

Futurs protocoles et essais cliniques en cours dans l'ATTR

Nicolas Piriou

CHU de Nantes – Centre de référence Cardiomyopathies



Journée organisée par :



R'EPOF



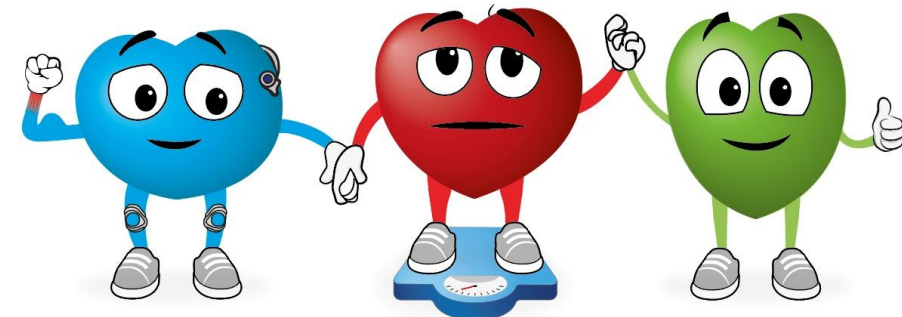
www.masterclass-amylose.com





Liens d'intérêts

- Alnylam
- Pfizer
- Astra Zeneca
- Pfizer



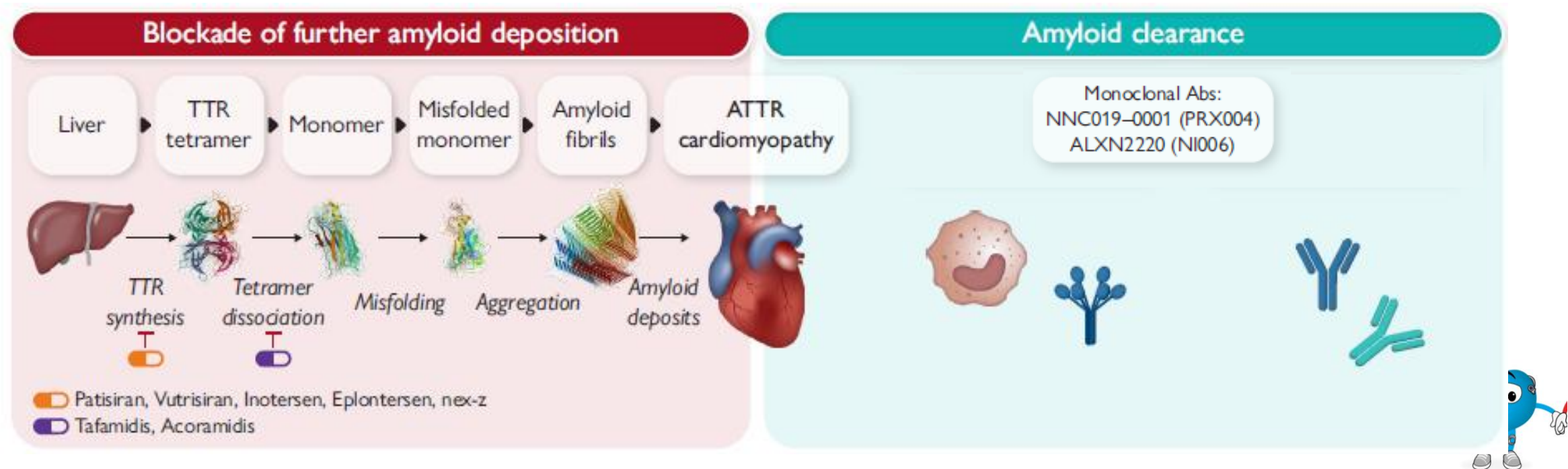
R[®] EPOF

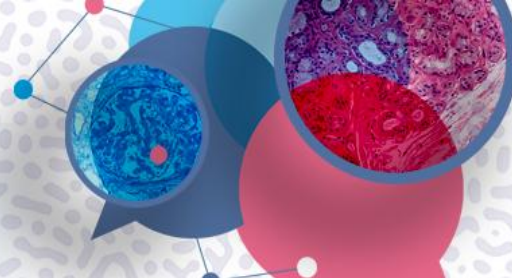
EPOF

EPON

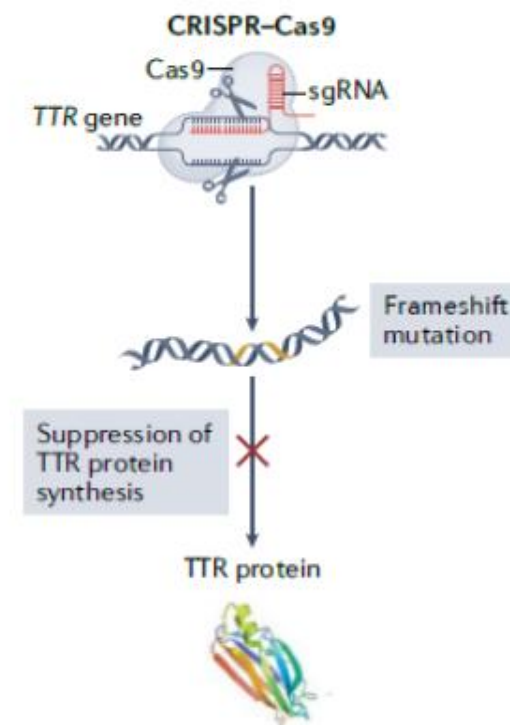
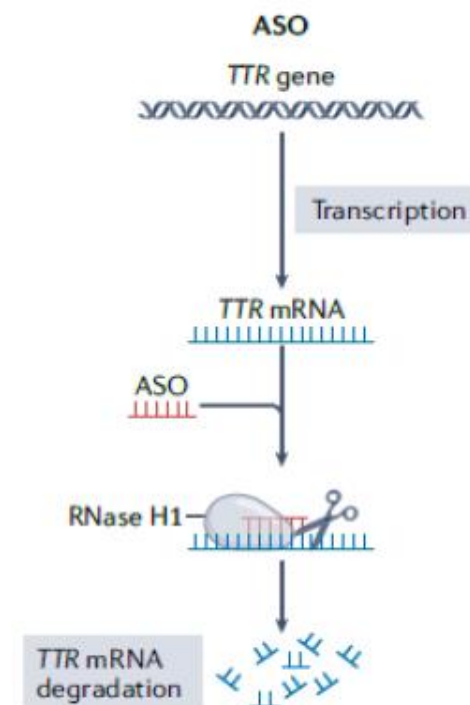
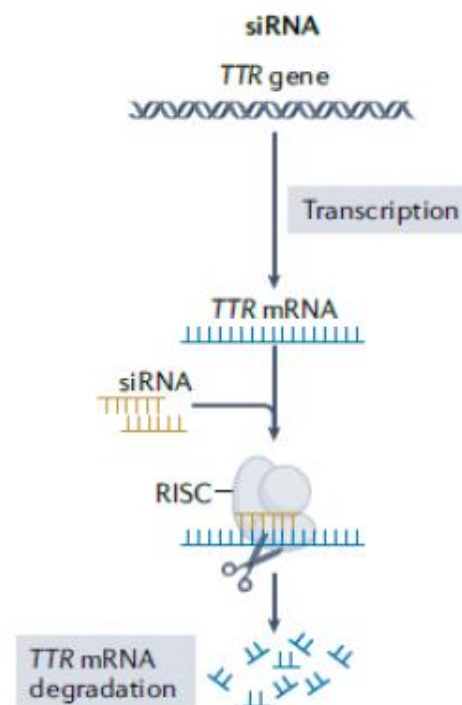
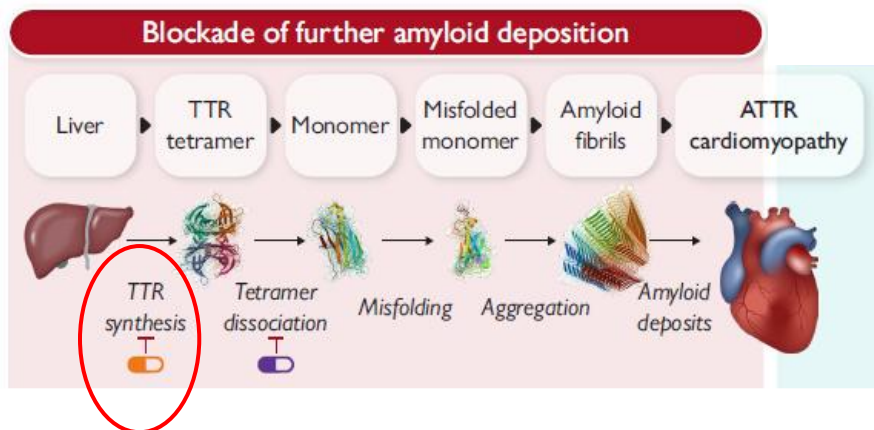


Explorer de nouvelles voies thérapeutiques, de nouvelles molécules, de nouvelles stratégies

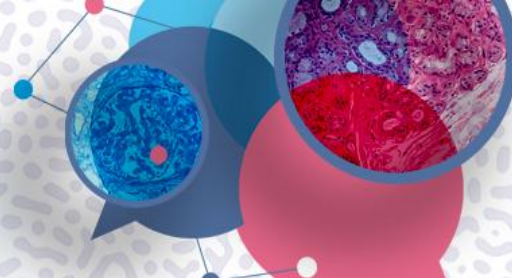




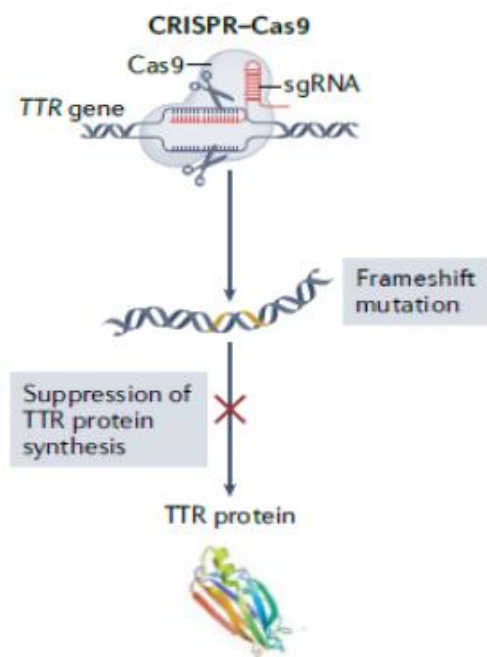
Essais en cours sur la voie du Silencage TTR



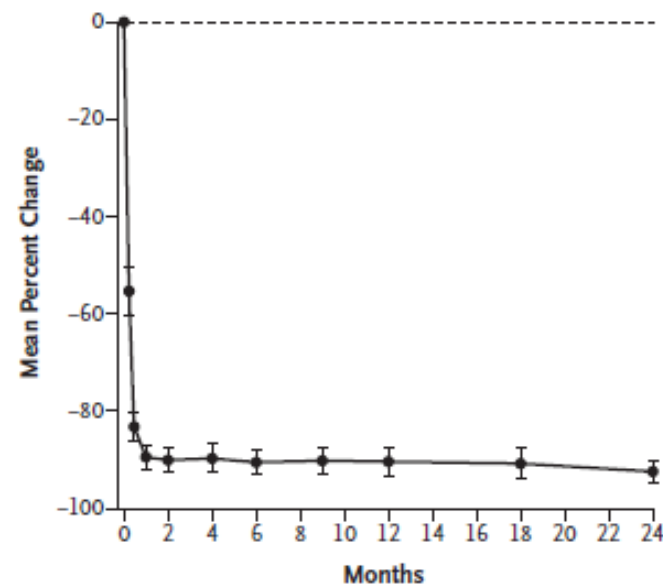
Nat Rev Cardiol. 2022 Oct;19(10):655-667



CRISPR-Cas 9 TTR gene editing (Nexiguran Ziclumeran)



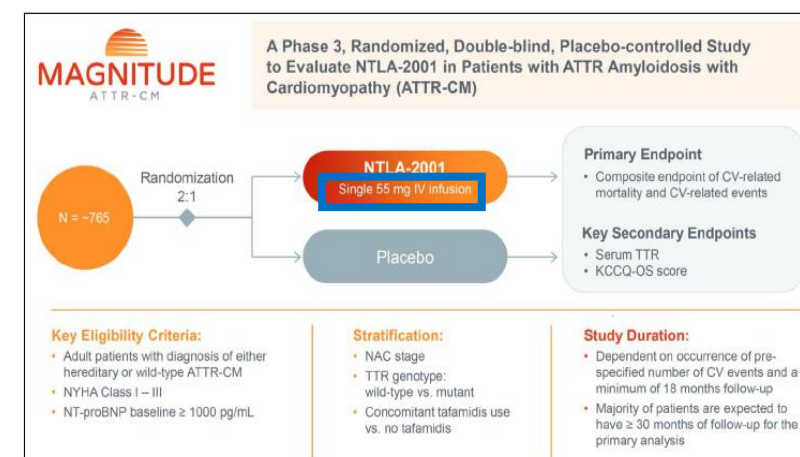
A Percent Change in Serum TTR Level from Baseline



No. of Patients 36 35 36 36 36 36 26 11

Figure 1. Reduction in Serum Transthyretin Level.

Magnitude – Phase 3 Trial of CRISPR in ATTR-CA



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34 patients : 2 avec élévation des transaminases reliée au traitement



Un nouveau siRNA : Nucleciran

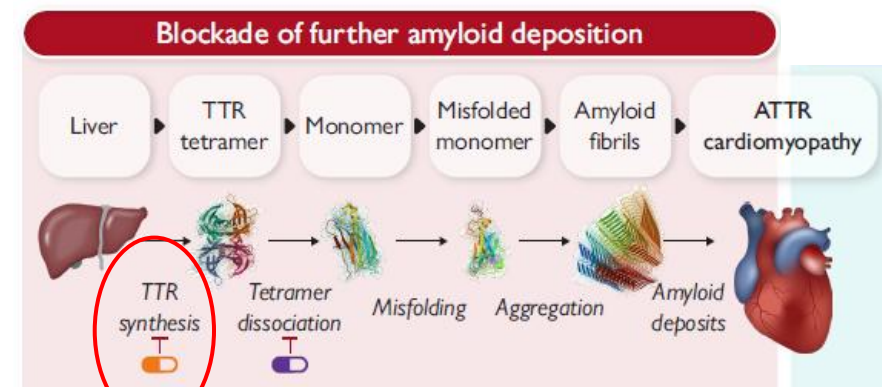
Nucleciran is a synthetic siRNA conjugated to GalNAc, which enables highly efficient delivery to the liver.

- GalNAc, a carbohydrate (sugar) molecule, is the ligand for the asialoglycoprotein receptor (ASGPR), which is highly and specifically expressed by hepatocytes.

Long-acting SC-administered
GalNAc-conjugated siRNA
targeting liver-expressed
mRNA for TTR

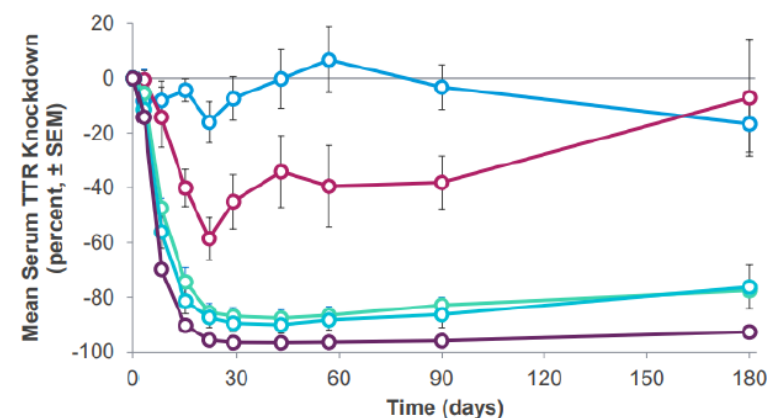
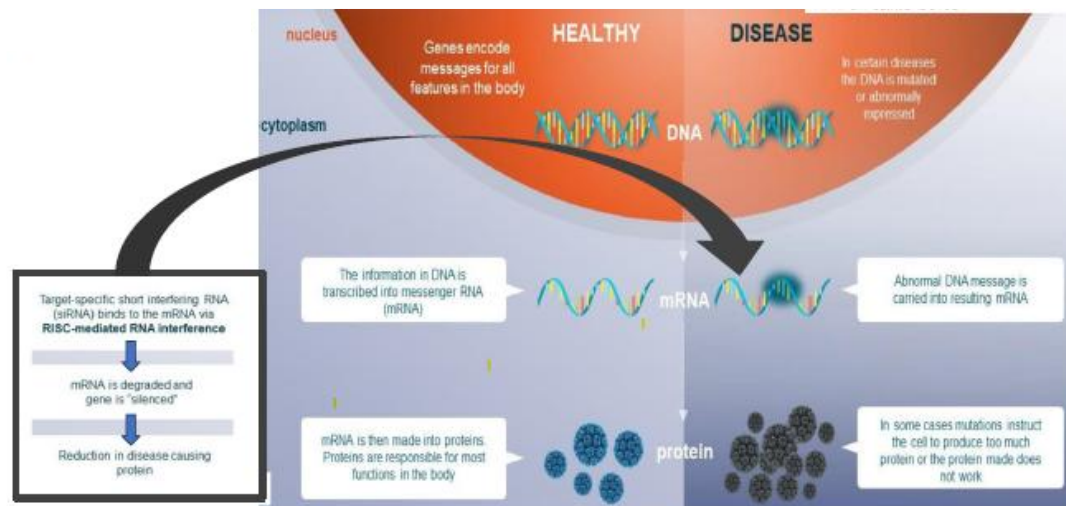


Alnylam



Phase 1 data supports best-in-class profile

TRITON-CM
ATTR-CM CLINICAL STUDY



- Single 300 mg dose resulted in rapid, deep, and durable TTR reduction:
 - >90% at Day 15
 - 97% at Day 29
 - 93% at Day 180
- Safety profile:
 - All doses of nucleciran have been **well tolerated**; no adverse events considered related to study drug by investigator
- Frequency of administration:
 - Data support **every 6 months** subcutaneous dosing

TRITON-CM Study Design



Patient Population: N≈1250

- Adults (18–85 years) with wild-type or variant ATTR-CM
- NYHA class I–III
- End-diastolic interventricular septal wall thickness >12 mm for males and >11 mm for females by echocardiography
- NT-proBNP >300 and <8500 ng/L at screening^a
- Background TTR stabilizer permitted

2:1 RANDOMISATION

Nucresiran
SC q6M
300 mg
N≈840

or

Placebo
SC q6M
N≈410

Primary Endpoint

- Composite of all-cause mortality and recurrent CV events (event-driven)

Secondary Endpoints

- Time to first CV event (CV hospitalizations and urgent HF visits) or all-cause mortality
- All-cause mortality
- Recurrent CV events
- Change from baseline in KCCQ-OS

Nucresiran
SC q6M
300 mg



Other Key Inclusion Criteria

- Medical history of HF with ≥1 prior hospitalization for HF OR clinical evidence^b of HF that requires treatment with a diuretic
- Demonstration of ATTR cardiomyopathy by one of the following:
 - Documented TTR amyloid deposits in cardiac tissue regardless of MGUS status
 - In the absence of MGUS, ^{99m}Tc scintigraphy with Grade 2 or 3 cardiac uptake
 - In the presence of MGUS, documentation of TTR protein in noncardiac tissue AND Grade 2 or 3 cardiac uptake on ^{99m}Tc scintigraphy

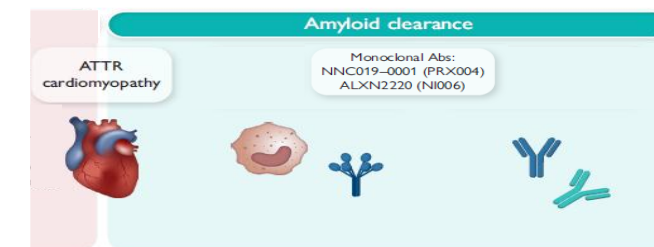
Key Exclusion Criteria

- NYHA class IV HF; or NYHA class III heart failure AND ATTR Amyloidosis Disease Stage 3^c
- Polyneuropathy Disability Score ≥IIIa at screening visit^d
- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m²
- Non-TTR cardiomyopathy, hypertensive cardiomyopathy, cardiomyopathy due to valvular heart disease, or cardiomyopathy due to ischemic heart disease
- Received prior TTR-lowering therapy OR plan for or anticipate beginning treatment during screening or the first 24 months following randomization

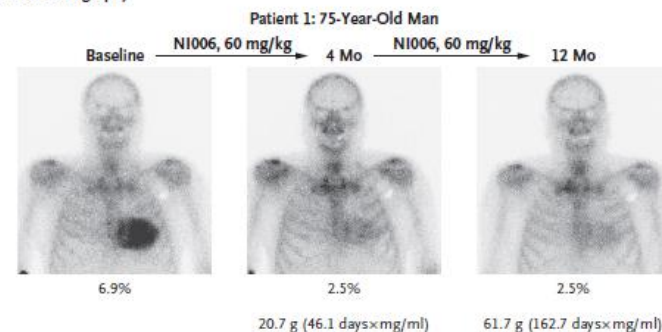
^aNT-proBNP >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation. ^bManifested by signs and symptoms of volume overload or elevated intracardiac pressures.

^cDefined as NT-proBNP >3000 ng/L and eGFR <45 mL/min. ^dRequires cane or stick to walk or is wheelchair-bound due to polyneuropathy.

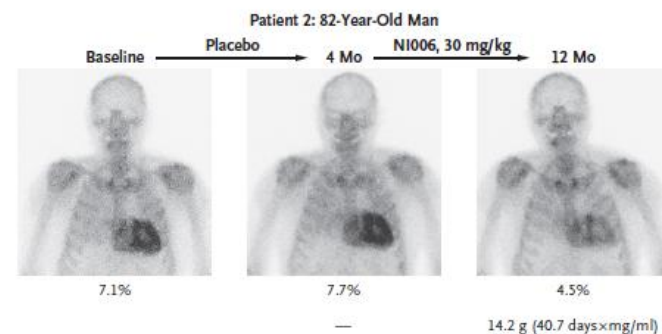
La voie des dépléteurs



Cardiac Tracer Uptake on Scintigraphy



Ratio in Heart to Whole Body
Total NI006



Ratio in Heart to Whole Body
Total NI006

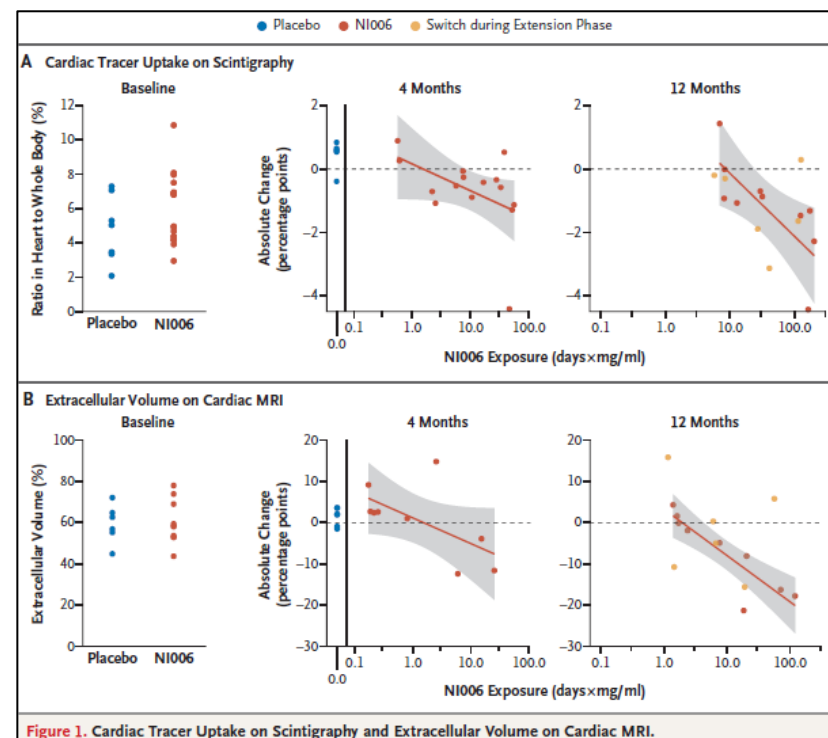


Figure 1. Cardiac Tracer Uptake on Scintigraphy and Extracellular Volume on Cardiac MRI.

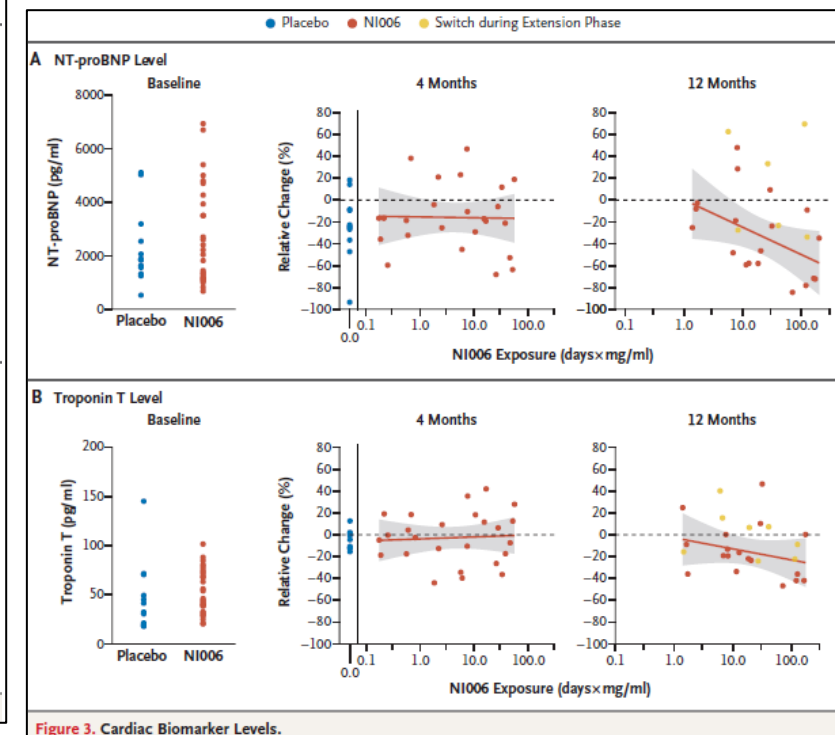
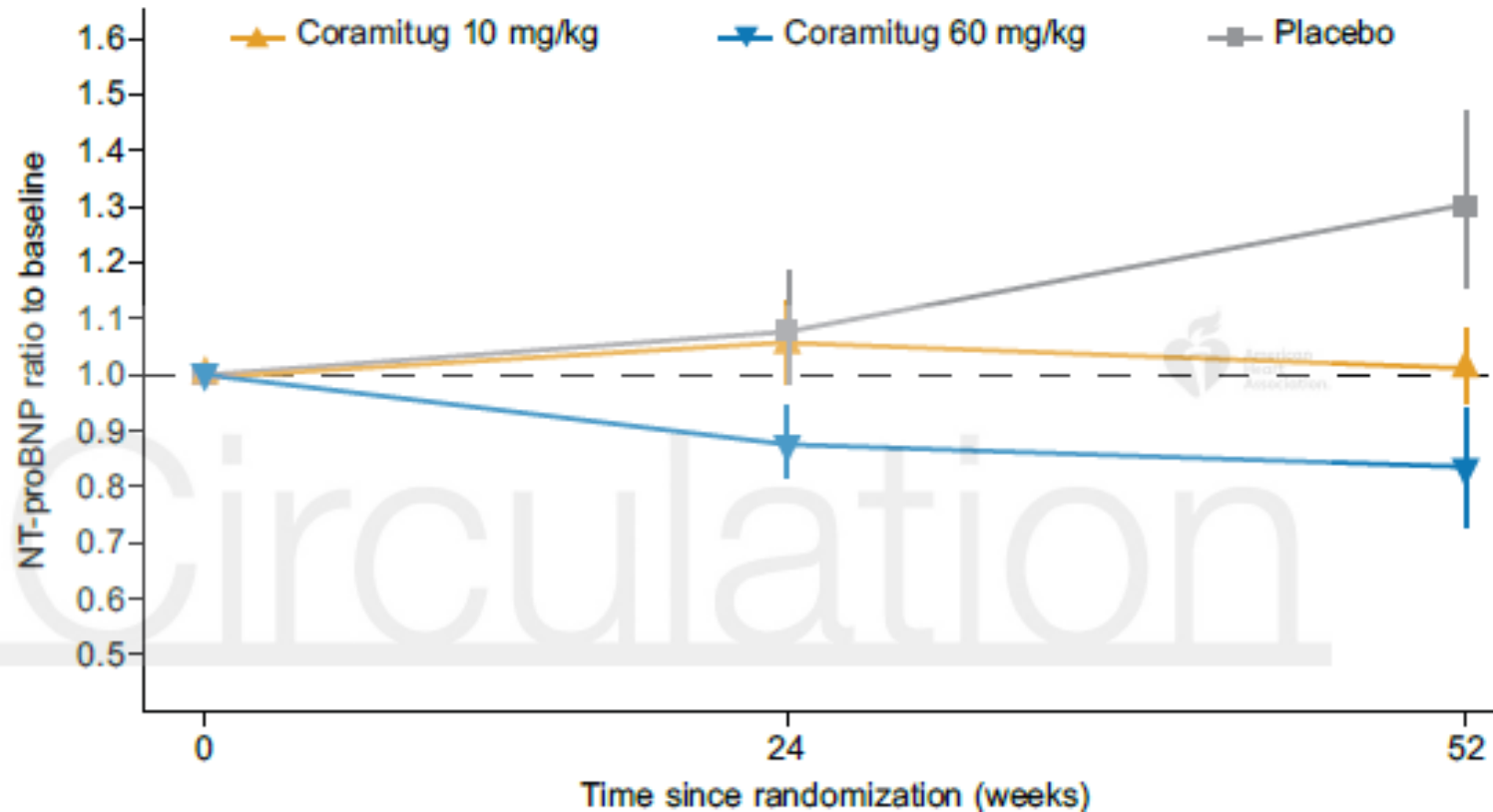


Figure 3. Cardiac Biomarker Levels.

P.Garcia-Pavia et al. NEJM 2023



Coramitug : données de phase 2

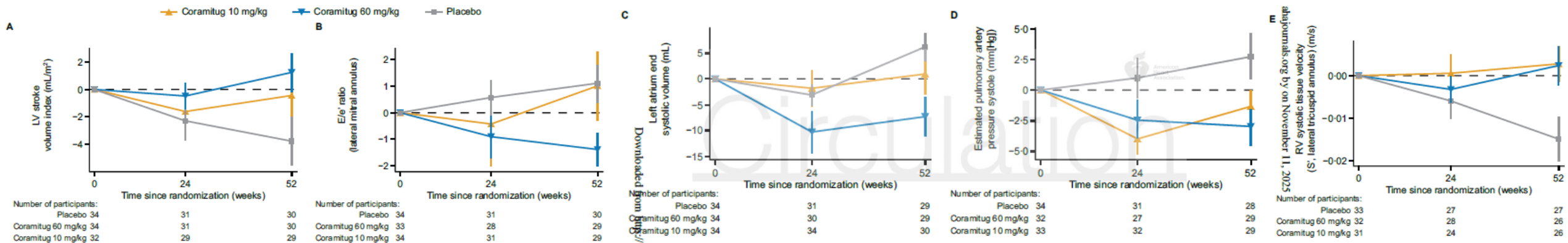
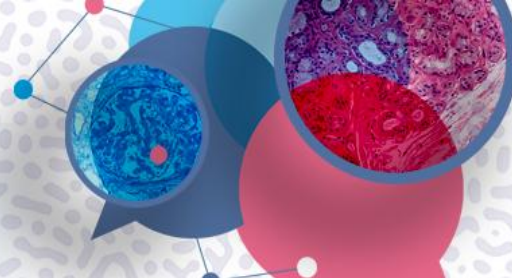


**Pas de différence d'effet sur le 6MWT
vs placebo**



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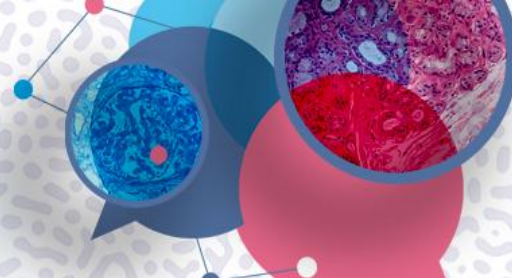
M.Fontana et al. Circulation 2025



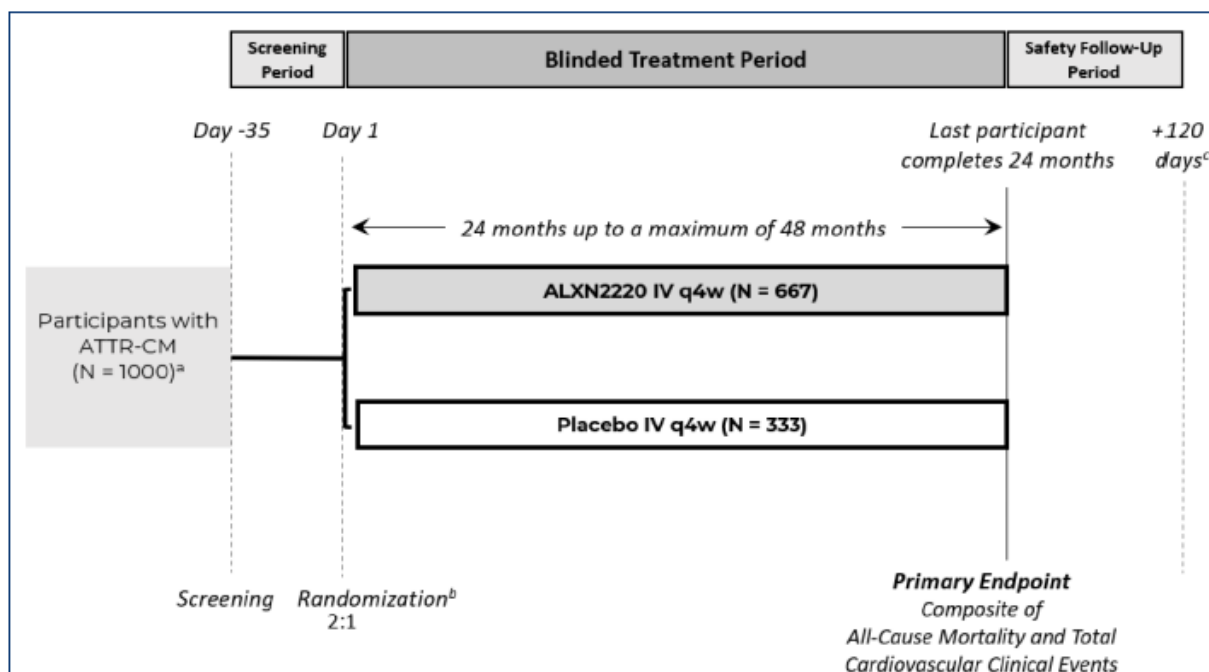
M.Fontana et al. Circulation 2025



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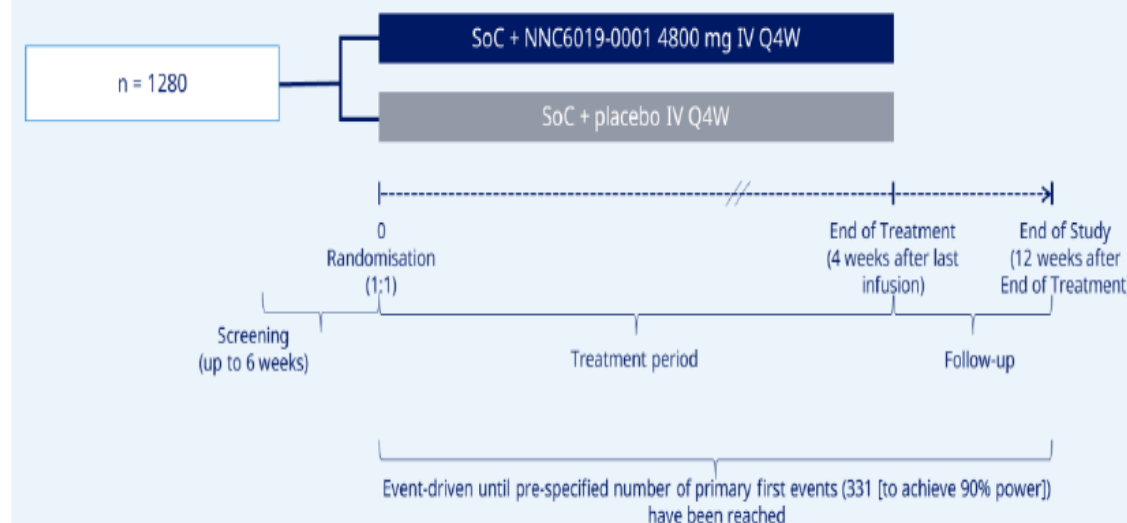


Les dépléteurs en Phase 3



Acronym: CLEOPATTRA

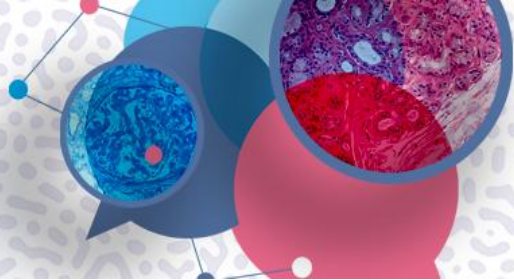
Short Title: CLEOPATTRA: A research study to look at the effects of treatment with a medicine called coramitug (NNC6019-0001) in people with heart failure due to ATTR amyloidosis.



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.	Composite of all-cause mortality, and total CV clinical events during the blinded treatment period. (Anderson-Gill model with robust variance)

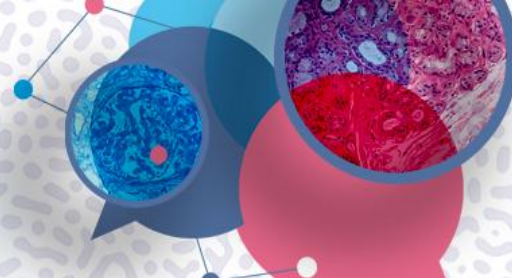
Objectives	Endpoints	
Primary	Title	Time frame
To demonstrate superiority of NNC6019-0001 versus placebo, both added to SoC ^a , in reducing the CV death & morbidity in participants with ATTRwt-CM or ATTRv-CM	Primary: The composite outcome of: • CV death ^b • Recurrent CV events (CV hospitalisation ^{b,c} and urgent HF visits ^b)	From baseline (week 0) up to EOS ^d



Les essais de stratégie thérapeutique



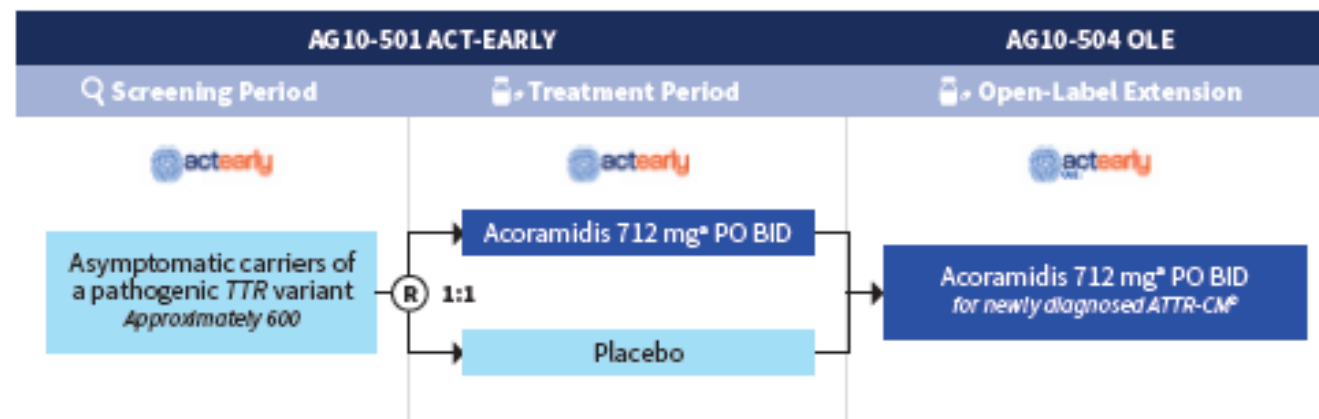
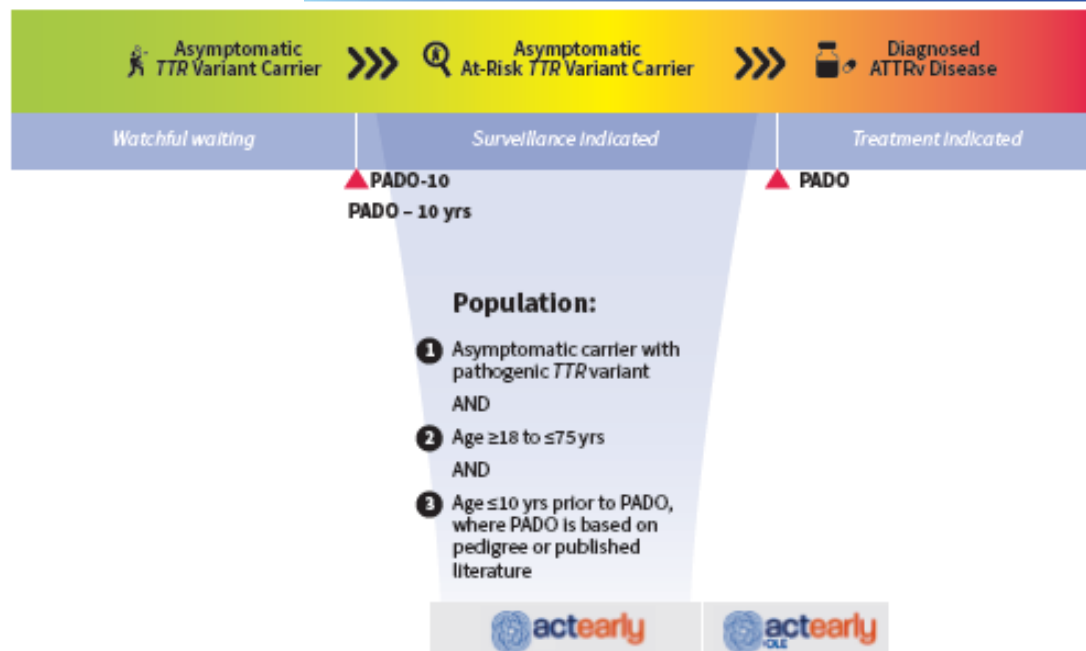
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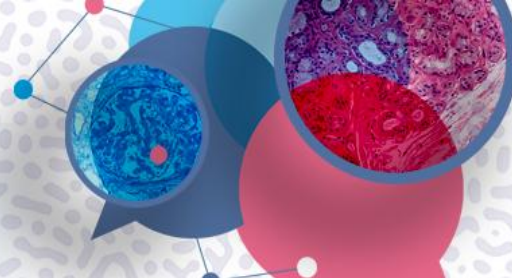


Traitement PRÉ-SYMPTOMATIQUE des apparentés porteurs du variant génétique pathogène

Rationale and Design of ACT-EARLY, the Acoramidis Transthyretin Amyloidosis Prevention Trial

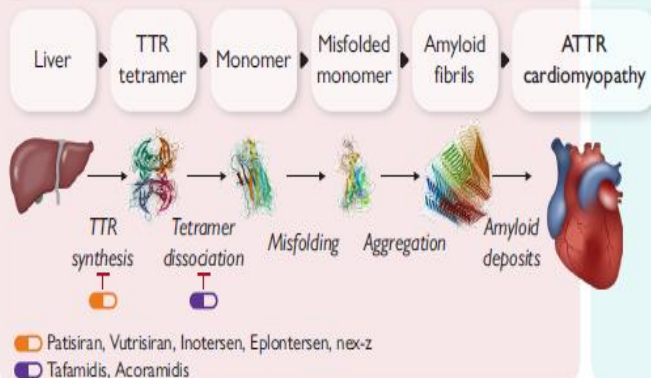
Pablo Garcia-Pavia¹, Julian D. Gillmore², David Adams³, Isabel Conceicao⁴, Teresa Coelho⁵, Daniel P. Judge⁶, Mathew S. Maurer⁷, Frederick L. Ruberg⁸, Scott Solomon⁹, Ahmad Masri¹⁰, Thibaud Damy¹¹, Marianna Fontana¹², Mary M. Reilly¹³, Nityasha Sarawat¹⁴, Peter van der Meer¹⁵, Mazen Hanna¹⁶, Morie Gertz¹⁷, Xiaofan (Martha) Cao¹⁸, Ted Lystig¹⁹, Uma Sinha²⁰, Adam Castaño²¹, Leonid Katz²², Jonathan C. Fox²³





L'arrivée des essais de COMBINAISONS thérapeutiques

Blockade of further amyloid deposition

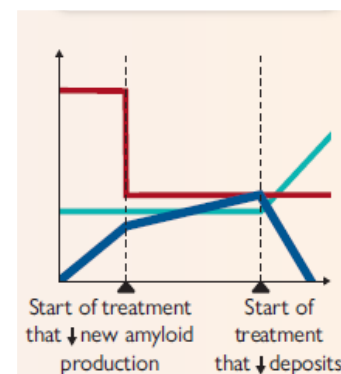


Amyloid clearance

Monoclonal Abs:
NNC019-0001 (PRX004)
ALXN2220 (NI006)



Balance between amyloid deposition and clearance: theoretical models

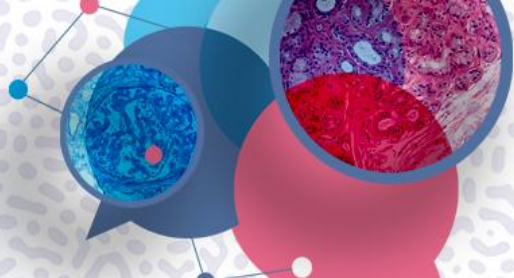


— Rate of amyloid production
— Amyloid burden
— Rate of amyloid clearance

Adapted from M.Fontana et al. Eur Heart J 2025

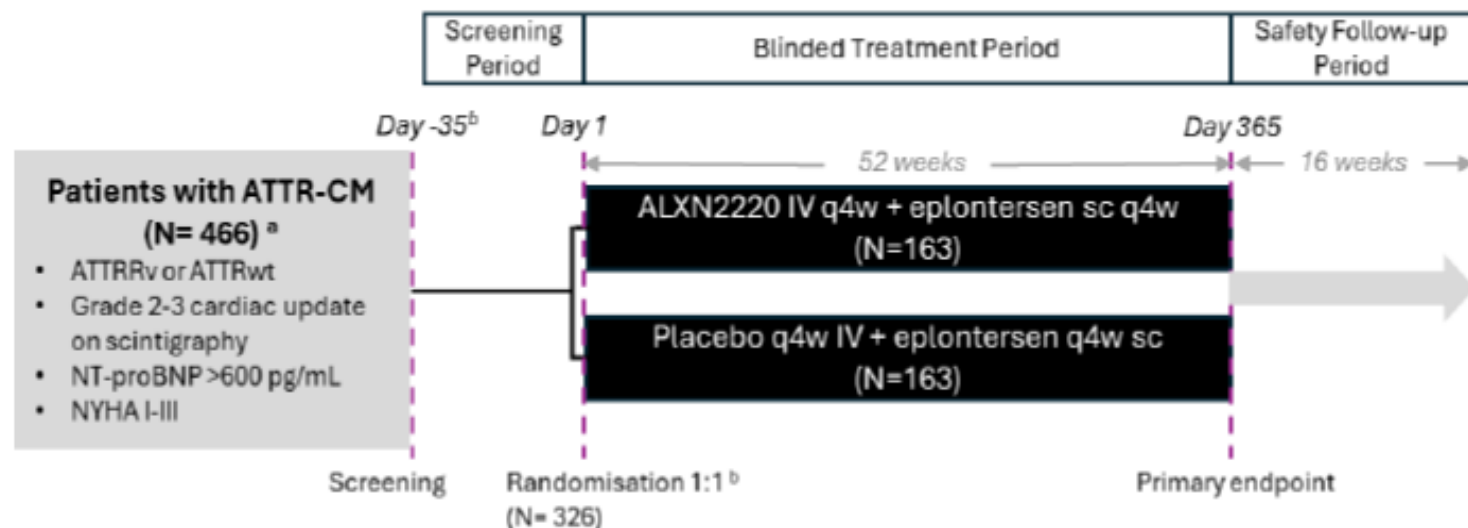


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A Phase 2b, Randomized, Double-blind, Active-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Eplontersen and ALXN2220 Compared to Eplontersen and Placebo in Adult Participants with Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR-CM)

Brief Title: Efficacy and Safety of Eplontersen and ALXN2220 for the Treatment of ATTR-CM



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Remerciements

Platinum sponsors



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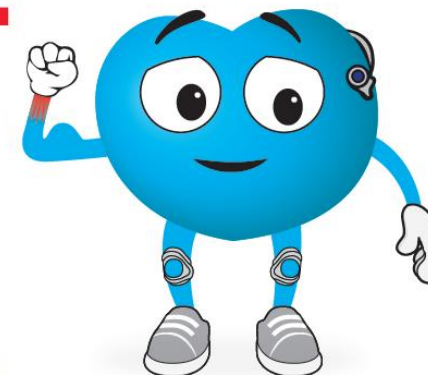
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Les atteintes rhumatologiques (synoviales) de l'amylose surviennent plusieurs années avant l'**insuffisance cardiaque (EPOF)**

R' EPOF

- Surdit 
- Canal carpien
- Doigt   ressaut
- Rupture du tendon du long biceps
- Canal lombaire  troit
- Proth se de hanche/genou
- Essoufflement
- Prise de poids
-  d mes
- Fatigue



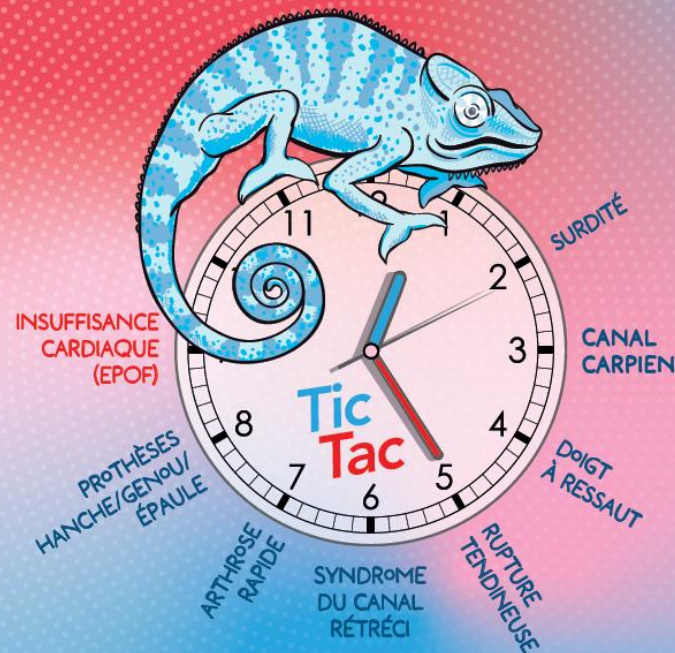
Et si c tait une
Amylose Cardiaque   transthyr tine ?



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AMYLOSES
CARDIAQUES

ÉVÉNEMENT HYBRIDE

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FAITES-VOUS DÉPISTER !Rejoignez la Campagne d'Information
et de Dépistage 2026 de la Maladie Caméléon

TIC-TAC,
Il est temps de changer de **TAC-TIC,**
Passons du **TACØTAC !!!**



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