Breaking evolution in amyloidosis

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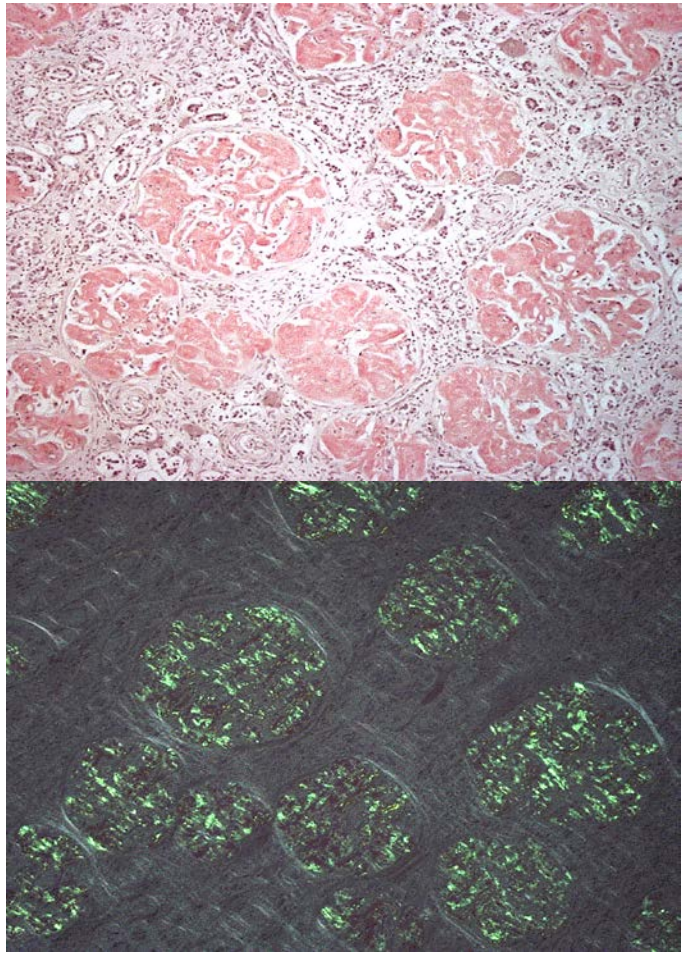
Amyloid & Amyloidosis

- Abnormal extracellular fibrillar protein deposit in tissues
- Pathognomonic green birefringence after Congo red staining
- >30 different amyloid proteins

Protein	Amyloid type	Clinical disease
Light chain	AL amyloidosis	Any organ
Amyloid A protein	AA amyloidosis	Kidneys
TTR	ATTR amyloidosis	Heart & nerves



Merlini G. Hematology Am Soc Hematol Educ Program 2017;1:1–12
Sipe *et al.* Amyloid 2014;21:221–4

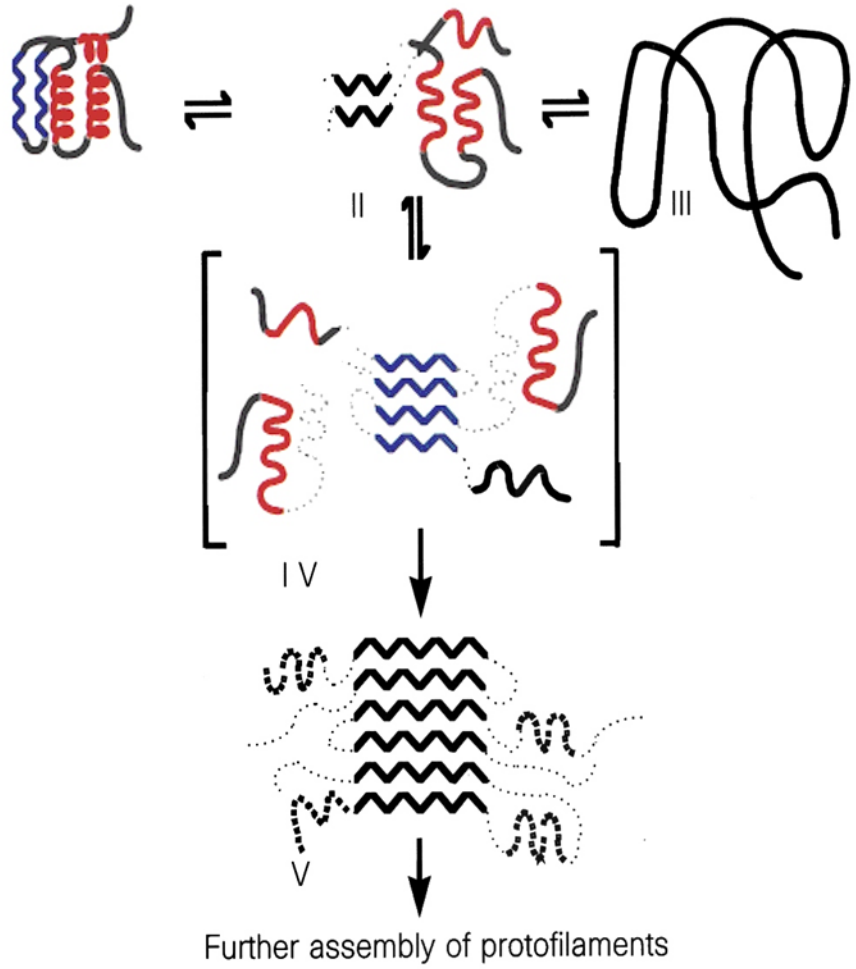
Amyloid fibrillogenesis *in vivo*

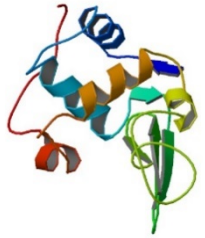
- Sustained high concentration of structurally normal protein: SAA, B_2M
- Production of structurally abnormal protein: mutated TTR, fibrinogen, apoAI, lysozyme, gelsolin, B_2M
- Normal concentration and structurally normal protein but at old age: wild-type ATTR amyloidosis

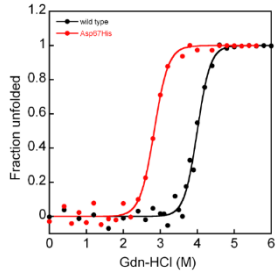
Misfolding & aggregation with typical cross-β polypeptide core structure

Instability of the folded state

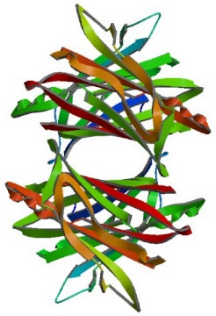
Lessons from hereditary amyloidoses

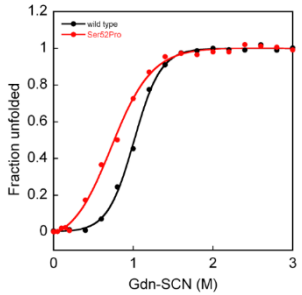




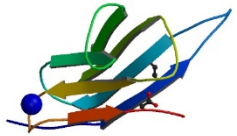


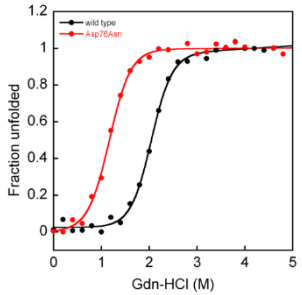
Lysozyme





TTR





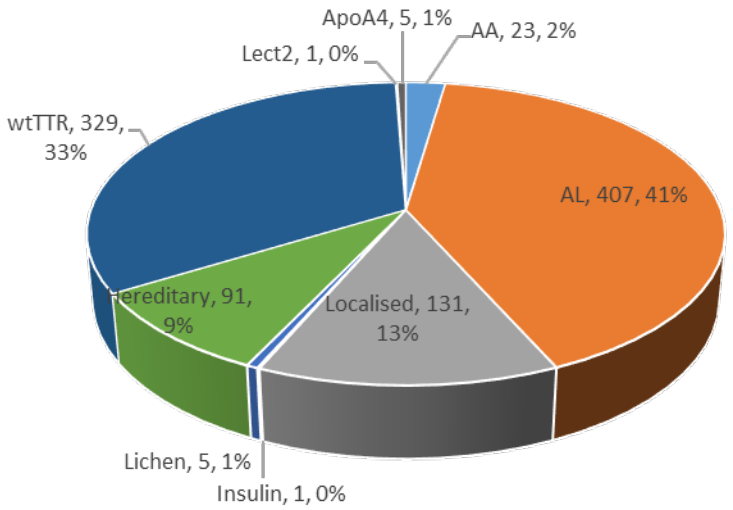
B_2M

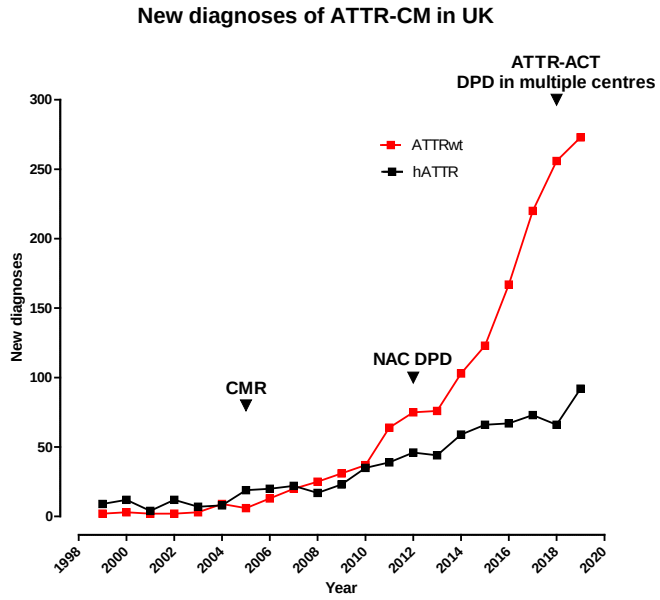
Booth *et al*, Nature, 1997:385:787-93
Valleix *et al*, N Engl J Med 2012;366:2276-83

Transthyretin (ATTR) amyloidosis

- Wild-type ATTR amyloidosis (ATTRwt) is a cardiomyopathy
  - Increasingly recognized cause of heart failure in over 50s
  - Almost certainly the commonest type of systemic amyloidosis
  - Progressive and fatal within 2-7 years

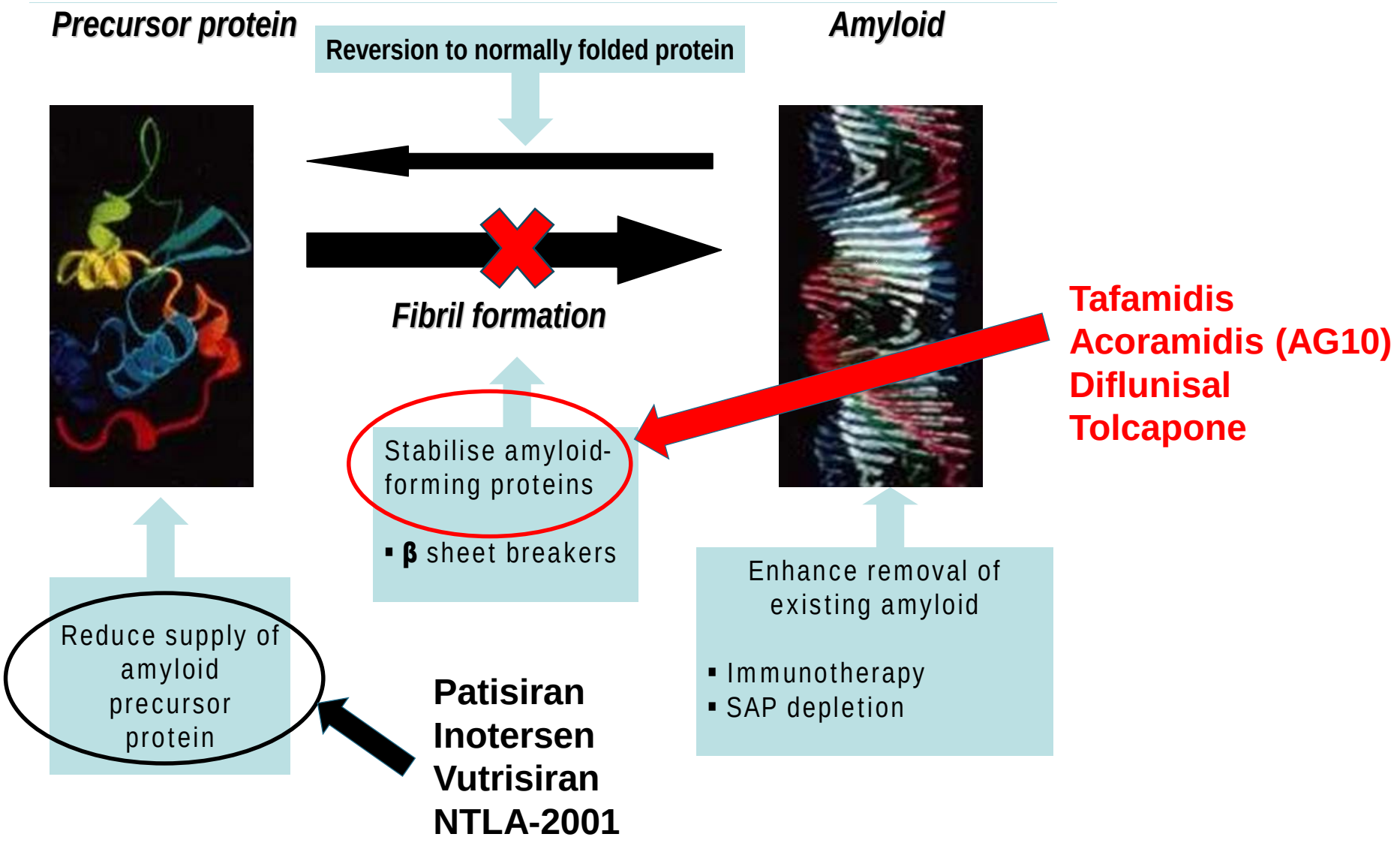
- Hereditary ATTR amyloidosis (ATTRv) usually causes cardiomyopathy and polyneuropathy
  - Progressive polyneuropathy with high disease burden
  - Fatal within 2-15 years

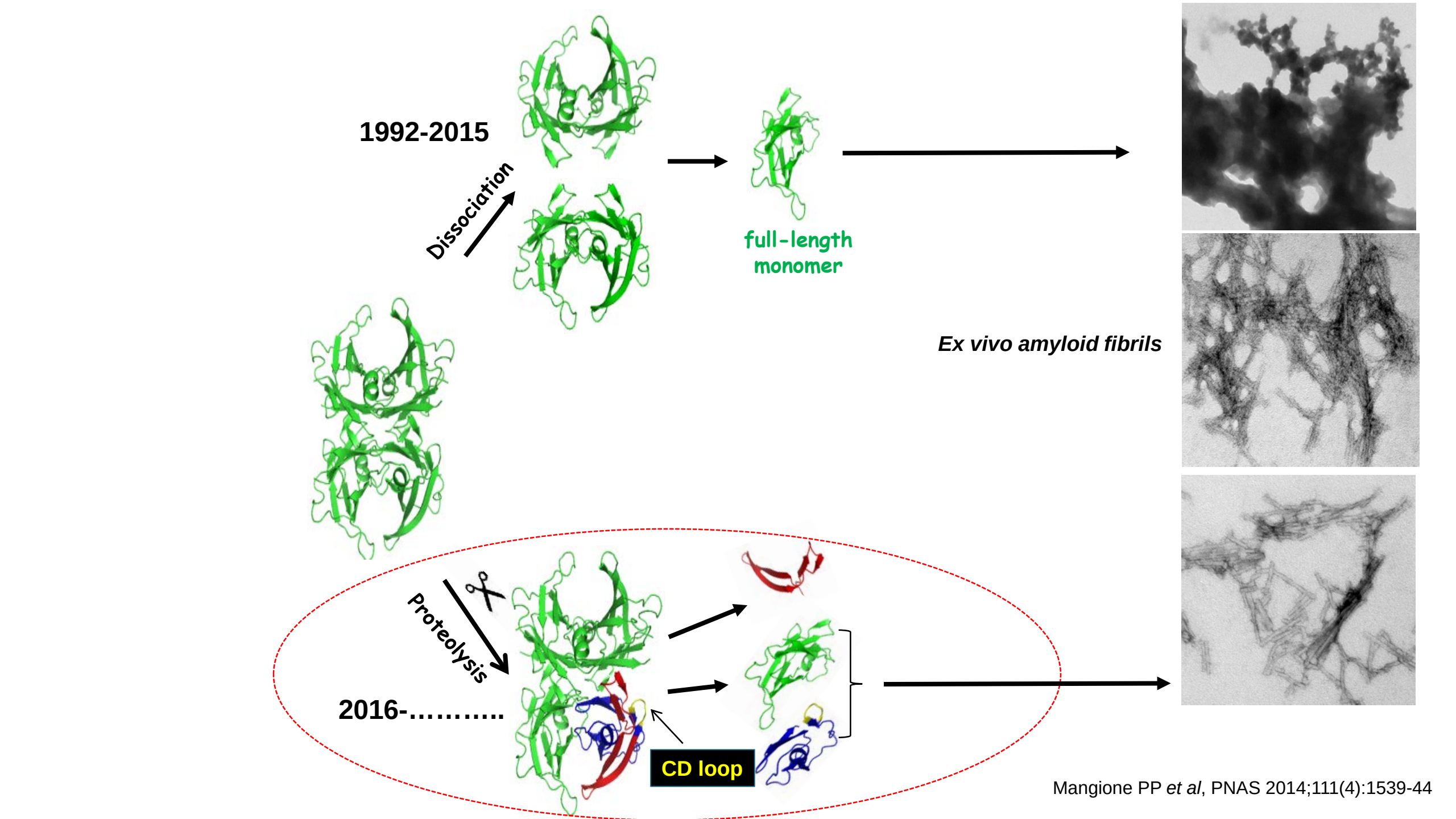




Lane T *et al,* Circulation 2019;140:16–26
Pinney *et al,* J Am Heart Assoc 2013;2: e000098
Tanskanen *et al,* Ann Med 2008;40:232–9
Rowczenio *et al,* Orphanet J Rare Dis. 2017;12(Suppl 1):165

Disease-modifying treatment strategies in (ATTR) amyloidosis



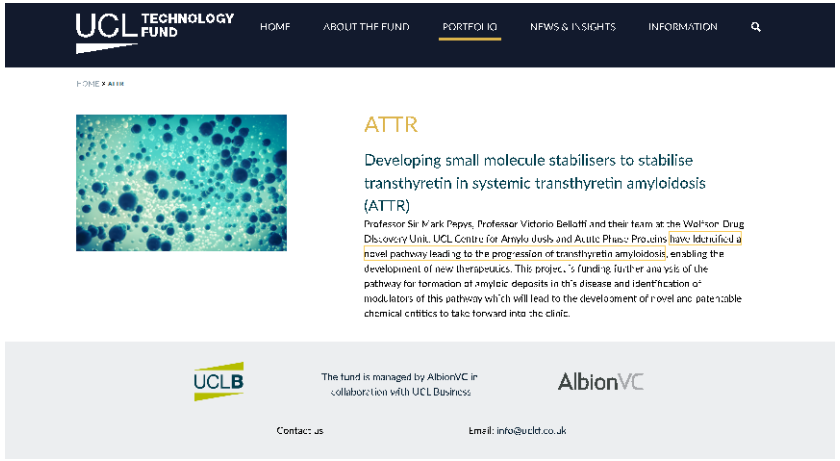


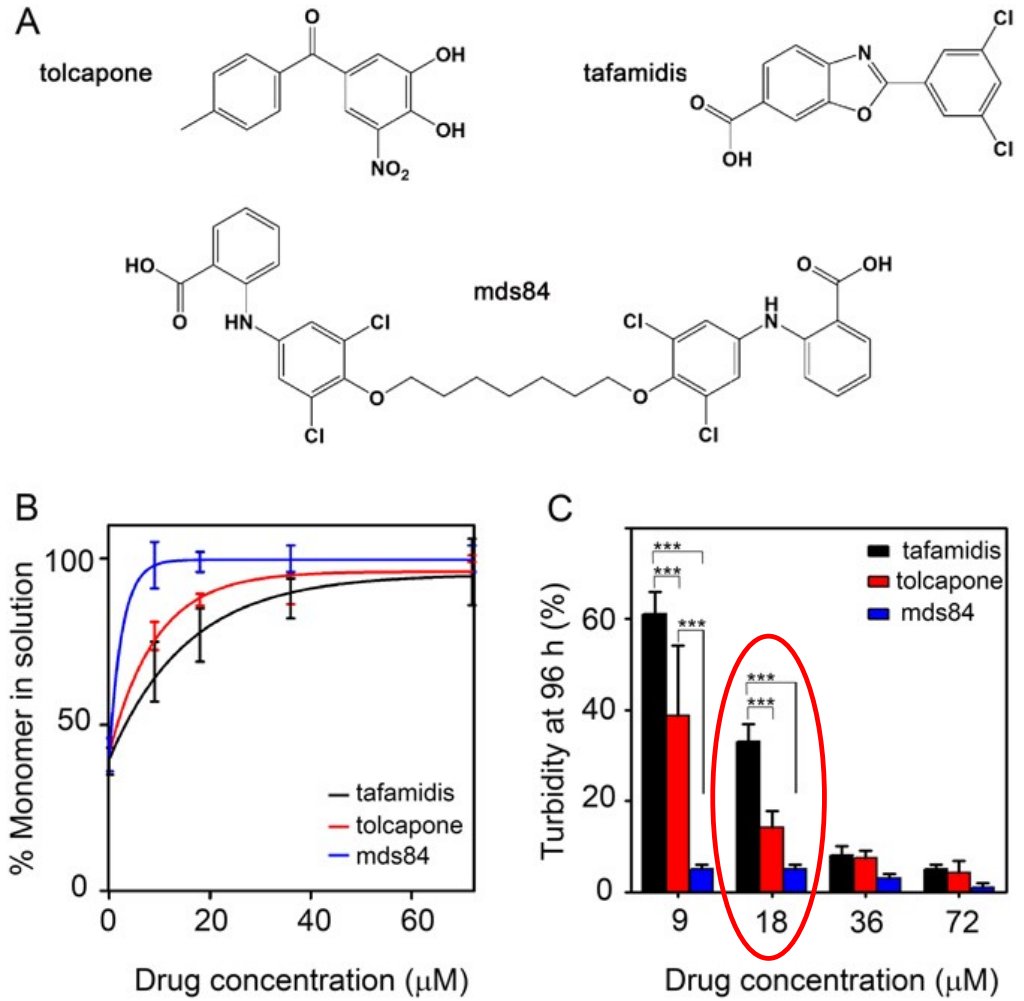
Mangione PP *et al*, PNAS 2014;111(4):1539-44

Inhibition of the mechano-enzymatic amyloidogenesis of transthyretin

Role of

- ligand affinity
- binding cooperativity
- occupancy of the inner channel





Bivalent inhibitors of MechanoEnzymatic mechanism

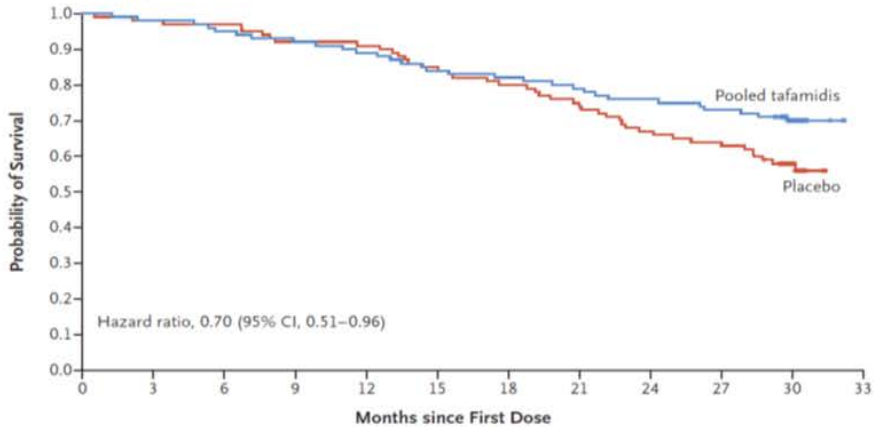
Verona G *et al*, *Sci Rep* 2017;**7:**182

ATTR-ACT study results

A Primary Analysis, with Finkelstein–Schoenfeld Method

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Mo 30	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30
				no. (%)	*per patient per yr*
Pooled Tafamidis	264	<0.001	1.70 (1.26–2.29)	186 (70.5)	0.30
Placebo	177			101 (57.1)	0.46

B Analysis of All-Cause Mortality



No. at Risk (cumulative no. of events)

Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

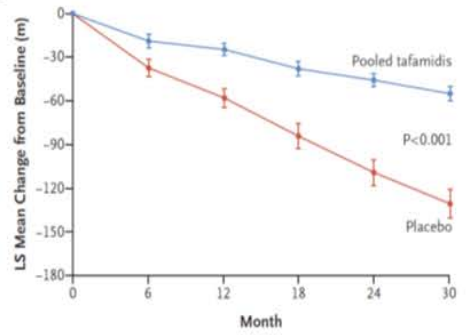
C Frequency of Cardiovascular-Related Hospitalizations

	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations	Cardiovascular- Related Hospitalizations	Pooled Tafamidis vs. Placebo Treatment Difference
		total no. (%)	*no. per yr*	*relative risk ratio (95% CI)*
Pooled Tafamidis	264	138 (52.3)	0.48	0.68 (0.56–0.81)
Placebo	177	107 (60.5)	0.70	

Figure 2. Primary Analysis and Components.

Panel A shows the results of the primary analysis as determined with the use of the Finkelstein–Schoenfeld method. Panel B shows an analysis of all-cause mortality for pooled tafamidis and for placebo, a secondary end point. Panel C shows the frequency of cardiovascular-related hospitalizations, also a secondary end point.

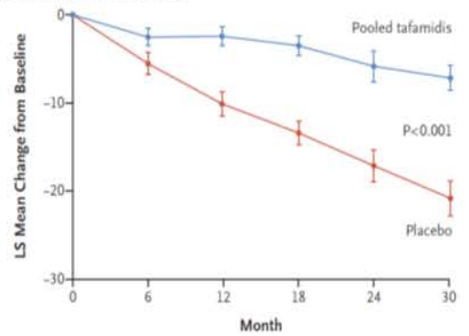
A Change from Baseline in 6-Minute Walk Test



No. of Patients

Tafamidis	264	233	216	193	163	155
Placebo	177	147	136	111	85	70

B Change from Baseline in KCCQ-OS



No. of Patients

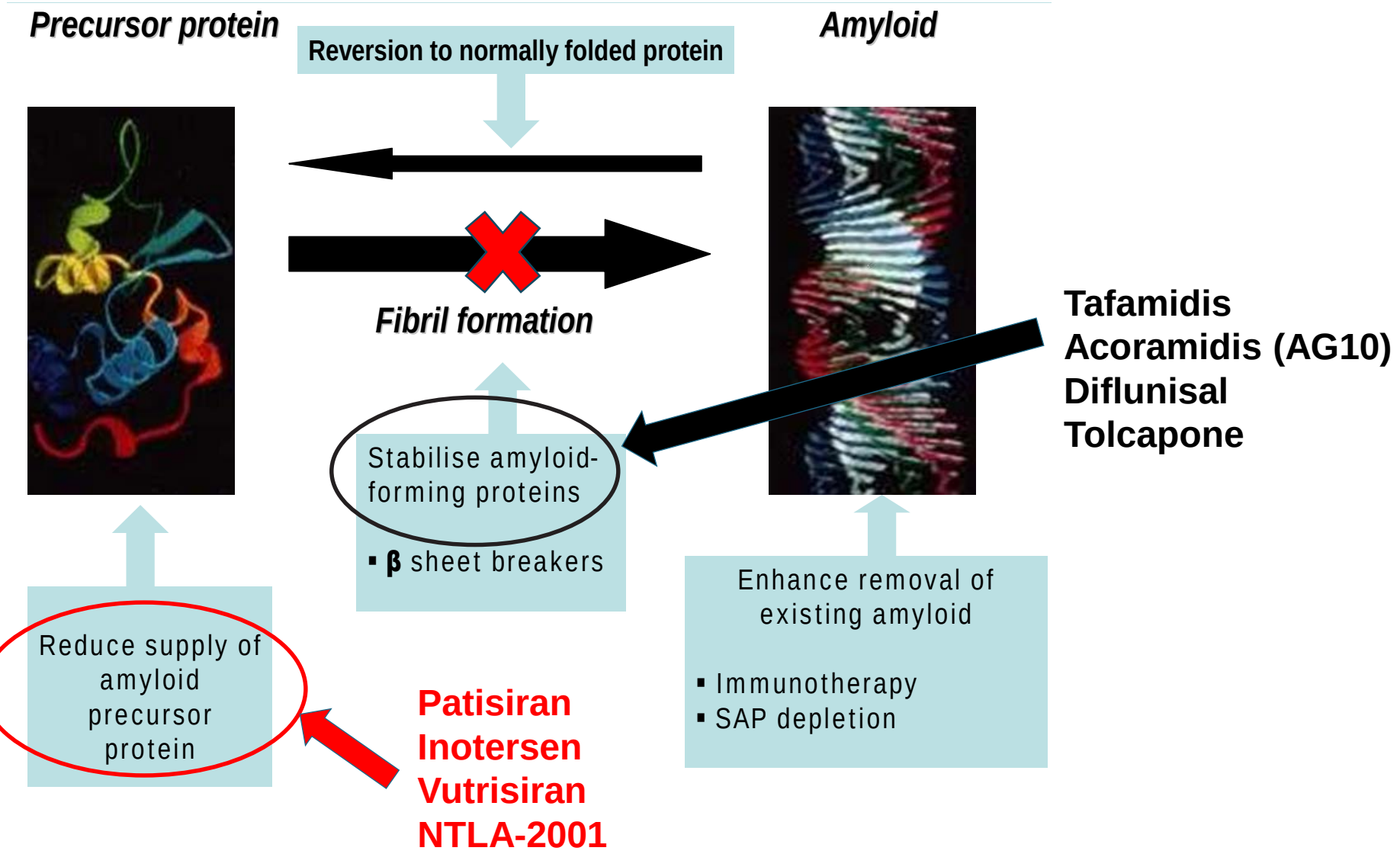
Tafamidis	264	241	221	201	181	170
Placebo	177	159	145	123	96	84

Figure 4. Key Secondary End Points.

Panel A shows the least-squares (LS) mean (±SE) change from baseline to month 30 in the distance walked in the 6-minute walk test in the pooled tafamidis group as compared with the placebo group. Panel B shows the LS mean (±SE) change from baseline for both groups in the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score, in which higher scores indicate better health status. I bars indicated standard errors.

Maurer MS *et al,* N Engl J Med 2018;379(11):1007–1016

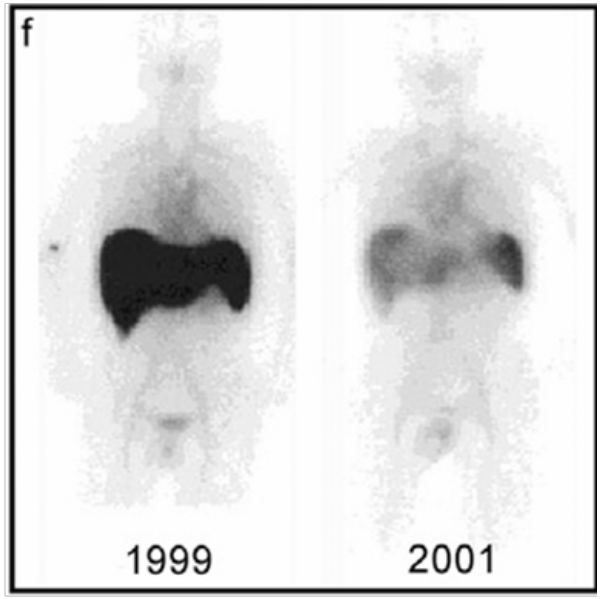
Disease-modifying treatment strategies in (ATTR) amyloidosis



Dynamic nature of amyloid deposits

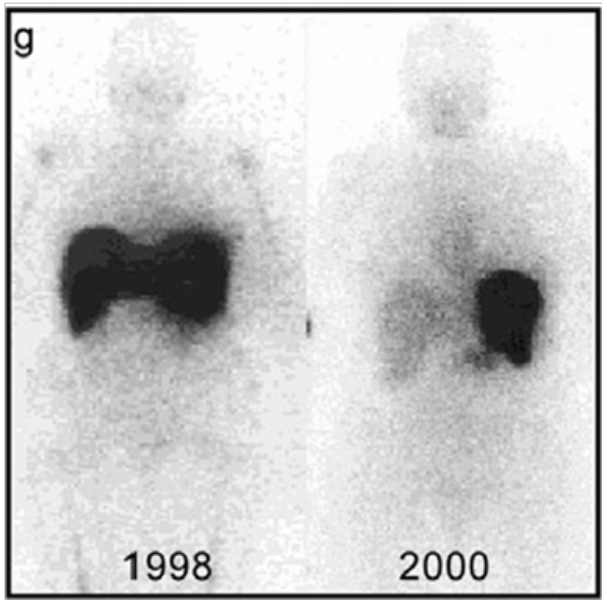
Regression of visceral amyloid deposits

AA amyloidosis[1]



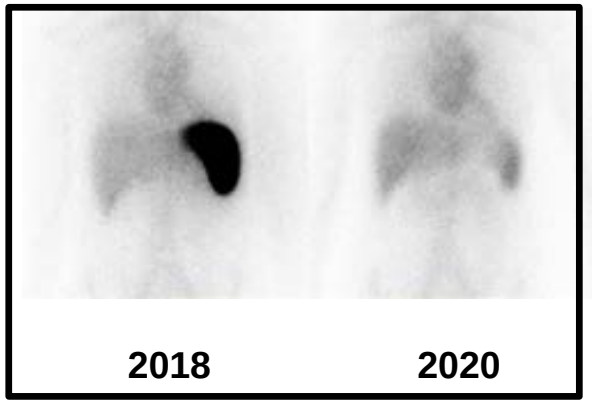
SAA suppression

AL amyloidosis[2]



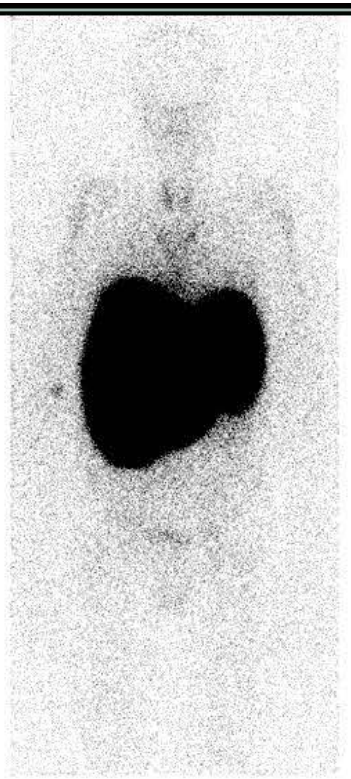
Complete hematologic response

ATTR amyloidosis[3]



TTR knockdown with patisiran

[1]Gillmore JD *et al*, Lancet 2001;358:24-29
[2]Lachmann HJ *et al*, BJH 2003;122:78-84
[3]Patel R *et al,* Amyloid 2021;28:269-270



July 2003

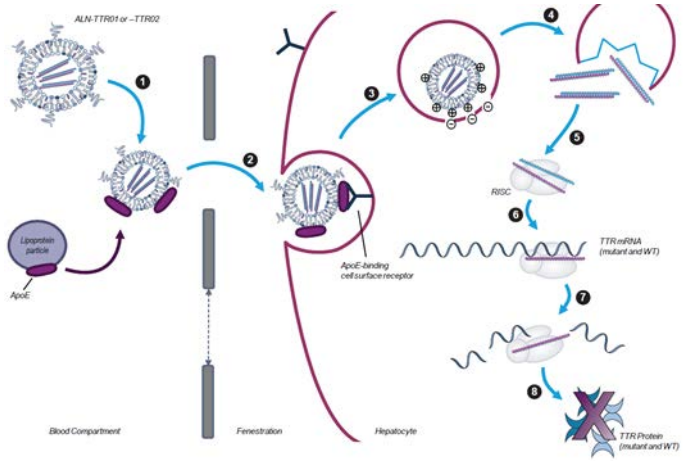
AMYLOID
W/B O

TTR-lowering RNAi therapy - Alnylam

Design

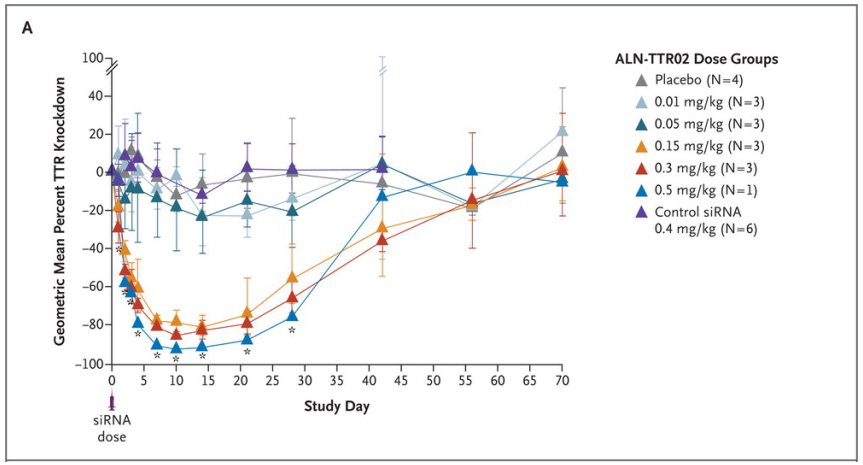
Phase 1 - Healthy volunteer study

Dose escalation study



Results

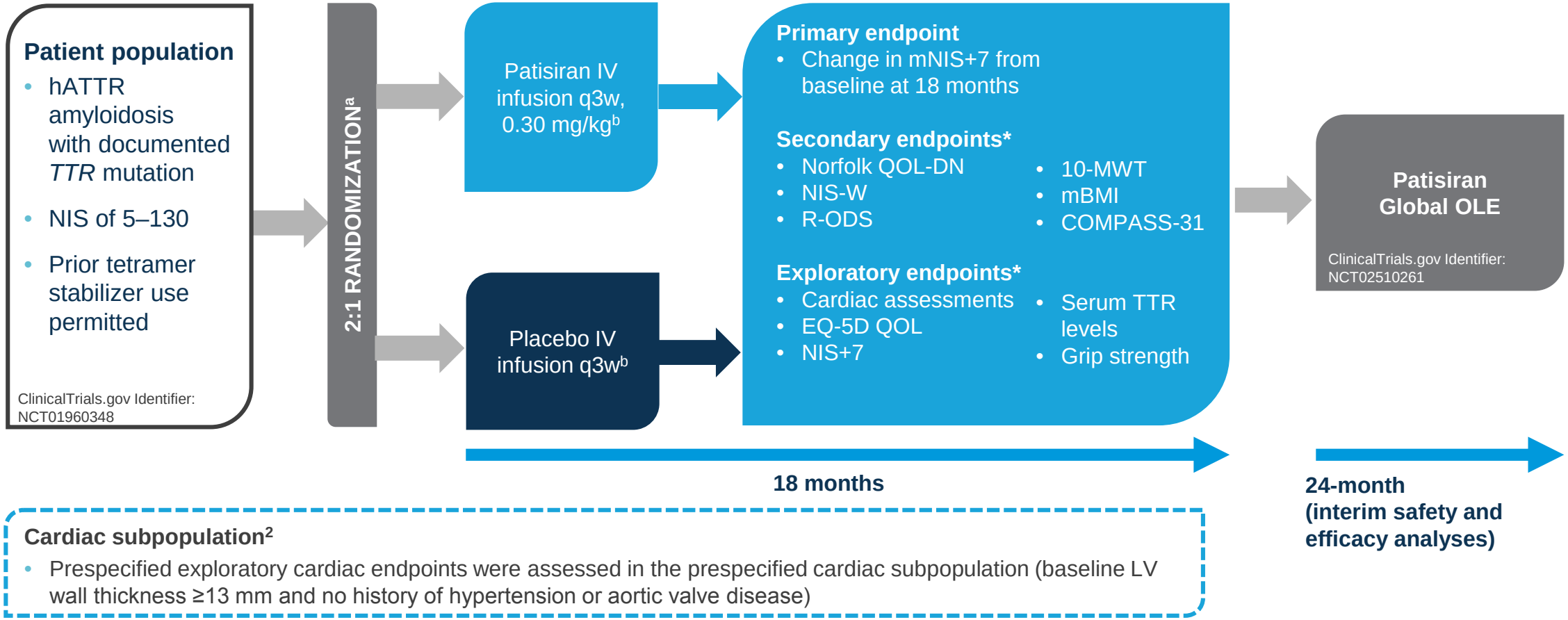
- Plasma TTR concentration reduced by ~80%
- Mild injection site reactions only toxicity



Coelho T *et al,* N Engl J Med 2013;369:819-829

APOLLO: A large, global study in hATTR amyloidosis with neuropathy

Phase 3 study design[1]



Cardiac subpopulation[2]

- Prespecified exploratory cardiac endpoints were assessed in the prespecified cardiac subpopulation (baseline LV wall thickness ≥13 mm and no history of hypertension or aortic valve disease)

[a]Stratification factors for randomization: NIS: <50 vs ≥50, early-onset V30M (<50 years of age at onset) vs all other mutations (including late-onset V30M), and previous tetramer stabilizer use (tafamidis or diflunisal) vs no previous tetramer stabilizer use; [b]To reduce likelihood of infusion-related reactions, patients received the following premedication or equivalent at least 60 minutes before each study drug infusion: dexamethasone; oral acetaminophen/paracetamol; H2 blocker (e.g. ranitidine or famotidine); and H1 blocker (e.g. diphenhydramine); *Evaluated change from baseline to 18 months for each endpoint

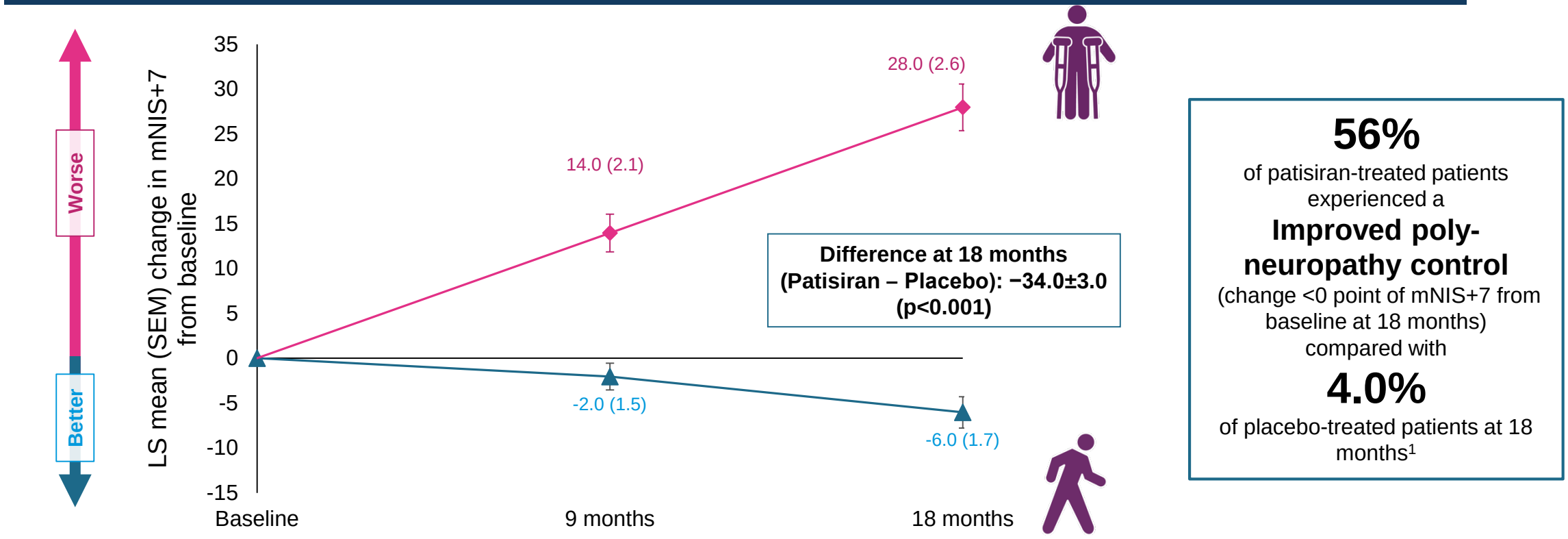
10-MWT, 10-meter walk test; COMPASS-31, composite autonomic symptom score 31; EQ-5D QOL, EuroQol 5-Dimensions quality of life questionnaire; hATTR, hereditary transthyretin amyloidosis; IV, intravenous; LV, left ventricular; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; NIS-W, Neuropathy Impairment Score – Weakness; Norfolk QOL-DN, Norfolk Quality of Life Questionnaire–Diabetic Neuropathy; OLE, open-label extension; q3w, once every 3 weeks; R-ODS, Rasch-built Overall Disability Scale; TTR, transthyretin

1. Adams D et al. BMC Neurology 2017;17:181; 2. Adams D et al. N Engl J Med 2018;379:11–21.

APOLLO: Polyneuropathy score was improved from baseline by patisiran treatment[1]

Progression of polyneuropathy in the placebo arm was consistent with the natural progression of the disease described in previous studies[1–3]

APOLLO: Change in mNIS+7 from baseline to 18 months (primary endpoint)[1]



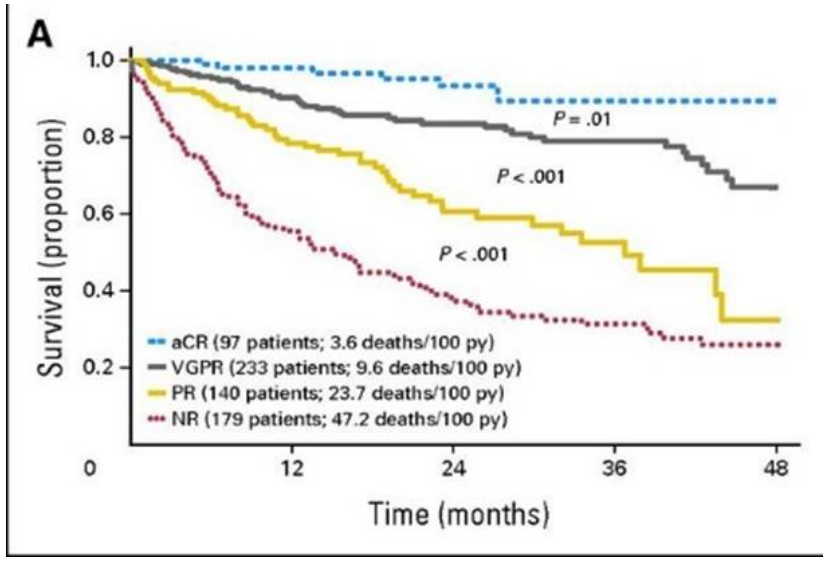
56%
of patisiran-treated patients experienced a
Improved poly-neuropathy control
(change <0 point of mNIS+7 from baseline at 18 months)
compared with
4.0%
of placebo-treated patients at 18 months[1]

LS, least squares; mNIS+7, modified Neuropathy Impairment Score +7; SEM, standard error of mean

1. Adams D et al. N Engl J Med 2018;379:11−21; 2. Koike H et al. Neurol Neurosurg Psychiatry 2012;83:152−8. 3. Berk J et al. JAMA 2013;310:2658−67.

Importance of magnitude of knockdown of fibril precursor protein in amyloidosis

AL amyloidosis



AA amyloidosis

Table 3. Unadjusted Relative Risk of Death Associated with the Most Recent Median Annual SAA Concentration during Follow-up.*

SAA Octile (mg/liter)	Relative Risk (95% CI)	P Value
<4	1.0	
≥4 to <9	3.9 (1.5–10.4)	0.007
≥9 to <16.7	5.1 (2.7–9.4)	0.003
≥16.7 to <28	7.0 (3.7–13.4)	0.07
≥28 to <45.6	9.1 (4.8–17.2)	0.008
≥45.6 to <87	12.1 (6.9–21.4)	<0.001
≥87 to <155	17.0 (8.6–33.8)	<0.001
≥155	17.7 (8.7–36.0)	<0.001

* The SAA value is the median concentration within each 12-month period and was incorporated into the Cox regression model as a time-dependent covariate.

ATTR amyloidosis

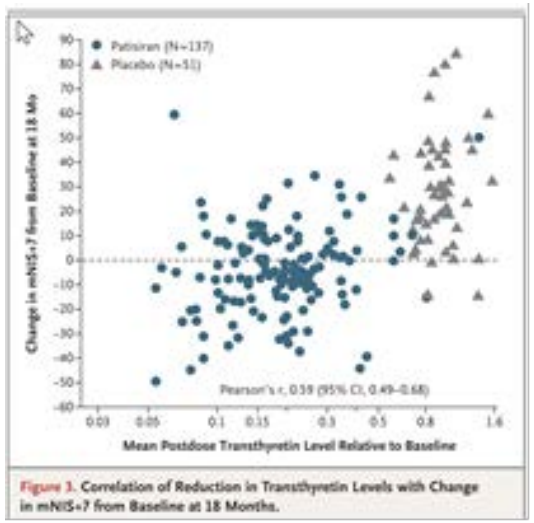


Figure 3. Correlation of Reduction in Transthyretin Levels with Change in mNIS+7 from Baseline at 18 Months.

Palladini G *et al*, JCO 2012;30:4541-4549

Lachmann HJ *et al,* NEJM 2007:356;2361-71

Adams D *et al*, NEJM 2018;379:11–21

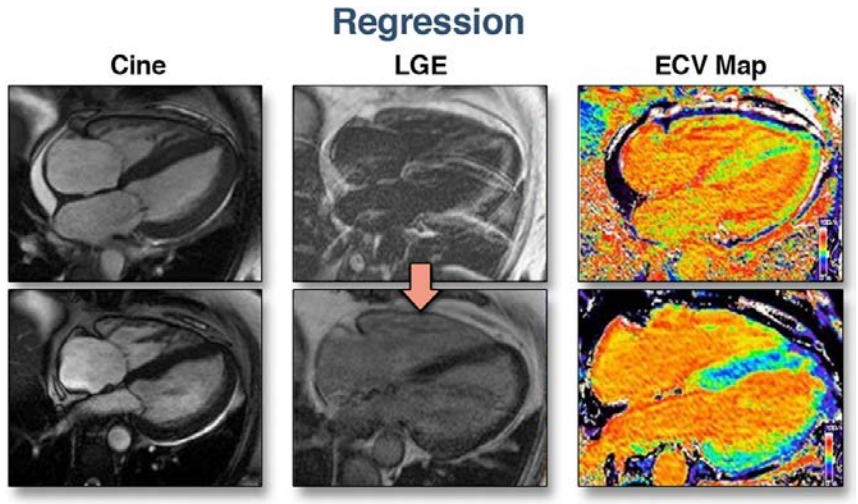
Regression of cardiac AL amyloid deposits

Table 2 Biomarkers, echocardiographic and cardiovascular magnetic resonance findings in patients with AL according to extracellular volume changes by cardiovascular magnetic resonance at 1-year post-chemotherapy

	Regressors (*N* = 27)			Stable (*N* = 67)			Progressors (*N* = 27)		
	Baseline	1 year	*P*-value	Baseline	1 year	*P*-value	Baseline	1 year	*P*-value
Clonal response		CR = 20 (74%) VGPR = 7 (26%)			CR = 24 (36%) VGPR = 24 (36%) PR = 12 (18%) NR = 7 (10%)			CR = 6 (22%) VGPR = 4 (15%) PR = 14 (52%) NR = 3 (11%)	

Table 3 Biomarkers, echocardiographic and cardiovascular magnetic resonance findings in patients with systemic light-chainaccording to extracellular volume changes by cardiovascular magnetic resonance at 2 years post-chemotherapy

	Regressors (*N* = 41)			Stable (*N* = 52)			Progressors (*N* = 15)		
	Baseline	2 years	*P*-value	Baseline	2 years	*P*-value	Baseline	2 years	*P*-value
Clonal response		CR = 30 (73%) VGPR = 11 (27%)			CR = 24 (46%) VGPR = 18 (35%) PR = 8 (15%) NR = 2 (4%)			CR = 1 (7%) VGPR = 2 (13%) PR = 10 (67%) NR = 2 (13%)	



Martinez-Naharro A *et al,* EHJ 2022 (In Press)

Potential for gene editing to address unmet need For ATTR amyloidosis

- Existing gene silencing therapies knock serum TTR down by ~80% (mean) and benefit neuropathy[1,2] and cardiomyopathy[3] in ATTRv
- Some patients on these treatments continue to experience debilitating effects and die from their disease
- Gene silencing therapies have to be administered repeatedly and lifelong
- Greater TTR knockdown is expected to achieve better clinical outcomes, and may potentially reverse the disease

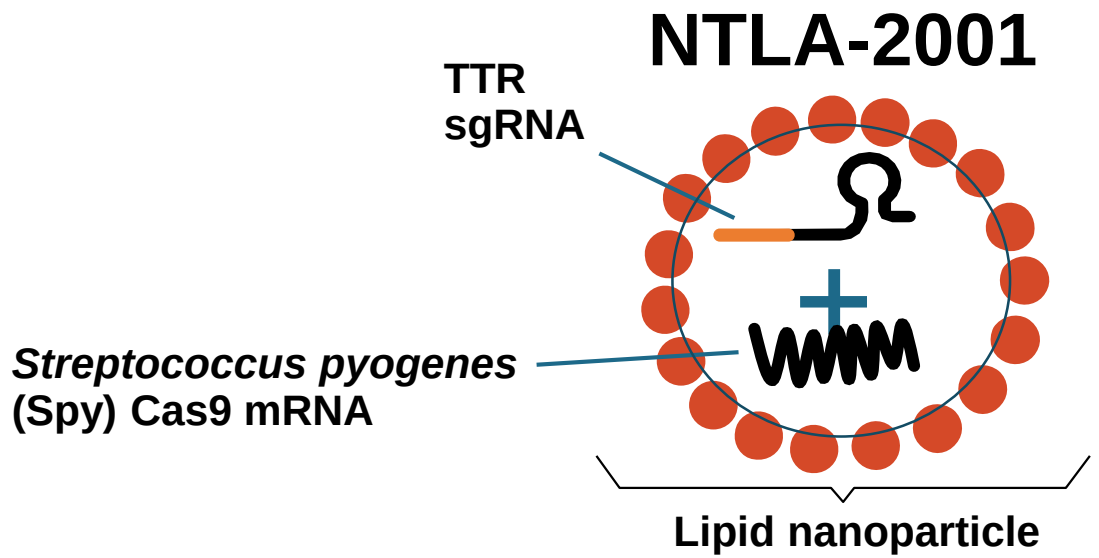
- Editing of the *TTR* gene is an attractive alternative therapeutic strategy

➢ **Potentially providing permanent, profound TTR knockdown, without the need for chronic therapy**

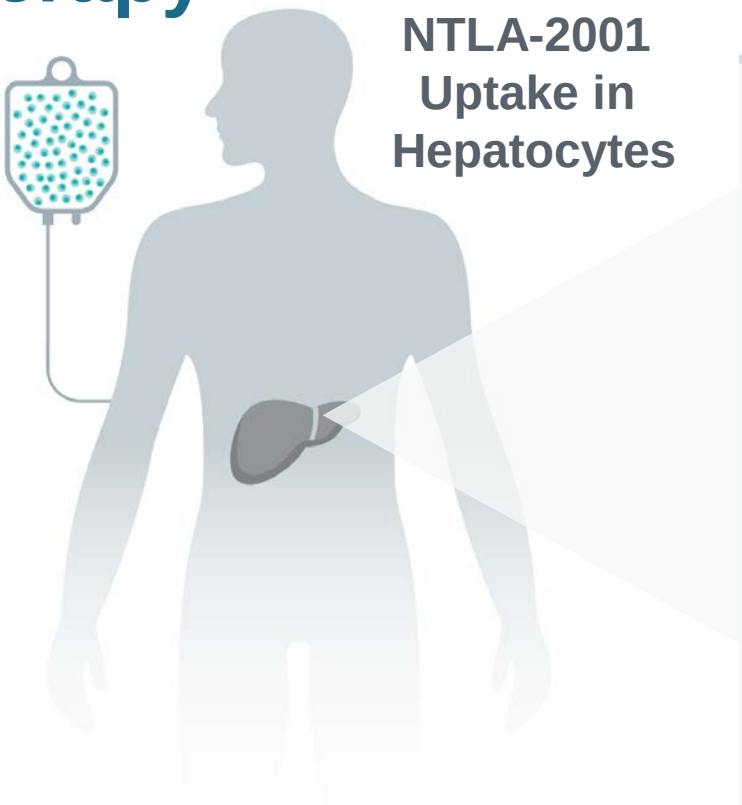
1. Adams D *et al*, NEJM 2018;379:11–21
2. Benson M *et al,* NEJM 2018;379:22-31
3. Solomon SD *et al,* Circulation 2019;139:431–443

CRISPR/Cas9-based gene editing

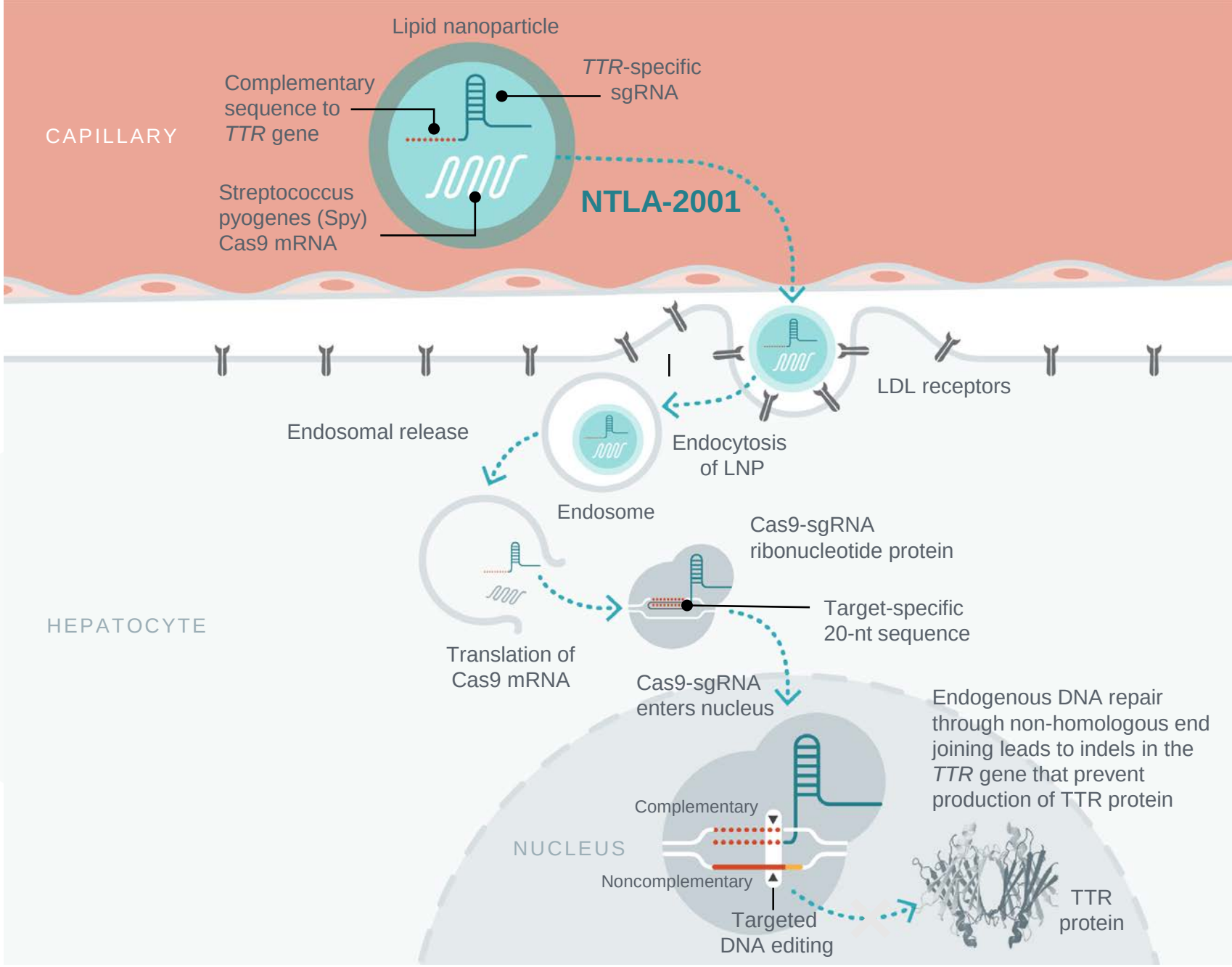
- CRISPR is a naturally occurring biological defence mechanism in bacteria
- Doudna & Charpentier showed how it could be used as a ‘cut and paste’ tool for editing gene sequences
- Nobel prize for Chemistry, 2020
- NTLA-2001 is the first investigational in vivo CRISPR-Cas9 based therapeutic
- **BUT** importantly, therapeutic platform is modular



NTLA-2001 is a novel, investigational CRISPR/Cas9-based *in vivo* gene editing therapy



NTLA-2001 Uptake in Hepatocytes



This presentation includes data for an investigational product not yet approved by regulatory authorities.

LNP, lipid nanoparticle; **sgRNA**, single guide RNA; **TTR**, transthyretin

Rigorous process to select sgRNA for NTLA-2001 to achieve both potent on-target and no detectable off-target editing

1 IDENTIFICATION

Conduct computational analysis to identify potential CRISPR-candidate sites for knockout and then eliminate sites containing *TTR* pathogenic variants, common SNPs and sequences with high off-target potential

2 CANDIDATE ASSESSMENT

Synthesize pool of initial sgRNAs and test rigorously for knockout efficiency, off-target editing and genotoxicity (including SVs), using human cells and animal models

- Multiple methods: *in silico*, biochemical/cell-based assays and image-based methods

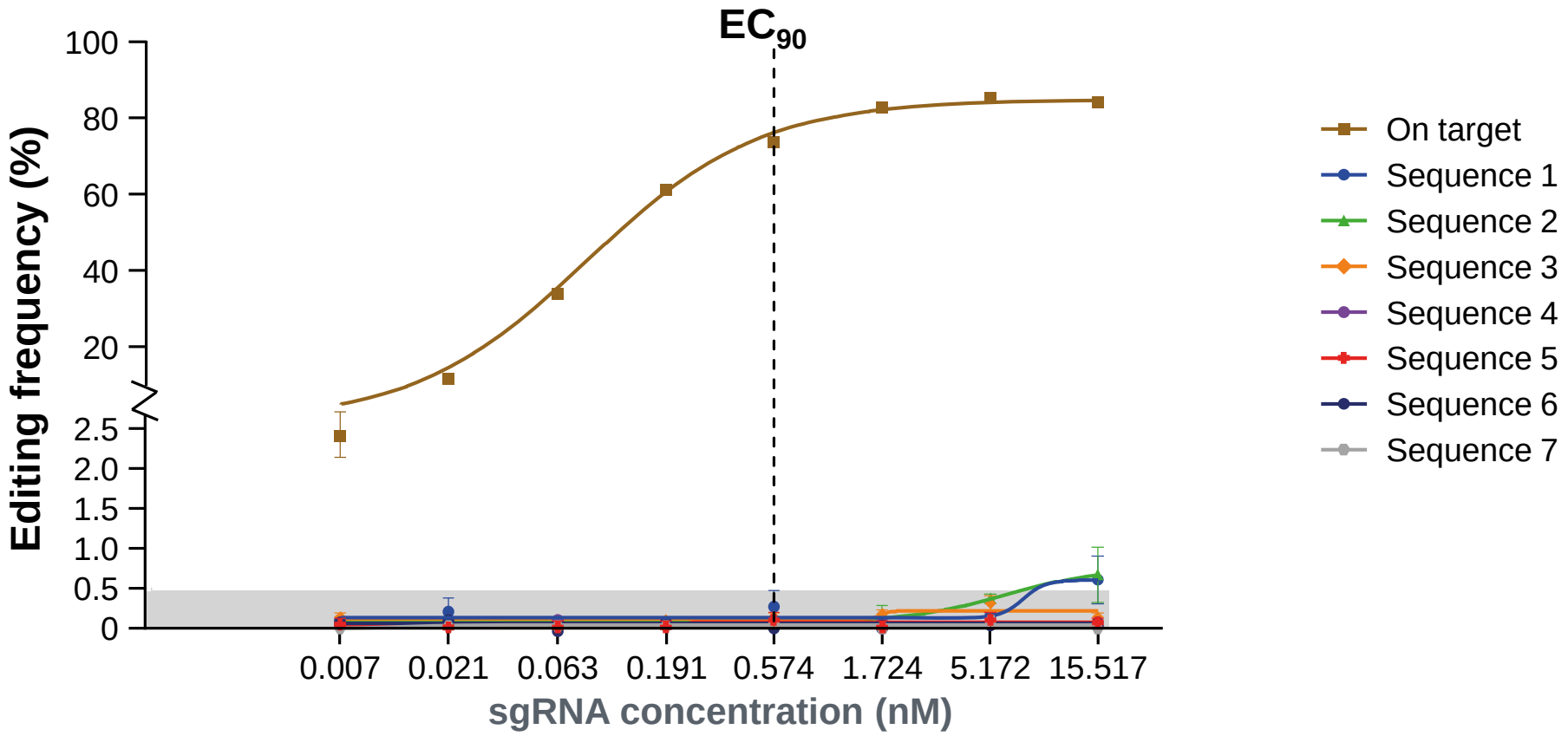
3 VALIDATION AND FINAL SELECTION

Select sgRNA with the highest on-target knockout efficiency and no detectable off-target potential at multiples of human therapeutic dose

This presentation includes data for an investigational product not yet approved by regulatory authorities.

sgRNA, single guide RNA; **SNPs**, single nucleotide polymorphisms
SV, structural variants; **TTR**, transthyretin

In Vitro: No detectable off-target editing with pharmacologic concentration of sgRNA

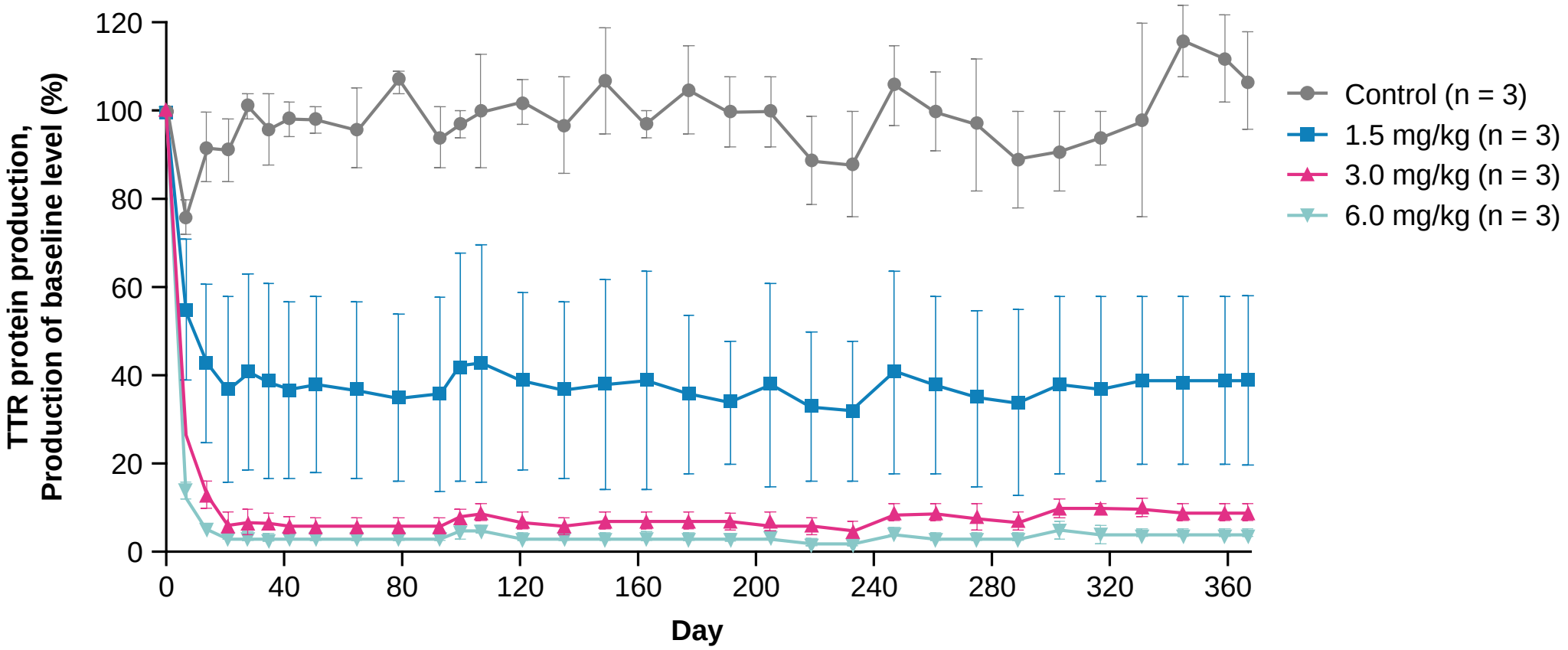


This presentation includes data for an investigational product not yet approved by regulatory authorities.

EC_{90}, concentration inducing 90% of maximal effect; **sgRNA**, single guide RNA

Gillmore JD *et al.* NEJM;2021;385:493-502

Pre-clinical *in vivo* study in NHP

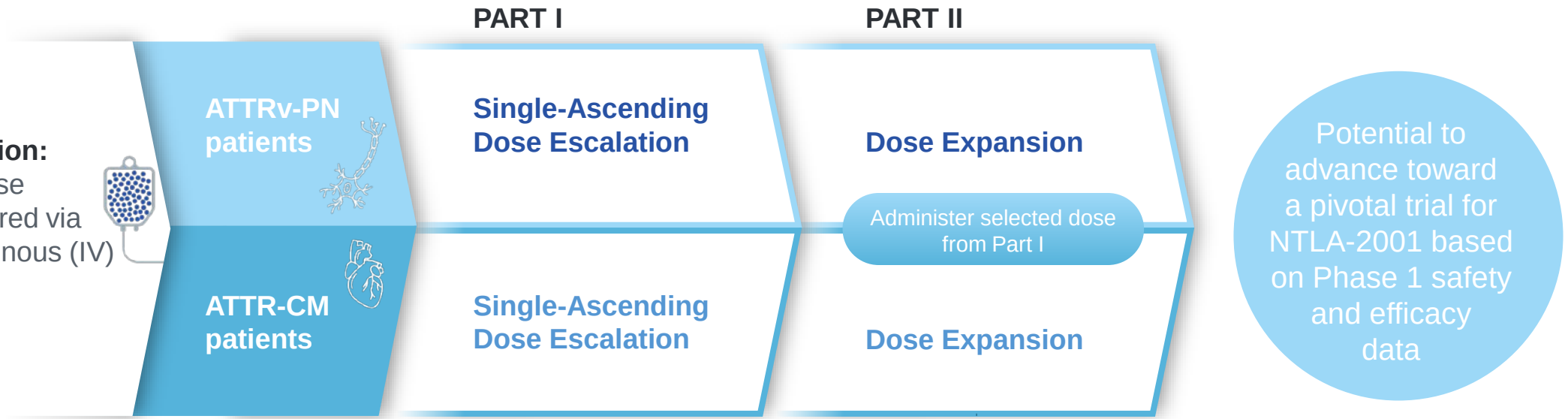


Durable, >95% TTR reduction after a single dose

NHP; non-human primate, TTR, transthyretin

NTLA-2001 expanded Phase 1 study

Two-part, open-label, multi-center study in adults with hereditary ATTR with polyneuropathy (ATTRv-PN) or ATTR amyloidosis with cardiomyopathy (ATTR-CM)



PRIMARY OBJECTIVES

Evaluate safety, tolerability, PK and PD

- *Measure serum TTR levels*

SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of:

- *Neurologic function in subjects with ATTRv-PN*
- *Cardiac disease in subjects with ATTR-CM*

Clinicaltrials.gov ID: NCT0460105

PK, Pharmacokinetics; **PD**, Pharmacodynamics

The trial consent process

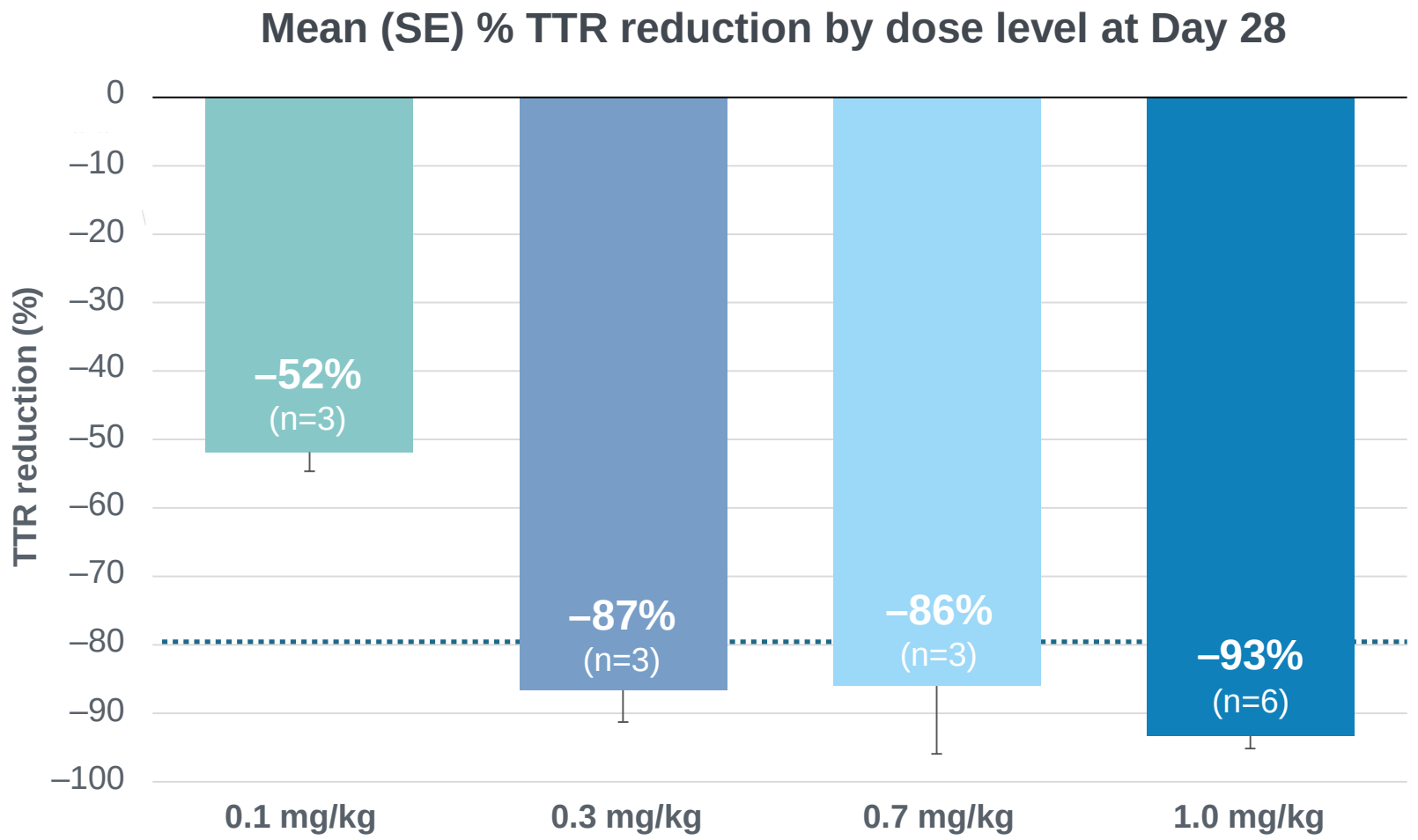
- First ever human to receive a drug which permanently ‘edits’ a gene in the body
- Risk of short term toxicity (hepatotoxicity, infusion reaction or cytokine activation)
- Risk of long term toxicity (off target editing and cancer)
- Uncertain biochemical effect but at low dose, likely modest (re-treatment possible?)
- At therapeutic dose, risk of profound TTR knockdown (RNAi experience)
- Uncertain clinical effect (hypothesis rather than fact)
- Uncertain biochemical & clinical duration
- But possibility of single infusional ‘Rolls Royce’ treatment

ATTRv-PN: NTLA-2001 generally well tolerated at all dose levels through the follow-up period

- **Across all dose levels, the most frequent adverse events* were headache, infusion-related reactions, back pain, rash† and nausea**
  - Majority of adverse events were mild in severity with 73% (n=11) of patients reporting a maximal adverse event severity of Grade 1
  - All infusion-related reactions were considered mild, resolving without clinical sequelae
  - All patients received a complete study dose of NTLA-2001
- **A single possibly-related Grade 3 event (SAE) of vomiting was reported at the 1.0 mg/kg dose in a patient with underlying gastroparesis**
  - 1.0 mg/kg dose level expanded per protocol to 6 patients to further characterize safety and PD
- **Maximally tolerated dose was not reached**

Data Cut Off: May 16, 2022
Median follow-up for all subjects is 6 months
* Related and unrelated events in more than 2 patients
† Date of onset D6–D145; all mild in severity
PD, pharmacodynamics; SAE, serious adverse event
Source: Intellia Therapeutics - As presented on June 24 at EASL's International Liver Congress 2022

Dose-dependent reductions in serum TTR



Dashed line represents the targeted minimum reduction

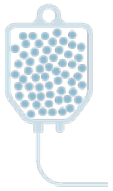
SE, standard error; TTR, transthyretin

Source: Intellia Therapeutics - As presented on June 24 at EASL's International Liver Congress 2022

NTLA-2001 Phase 1 study: Cardiomyopathy arm

Hereditary transthyretin amyloidosis with cardiomyopathy (ATTRv-CM) or wild-type cardiomyopathy (ATTRwt-CM), NYHA Class I - III

Intervention:
Single dose administered via an intravenous (IV) infusion



PART I – DOSING COMPLETE
Single-Ascending Dose

- 1.0 mg/kg NYHA Class I/II (n=3)
- 0.7 mg/kg NYHA Class III (n=6)
- 0.7 mg/kg NYHA Class I/II (n=3)

PART II
Dose Expansion

- 55 mg

PRIMARY OBJECTIVES

Evaluate safety, tolerability, PK and PD

- *Measure serum TTR levels*

SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of cardiac disease

- *Cardiac imaging, biomarkers, cardiopulmonary exercise test, 6MWT*

Clinicaltrials.gov ID: NCT04601051

NYHA, New York Heart Association; **PK,** Pharmacokinetics; **PD,** Pharmacodynamics; **6MWT**, 6 Minute Walk Test

Patient demographics & characteristics

Parameter	NYHA Class I/II 0.7 mg/kg n = 3	NYHA Class III 0.7 mg/kg n = 6	NYHA Class I/II 1.0 mg/kg n = 3	All patients N = 12
Median age, years (min, max)	74 (71, 75)	78 (75, 86)	71 (68, 72)	75 (68, 86)
Sex, n (%)				
Male	3 (100%)	6 (100%)	3 (100%)	12 (100%)
Median weight, kg (min, max)	85 (63, 88)	86 (71, 106)	85 (75, 88)	85 (63, 106)
***TTR* genotype, n (%)**				
p.V142I	–	–	1 (33%)	1 (8%)
p.T80A	–	1 (17%)	–	1 (8%)
WT	3 (100%)	5 (83%)	2 (67%)	10 (83%)
NYHA classification, n (%)				
I	1 (33%)	–	–	1 (8%)
II	2 (67%)	–	3 (100%)	5 (42%)
III	–	6 (100%)	–	6 (50%)
Median NT-proBNP, ng/L (min, max)	2480 (2103, 3637)	2463 (2112, 16690)	2408 (1607, 3474)	2461 (1607, 16690)

This presentation includes data for an investigational product not yet approved by regulatory authorities.

Data Cut Off: August 25, 2022

NT-proBNP, N-terminal prohormone of brain natriuretic peptide; **NYHA**, New York Heart Association; **TTR**, Transthyretin

NTLA-2001 was generally well-tolerated across all cohorts through the follow-up period

- **Across all cohorts, majority of adverse events were mild in severity**
  - 25% (n=3) of patients reported no AEs and 67% (n=8) reported mild or moderate AEs as their highest severity
  - Infusion-related reactions were reported in 2 patients
  - All patients received a complete study dose of NTLA-2001
- **A single Grade 3 infusion-related reaction was reported at the 0.7 mg/kg dose in a NYHA Class III patient and resolved without any clinical sequelae**
  - NYHA Class III 0.7 mg/kg dose level cohort expanded per protocol to 6 patients to further characterize safety and PD
  - No additional patients reported a treatment-related AE higher than Grade 1
- **No clinically significant laboratory findings**
  - Transient Grade 1 liver enzyme elevations observed

This presentation includes data for an investigational product not yet approved by regulatory authorities.

Data Cut Off: August 25, 2022
Median follow-up for all subjects is 5.5 months
AE, adverse event; **PD**, pharmacodynamics

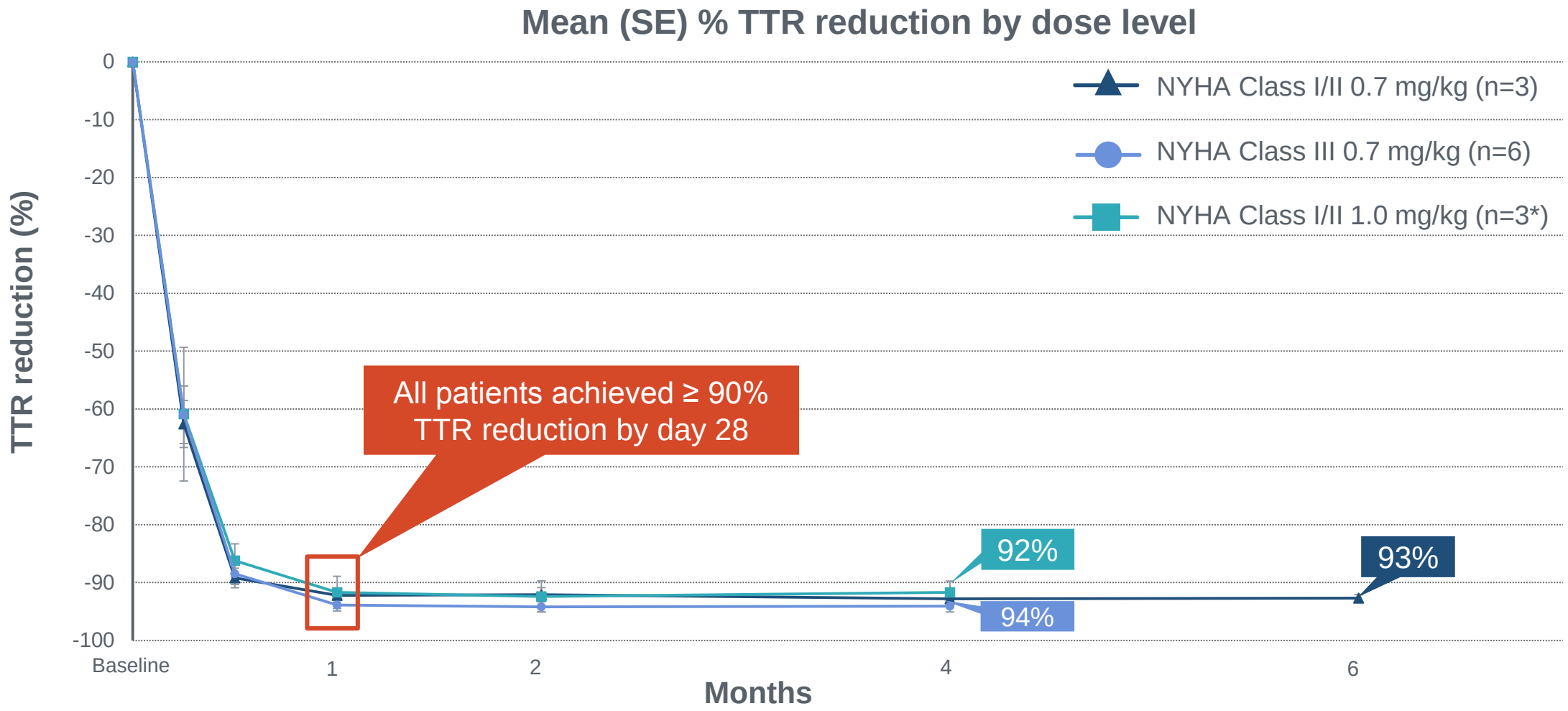
Majority of adverse events were mild in severity

Parameter	NYHA Class I/II 0.7 mg/kg n = 3			NYHA Class III 0.7 mg/kg n = 6			NYHA Class I/II 1.0 mg/kg n = 3			All Patients N = 12		
	Gr. 1	Gr. 2	Gr. 3	Gr. 1	Gr. 2	Gr. 3	Gr. 1	Gr. 2	Gr. 3	Gr. 1	Gr. 2	Gr. 3
Patients with at least one TEAE	2	–	–	3	1*	1	1	1†	–	6	2	1
Infusion-related reaction	–	–	–	–	–	1	1	–	–	1	–	1
COVID-19	–	–	–	1	–	–	1	–	–	2	–	–

Data Cut Off: August 25, 2022
TEAEs occurring in ≥ 2 Patients
Patients counted once per row, per dose level, at highest grade reported
*Gr.2 urinary retention and Gr.2 epistaxis in same patient
†Gr.2 herpes zoster and Gr.2 inguinal hernia in same patient
Gr., Grade; **TEAE**, treatment emergent adverse event

This presentation includes data for an investigational product not yet approved by regulatory authorities.

Rapid and deep serum TTR reduction sustained through 4-6 months across all patients



This presentation includes data for an investigational product not yet approved by regulatory authorities.

Data Cut Off: August 25, 2022
SE, standard error; **TTR**, transthyretin
*n=2 at Month 2 (missed patient visit)

Deep, consistent and durable TTR reductions achieved at both 0.7 and 1.0 mg/kg doses

- Mean TTR reduction >90% across all therapeutic doses by day 28 and sustained through data cut-off
- NTLA-2001 was generally well-tolerated at all doses
  - Majority of adverse events were mild
  - No clinically significant laboratory findings observed
- Similar results in ATTR-PN & ATTR-CM patients (across all NYHA Classes)

NTLA-2001 is the first systemically administered drug to result in knockout of a gene in humans

These data demonstrate the promise of CRISPR-based *in vivo* genome editing in humans

Considerations for potential future applications of *in vivo* CRISPR-based gene editing

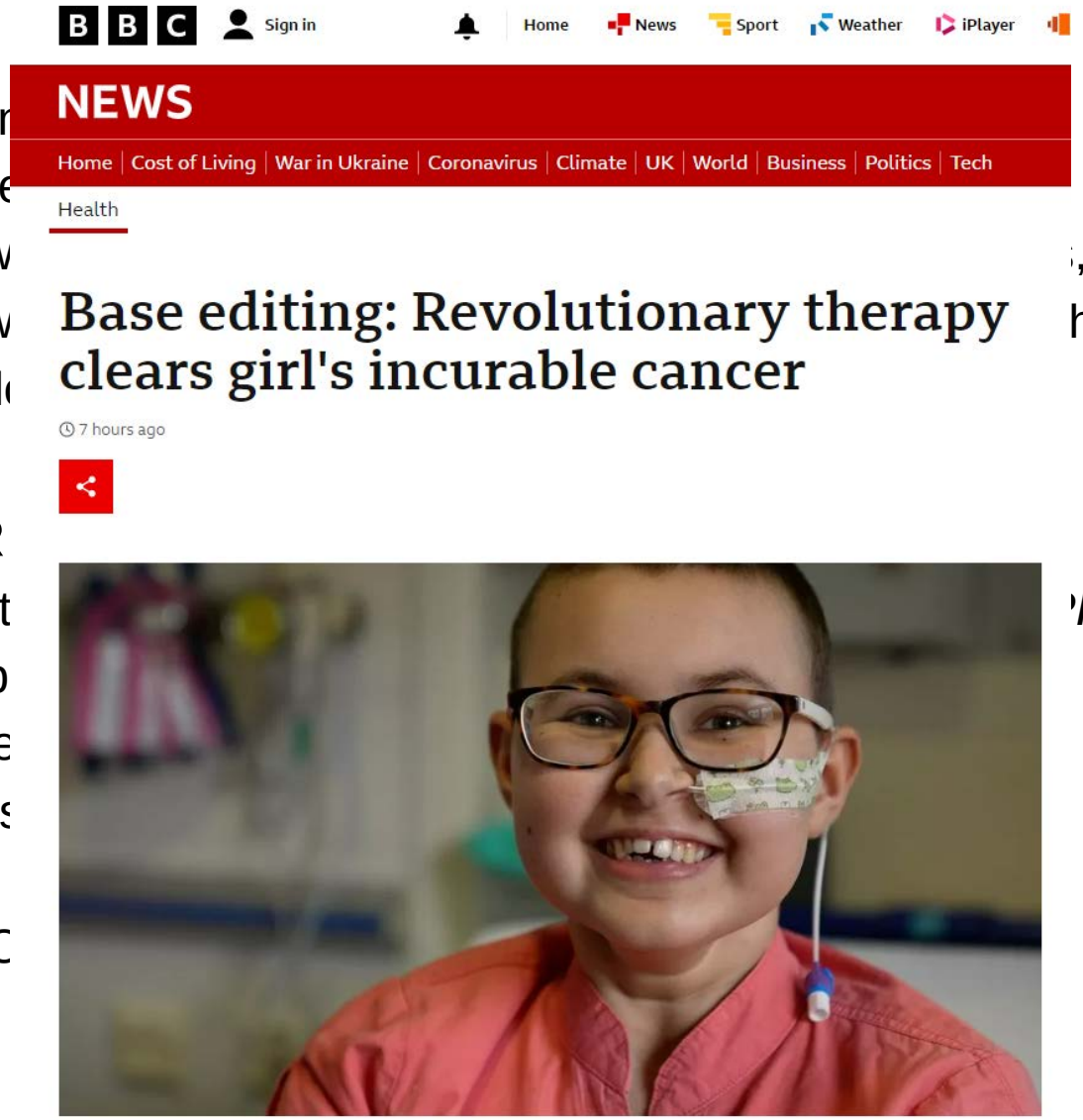
- Why ATTR amyloidosis?
  - Unequivocal link betwee
  - Circulating TTR exclusive
  - Knockdown of TTR know
  - Knockdown of TTR know
  - Knockout editing technol

, experience with RNAi)

h RNAi)

- Future potential CRISPR
  - Knockout editing (heredit
  - Knockin editing (haemop
  - Base editing (single base
  - Prime editing (editing of s
  - Multiplex editing (editing
  - CRISPR activation and C

INA1; HIV)



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