

Futurs protocoles et essais cliniques en cours dans l'ATTR

Nicolas Piriou

CHU de Nantes – Centre de référence Cardiomyopathies



Journée organisée par :

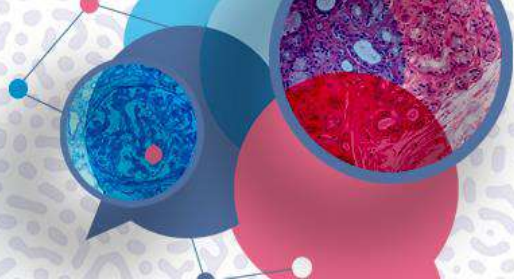


R'EPOF



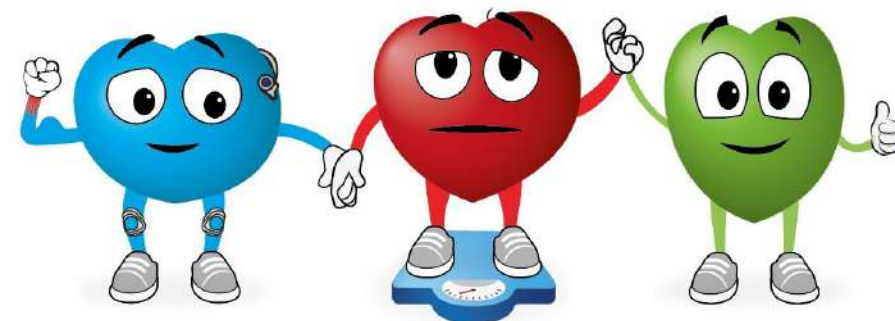
www.masterclass-amylose.com





Liens d'intérêts

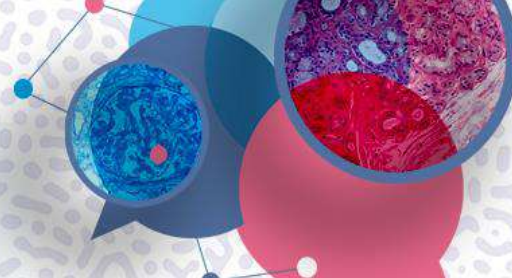
- Alnylam
- Pfizer
- Astra Zeneca
- Pfizer



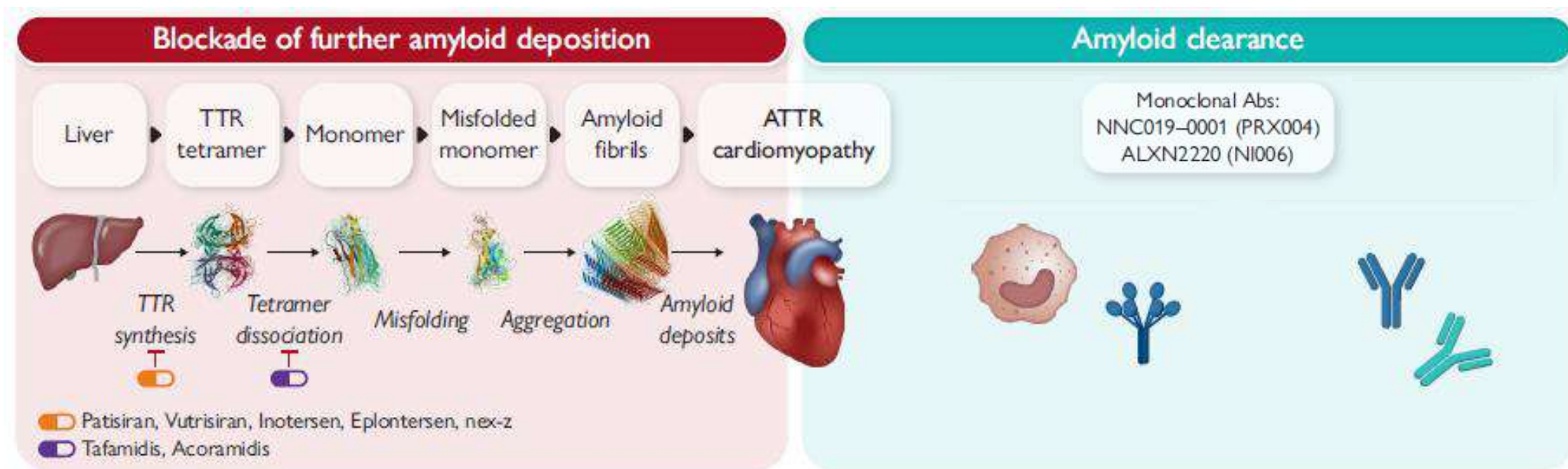
R'EPOF

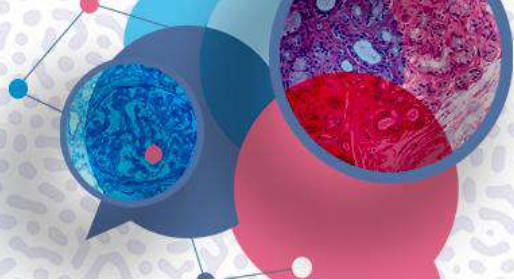
EPOF

EPON

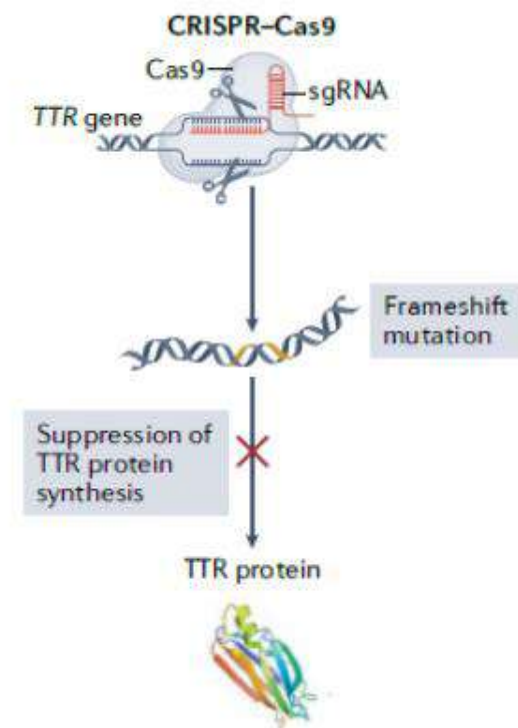
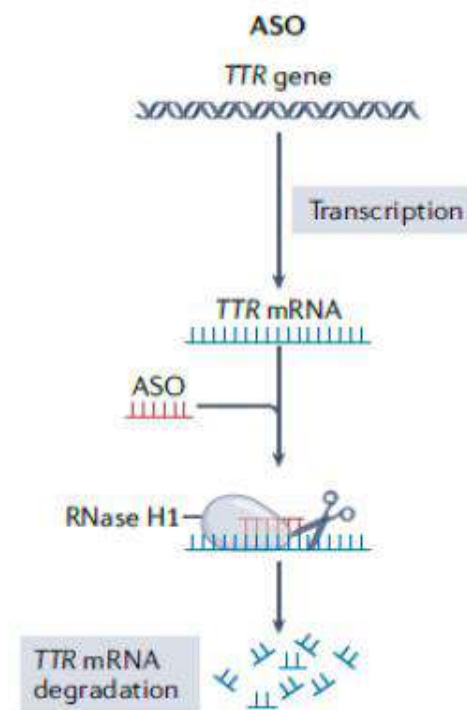
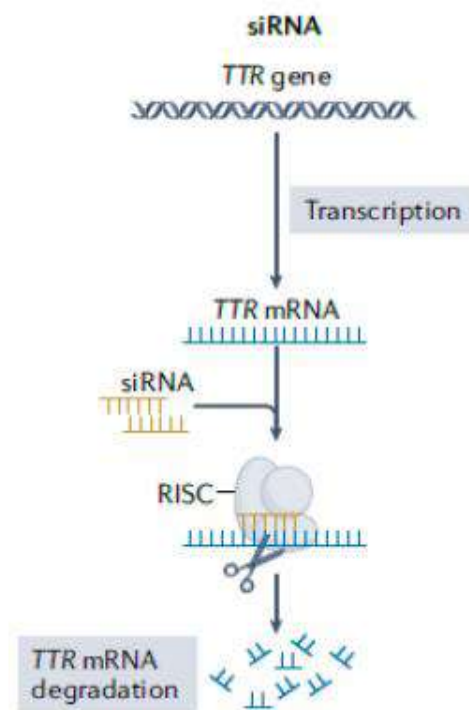
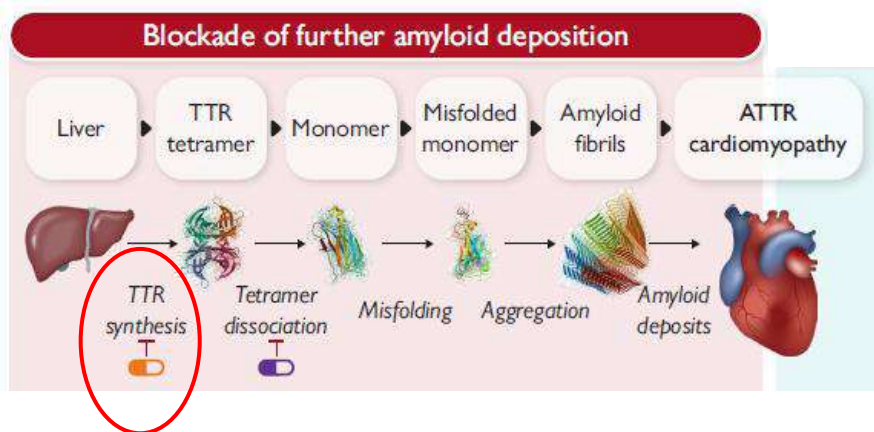


Explorer de nouvelles voies thérapeutiques, de nouvelles molécules, de nouvelles stratégies

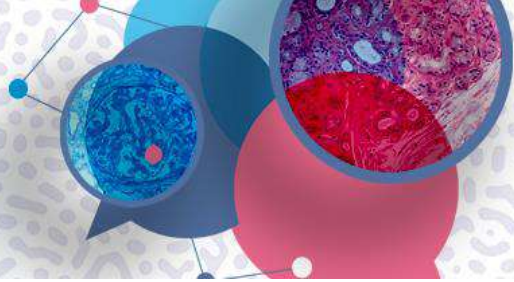




Essais en cours sur la voie du Silencage TTR

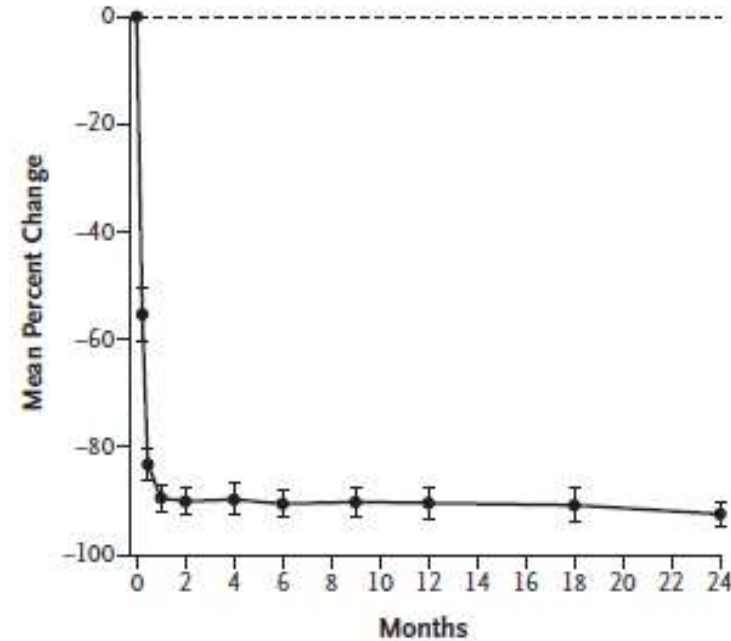
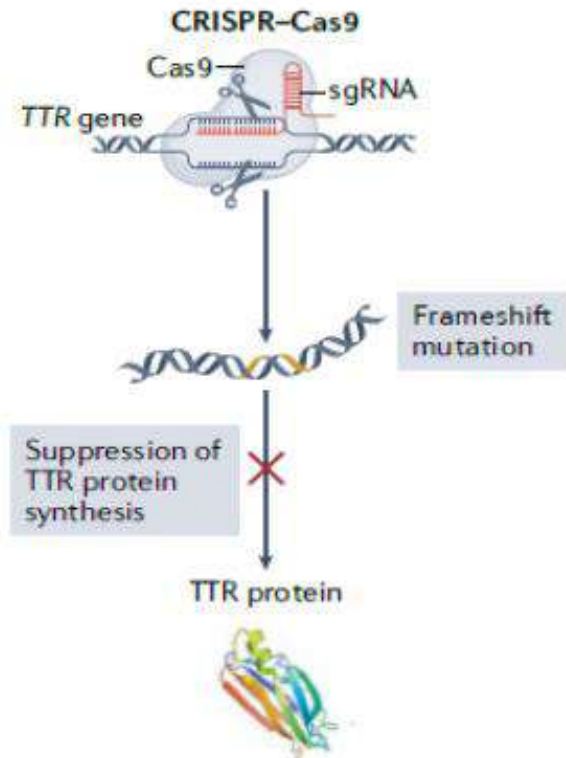


Nat Rev Cardiol. 2022 Oct;19(10):655-667



CRISPR-Cas 9 TTR gene editing (Nexiguran Ziclumeran)

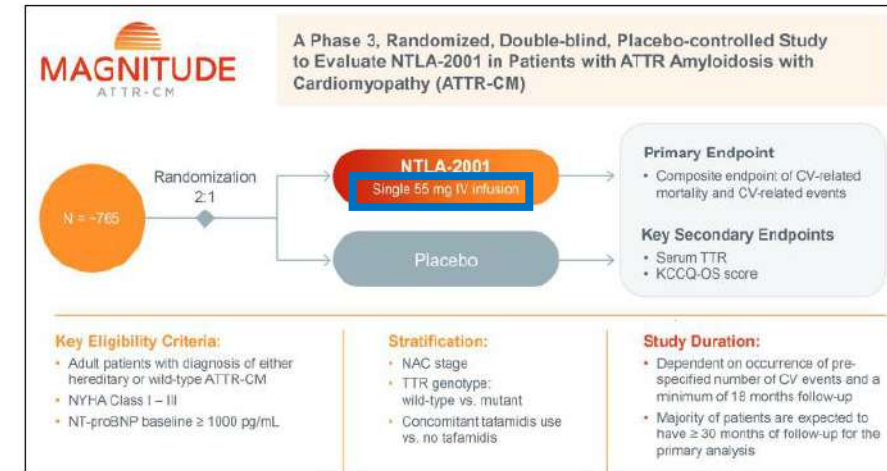
A Percent Change in Serum TTR Level from Baseline



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



34 patients : 2 avec élévation des transaminases reliée au traitement



Un nouveau siRNA : Nucleciran

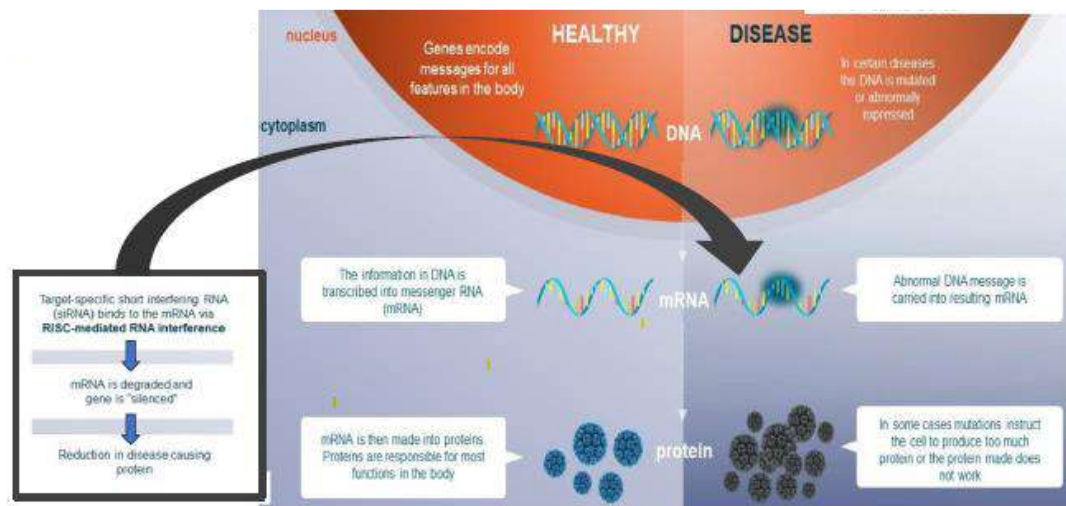
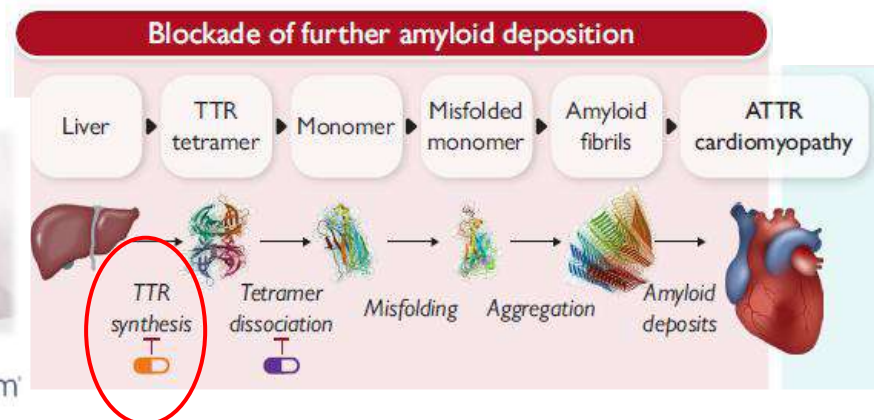
Nucleciran is a synthetic siRNA conjugated to GaINAc, which enables highly efficient delivery to the liver.

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

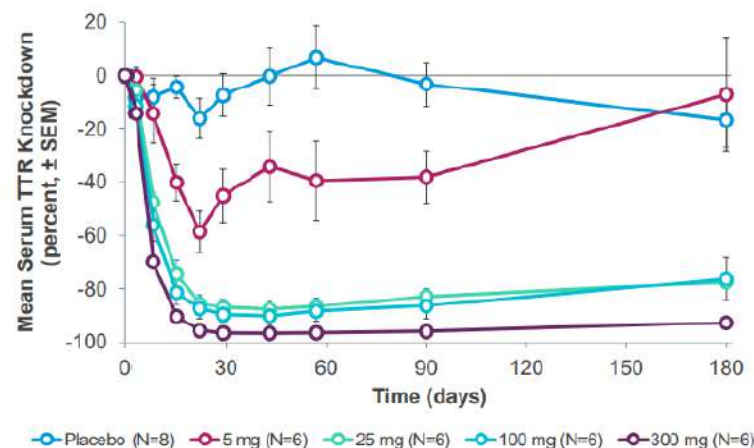
Long-acting SC-administered
GaINAc-conjugated siRNA
targeting liver-expressed
mRNA for TTR



Alnylam



Phase 1 data supports best-in-class profile

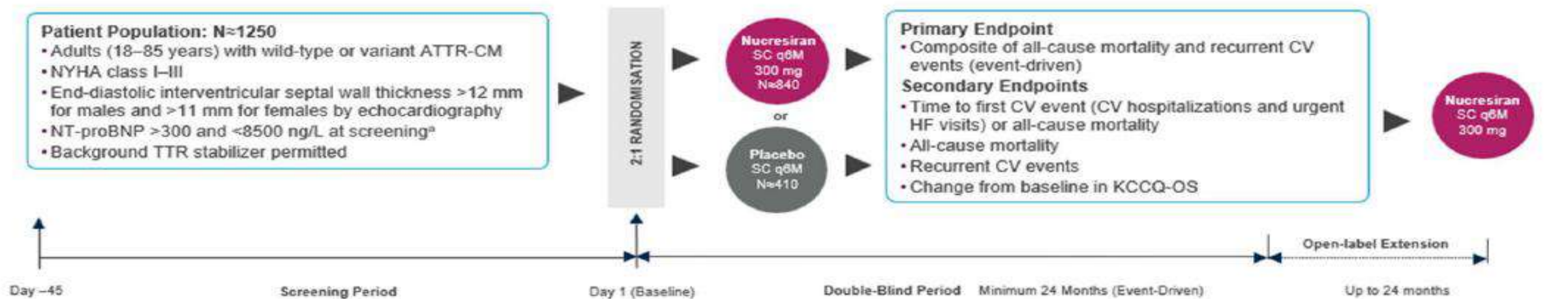


- Single 300 mg dose resulted in rapid, deep, and durable TTR reduction:
 - >90% at Day 15
 - 97% at Day 29
 - 93% at Day 180
- Safety profile:
 - All doses of nucleciran have been **well tolerated**; no adverse events considered related to study drug by investigator
- Frequency of administration:
 -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

TRITON-CM
ATTR-CM CLINICAL STUDY



TRITON-CM Study Design



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

Amyloid clearance

ATTR
cardiomyopathy

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



Cardiac Tracer Uptake on Scintigraphy

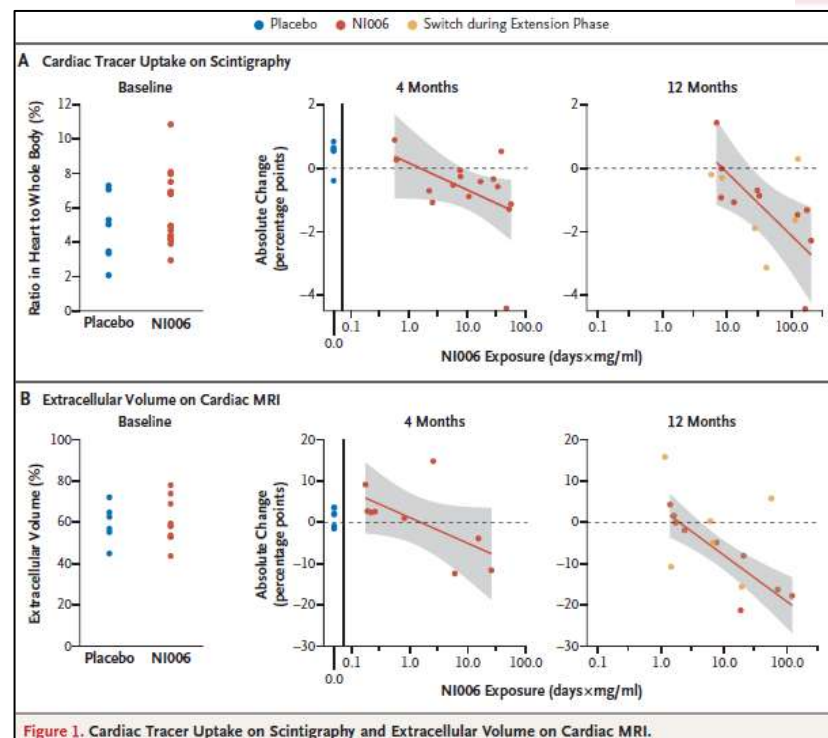
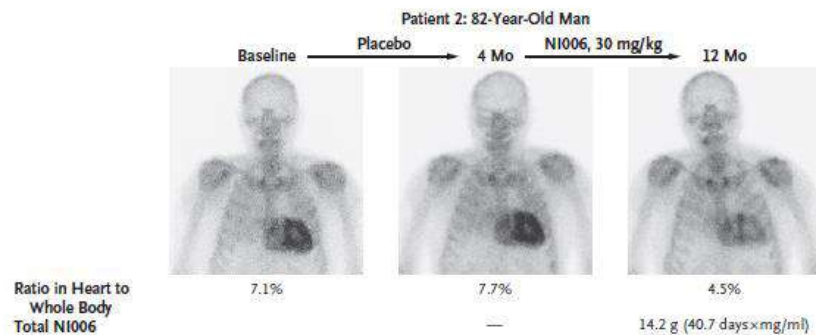
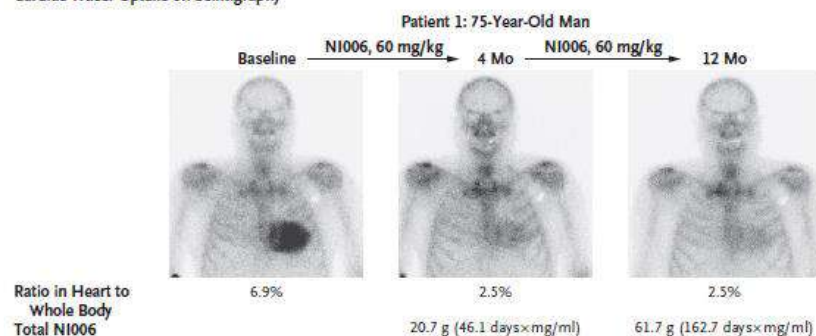


Figure 1. Cardiac Tracer Uptake on Scintigraphy and Extracellular Volume on Cardiac MRI.

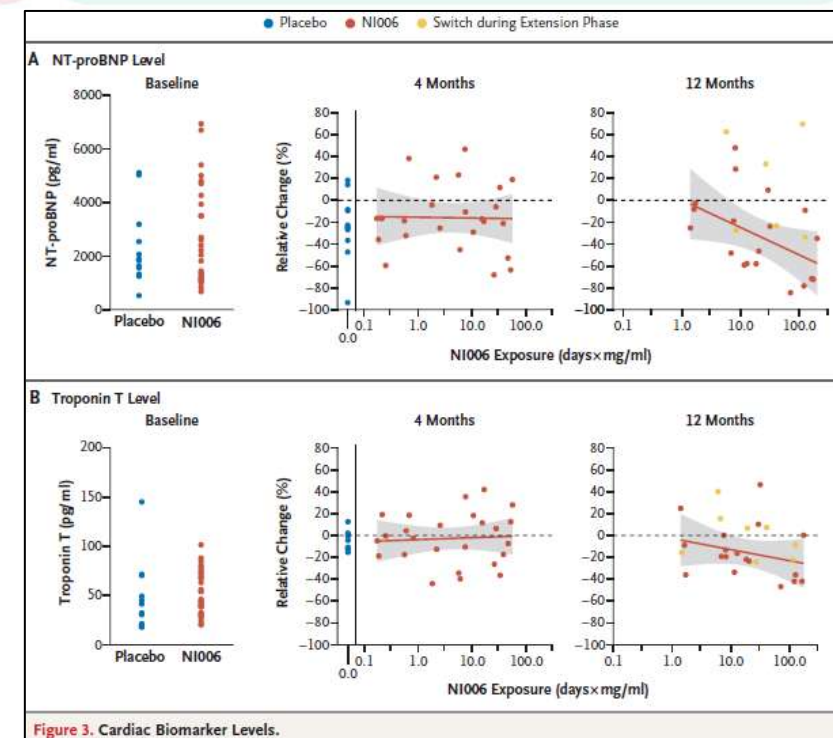
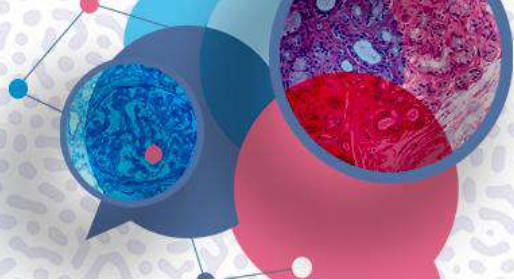
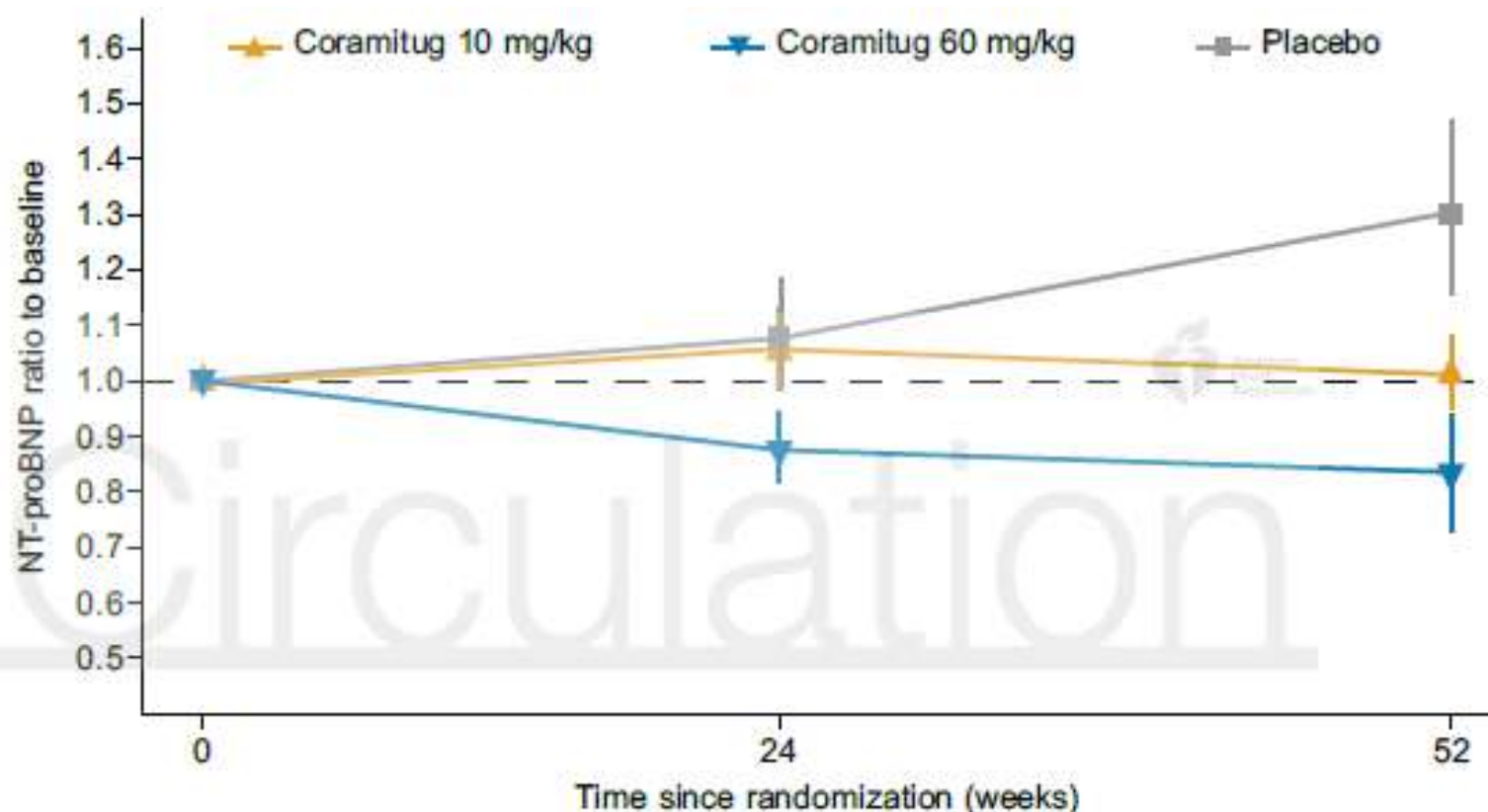


Figure 3. Cardiac Biomarker Levels.

P.Garcia-Pavia et al. NEJM 2023



Coramitug : données de phase 2

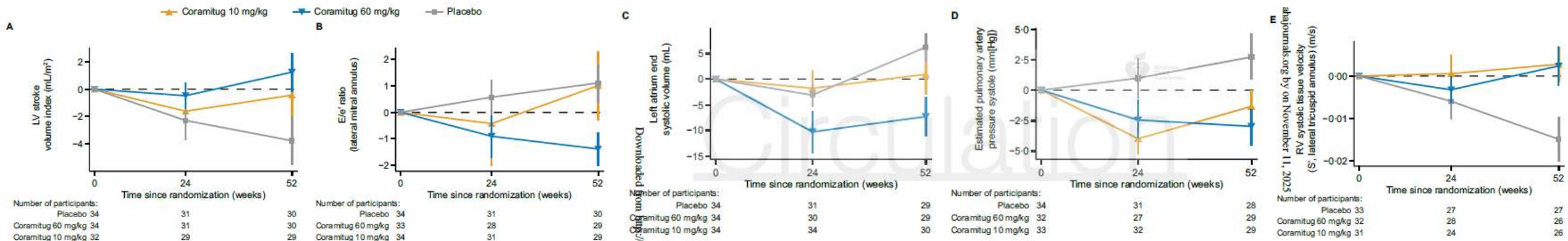
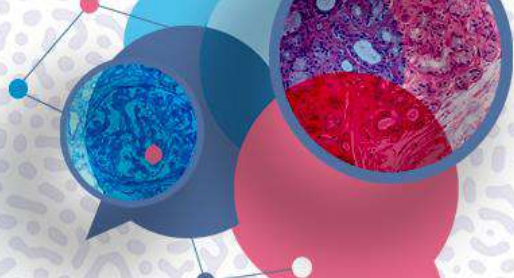


Pas de différence d'effet sur le 6MWT
vs placebo



R'EPOF

M.Fontana et al. Circulation 2025



M.Fontana et al. Circulation 2025

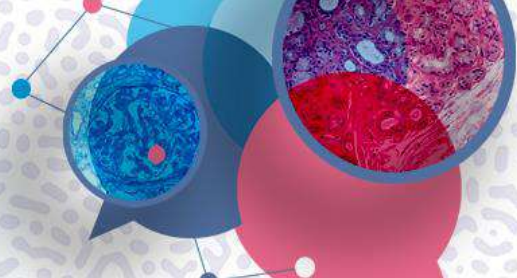


R'EPOF

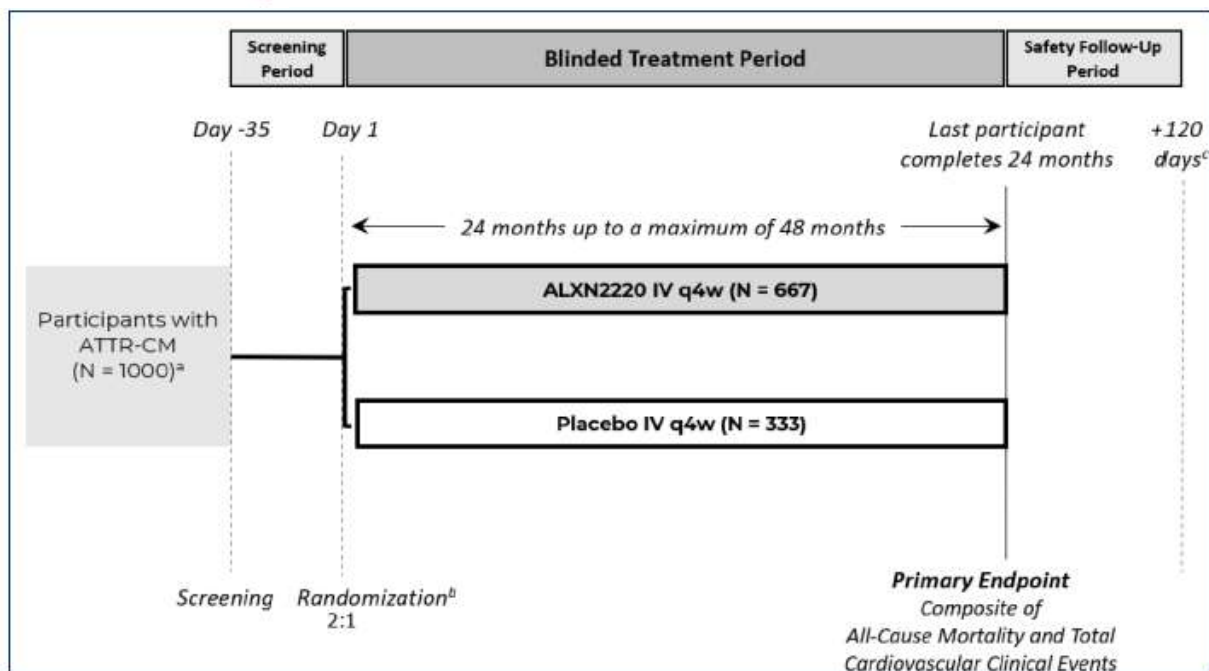


www.reseau-amylose.org



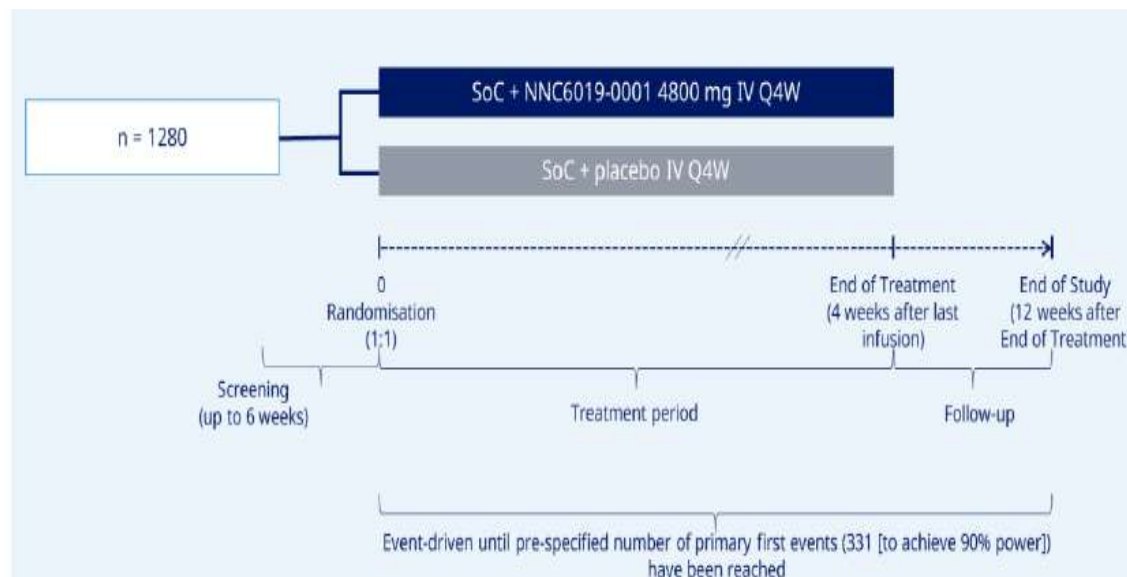


Les Dépléteurs en Phase 3



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

Primary

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

Endpoints

Title

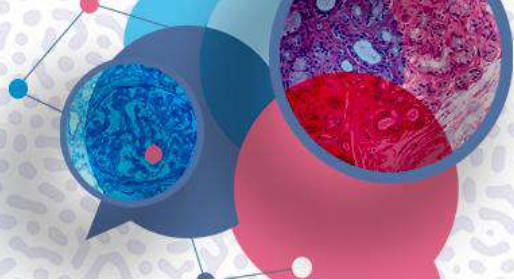
Primary:

The composite outcome of:

- CV death^b
- Recurrent CV events (CV hospitalisation^{b, c} and urgent HF visits^b)

Time frame

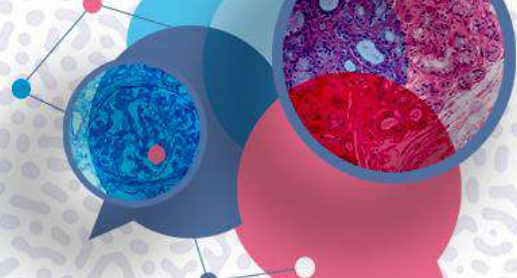
From baseline (week 0) up to EOS^d



Les essais de Stratégie thérapeutique



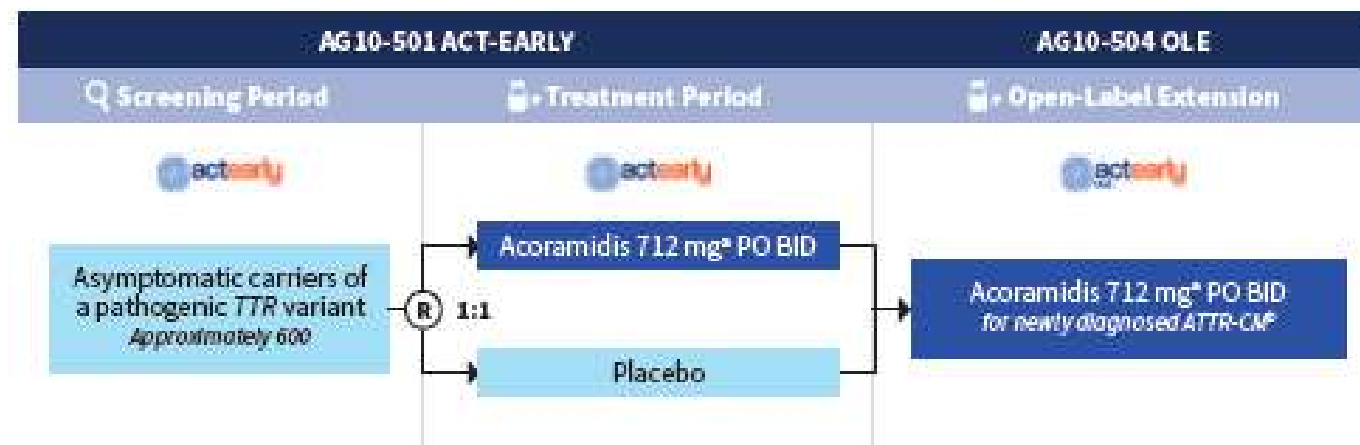
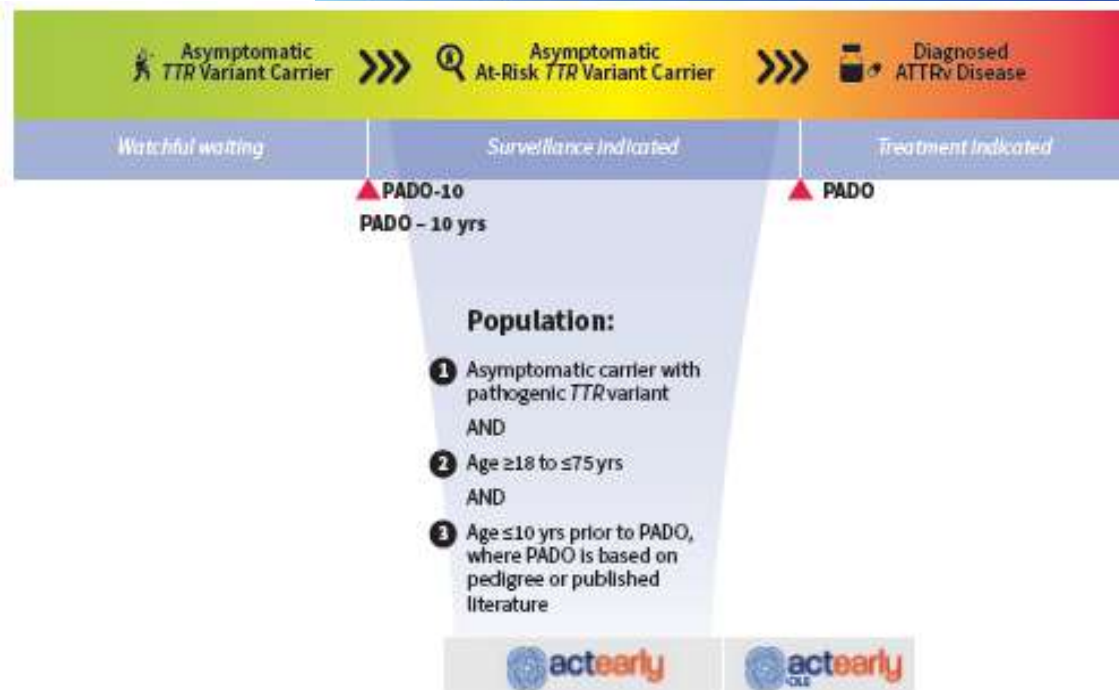
R'EPOF

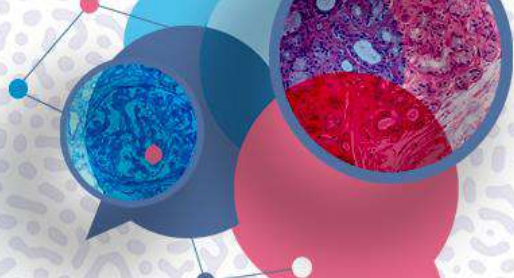


Traitement PRÉ-SYMPTOMATIQUE des apparentés porteurs du variant génétique pathogène

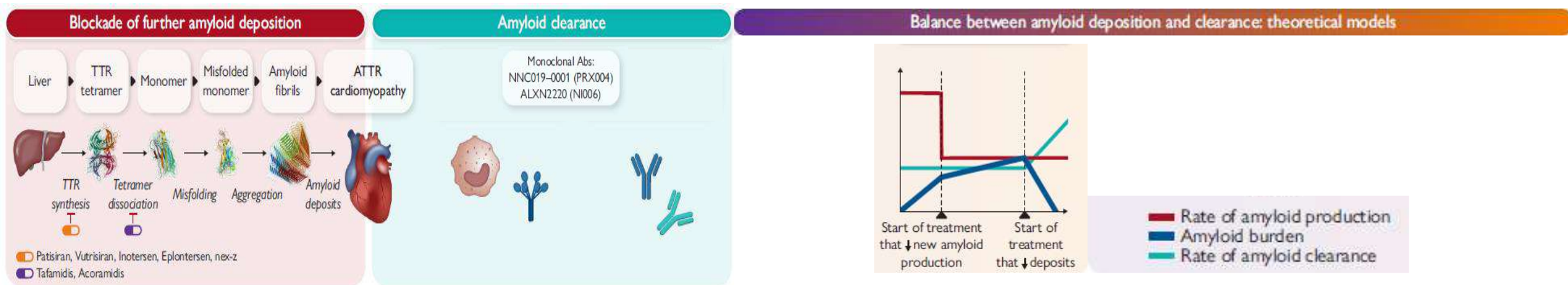
Rationale and Design of ACT-EARLY, the Acoramidis Transthyretin Amyloidosis Prevention Trial

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, Nitasha Sarswat¹⁴, Peter van der Meer¹⁵, Mazen Hanna¹⁶, Morie Gertz¹⁷, Xiaofan (Martha) Cao¹⁸, Ted Lysig¹⁹, Uma Sinha²⁰, Adam Castano²¹, Leonid Katz²², Jonathan C. Fox²³





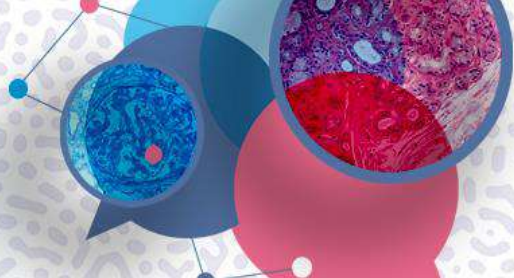
L'arrivée des essais de COMBINAISONS thérapeutiques



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

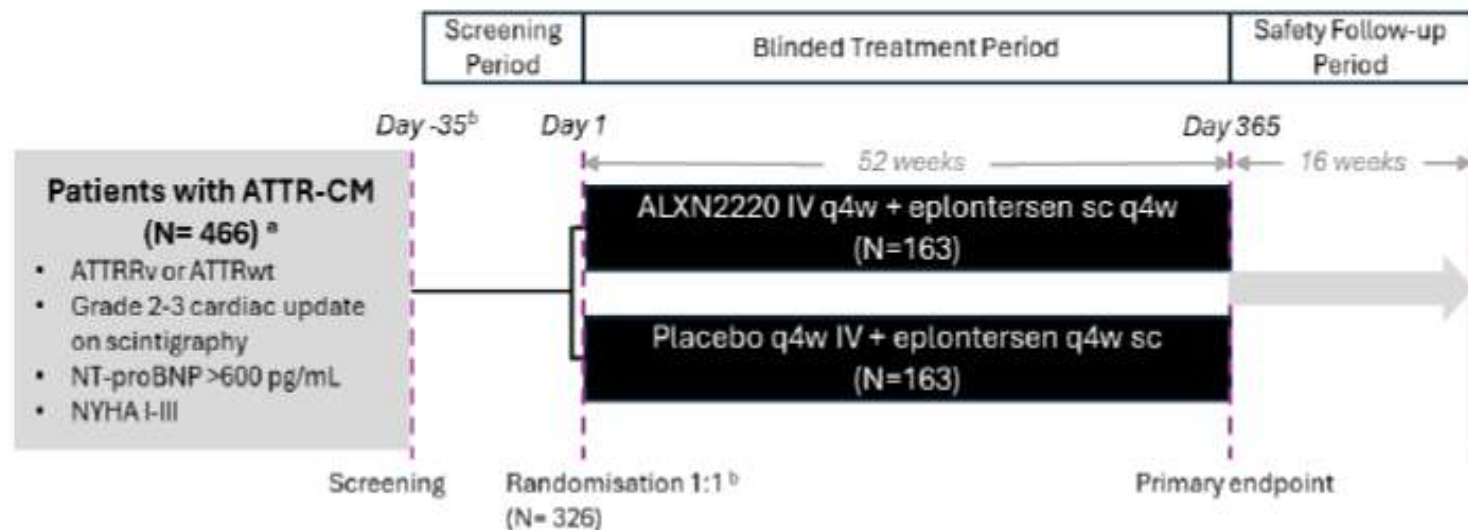


R'EPOF



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



R'EPOF



Remerciements

Platinum sponsors



Silver sponsor



Journée organisée par :



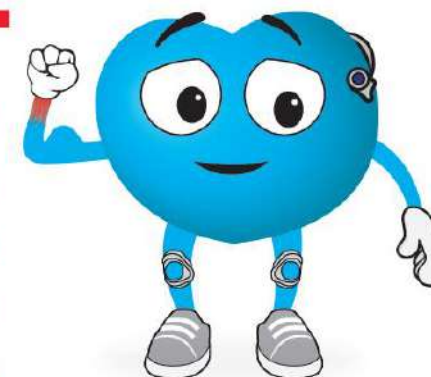
www.masterclass-amylose.com



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

R⁺ EPOF

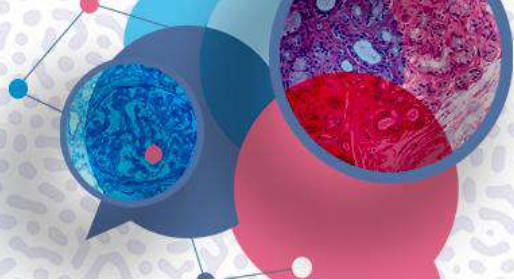
- Surdit 
- Canal carpien
- Doigt   ressaut
- Rupture du tendon du long biceps
- Canal lombaire  troit
- Proth se de hanche/genou
- Essoufflement
- Prise de poids
-  d mes
- Fatigue



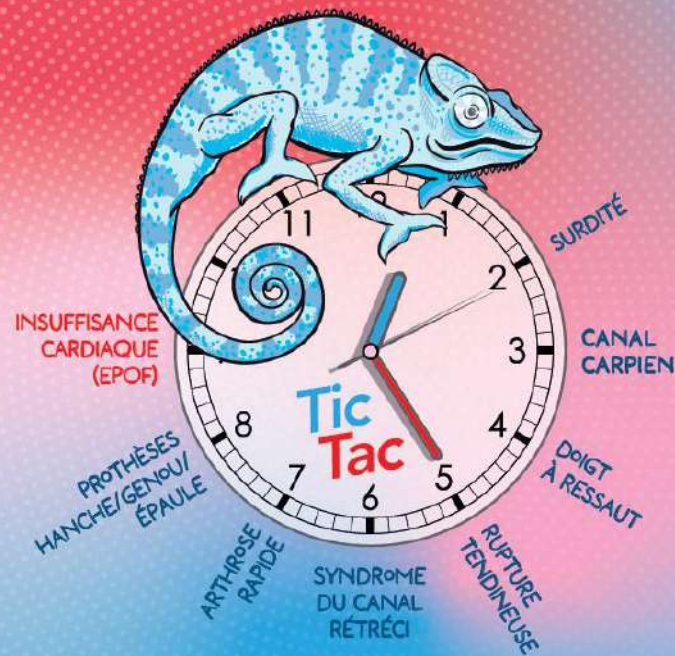
Et si c tait une
Amylose Cardiaque  
transthyr tine ?



R⁺EPOF



ET SI VOUS AVIEZ
LA MALADIE CAMÉLÉON ?



GAGNEZ DU TEMPS CONTRE L'AMYLOSE CARDIAQUE,
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 !!!**



R'EPOF