7e MASTERCLASS AMYLOSES CARDIAQUES

ÉVÉNEMENT HYBRIDE
PRÉSENTIEL
& DISTANCIEL

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www.masterclass-amylose.com

Immunothérapie anti-TTR

ALXN2022 Phase 2 et 3 et NOVO-NORDISC

Jean-Christophe Eicher

CHU François Mitterrand DIJON

Disclosures

☑ I have the following potential disclosure to report

Affiliation/Financial Relationship

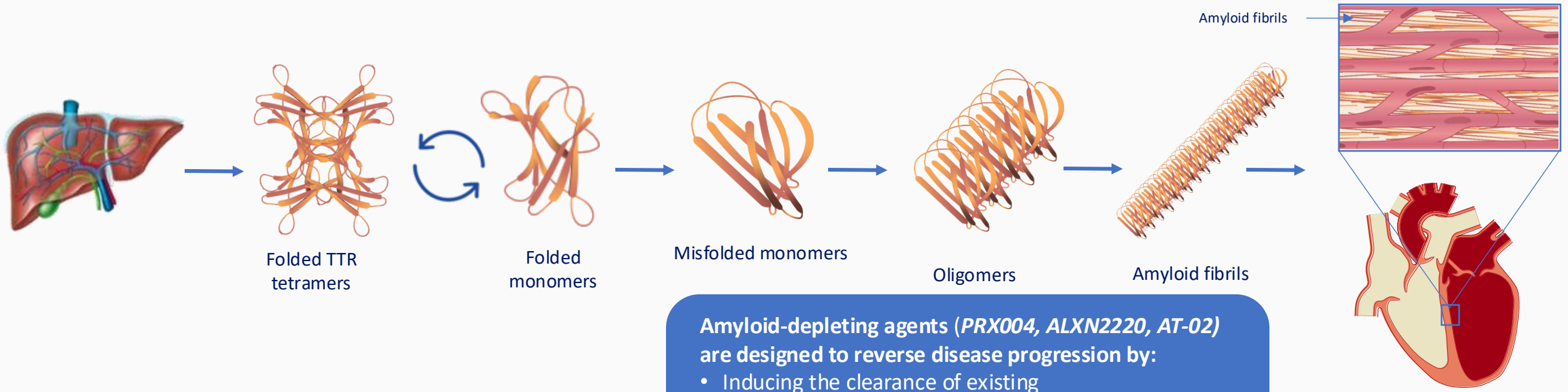
- Grant/Research Support
- Consulting Fees/Honoraria

Company

- Alnylam
- Amgen
- AstraZeneca
- Bayer
- Boehringer
- Corvia
- Novartis
- Pfizer
- Vifor

TTR-targeted therapeutic approaches for ATTR-CM

Amyloid depletion[1–4]



Amyloid-depleting agents (*PRX004, ALXN2220, AT-02*) are designed to reverse disease progression by:

- Inducing the clearance of existing amyloid deposits
- Preventing the formation of new amyloid fibrils

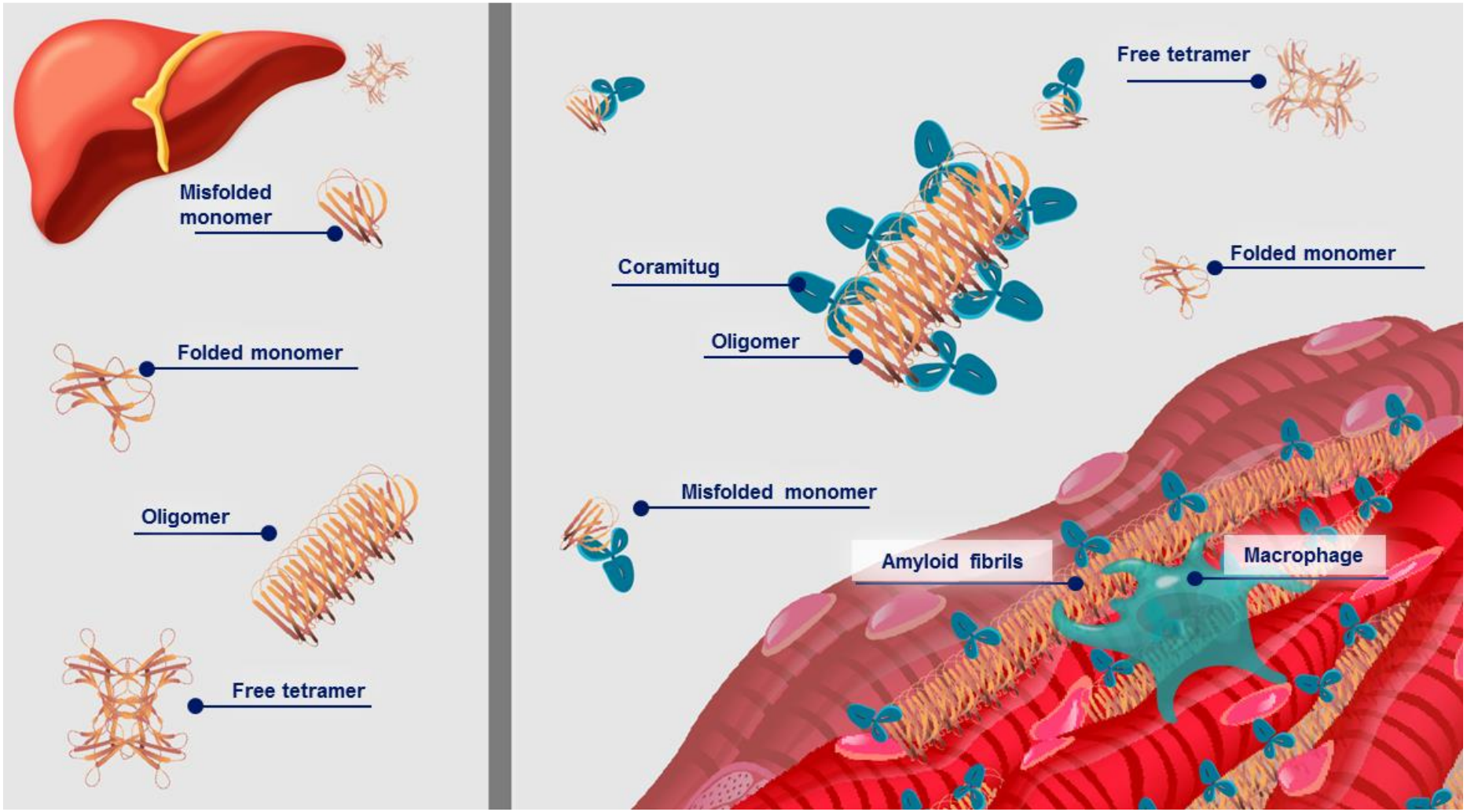

Misfolded monomer
Folded monomer
Oligomer
Free tetramer
Free tetramer
Coramitug
Folded monomer
Oligomer
Misfolded monomer
Amyloid fibrils
Macrophage

Table 1. Monoclonal antibody drugs in clinical trials for the treatment of ATTR, and related antibodies.

Antibody Name	Other Names	Epitope	Clinical Trial Numbers	Current Stage of Trial	Reference
ALXN-2220	NI006, NI301A, anti-TTR (41–45)	Residues 41–45	NCT06183931—Phase 3 NCT04622046—Phase 3—Japan	Phase 3	[10–12]
Coramitug	NNC6019-0001, PRX004, anti-TTR (89–97)	Residues 89–97	NCT03336580—Phase 1, terminated NCT05442047—Phase 2 NCT06260709—Phase 2—long term	Phase 2	[13–15]
RT24	anti-TTR (115–124)	Residues 115–124	-	-	[16]
anti-TTR (39–44)	-	Residues 39–44	-	-	[17–21]
anti-TTR (56–61)	-	Residues 56–61	-	-	[17]

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

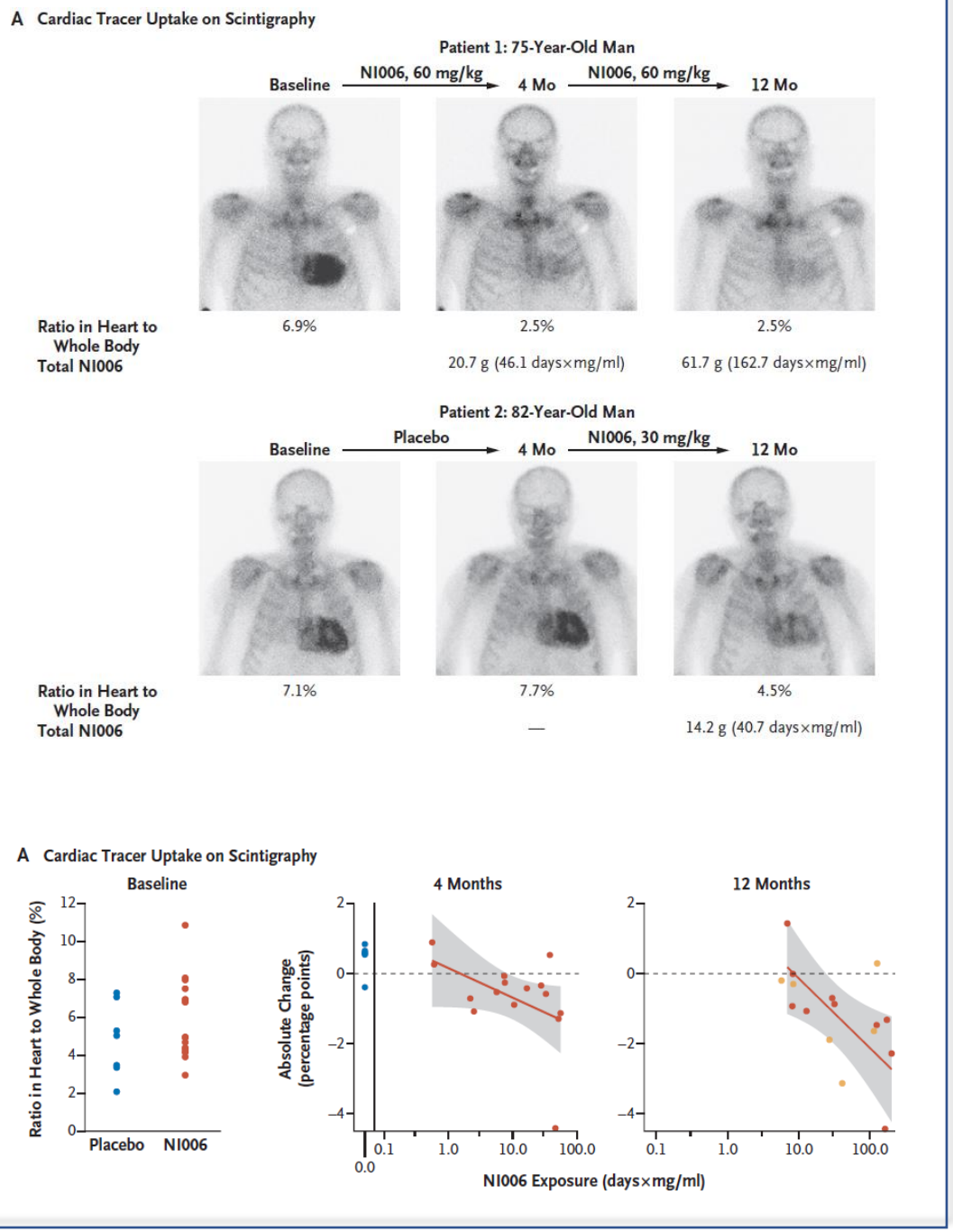
Pablo Garcia-Pavia, M.D., Ph.D., Fabian aus dem Siepen, M.D., Erwan Donal, M.D., Ph.D., Olivier Lairez, M.D., Peter van der Meer, M.D., Ph.D., Arnt V. Kristen, M.D., Michele F. Mercuri, M.D., Ph.D., Aubin Michalon, Ph.D., Robert J.A. Frost, M.D., Ph.D., Jan Grimm, Ph.D., Roger M. Nitsch, M.D., Christoph Hock, M.D., Peter C. Kahr, M.D., and Thibaud Damy, M.D., Ph.D.

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

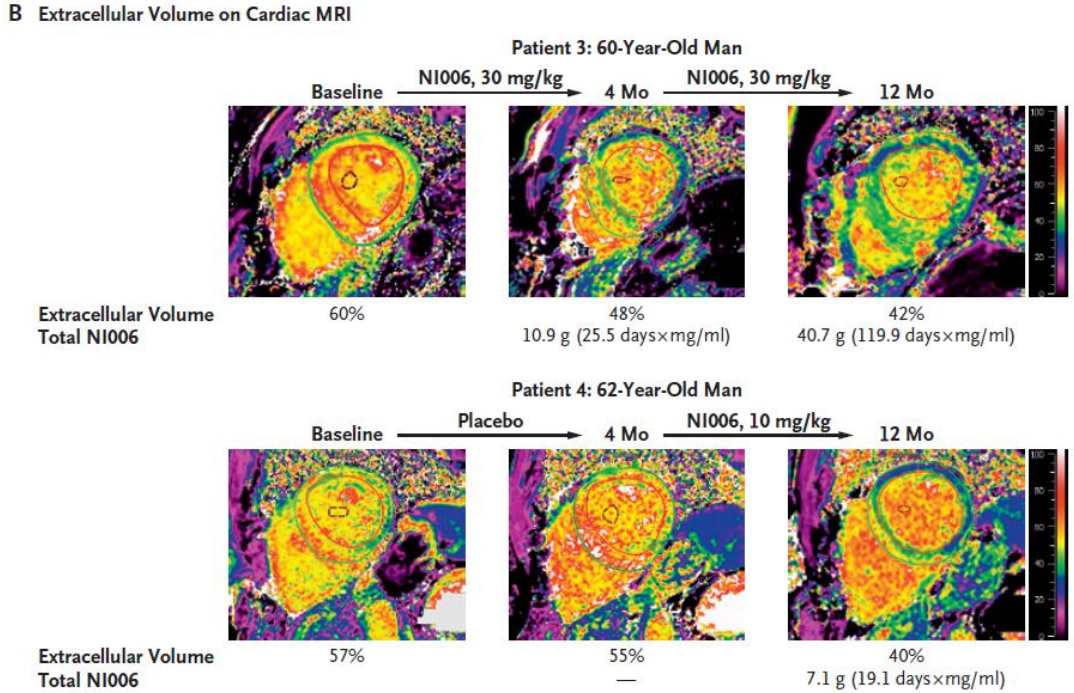
IV every 4 weeks, 2 months / OLE 8 months

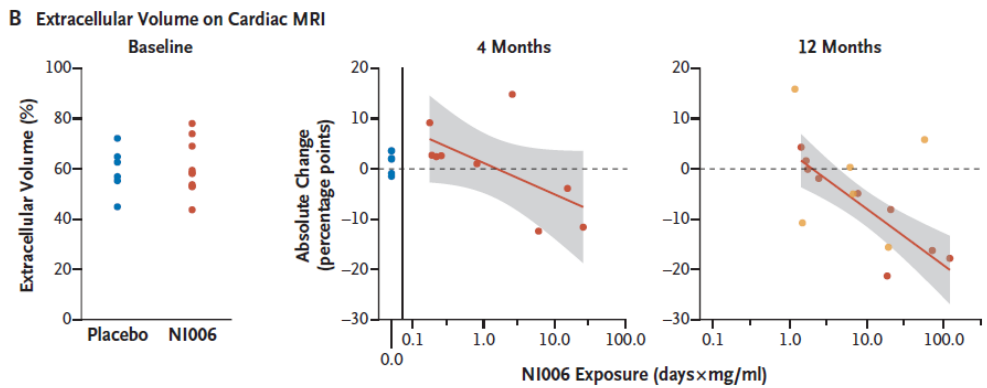
Patients with…	0.3 mg/kg n= 4	1 mg/kg n= 4	3 mg/kg n= 4	10 mg/kg n= 5	30 mg/kg n= 5	60 mg/kg n= 5	Placebo n= 13	Total N = 40
At least one AE	4 (24)	4 (14)	3 (22)	5 (30)	5 (37)	5 (25)	11 (39)	
Severe (grade III)	1 (1)	2 (2)	0	1 (1)	1 (1)	0	2 (2)	
Life threatening, death (grade ≥ IV)	0	0	0	0	0	0	0	
At 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	

- ALXN2220 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)
- **Non-serious musculoskeletal AEs** (e.g. arthralgias) were more commonly observed with high-dose ALXN2220 and in placebo patients after switch to ALXN2220 during OLE


A Cardiac Tracer Uptake on Scintigraphy
Patient 1: 75-Year-Old Man
Baseline
NI006, 60 mg/kg
4 Mo
NI006, 60 mg/kg
12 Mo
Ratio in Heart to Whole Body
Total NI006
6.9%
2.5%
20.7 g (46.1 days×mg/ml)
2.5%
61.7 g (162.7 days×mg/ml)
Patient 2: 82-Year-Old Man
Baseline
Placebo
4 Mo
NI006, 30 mg/kg
12 Mo
Ratio in Heart to Whole Body
Total NI006
7.1%
7.7%
—
4.5%
14.2 g (40.7 days×mg/ml)

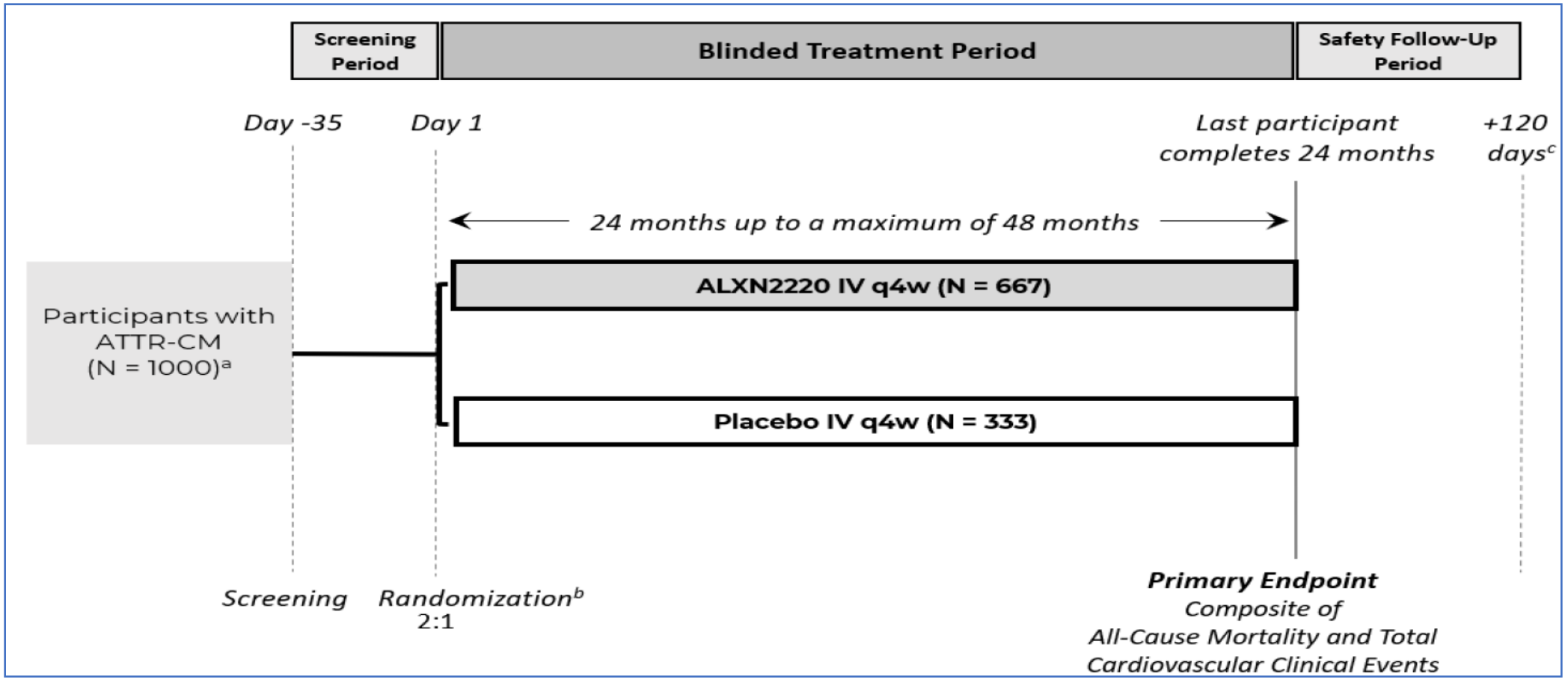
A Cardiac Tracer Uptake on Scintigraphy
Baseline
Ratio in Heart to Whole Body (%)
Placebo
NI006
4 Months
12 Months
Absolute Change (percentage points)
NI006 Exposure (days×mg/ml)


B Extracellular Volume on Cardiac MRI
Patient 3: 60-Year-Old Man
Baseline
NI006, 30 mg/kg
4 Mo
NI006, 30 mg/kg
12 Mo
Extracellular Volume
Total NI006
60%
48%
10.9 g (25.5 days×mg/ml)
42%
40.7 g (119.9 days×mg/ml)
Patient 4: 62-Year-Old Man
Baseline
Placebo
4 Mo
NI006, 10 mg/kg
12 Mo
Extracellular Volume
Total NI006
57%
55%
—
40%
7.1 g (19.1 days×mg/ml)


B Extracellular Volume on Cardiac MRI
Baseline
Extracellular Volume (%)
Placebo
NI006
4 Months
12 Months
Absolute Change (percentage points)
NI006 Exposure (days×mg/ml)

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

DepleTTR-CM Study



Key Inclusion Criteria

DepleTTR-CM Study

- Age ≥ 18 years to ≤ 90 years
- Participant and disease characteristics
  - Centrally confirmed diagnosis of ATTR-Cardiomyopathy (ATTR-CM) with either wild-type or variant genotype
- End-diastolic interventricular septal wall thickness ≥ 12 mm for men or ≥ 11mm for women on echocardiography measured at Screening
- NT-proBNP > 2000 pg/ml measured by a central laboratory at Screening
- Treatment with a loop diuretic therapy for at least 30 days prior to screening.
- History of heart failure as documented by one of the following events within 1 year prior to Screening:
  - Heart failure hospitalization
  - Urgent heart failure visit
  - Episode of volume overload documented by NT-proBNP > 2000 pg/ml (or equivalent BNP > 500 pg/mL)
- Life expectancy of ≥ 6 months as per Investigator's judgement
- NYHA Class II-IV at Screening
- Must agree to highly effective birth control if woman of child-bearing potential or non-sterile male

Key Exclusion Criteria

DepleTTR-CM Study

- Known leptomeningeal amyloidosis or light chain (AL) or secondary amyloidosis (AA)
- History of multiple myeloma
- Acute coronary syndrome, unstable angina, stroke, transient ischemic attack, coronary revascularization, cardiac device
- implantation, cardiac valve repair, or major surgery within 3 months of Screening
- Uncontrolled hypertension (average resting systolic blood pressure [BP] > 160mmHg or diastolic BP > 100 mmHg);
- Uncontrolled clinically significant cardiac arrhythmia, per Investigator's assessment.
- Left ventricular ejection fraction (LVEF) less than 30% on echocardiography assessment during screening

Primary objective

Objective	Endpoint
To assess the efficacy of ALXN2220 in the treatment of adult participants with ATTR-CM by evaluating the difference between the ALXN2220 and placebo groups as assessed by the composite endpoint of all-cause mortality (ACM), and the total cardiovascular (CV) clinical events.	Total Occurrence of ACM and CV clinical events during the Blinded Treatment Period

Secondary Objectives (not in hierarchical sequence for testing):

Objective	Endpoint
To assess the effects of ALXN2220 on symptoms, functionality, and health-related quality of life (QoL) as measured by the change from Baseline in Kansas City Cardiomyopathy Questionnaire- Overall Score (KCCQ-OS)	Change from Baseline in KCCQ-OS to 24 months
To assess the effects of ALXN2220 on CV related mortality	Time to CV related mortality
To assess the effects of ALXN2220 on change from baseline in 6MWT	Change from baseline in 6MWT to 24 months
To assess the efficacy of ALXN2220 by the rate of CV clinical events	Rate of CV clinical events
To assess the efficacy of ALXN2220 in the treatment of ATTR-CM as assessed by time to ACM	Time to ACM

Other Secondary objectives

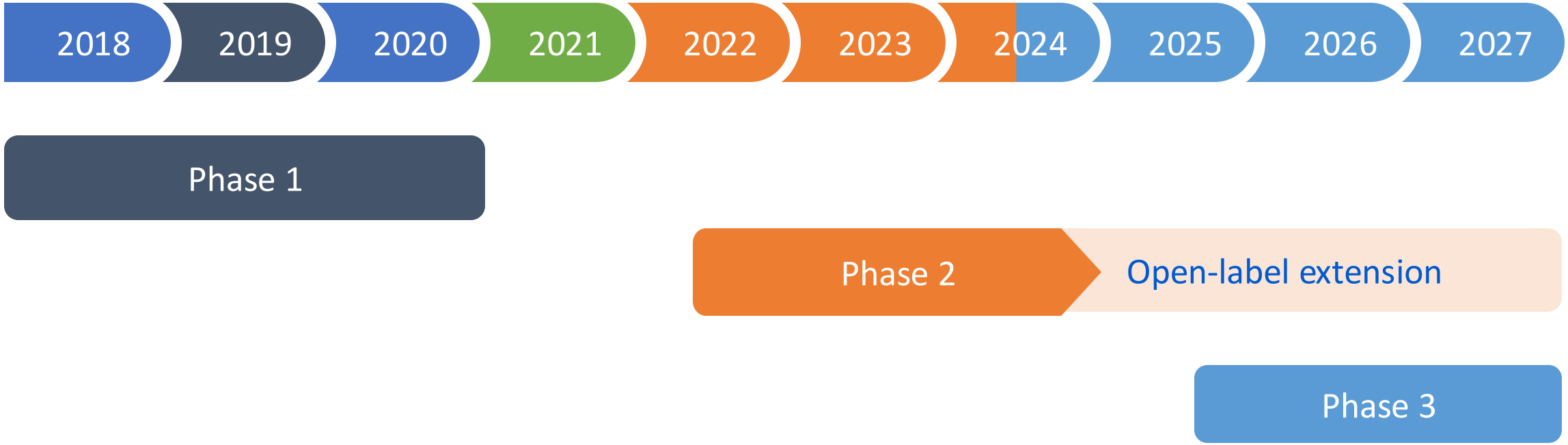
Safety

Objective	Endpoint
To assess the safety and tolerability of ALXN2220	Incidence of treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (SAEs). Changes from baseline in physical exam, vital signs, clinical laboratory tests, and 12 -lead electrocardiograms (ECGs)

Immunogenicity

Objective	Endpoint
To assess immunogenicity to ALXN2220	Anti-drug antibodies (ADA) incidence, response categories and titer

NNC6019-0001 clinical development



PRX004 in variant amyloid transthyretin (ATTRv) amyloidosis: results of a phase 1, open-label, dose-escalation study

Suhr OB. *Amyloid* 2024

IV every 28 days

0.1, 0.3, 1, 3, 10 or 30 mg/kg

21
participants included

3–17
infusions per participant

6
dose levels

~31
days' half-life with each dose

All six dose levels of coramitug ranging from 0.1–30 mg/kg were **well tolerated with no safety signals**.
The maximum tolerated dose was not reached

- A **dose-dependent decrease in circulating misTTR** was observed
- Coramitug was associated with a **mean change of –1.21% in GLS from baseline to 9 months**[1] indicating a possible benefit
- Coramitug demonstrated a **mean change of +1.29 in NIS from baseline to 9 months**[1] indicating stable peripheral nerve function

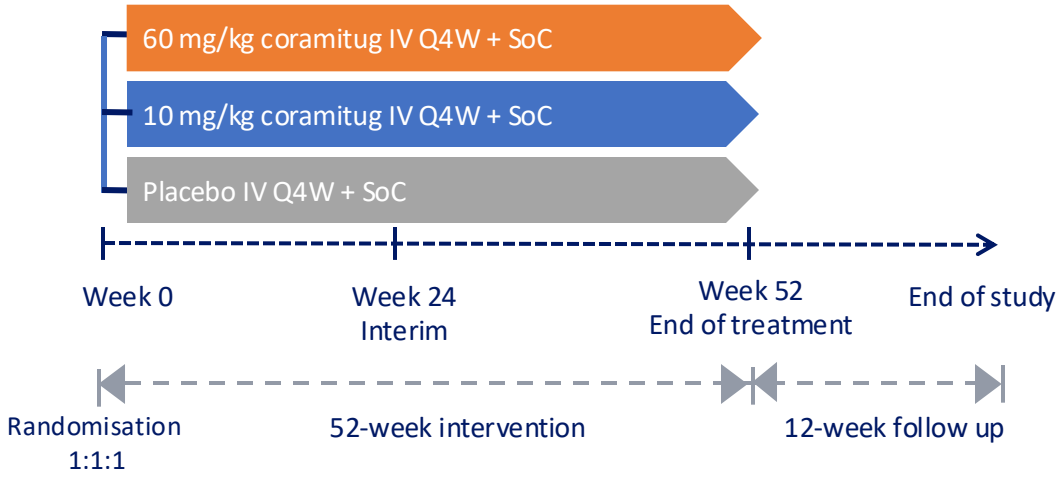
NN6019-4940 Phase 2 trial: Dose finding, proof of concept and safety

Trial design: NN6019-4940

Primary objective: To evaluate the impact of coramitug on functional endpoints and circulating/imaging biomarkers as well as its PK, safety and tolerability at two dose levels and to select the dose to be studied in Phase 3

Trial information
- Double blinded
- Stratification by disease type (ATTRwt versus ATTRv)
- Includes an initial sentinel dosing phase

N=105 patients
- ATTR-CM (variant or wild-type)
- NYHA class II–III
- LVWT ≥12 mm
- NT-proBNP ≥650 in sinus and >1000 pg/mL in atrial fibrillation
- 6MWD ≥150 m and ≤450 m
- eGFR ≥25 mL/min/1.73 m^2

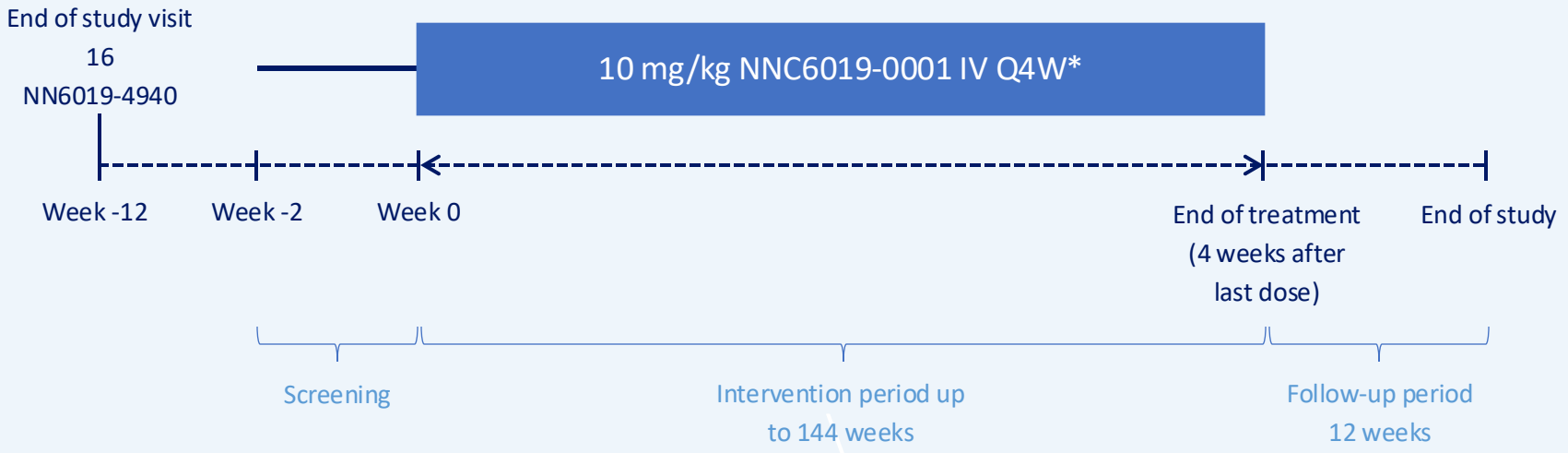


Key endpoints
- **Primary:** Change from baseline to Week 52 in:
  - 6MWD
  - NT-pro-BNP
- **Secondary:** ECV, KCCQ-CSS, GLS, troponin I, NIS, TEAEs, time to occurrence of all-cause mortality, number of CV events comprising hospitalisation due to CV events or urgent heart failure visits
- **Exploratory endpoints:** EQ-5D-5L, misTTR

NN6019-7565 Open-label extension

~80 patients

- Completed the phase 2 trial, NN6019-4940
- Attended the last study visit



Trial information:

- Initiation ~Jan 2024
- Open-label, no blinding (single-arm design)
- Blinding from phase 2 will be kept
- Dosing to start after the 12 weeks follow up
- N = ~80 (expected 20% drop-out from phase 2)

Trial rationale

- To obtain additional safety and efficacy data for NNC6019-0001 and to provide continued access to NNC6019-0001 for patients included in the phase 2 trial

Primary study objective

- To assess long-term safety and efficacy of NNC6019-0001 from baseline up to 36 months

Secondary study objectives

- To assess long-term effect of NNC6019-0001 on 6MWT, NT-proBNP, ECV, KCCQ-CSS, troponin I, GLS from baseline to 24 months, and time to occurrence of death, Htx or cardiac mechanical assist device from baseline up to 36 months

Primary endpoint

- Treatment-emergent adverse events

Secondary endpoints

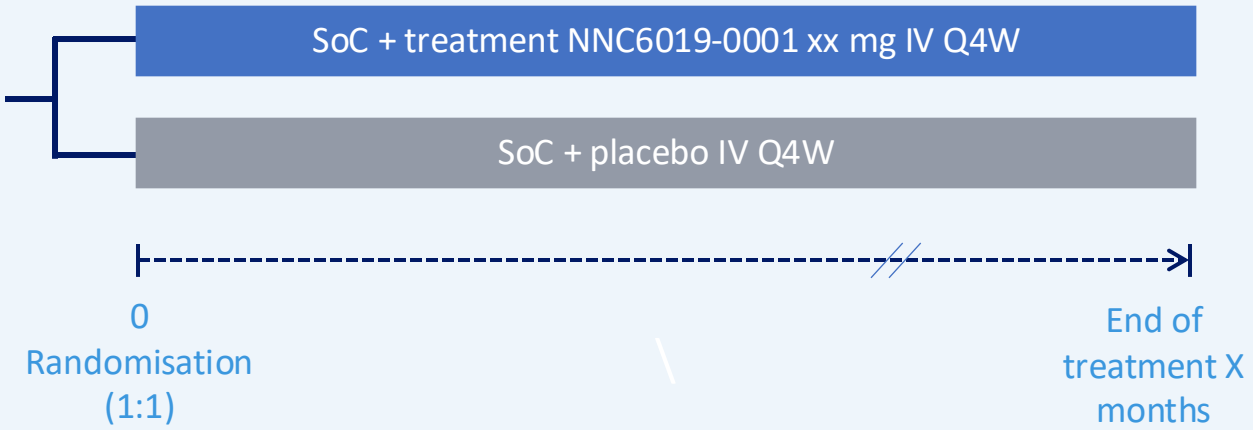
- Change from baseline in 6MWT, NT-proBNP, ECV, KCCQ-CSS, troponin I, GLS

NN6019-4958 phase 3

CVOT in patients with ATTR-CM

~1000 patients

- 18-90 years
- ATTR-CM (hereditary or wildtype)
- Heart failure requiring diuretics
- NT-proBNP≥ 1000 pg/mL
- 6MWT ≥50 m



Study information:

- Double blinded, randomised, placebo-controlled
- Event-driven
- 3.5 years of duration
- Recruitment time: 25 months
- 331 events to achieve 90% power
- 30% RRR
- Event rate 0.20
- Annual mortality rate 7%
  (1/3 of ATTR-ACT)

Primary objective

- To demonstrate superiority of NNC6019-0001 versus placebo, both added to standard of care, in reducing all-cause mortality and CV morbidity

Primary endpoints

- Number of occurrences of the composite endpoint: CV mortality, recurrent CV events (CV hospitalisations and urgent HF visits)

Secondary endpoints

- KCCQ, 6MWT, time to CV events, time to all-cause mortality, time to CV deaths, time to HHF or UHF, NT-proBNP, troponin I, GLS, safety and tolerability, mATTR

Merci pour votre attention !