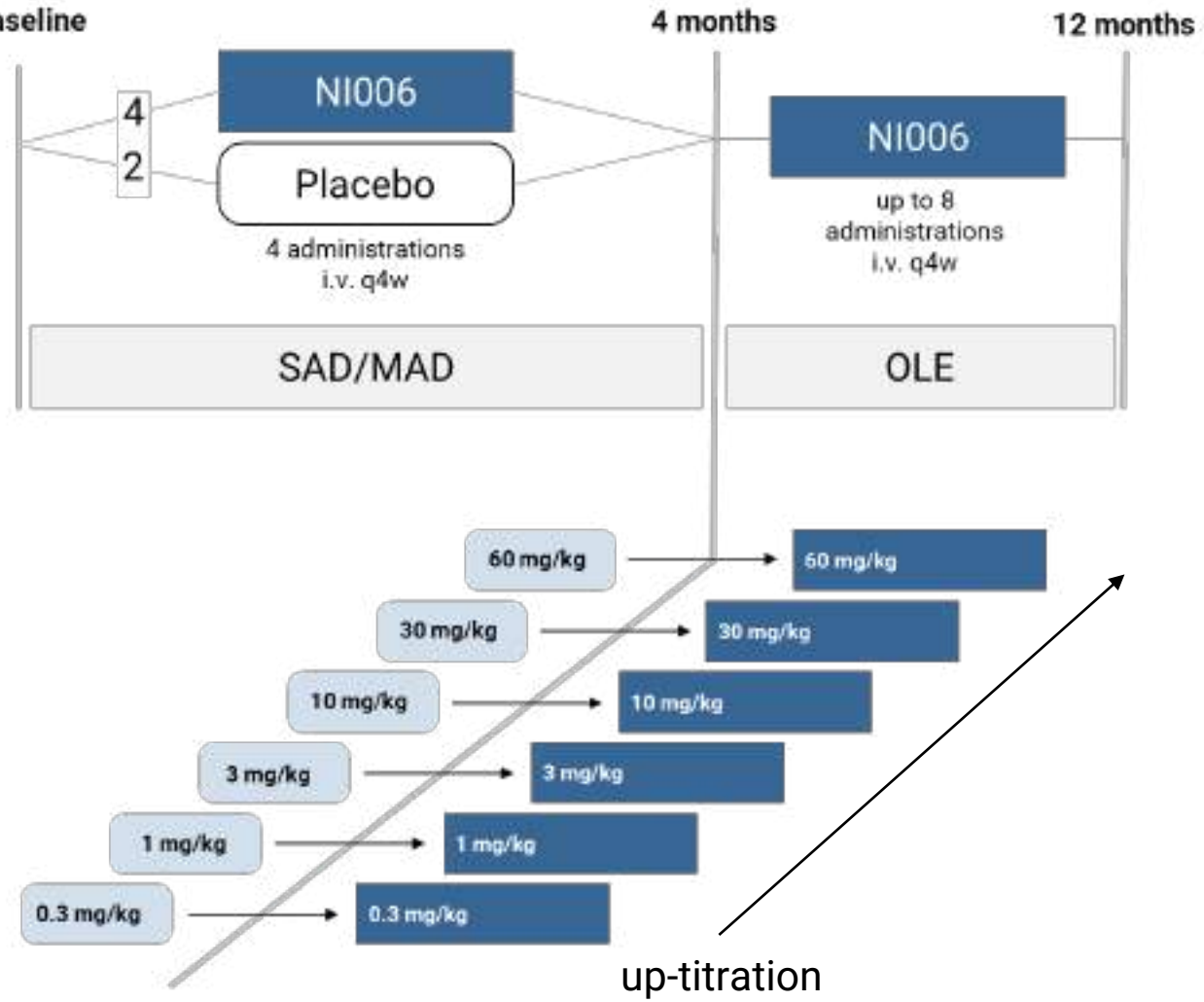
- Safety & tolerability

Secondary Outcomes

- Pharmacokinetics

Explor. Efficacy Assessments

- Scintigraphy or cardiac MRI
- Echocardiogram
- Biomarkers
- 6-MWT, QoL



NI006-101, NCT 04360434

Baseline demographics, disease characteristics and cardiac imaging

Characteristic	NI006 (N=27)	Placebo (N=13)
Age (years)	74 (70 – 77)	68 (67 – 74)
Male Sex	26 (96)	13 (100)
TTRwt genotype	23 (85)	10 (77)
Weight (kg)	85 (79 – 92)	75 (71 – 80)
NT-proBNP (pg/mL)	2029 (1433 – 3674)	1591 (1310 – 2107)
Troponin T (pg/mL)	52 (38 – 71)	33 (22 – 43)
eGFR (ml/min/1.73m^2)	63 (44 – 86)	79 (62 – 86)
NAC Stage		
Stage I	12 (44)	11 (85)
Stage II	13 (48)	2 (15)
Stage III	2 (7)	0
NYHA Class		
Class I	3 (11)	3 (23)
Class II	19 (70)	10 (77)
Class III	5 (19)	0

Characteristic	NI006 (N=27)	Placebo (N=13)
Coexisting Conditions		
Atrial fibrillation	17 (63)	10 (77)
Hypertension	18 (67)	7 (54)
Diabetes	4 (15)	2 (15)
Baseline medication		
Tafamidis	24 (89)	12 (92)
Echocardiographic Variables		
ED-IVS (mm)	15 (15 – 16)	16 (15 – 17)
LVEF (%)	62 (57 – 69)	72 (54 – 76)
Cardiac MRI		
Participants	10 (37)	6 (46)
ECV (%)	58.3 (53.2 – 66.6)	59.8 (55.7 – 64.3)
Scintigraphy		
Participants	17 (63)	7 (54)
H/WB ratio (%)	5.0 (4.4 – 7.0)	5.0 (3.4 – 6.2)

Numbers represent median (interquartile range) or n (percentage)

Safety & tolerability up to the highest dose level of 60 mg/kg

Adverse Event (AE) summary for 4-months SAD/MAD phase

Patients with…	0.3 mg/kg n= 4	1 mg/kg n= 4	3 mg/kg n= 4	10 mg/kg n= 5	30 mg/kg n= 5	60 mg/kg n= 5	Placebo n= 13
At least one AE	4 (24)	4 (14)	3 (22)	5 (30)	5 (37)	5 (25)	11 (39)
Severe (grade III)	1 (1)	2 (2)	0	1 (1)	1 (1)	0	2 (2)
Life threatening, death (grade ≥ IV)	0	0	0	0	0	0	0
At least one SAE	1 (1)	3 (3)	0	1 (3)	1 (1)	0	3 (3)
At least one related AE	0	1 (1)	1 (2)	1 (5)	2 (13)	1 (4)	0
At least one related SAE	0	0	0	0	0	0	0
AE leading to temporary d/c	0	0	0	0	0	0	1
AE leading to permanent d/c	0	0	0	2 [COVID-19, Arthralgias]	1 [COVID-19]	1 [Thrombo-cytopenia]	0

Numbers represent n of patients (n of events) [AE term]. Grading according to CTCAE.

- NI006 has a favorable safety profile up to the highest dose, no dose-limiting toxicity (DLT), no treatment related SAE
- No acute echocardiographic changes, no ECG changes/arrhythmias, no clinically meaningful changes in safety labs
- 2 cases of fatal disease progression in OLE in patients with advanced disease (1 placebo, 1 in 3 mg/kg cohort)
- 1 patient discontinued during OLE (COVID-19)
- Non-serious musculoskeletal AEs (e.g. arthralgias) were more commonly observed with high-dose NI006 and in placebo patients after switch to NI006 during OLE

Quantification of cardiac amyloid load using established imaging proxies

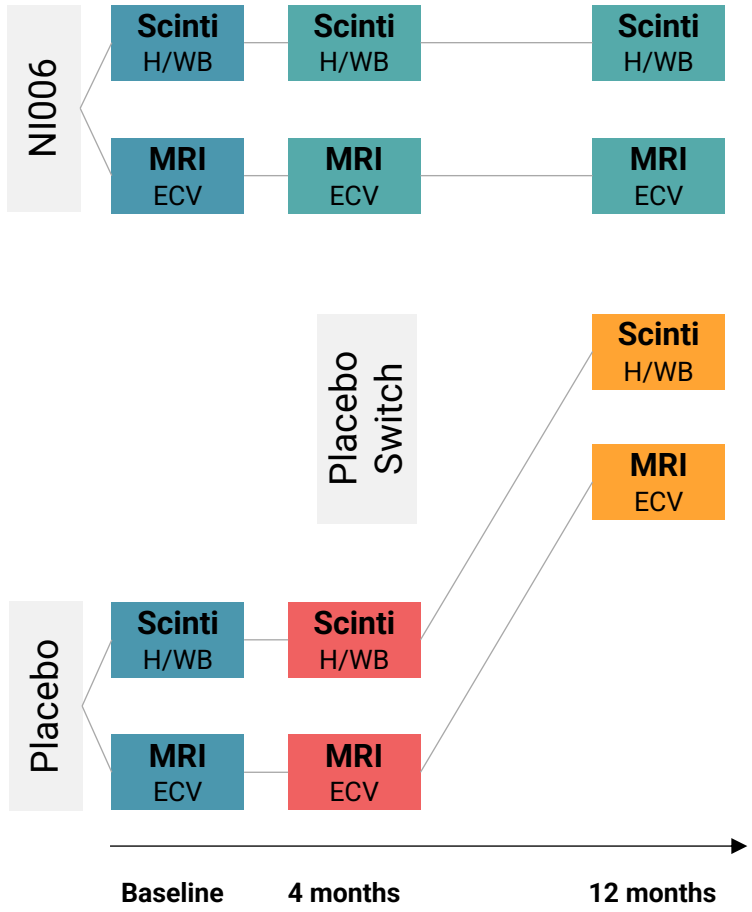
- Serial scintigraphy or cardiac MRI performed in all patients
- One imaging modality per patient, selected according to patient characteristics and local standards
- Harmonized acquisition protocol, central reading in blinded fashion

Planar scintigraphy (n=24)

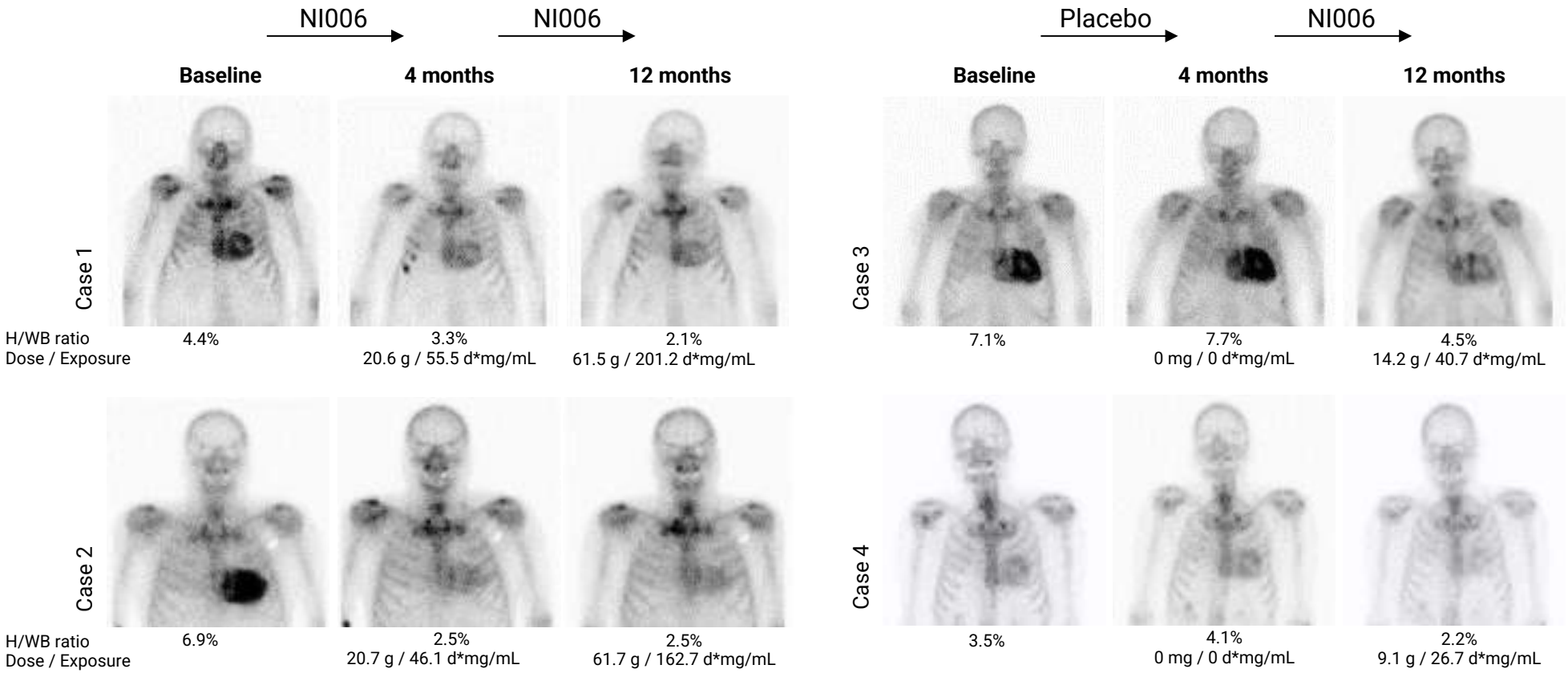
- Tracer uptake of heart over whole-body (H/WB) ratio assessed
- DPD (n=7) or HMDP (n=17) used as cardiac tracers

Cardiac MRI (n=16)

- Midventricular extracellular volume (ECV) assessed
- Calculated from pre-/post contrast T1 measurements of myocardium in short-axis view



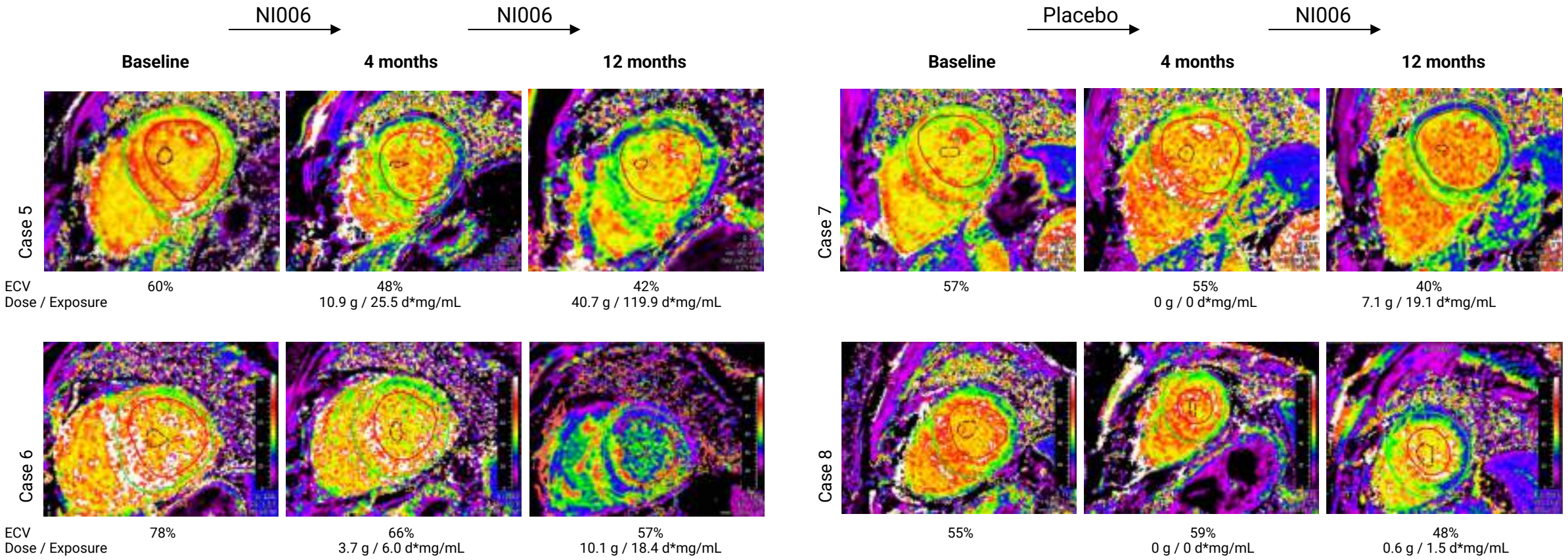
Reductions of cardiac tracer uptake on scintigraphy



- NI006 reduced cardiac uptake on scintigraphy as early as 4 months on treatment with NI006.
- After continued treatment for up to 12 months, cardiac tracer uptake was further reduced.
- Placebo participants showed reduced cardiac uptake after switch to NI006 during OLE.

H/WB ratio – heart to whole body ratio

Reductions in extracellular volume (ECV) on cardiac MRI



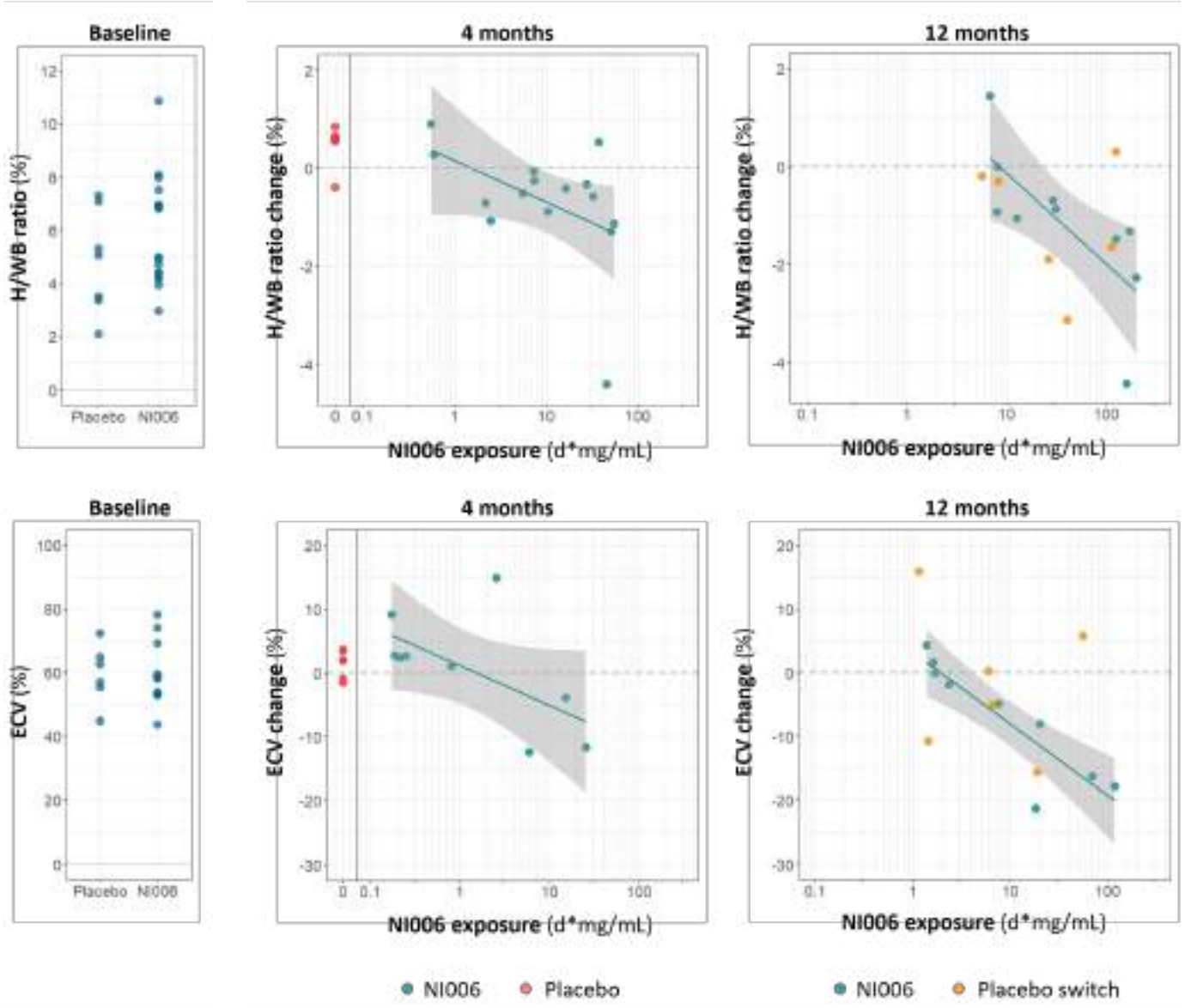
- NI006 reduced the ECV on cardiac MRI as early as 4 months on treatment with NI006.
- After continued treatment for up to 12 months, ECV was further reduced.
- Placebo participants showed reduced ECV after switching to NI006 during OLE.

ECV – extracellular volume

Exposure-response relationship for heart over whole-body ratio & ECV

Scinti-graphy

MRI



Pre-specified analysis according to NI006 dose:
High dose (≥10 mg/kg) vs Low dose (≤3 mg/kg)

H/WB ratio Median	NI006 0.3-3 mg/kg	NI006 ≥10 mg/kg
Baseline	5.0%	5.7%
4 months	5.9%	3.8%
12 months	5.3%	2.5%

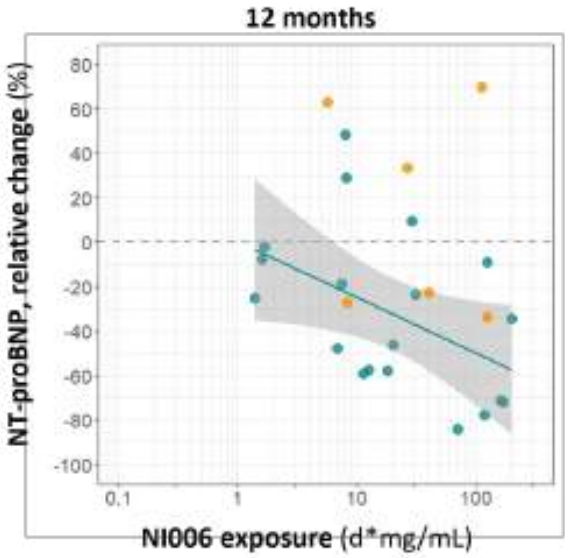
ECV Median	NI006 0.3-3 mg/kg	NI006 ≥10 mg/kg
Baseline	58.1%	59.4%
4 months	61.1%	49.0%
12 months	54.4%	41.6%

Linear regression lines with unadjusted 95% confidence intervals for patients randomized to NI006

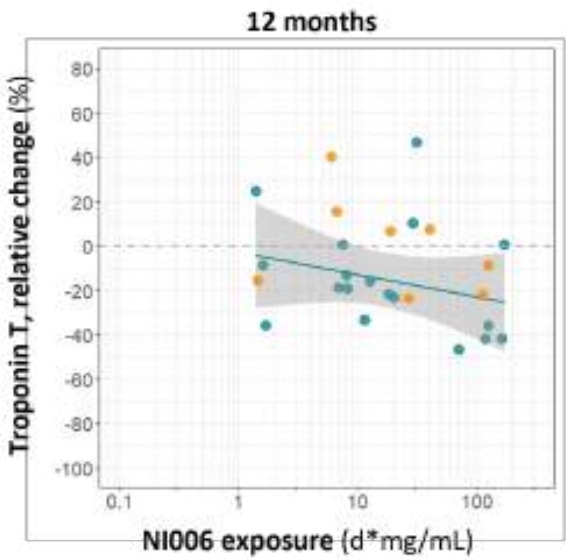
NI006-101, NCT 04360434

Changes in NT-proBNP, Troponin T and additional exploratory efficacy read-outs

NT-proBNP



Troponin T



NI006 Placebo switch

Pre-specified analysis according to NI006 dose:
High dose (≥10 mg/kg) vs Low dose (≤3 mg/kg)

Relative median change from baseline in patients with

	NI006 0.3-3 mg/kg	NI006 ≥10 mg/kg
NT-proBNP	-22%	-58%
Troponin T	-18%	-29%

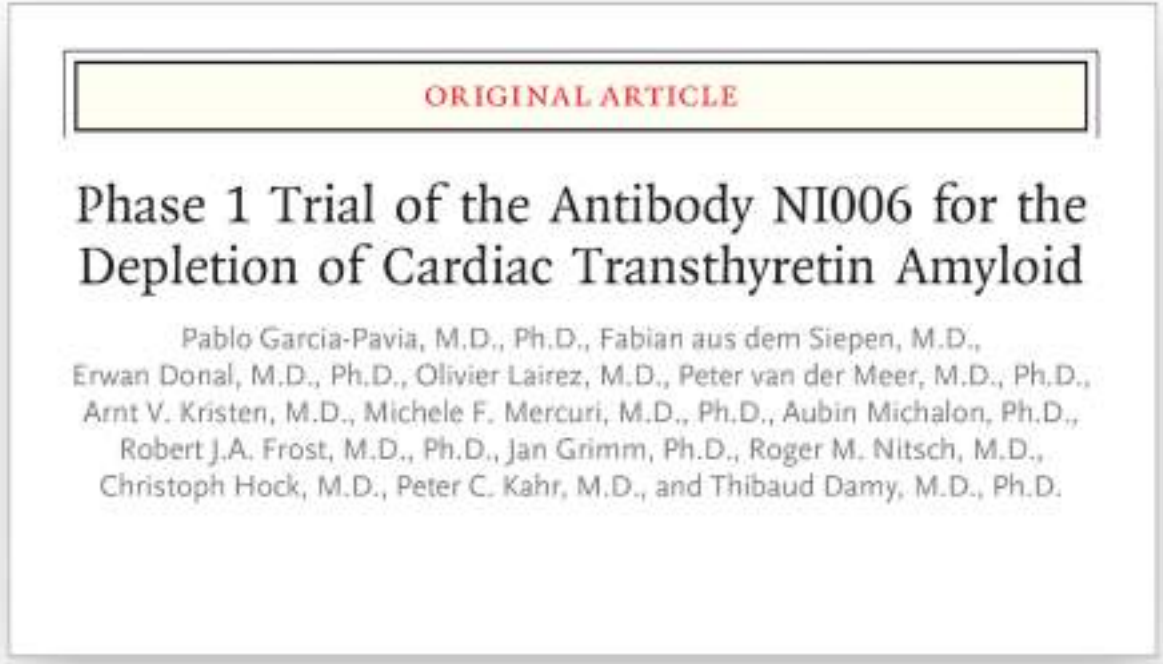
- Changes in imaging proxies of cardiac amyloid load were accompanied by reductions in cardiac biomarkers.
- Despite small sample size, echocardiographic findings (wall thickness, LVEF, diastolic function) and quality of life (KCCQ) also showed improvement at 12 months compared to baseline.

Linear regression lines with unadjusted 95% confidence intervals for patients randomized to NI006

NI006-101, NCT 04360434

Results of the Phase 1b study of NI006 in patients with ATTR-CM

- NI006 up to 60 mg/kg had a favorable safety profile over 12 months of treatment.
- Adverse events were mostly mild to moderate and could be managed.
- Imaging proxies of cardiac amyloid and changes in biomarkers suggest ATTR depletion.
- Study establishes initial proof of concept for cardiac TTR depletion using NI006.
- Data support further clinical investigation of NI006.



ALXN2220-ATTR-CM-301 : A phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of Amyloid Depleter ALXN2220 in adult participants with Transthyretin Amyloid Cardiomyopathy (ATTR-CM) deple TTR-CM Study