Introduction to RNA Interference (RNAi) Therapies in Development for TTR Amyloidosis (ATTR)

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About Alnylam

Our Vision

- Harnessing a Revolution in Biology for Human Health®

Our Commitment to You

- We understand the impact that ATTR can have on you and your family
- Improving the knowledge and treatment of ATTR is one of our highest commitments

Cambridge,
Massachusetts

Uxbridge,
United Kingdom

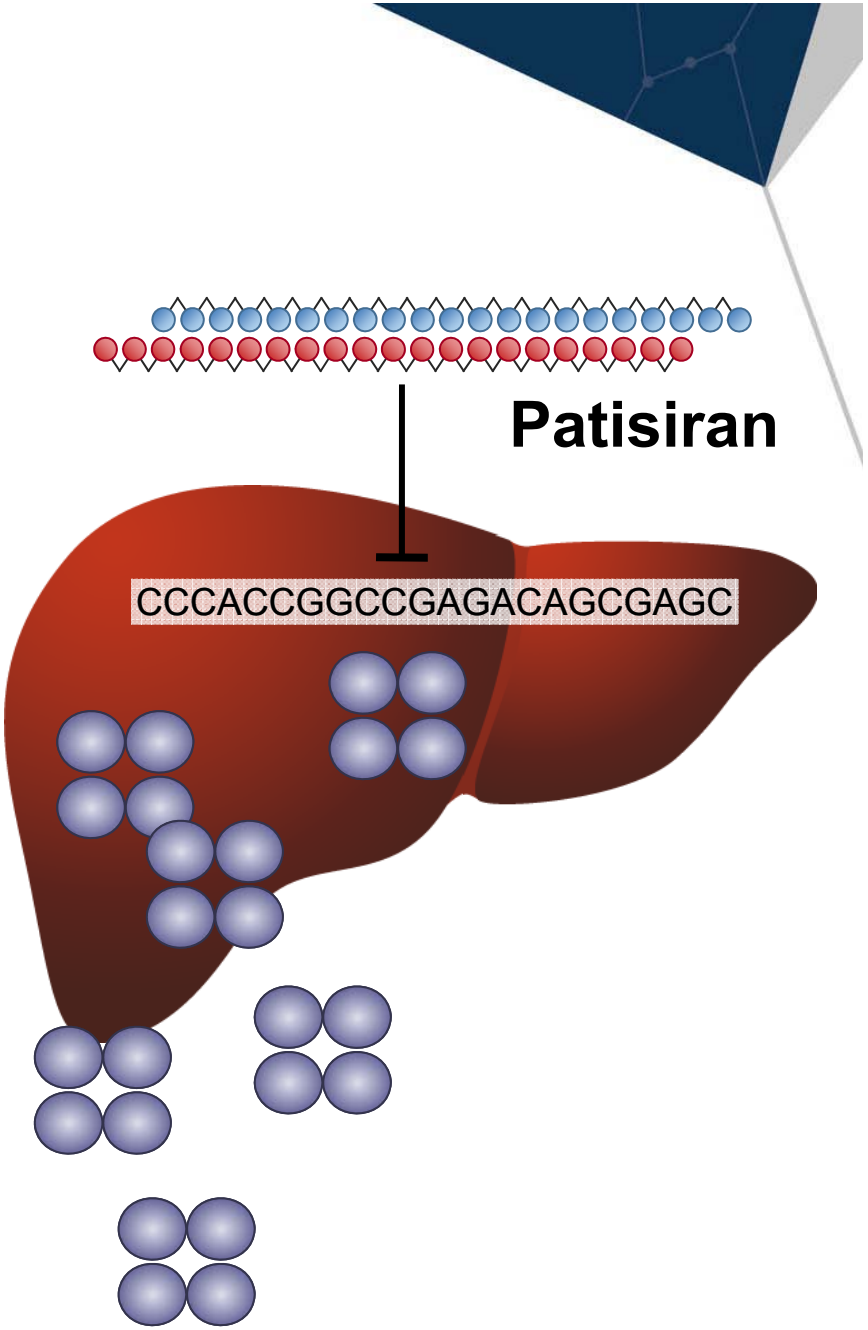
Patisiran (ALN-TTR02)

Investigational RNAi Therapy Under Evaluation for the Treatment of Familial Amyloidotic Polyneuropathy (FAP)

About Patisiran

How Patisiran May Work

- Patisiran uses the body's natural process called RNA interference (RNAi) to lower the levels of TTR protein that cause FAP
- Patisiran prevents the production of TTR protein
- This may slow or halt the progression of FAP
- Patisiran is given by IV infusion



Patisiran Clinical Development

Study	Participants	Status
Phase 1	17 healthy human volunteers	Completed[1]
Phase 2	29 adults with FAP	Completed[2]
Phase 2 Open-Label Extension (OLE)	27 adults with FAP who participated in the Phase 2 study	Enrollment Closed
Phase 3 Study: APOLLO	Target enrollment: 200 adults with FAP	Currently Enrolling

1. Coehlo, et al. NEJM (2013); 2. Suhr, et al. Orphanet (2015)

Phase 2 Open Label Extension (OLE) Study of Patisiran 12-month Preliminary Results

An Investigational RNAi Therapeutic for the Treatment of Familial Amyloidotic Polyneuropathy (FAP)

Patisiran Phase 2 OLE Study
Study Design

Study Participants
- All patients who participated in the double-blind Phase 2 study were able to enroll in the open-label extension (OLE) study

Investigational Drug
- Study participants receive patisiran via IV infusion every 3 weeks for up to 2 years
- There is no placebo control group

Study Objectives
- To understand the long-term (2 year) safety and tolerability of patisiran in adults with FAP
- To understand the effect of patisiran on:
  - TTR protein levels in the blood
  - Neurologic impairment (mNIS+7 and NIS)
  - Quality of Life

Suhr et al., ANA 2015

Patisiran Phase 2 OLE

Preliminary Study Results* – Demographics of Study Participants and Exposure to Patisiran

27 adults
Average age = 64

18 Men

9 Women

Stabilizer Use

20 participants taking tafamidis or diflunisal at study entry

14 participants taking tafamidis or diflunisal at time of analysis^

TTR Genotype

Val30Met(V30M)= 20
Ser77Tyr(S77Y)= 2
Ser77Phe(S77F)= 2
Tyr116Ser(Y116S)=1
Phe64Leu(F64L)= 1
Arg54Thr(R54T)= 1

16.9 months average study treatment duration at time of analysis*

A total of 669 doses of patisiran have been given to the 27 study participants*
The average number of doses per study participant is 25.

^6 subjects reported stabilizer use (5 on diflunisal, 1 on tafamidis) at the time of first dose but subsequently stopped approximately 1 to 18 months into the study.
Suhr et al., ANA 2015
**Data as of July 15, 2015*

Patisiran Phase 2 OLE

Preliminary Study Results* – Safety and Tolerability

>1 year of dosing patisiran 0.3 mg/kg every 3 weeks has been generally well tolerated

No clinically significant changes in liver function, kidney function or hematological parameters were observed

5 patients (18.5%) with 7 serious adverse events deemed unrelated to the study drug**

The 2 most common drug-related adverse events:
- **Flushing: 6 patients (22.2%)**
- **Mild skin reactions at the site of the infusion: 5 patients (18.5%)**

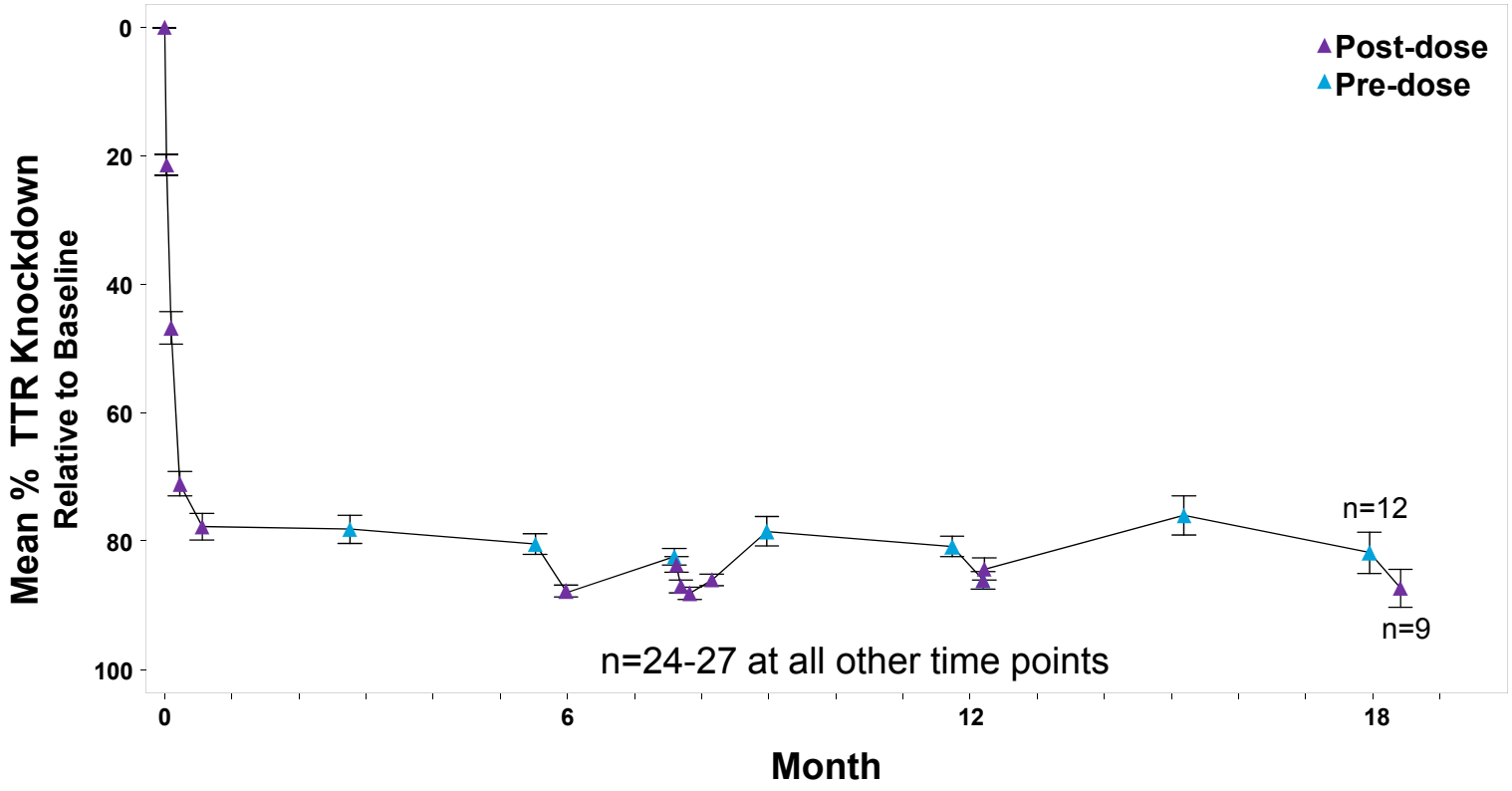
26 of 27 patients continue on study

**One discontinuation for gastroesophageal cancer at ~20 months deemed unrelated to study drug; patient subsequently died Aug 2015

Suhr et al., ANA 2015
**Data as of July 15, 2015*

Patisiran Phase 2 OLE

Preliminary Study Results* – TTR Lowering in the Blood

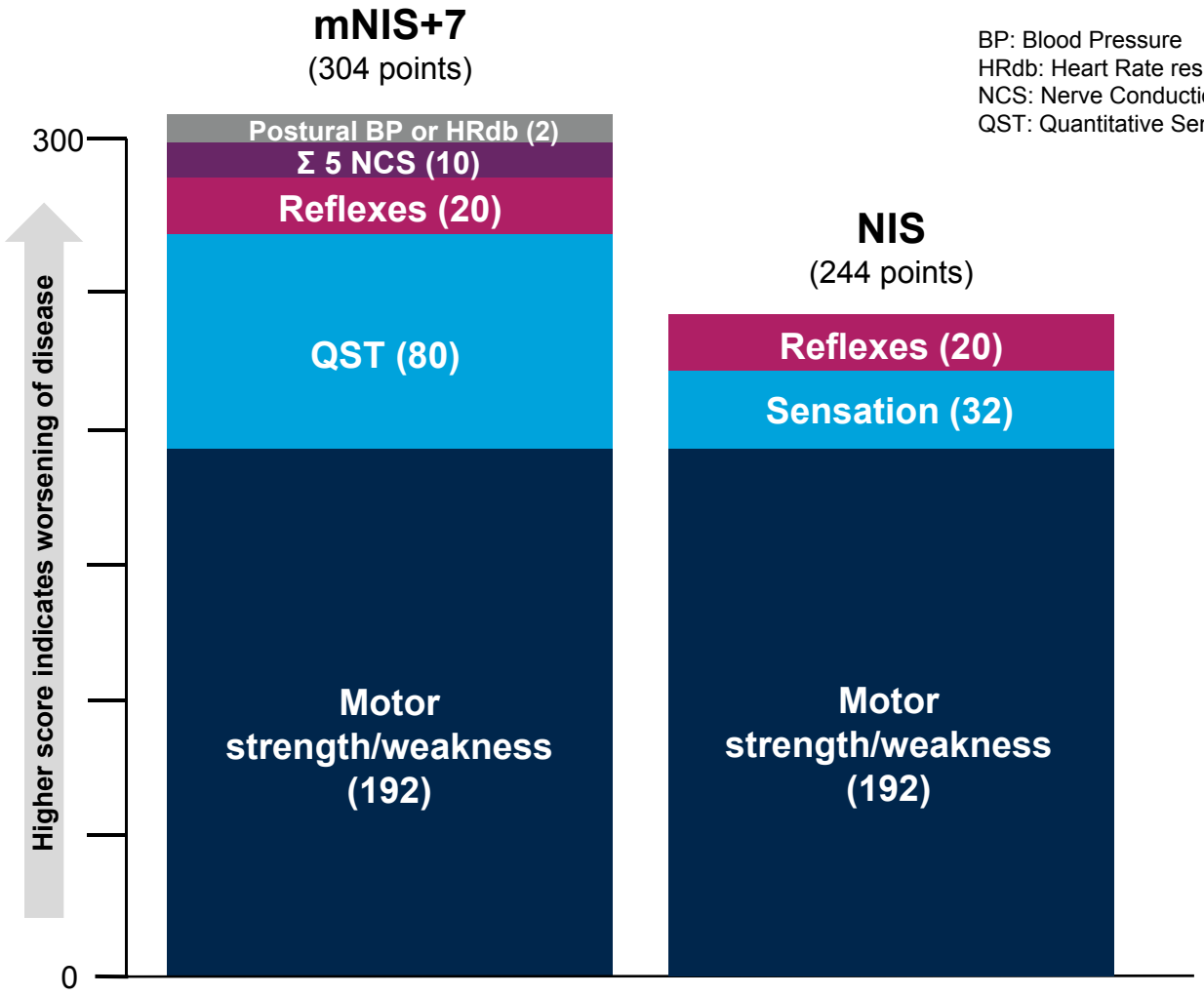


Knockdown *represents the lowering of TTR protein levels in the blood*

Patisiran lowered the amount of TTR protein in the blood by approximately 80% over 18 months

Suhr et al., ANA 2015
**Data as of July 15, 2015*

Neuropathy Impairment Scores
Used in FAP Trials



BP: Blood Pressure
HRdb: Heart Rate response to Deep Breathing
NCS: Nerve Conduction Studies
QST: Quantitative Sensory Testing

Adams D et al., *Neurology. 85;675-682* (2015)

Patisiran Phase 2 OLE Preliminary Study Results*

Change in mNIS+7 at 6 and 12 Months

	Change from Baseline to Month 6 (n=27)		Change from Baseline to Month 12 (n=27)	
mNIS+7 component	**Mean (SEM)**	**Median (range)**	**Mean (SEM)**	**Median (range)**
Total+	**-1.4 (2.1)**	**-2.0 (-25.4, 22)**	**-3.1 (2.3)**	**-2.5 (-29.8, 24.0)**
NIS-weakness	**0.2 (1.2)**	**0 (-9.9, 16)**	**0 (0.7)**	**0 (-10.4, 8.3)**
NIS-reflexes	**-0.7 (0.5)**	**0 (-8, 3)**	**0.1 (0.5)**	**0 (-9.0, 4.0)**
QST#	**-1.1 (1.5)**	**-1.5 (-15, 16)**	**-3.4 (1.9)**	**-2.5 (-23.0, 19.0)**
NCS Σ5	**0.2 (0.1)**	**0 (-1.5, 1.5)**	**-0.1 (0.2)**	**0 (-2.0, 3.5)**
Postural BP	**0 (0.1)**	**0 (-1, 1)**	**0 (0.1)**	**0 (-1.5, 2.0)**

+Partial imputation was used to recover mNIS+7 data points where components were missing at one or more replicate measurements (per patient/visit)
QST: N=26 for 6 and 12-mo. comparisons.

Suhr et al., ANA 2015
**Data as of July 15, 2015*

Patisiran Phase 2 OLE Preliminary Study Results*
ΔNIS and ΔmNIS+7 Across FAP Studies~

		Natural History (nonlinear)#1	Diflunisal Phase 3+2	Patisiran Phase 2 OLE†*
12 Months	Mean (SEM) ΔmNIS+7^	17.8 (8.5)	PBO: 14.0 (2.2) Drug: 7.0 (1.9)	**-3.1 (2.3)**
	Mean (SEM) ΔNIS	14.3 (6.8)	PBO: 10.1 (3.2) Drug: 4.1 (2.9)	**0.2 (1.1)**

~ Assessments drawn from studies in patients with similar baseline characteristics and not based on head-to-head studies

^ Translated algebraically from NIS (Natural History study) or NIS+7 (Diflunisal study)[1]

Predicted progression of median NIS value from Gompertz curve fit[1]

+ Linear interpolation from 2-year NIS progression measurement in longitudinal analysis set

† n=27; patisiran results similar in patients with/without concurrent TTR stabilizer therapy; mNIS+7 using full mNIS+7 set (with partial imputation for 2 patients)

SEM: Standard Error of the Mean

[1]Adams D et al., *Neurology. 85;675-682* (2015)
[2]Berk JL *et al., JAMA.* 310:2658-67 (2013)
*Data as of July 15, 2015

Summary

Familial Amyloidotic Neuropathy (FAP)

- Caused by TTR amyloid that accumulates primarily in the nervous system, damaging the nerves in many parts of the body

Patisiran

- An investigational RNAi therapeutic specifically designed to target TTR mRNA
- Approximately 80% reduction of both wild type and mutant TTR observed in TTR-FAP participants in the Phase 2 OLE study*, including those on a tetramer stabilizer
- Patisiran generally well tolerated in patients with FAP out to 21 months
- In aggregate, results consistent with therapeutic hypothesis that TTR knockdown has potential to halt neuropathy progression

Clinical Trials

- Alnylam has completed the Phase 1 and Phase 2 clinical trials. The Phase 2 open label extension (OLE) study is ongoing
- A Phase 3 study called APOLLO is being conducted in up to 200 participants in over 15 countries to evaluate the safety and efficacy of patisiran in patients with FAP

Suhr et al., ANA 2015
**Data as of July 15, 2015*

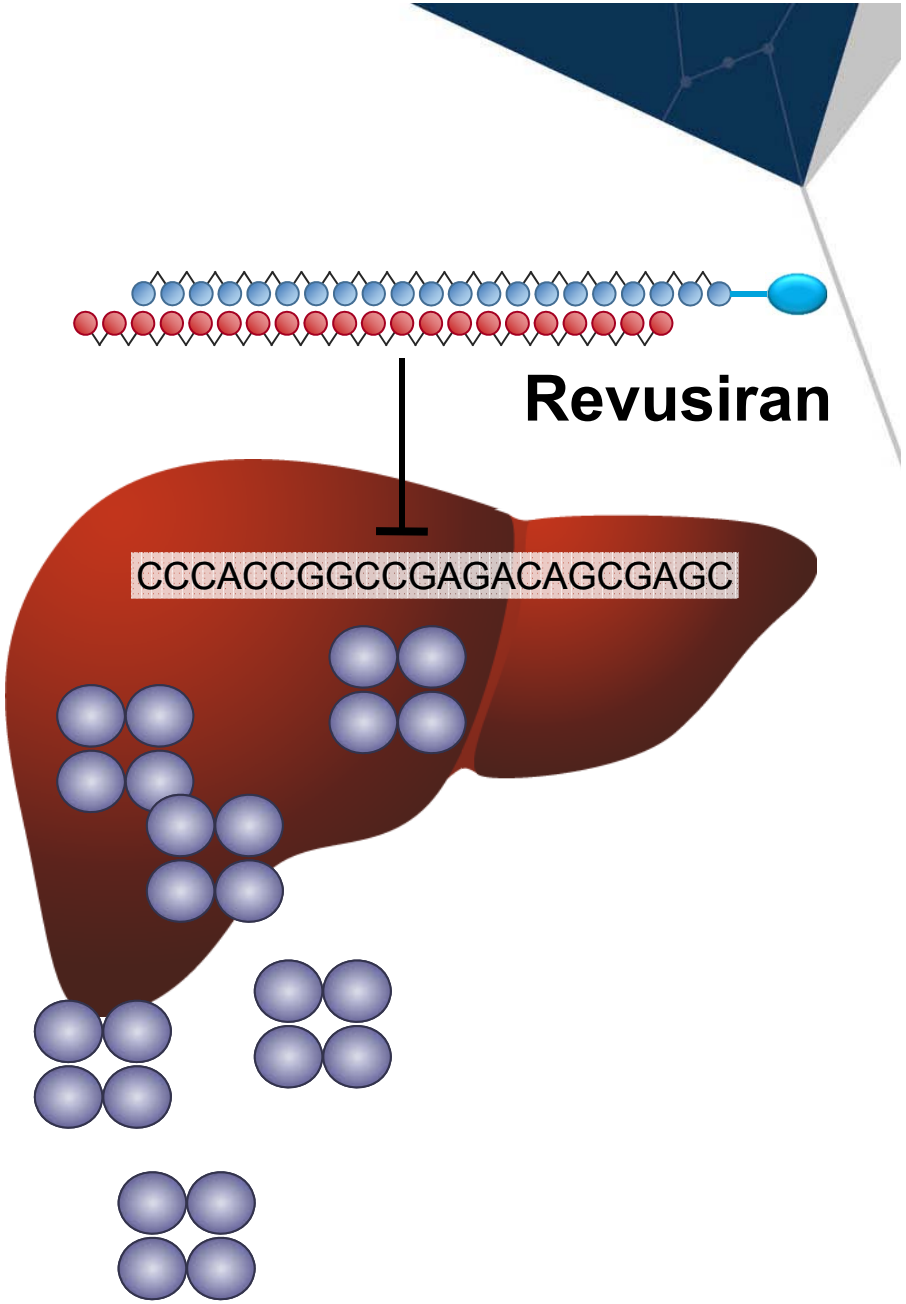
Revusiran (ALN-TTRsc)

Investigational RNAi Therapy Under Evaluation for the Treatment of Familial Amyloidotic Cardiomyopathy (FAC)

About Revusiran

How Revusiran May Work

- Revusiran uses the body's natural process called RNA interference to lower the levels of TTR protein that cause familial amyloidotic cardiomyopathy (FAC)
- Revusiran prevents the production of TTR protein
- This may slow or halt the progression of FAC
- Revusiran is given by subcutaneous injection (under the skin)



Revusiran Clinical Development

Study	Participants	Status
Phase 1	84 healthy human volunteers	Completed[1]
Phase 2	14 adults with FAC 12 adults with senile systemic amyloidosis (SSA)	Completed[2]
Phase 2 Open-Label Extension (OLE)	14 adults with FAC and 11 adults with SSA who participated in the Phase 2 study	Enrollment Closed
Phase 3 Studies: ENDEAVOUR	Target enrollment: 200 adults with FAC	Currently enrolling

1. Zimmerman, *HFSA* (2013); 2. Gilmore, *ACC*, March 2015

Revusiran Phase 2 Study Design

Study Participants

- 26 adults with ATTR cardiomyopathy

Investigational Drug

- All study participants received the investigational drug via subcutaneous (SC) injection, under the skin, up to 10 times in a 5 week period
- Dose/regimen: 5.0 or 7.5 mg/kg, daily x 5, followed by weekly x 5
- There was no placebo control group

Study Design

- Open-label, multi-dose study in patients with ATTR cardiomyopathy
  - New York Heart Association class ≤ 3 (stable CHF)
  - Concomitant tafamidis, diflunisal, doxycycline/TUDCA* allowed

Study Objectives

- To understand the safety and tolerability of multiple doses of revusiran in adults with ATTR cardiomyopathy
- To understand the effect of revusiran on:
  - TTR protein levels in the blood
  - 6-minute walk test
  - Quality of Life

*Tauroursodeoxycholic acid

Gilmore, *ACC*, March 2015

Revusiran Phase 2 Study*
Demographics of Study Participants

26 adults Average age = 68	Race	Stabilizer Use	TTR Genotype
23 Men 3 Women	22 White 4 African American	22 participants not taking a stabilizer 4 participants taking diflunisal (250 mg BID)	T60A = 7 V122I = 5 S77Y = 1 I84S = 1 WT = 1

**Results as of March 15, 2015*

Gilmore, *ACC*, March 2015

Revusiran Phase 2 Study*
Study Results – Safety and Tolerability

26 patients received revusiran
A total of 258 doses were given in this study

All treatment emergent adverse events were mild or moderate in severity

No clinically significant changes in liver function, kidney function, other laboratory chemistries, or hematological parameters were observed

Mild skin reactions at the injection site: 4 patients (15%) (skin reddening [3] and rash [1])

Transient mild liver function test changes: 4 patients (15%)

Note: As of 11 Aug 2015, 3 of the 25 patients in the ongoing Phase 2 open-label extension (OLE) study have discontinued from the study due to injection site reactions (ISRs).

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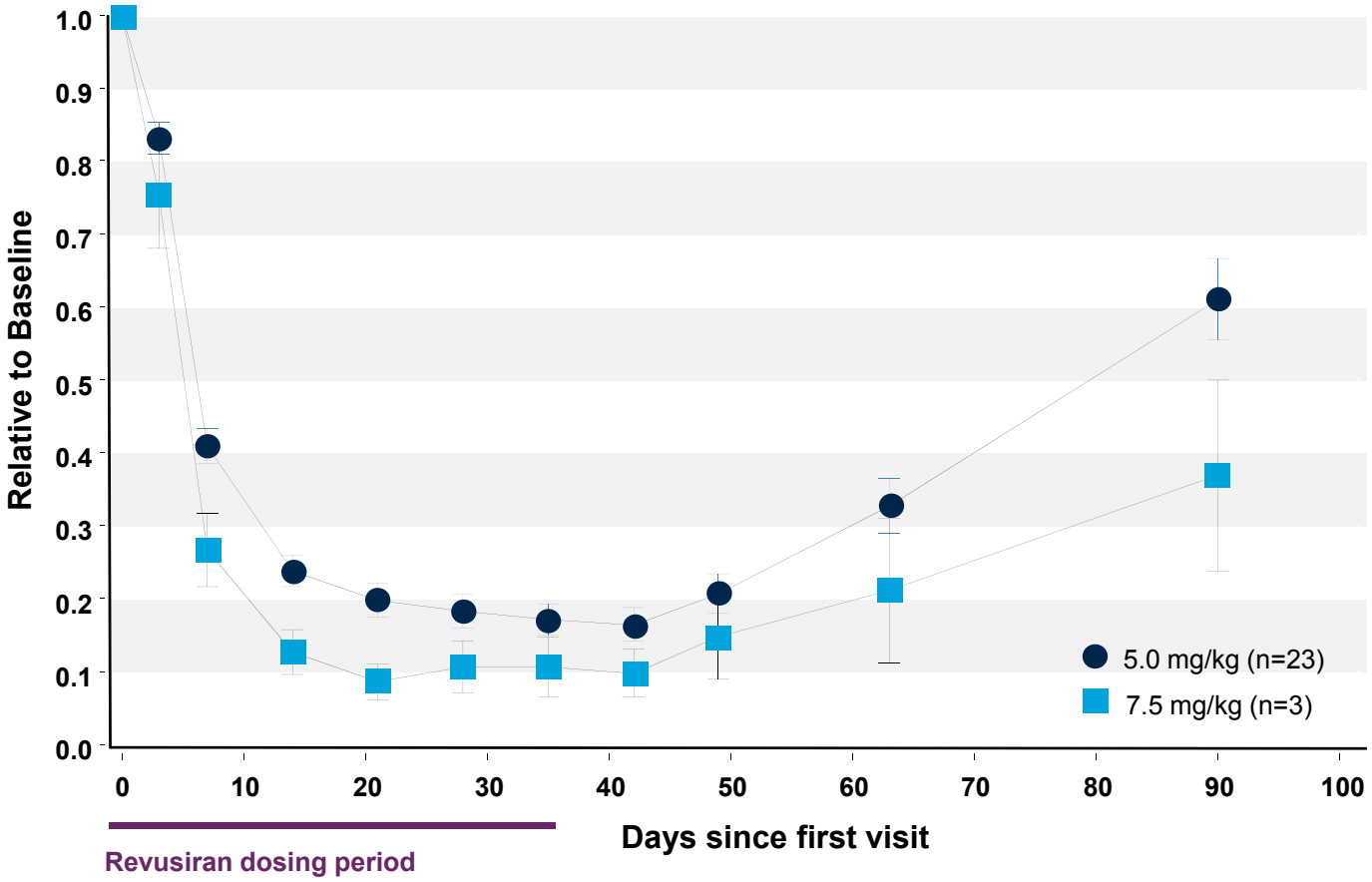
**Results as of March 15, 2015*

Revusiran Phase 2 Study Results*

TTR Lowering by Dose Group



Knockdown *represents the lowering of TTR protein levels in the blood*

- Individual Max Knockdown %: 98.2
- Mean Knockdown %: ~86 ± 9

**Results as of March 15, 2015*

Gilmore, *ACC*, March 2015

Summary

ATTR Cardiomyopathy

- Caused by TTR amyloid that accumulates primarily in the heart and nervous system

Revusiran

- An investigational RNAi therapeutic specifically designed to target TTR mRNA
- Multiple doses of revusiran generally well tolerated in patients with ATTR cardiomyopathy in Phase 2*
- 3 patients in the ongoing Phase 2 open-label extension (OLE) study have discontinued due to injection site reactions
- ~86% reduction of TTR observed in patients with ATTR cardiomyopathy in the Phase 2 study

Clinical Trials

- Alnylam has completed the Phase 1 and Phase 2 clinical trials. The Phase 2 open label extension (OLE) study is ongoing
- A Phase 3 study called ENDEAVOUR is being conducted in up to 200 participants in approximately 10 countries to evaluate the safety and efficacy of revusiran in patients with FAC

**Results as of March 15, 2015*

Gilmore, *ACC*, March 2015

Alnylam Assist™

Free Third-party TTR amyloidosis (FAP & FAC) diagnostic testing

Alnylam Assist™

Dedicated support program for patients and families in the US affected by ATTR

- Physicians must register with Alnylam Assist
- Free third-party diagnostic testing through an independent laboratory
- Testing is available to anyone who maybe experiencing symptoms of FAP or FAC
- Results are sent to your doctor. Alnylam does not receive any personally identifiable information

Early diagnosis can help patients with FAP and FAC get the help and support they need.

About Alnylam

Our Commitment to You

- We understand the impact that ATTR can have on you and your family

- Improving the knowledge and treatment of ATTR is one of our highest commitments

Thank You

APOLLO Phase 3 Study

Study Design

Patient Population
- FAP: any TTR mutation, Stages 1 and 2
- Neurological impairment score (NIS) of 5-130
- Prior tetramer stabilizer use permitted

▶ **2:1 RANDOMIZATION**

- ▶ **Patisiran IV infusion q3W, 0.3 mg/kg**
- ▶ **Placebo IV infusion q3W**

Primary Endpoint
- mNIS+7 at 18 months

Secondary Endpoints
- Norfolk QOL-DN
- NIS-weakness
- mBMI
- 10-meter walk test
- COMPASS-31

Exploratory Endpoints
- EQ-5D QOL
- NIS+7
- Serum TTR levels
- Cardiac assessments
- Grip strength
- Rausch-built Overall Disability Scale

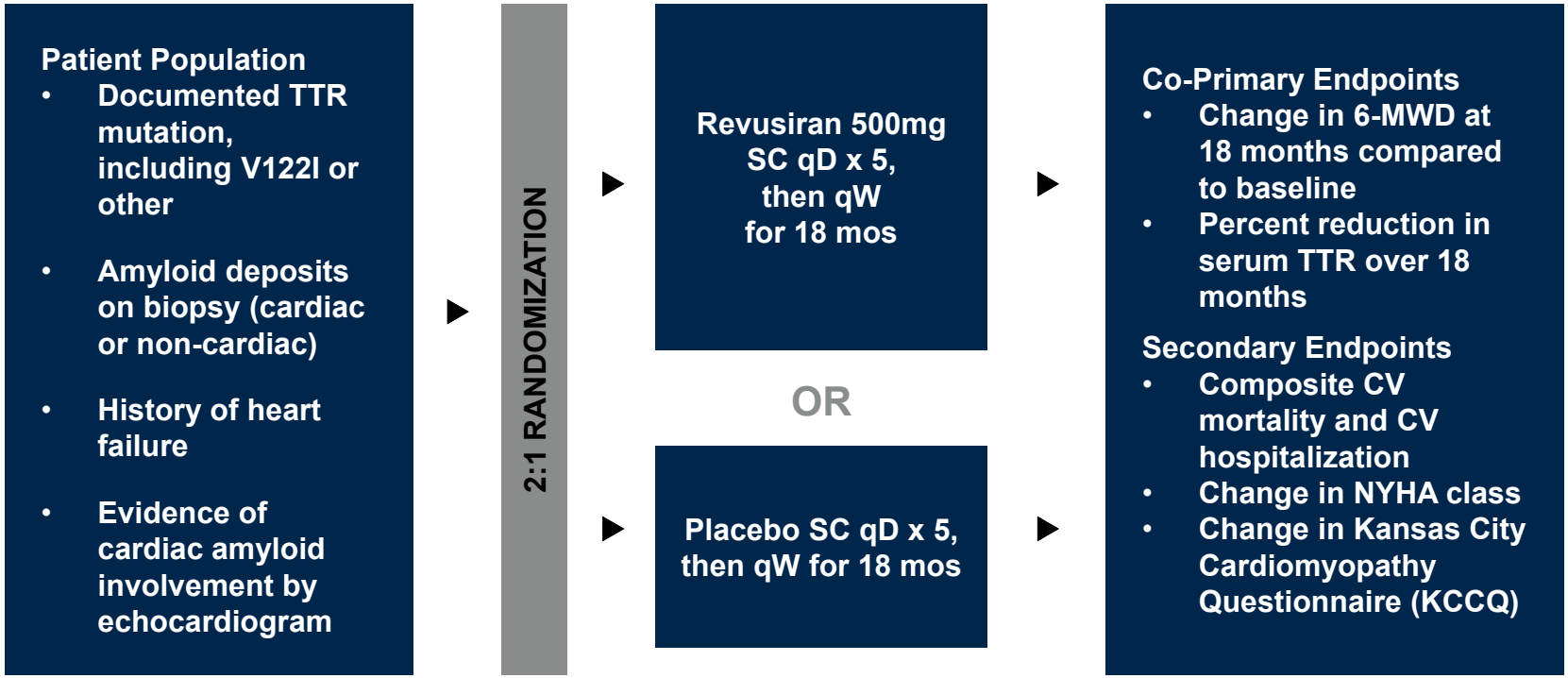
All completers eligible for patisiran treatment on Phase 3 OLE study

Statistical Considerations

- Placebo-estimated mNIS+7 progression rate of 17.8 points/yr derived from natural history study of 283 patients with FAP
- Study with 90% power to detect as little as 37.5% difference in ΔmNIS+7 between treatment groups with 2-sided alpha=0.05
- Blinded interim analysis of variance for sample size adjustment

Alnylam PHARMACEUTICALS

ENDEAVOUR Phase 3 Study Design



All completers eligible for revusiran treatment on Phase 3 OLE study

Statistical Considerations

- Placebo-estimated decline in 6-MWD of ~140 meters over 18 months in natural history study of 137 patients with FAC (n=39 for 6-MWD data)
- 90% Power to detect as little as 39% difference in 18 mo change from baseline 6-MWD between treatment groups with significance level of p <0.05
- Unblinded interim analysis for futility when ~50% of patients reach 18 mos

Alnylam PHARMACEUTICALS