Amyloidosis Research Consortium

# Wild Type ATTR Amyloidosis

## Treatment Options in 2025

**Presented by:**

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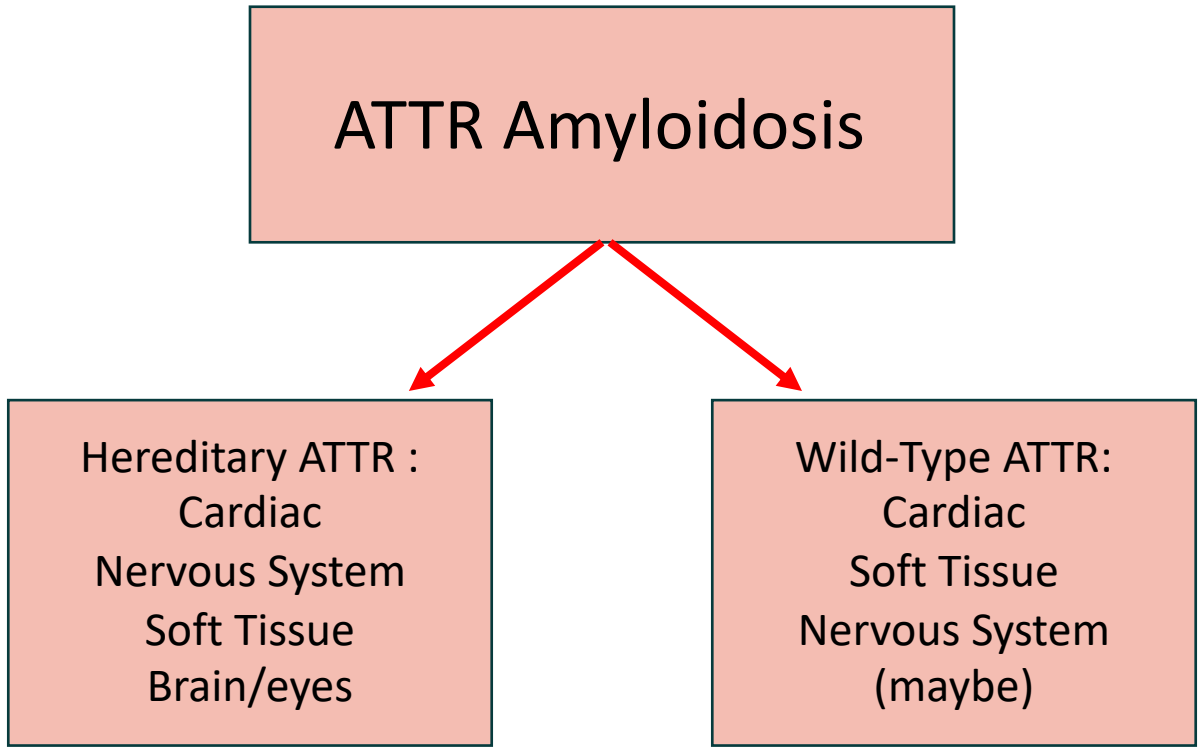
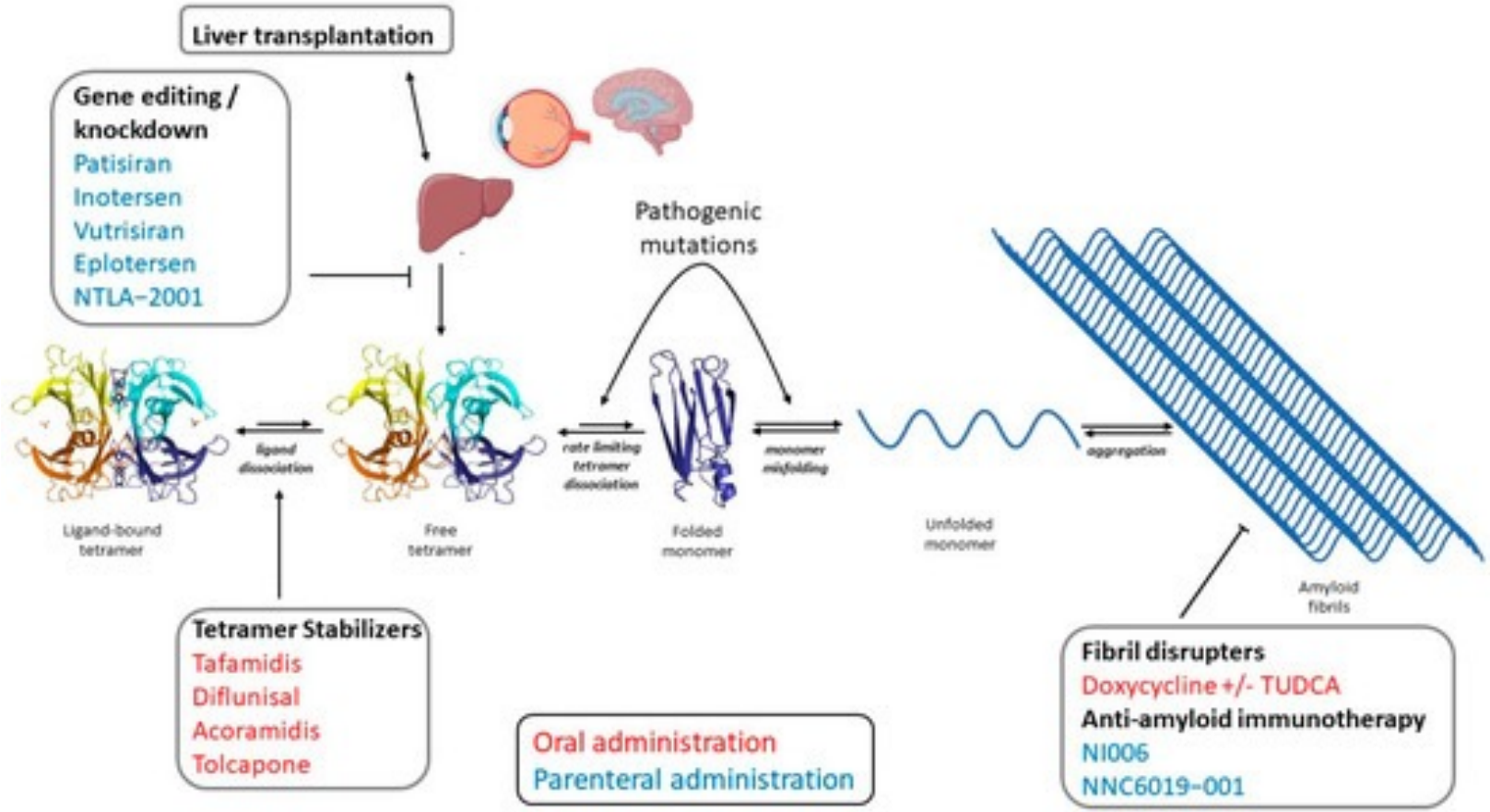
# Common Manifestations of ATTR Amyloidosis



# How Do We Treat ATTR Amyloidosis?

# Treatment strategies for ATTR amyloidosis




Nuvolone M, Girelli M and Merlini G. *Int. J. Mol. Sci.* 2022

# Therapeutic approaches to ATTR amyloidosis

| Type of Amyloidosis | Treatment Options |
|---|---|
| ATTRwt Cardiac Amyloidosis or ATTRv Cardiac Amyloidosis | 1). FDA-approved TTR stabilizer tafamidis<br>2). FDA-approved TTR stabilizer: acoramidis<br>3). Off-label TTR stabilizer diflunisal<br>4). FDA-approved vutrisiran (TTR gene silencer)<br>5). NTLA2001 CRISPR clinical trial<br>6). Anti-fibril antibody clinical trials |
| ATTRv Peripheral Neuropathy Without Significant Cardiac involvement | FDA-approved TTR gene silencers:<br>1). RNAi: patisiran IV or vutrisiran SQ<br>2). ASO: inotersen SQ or epiontersen SQ<br>3). Possible option for early disease: TTR stabilizer (diflunisal) |

# ATTR Cardiac Amyloidosis: Wild-Type or Hereditary

# Cardiac Amyloidosis: TTR Stabilizers

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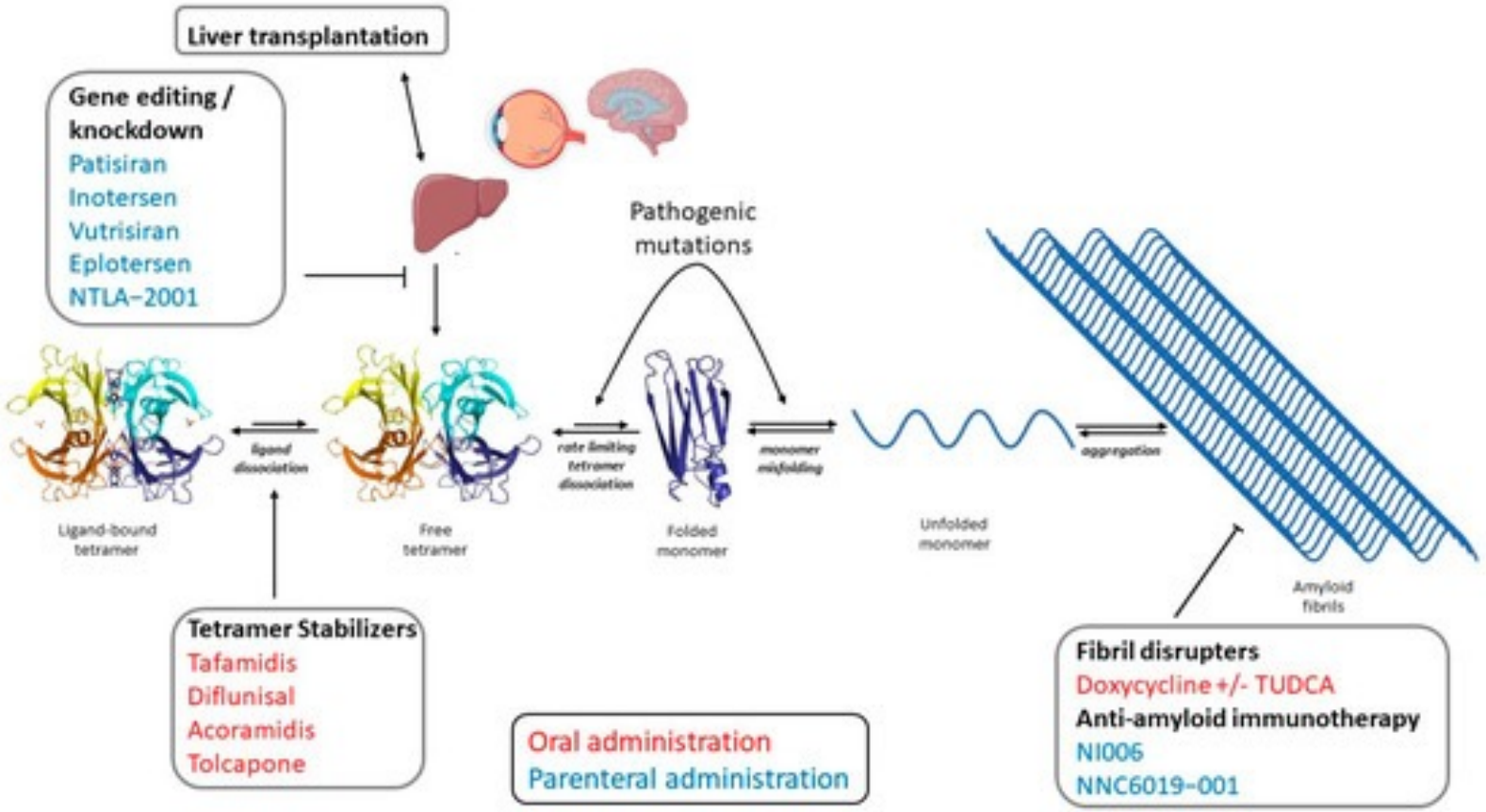
- Oral pills
- Tafamidis (once a day), acoramidis (twice a day), off-label diflunisal (twice a day)
- Well-tolerated
- Major side effect of tafamidis and acoramidis: financial toxicity
- Diflunisal: kidney side effects, GI (acid reflux)
- Benefit after 18 months of treatment: likely slower progression

# Cardiac Amyloidosis: TTR Stabilizers

- Tafamidis: most benefit in early stage disease, wild-type disease and tafamidis meglumine 80 mg daily (tafamidis 61 mg daily)
- Acoramidis: more potent TTR stabilizer, unclear comparative effectiveness vs tafamidis
- Real world: choose agent based on price
- Diflunisal requires renal function monitoring
- Off-label use of diflunisal in prophylaxis

# Treatment strategies for ATTR amyloidosis




Nuvolone M, Girelli M and Merlini G. *Int. J. Mol. Sci.* 2022

# TTR Gene Silencing: Shutting Down The TTR Factory

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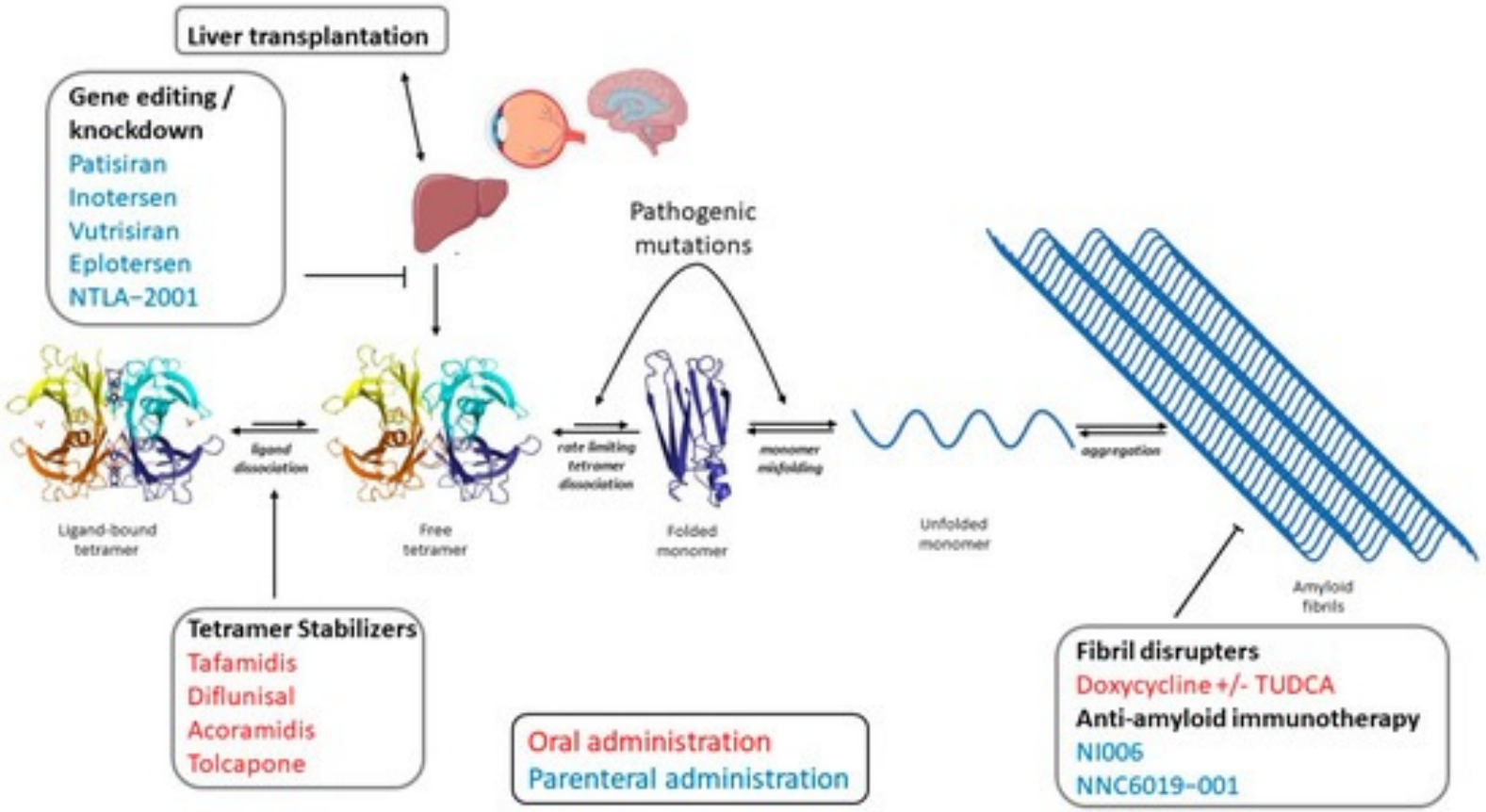
- Patisiran (ONPATTRO): IV infusion once every 3 weeks
- Vutrisiran (AMVUTTRA): subcutaneous injection once every 3 months
- Eplontersen (WAINUA): subcutaneous injection once a month (trial ongoing)
- Nexiguran ziclumeran (NTLA 2001 or nex-z): CRISPR-based gene editing, IV dose once (trial ongoing)

# Summary of TTR Gene Silencing for ATTR Cardiac Amyloidosis

- **APOLLO B:** patisiran resulted in less decline in 6 MWT duration, no change in mortality at 12 months; **not FDA approved**
- **HELIOS B:** vutrisiran resulted in lower risk of death in the monotherapy arm and the overall population (including tafamidis) at 36 months; **FDA approved on March 20th, 2025**
- **MAGNITUDE:** phase 3 ongoing; interim results of phase 1 with significant reduction in TTR levels, stable NT-proBNP at 12 months (with trend towards improvement)

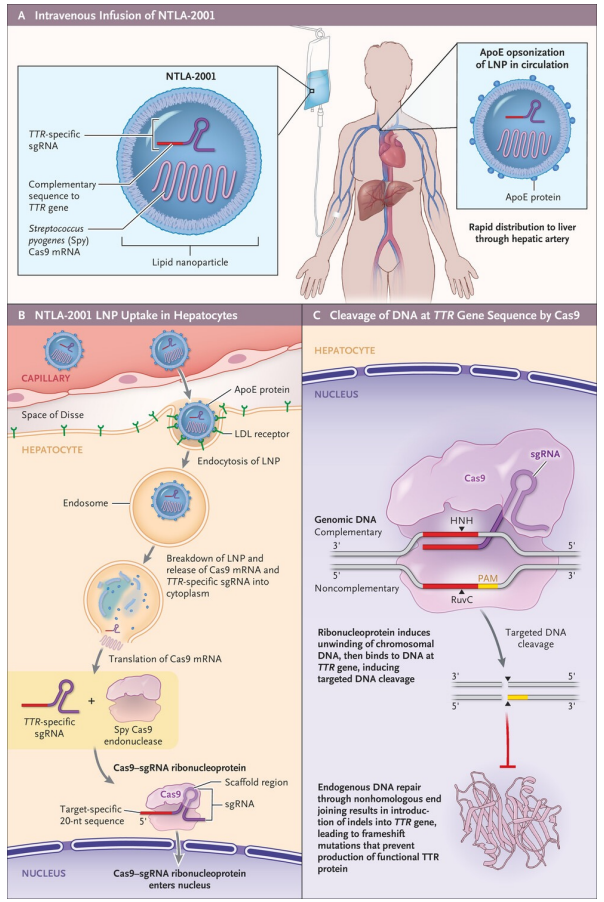
# Treatment strategies for ATTR cardiac amyloidosis




Nuvolone M, Girelli M and Merlini G. *Int. J. Mol. Sci.* 2022

# CRISPR: The ultimate gene silencer

- Phase 1 study of 36 subjects with ATTR-CM
- Significant (89%) decrease in TTR levels from baseline at 12 months
- Mild adverse events: infusion site reaction and mildly elevated liver enzymes
- NT-proBNP levels stable at 12 months with trend towards improvement

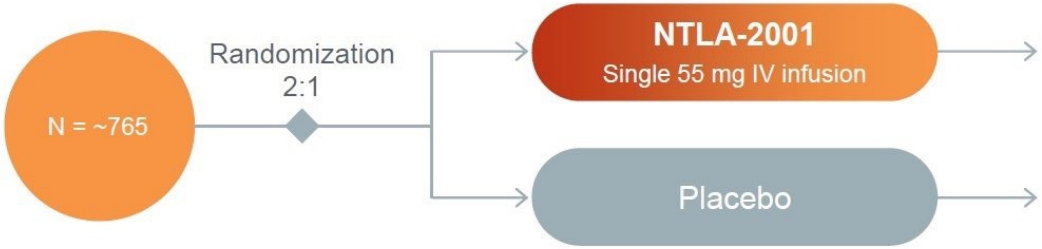



Fontana M et al. NEJM 2024

# MAGNITUDE: Phase 3 RCT of NTLA-2001 vs placebo

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)**




**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

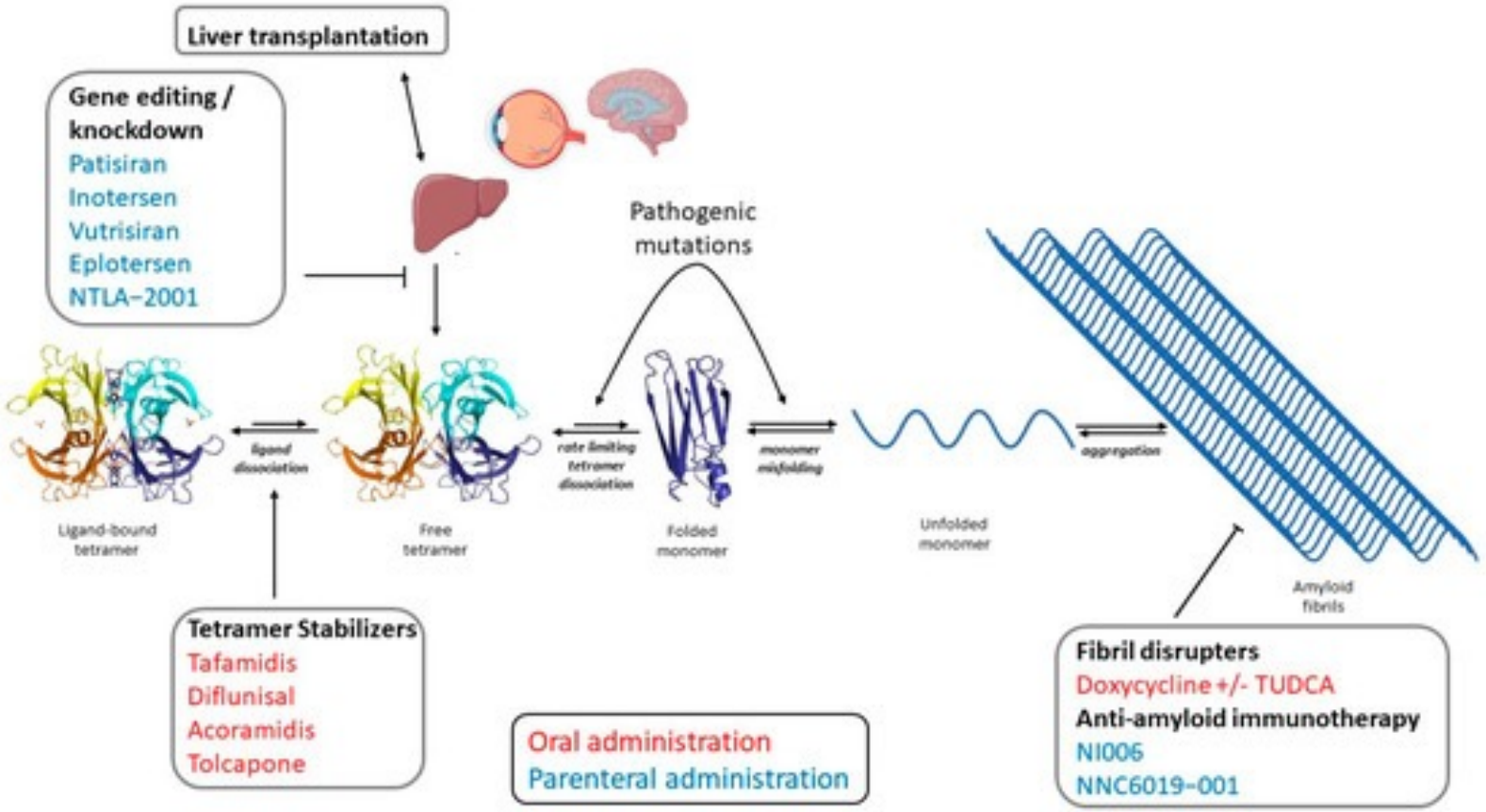
**Study Duration:**

- 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

Clinicaltrials.gov ID: NCT06128629

REGENERON Intellia THERAPEUTICS

# Treatment strategies for ATTR cardiac amyloidosis




Nuvolone M, Girelli M and Merlini G. *Int. J. Mol. Sci.* 2022

# Anti-TTR fibril antibody to reduce cardiac amyloid fibril burden

Phase 1 double-blind trial of NI006 (now ALXN2220) every 4 weeks vs placebo (2:1 Ratio) in 40 patients in a dose-escalation protocol

Subjects treated for 4 months

No apparent serious adverse events

Cardiac uptake by scintigraphy and ECV by CMR reduced in treatment arm at 12 months

Cardiac biomarkers reduced in treatment arm

Garcia-Pavia P et al. NEJM 2023

# DepleTTR-CM: Phase 3 Trial of ALXN2220 vs placebo in ATTR cardiac amyloidosis

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RCT of ALXN2220 vs placebo in a 2:1 ratio

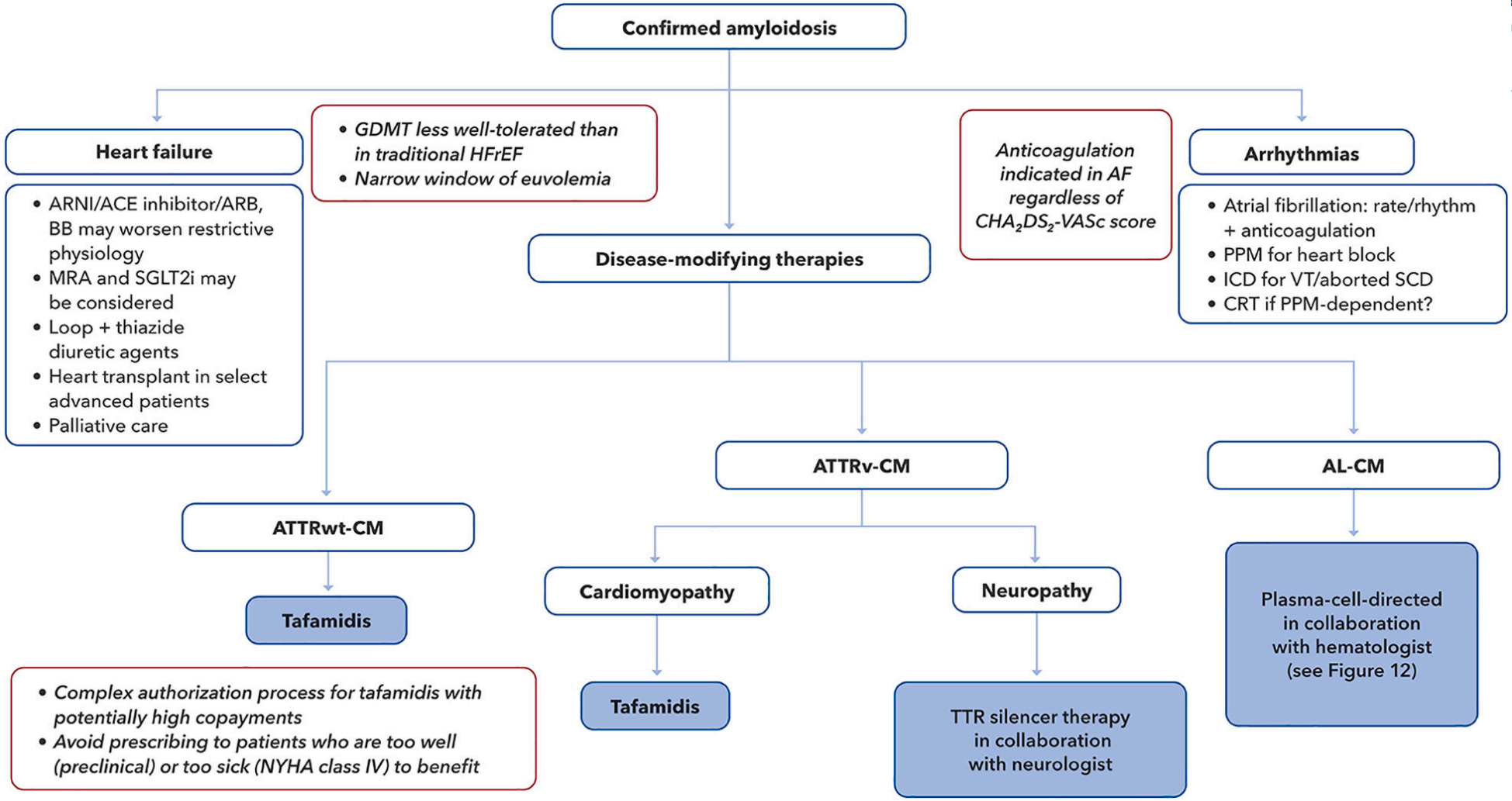
ALXN2220 vs placebo weight-based infusion every 4 weeks for at least 24 months up to a 48 months

Primary endpoint: composite of all-cause mortality and CV events

Secondary endpoints:  change from baseline in KCCQ-OS at month 24, time to CV-related mortality, change from baseline in 6MWT, rate of CV events, time to all-cause mortality

# ATTR Amyloidosis Treatment Algorithm

Kittelson M, Ruberg FL et al. JACC 2023




Kittelson M, Ruberg FL et al. *JACC* 2023; 81:1076-1126

# Summary

Tafamidis and acoramidis are FDA- and EMA-approved TTR stabilizers for ATTR cardiac amyloidosis

Vutrisiran (gene silencer) recently FDA-approved for ATTR cardiac amyloidosis

Patisiran, vutrisiran, inotersen, eplontersen are all FDA-approved for ATTRv peripheral neuropathy (covered in other webinars)

Ongoing clinical trials of eplontersen (CARDIO-TTRansform), CRISPR-cas9 based TTR gene silencing (MAGNITUDE) and anti-TTR  fibril antibody therapy (DepleTTR-CM)

# Thank You!