7e MASTERCLASS AMYLOSES CARDIAQUES
ÉVÉNEMENT HYBRIDE
PRÉSENTIEL
& DISTANCIEL
Mercredi 11 décembre 2024
Fondation Biermans-Lapôtre ■ PARIS
www.masterclass-amylose.com

Essais lancés et à venir dans les ATTR-CM

Recombinaison ARN et ADN

Cardio-TTRansform et INTELLIA-CRISPR-CAS9

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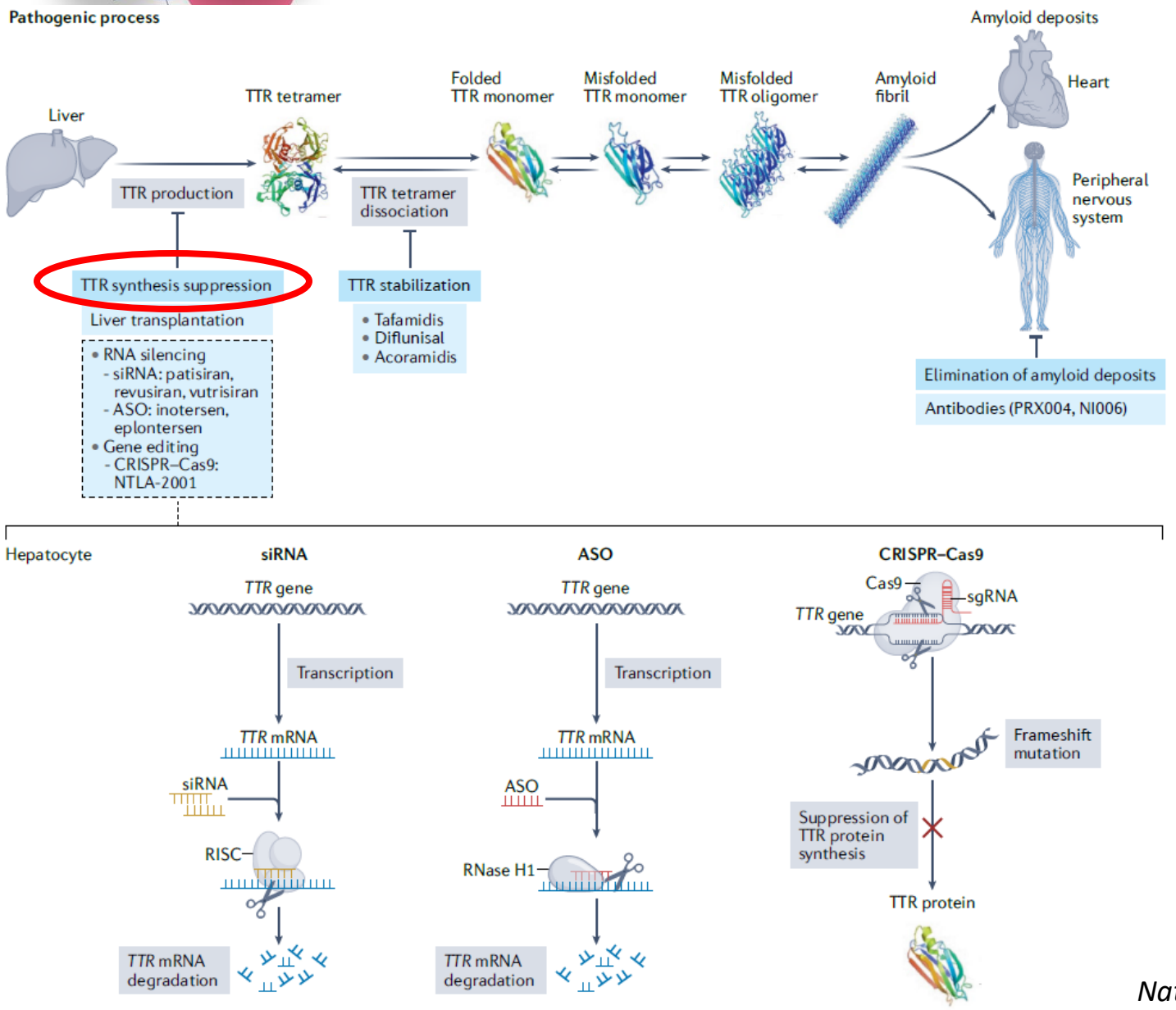
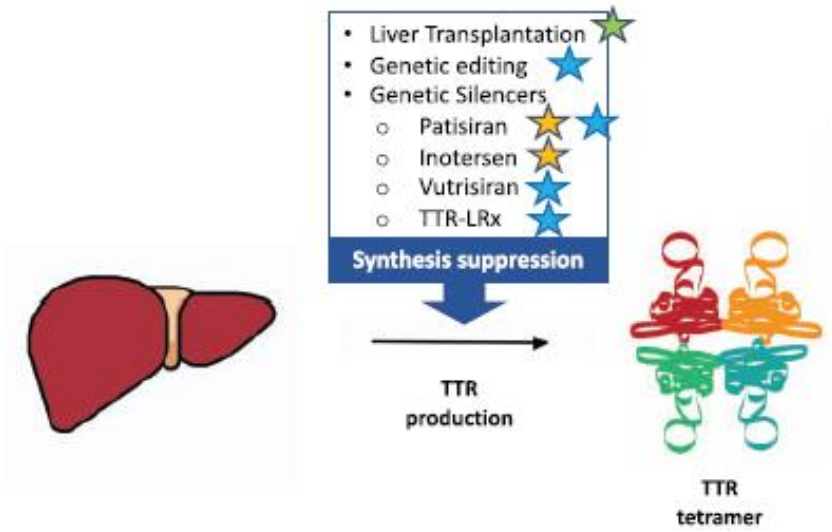
Liens d'intérêt

- Pfizer
- Alnylam



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

Encore des questions ?



➔ Efficacité et sécurité des oligonucléotides antisens ?

➔ Combinaison d'un inhibiteur de synthèse de Transthyrétine et d'un stabilisateur ?

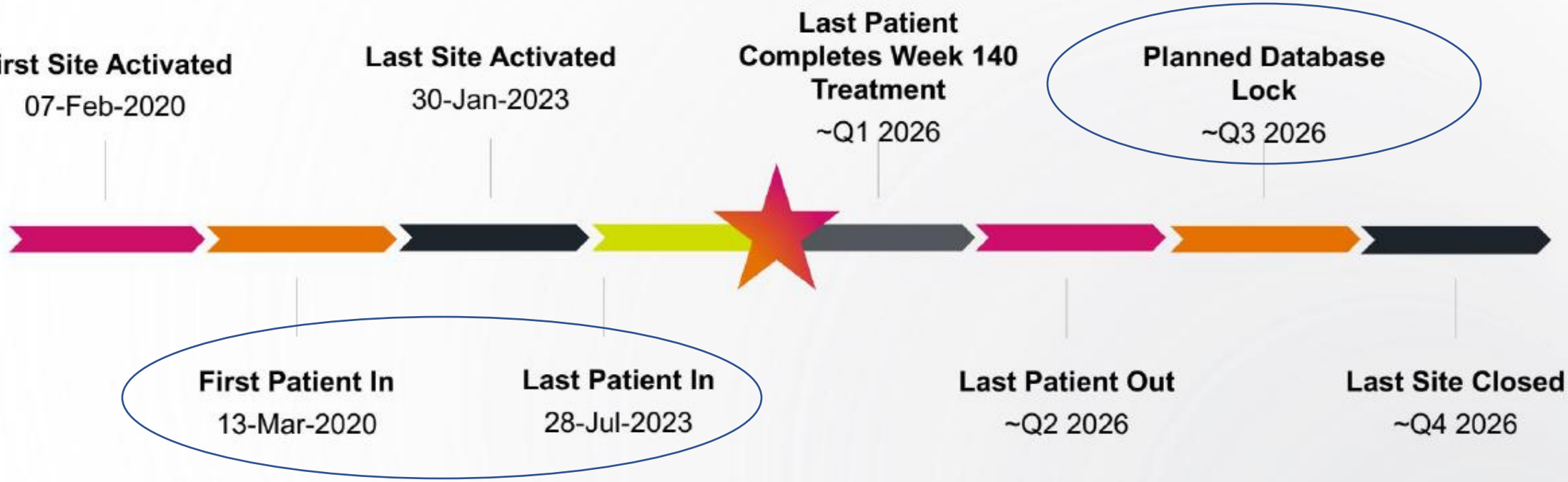
➔ Sécurité et efficacité des CRISPR ?

cardio TTRansform

A Phase 3 Global, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Transthyretin-Mediated Amyloid Cardiomyopathy

Eplontersen

CS2 Global Study Timelines



Largest, Most Comprehensive Phase 3 Study in Patients with ATTR Cardiomyopathy

cardio TTRansform

DESIGN

A global, randomized, double-blind, placebo-controlled study in >1,400 patients with hereditary or wild-type TTR amyloid cardiomyopathy

Imaging sub-studies in ATTR-CM to assess the effects on cardiac structure and function

PRIMARY ENDPOINT

Cardiovascular death & frequency of cardiovascular clinical events at Week 140 (~32 months)

HELIOS·B

Essai randomisé en double aveugle chez les patients avec ATTR-CM

HELIOS·B

N = 655
Population de patients

- Amylose ATTR; wtATTR ou ATTRv quelle que soit la mutation
  - **≤ 30% d'utilisation de tafamidis à la baseline**
- Cardiomyopathie confirmée et historique d'insuffisance cardiaque symptomatique
- NYHA ≤ III;
- PND I ou II à la visite d'inclusion

1:1 RANDOMISATION

Vutrisiran
SC q3M
25 mg

or

Placebo
SC q3M

Critère d'évaluation principal
Résultat composite de la mortalité toutes causes confondues et des hospitalisations CV récurrentes (lorsque le dernier patient atteint le 30e mois).

Critères d'évaluation secondaires

- Distance au TDM6
- Score au questionnaire sur la cardiomyopathie de Kansas City (KCCQ OS)
- Épaisseur moyenne de la paroi du ventricule gauche (VG)
- Déformation longitudinale globale
- Critère composite de mortalité toutes causes confondues et des hospitalisations récurrentes toutes causes confondues
- Mortalité toutes causes confondues
- Hospitalisations CV récurrentes
- NT-proBNP

- https://www.clinicaltrials.gov/ct2/show/NCT04153149

Contemporary Population with Baseline Characteristics Balanced Across Arms

HELIOS-B

Overall Population

Parameter		Overall Population	
		Placebo (N=328)	Vutrisiran (N=326)
Age (years), median (range)		76 (46, 85)	77 (45, 85)
Male sex, n (%)		306 (93.3)	299 (91.7)
hATTR amyloidosis, n (%)		39 (11.9)	37 (11.3)
NYHA class, n (%)	I	35 (10.7)	49 (15.0)
	II	258 (78.7)	250 (76.7)
	III	35 (10.7)	27 (8.3)
ATTR disease stage, n (%)	1	229 (69.8)	208 (63.8)
	2	87 (26.5)	100 (30.7)
	3	12 (3.7)	18 (5.5)
Baseline 6-MWT, meters, mean (SD)		377 (96)	372 (104)
Baseline KCCQ-OS, points, mean (SD)		72.26 (19.92)	72.96 (19.44)
Baseline NT-proBNP, ng/L, median (IQR)		1801 (1042, 3082)	2021 (1138, 3312)
Baseline Troponin I, ng/L, median (IQR)		65.2 (41.1, 105.5)	71.9 (44.9, 115.9)

Substantial use of effective background medications

- **Tafamidis**
  - Baseline ~40% in both treatment arms
  - Drop-in on monotherapy population during DB period ~21% and ~22% for placebo and vutrisiran, respectively
- **SGLT2 inhibitors**
  - Baseline ~3% in both treatment arms
  - Drop-in during DB period ~35% and ~31% for placebo and vutrisiran, respectively

Substantial use of diuretics

- Baseline ~80% in both treatment arms
- Outpatient initiation or intensification of diuretics after first dose was ~56% and ~48% for placebo and vutrisiran, respectively

Patients were not randomised to baseline tafamidis; patients on baseline tafamidis were generally healthier based on NYHA class, NT-proBNP, 6-MWT, and KCCQ-OS score

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Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; DB, double-blind; hATTR, hereditary transthyretin amyloidosis; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; SGLT2, sodium-glucose cotransporter-2.

Study Design

cardio TTRansform

- Patients will be stratified at Randomization based on
  - NYHA Classification (I and II vs. III)
  - ATTR mutation status (mutated vs. wild-type)
  - 6MWT distance (6MWT ≤ 350 meters vs. > 350 meters)
  - **Current treatment with tafamidis (Yes vs. No)**

- Concomitant administration of SoC therapies is allowed, per Investigator's discretion, if locally approved, accessible, and consistent with local clinical practice (except ASO and siRNA compounds, diflusinal, doxycycline, and/or non-dihydropyridine calcium-channel blocker [e.g. verapamil diltiazem]).

- Patients will also receive supplemental doses of the RDA of vitamin A.

CS2 Global Enrollment Status – As of 31May2024

Status	Patients Actuals
Randomized	1,438

Country	Patients Randomized	
ARGENTINA	11	☑ 2021
AUSTRALIA	71	☑ 2020
AUSTRIA	49	☑ 2020
BELGIUM	19	☑ 2021
BRAZIL	85	
CANADA	57	☑ 2021
CZECH REPUBLIC	30	☑ 2020
DENMARK	13	☑ 2021
FRANCE	49	☑ 2021
GERMANY	52	☑ 2020
GREECE	16	☑ 2021
ISRAEL	11	☑ 2021
ITALY	59	☑ 2021
JAPAN	25	☑ 2021
POLAND	8	☑ 2020
PORTUGAL	36	☑ 2020
SPAIN	134	2023
SWEDEN	27	☑ 2020
UK	185	2024
USA	501	☑ 2019
Total	**1,438**	

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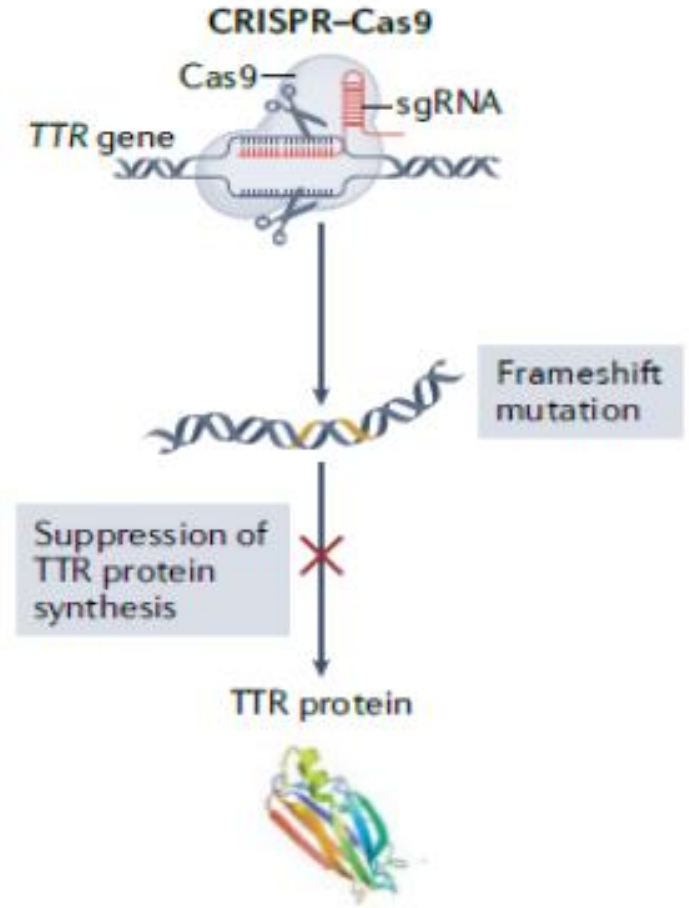
800-1000 patients sous tafamidis ?

Genome editing / CRISPR-CAS9



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

CRISPR-Cas9 Gene Editing with Nexiguran Ziclumeran for ATTR Cardiomyopathy

Marianna Fontana, M.D., Ph.D., Scott D. Solomon, M.D., Jessica Kachadourian, Pharm.D., Liron Walsh, M.D., Ricardo Rocha, M.D., David Lebwohl, M.D., Derek Smith, M.S., Jörg Täubel, M.D., Edward J. Gane, M.B., Ch.B., Björn Pilebro, M.D., David Adams, M.D., Ph.D., Yousuf Razvi, M.B., Ch.B., Joy Olbertz, Ph.D., Pharm.D., Alexandra Haagensen, M.D., Peijuan Zhu, Ph.D., Yuanxin Xu, M.D., Ph.D., Adia Leung, M.S., Alison Sonderfan, M.S., R.D., David E. Gutstein, M.D., and Julian D. Gillmore, M.D., Ph.D.

16 novembre 2024

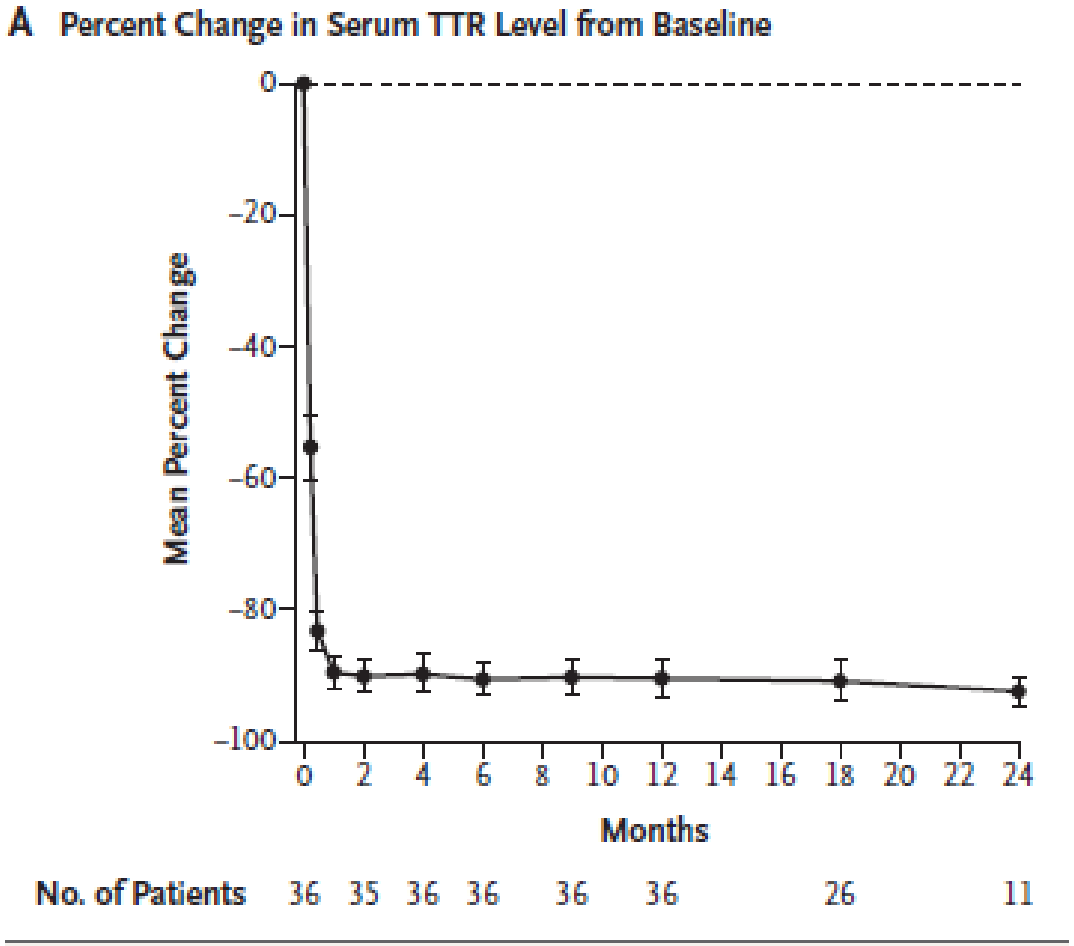
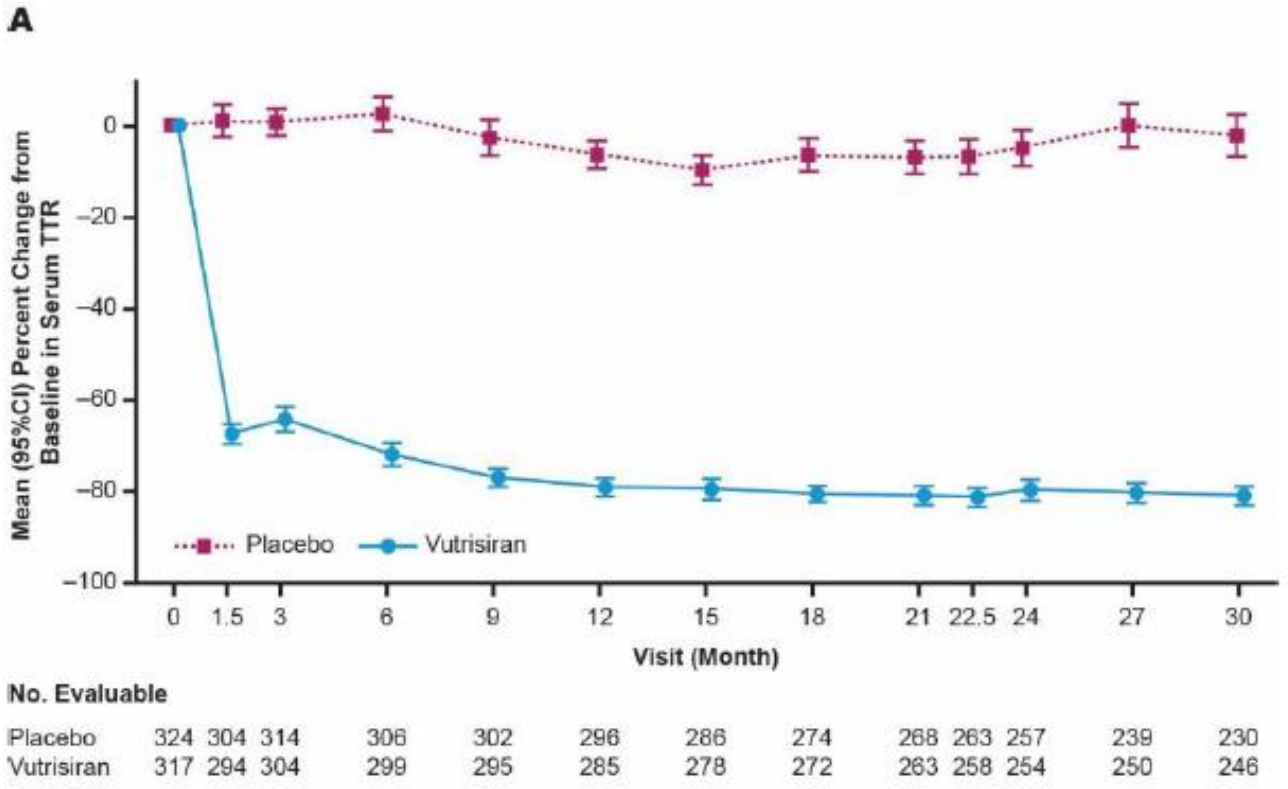


Figure 1. Reduction in Serum Transthyretin Level.



34 patients : 2 avec élévation des transaminases reliée au traitement

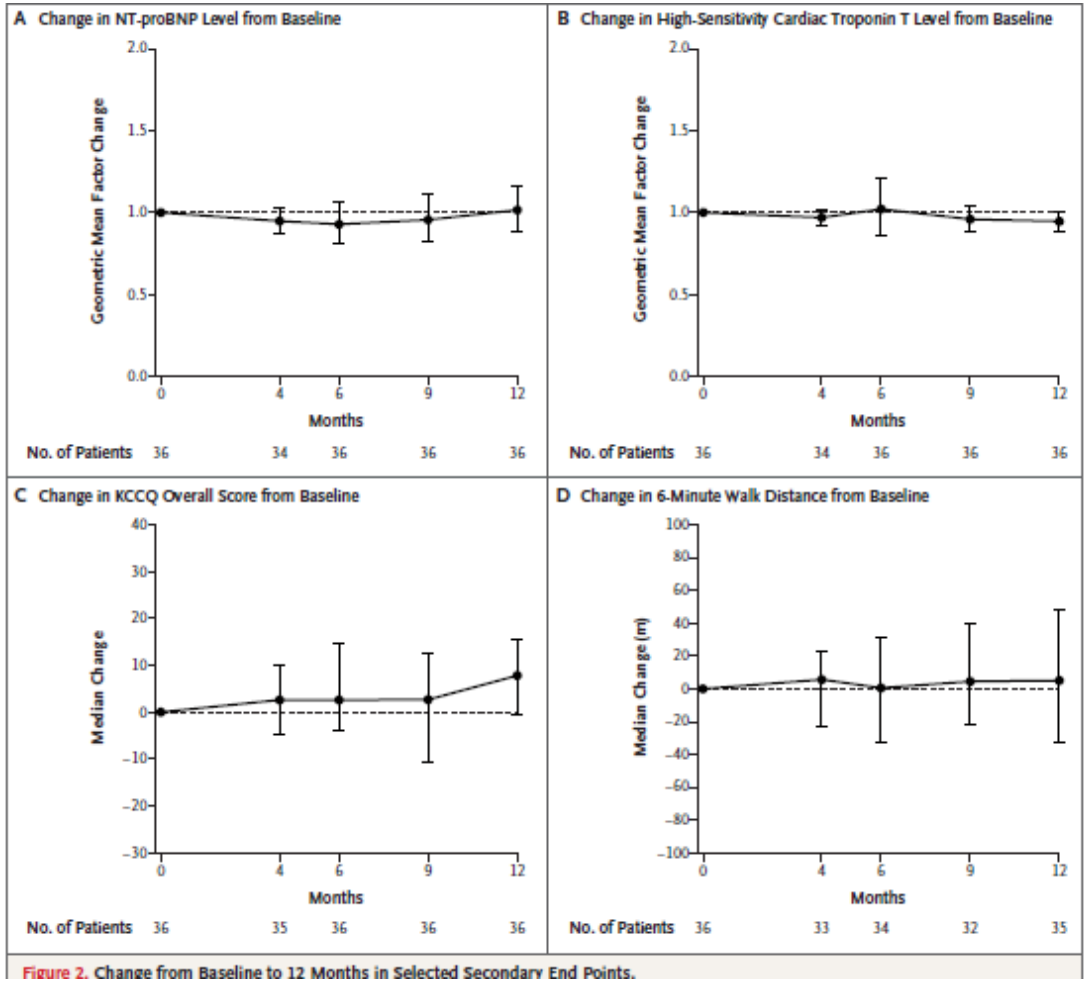


Figure 2. Change from Baseline to 12 Months in Selected Secondary End Points.

Magnitude – Phase 3 Trial of CRISPR in ATTR-CA

MAGNITUDE
ATTR-CM

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate NTLA-2001 in Patients with ATTR Amyloidosis with Cardiomyopathy (ATTR-CM)

N = ~765

Randomization 2:1

NTLA-2001
Single 55 mg IV infusion

Placebo

Primary Endpoint
- Composite endpoint of CV-related mortality and CV-related events

Key Secondary Endpoints
- Serum TTR
- KCCQ-OS score

Key Eligibility Criteria:
- Adult patients with diagnosis of either hereditary or wild-type ATTR-CM
- NYHA Class I – III
- NT-proBNP baseline ≥ 1000 pg/mL

Stratification:
- NAC stage
- TTR genotype: wild-type vs. mutant
- Concomitant tafamidis use vs. no tafamidis

Study Duration:
- Dependent on occurrence of pre-specified number of CV events and a minimum of 18 months follow-up
- Majority of patients are expected to have ≥ 30 months of follow-up for the primary analysis

Merci de votre attention