Phase 2 Open-Label Extension Study of Revusiran

An Investigational RNAi Therapeutic for the Treatment of Patients with Transthyretin Cardiac Amyloidosis

03 November 2015

Alnylam® PHARMACEUTICALS

Background

Epidemiology

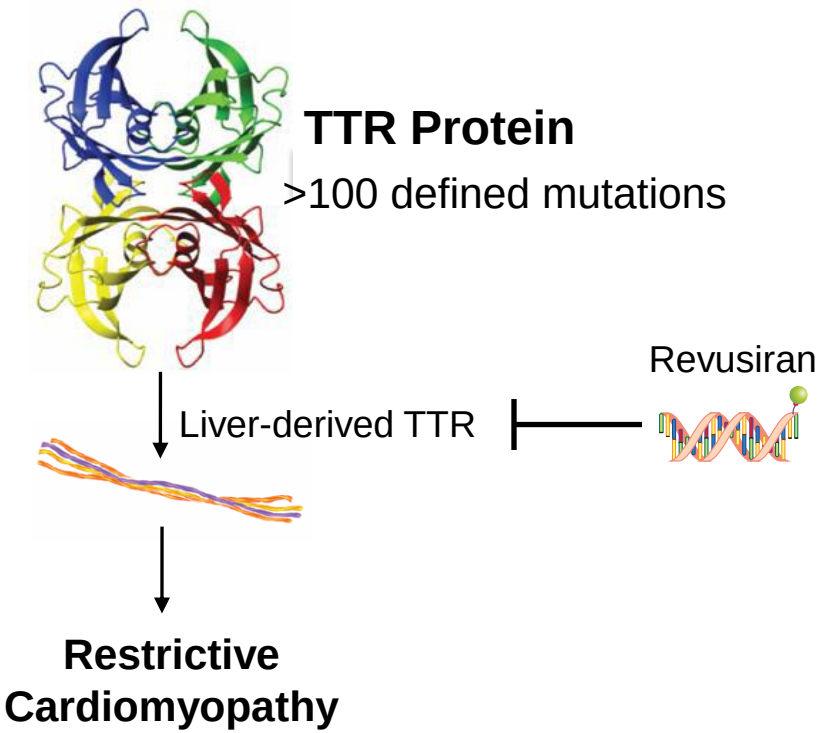
- Orphan disease
- Estimated >40,000 FAC patients WW
  - Currently underdiagnosed
- Cardiac-predominant TTR genotypes in US/EU
  - V122I is most common mutation; occurs in ~4% of African-Americans
  - T60A most common mutation in UK/Irish population
- Growing recognition of WT TTR (SSA) worldwide

Clinical pathology

- Onset >65 yrs
- Cardiac amyloid deposition leads to cardiac wall thickening, atrial arrhythmias, conduction disease and heart failure
- Fatal within 2.5-5 years of diagnosis depending on TTR variant

Limited treatment options

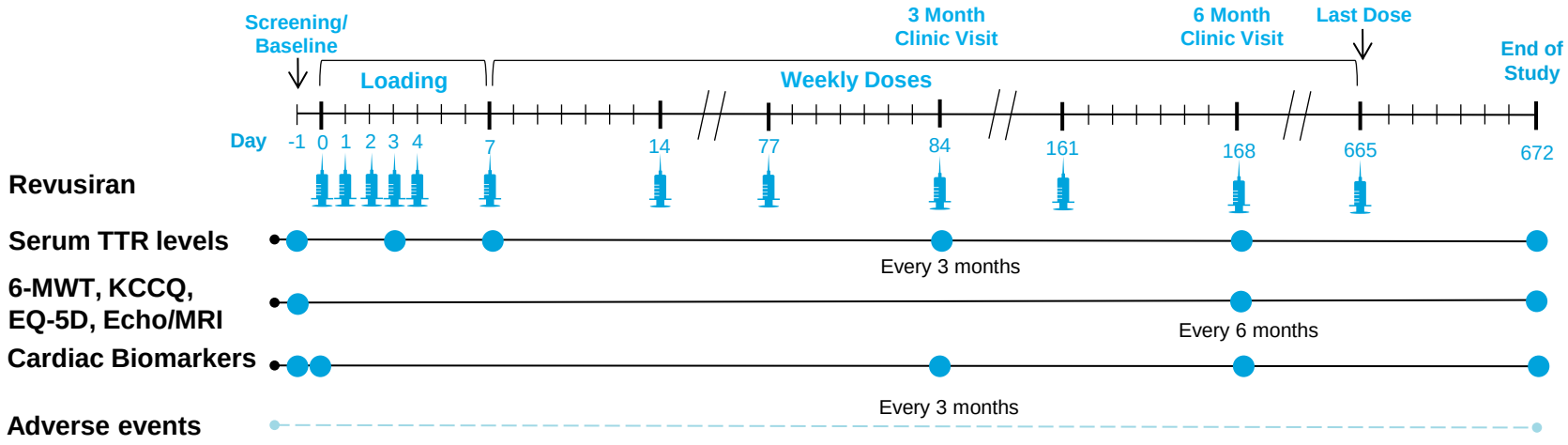
- Medical management of heart failure symptoms
- Heart transplant or combined heart/liver transplant performed in small number of patients young enough (<70 yrs) to undergo procedure



Revusiran in Clinical Development

- GalNAc-siRNA targeting TTR for SC dosing
- Phase 2 study completed
- Phase 2 extension study ongoing
- Phase 3 ENDEAVOUR trial in FAC ongoing

Revusiran Ph2 OLE Study Design



FAC and SSA patients previously enrolled in Phase 2 study eligible to enter Phase 2 OLE study

- Up to 2 years of dosing with clinical endpoints evaluated every 6 months
  - Clinical endpoints include those evaluated in the ENDEAVOUR Phase 3 Study
  - Dose/regimen: 500 mg, daily x 5, followed by weekly
- Study Objectives
  - Primary: Safety and tolerability of long term dosing with revusiran
  - Secondary: Effect on serum TTR and on mortality, hospitalization and 6-minute walk distance (6-MWD)
  - Tertiary: Pharmacokinetics and effects on cardiac biomarkers, cardiac imaging, NYHA class, KCCQ, and Quality of Life (EQ-5D)

Timelines are not to scale

Alnylam® PHARMACEUTICALS

Revusiran Ph2 OLE Preliminary Results*

Demographics and Exposure

Characteristics		FAC (n=14)	SSA (n=11)	Total (n=25)
Median Age (range)		66 years (53–79)	73 years (65–79)	70 years (53–79)
Male Gender		11 (79%)	11 (100%)	22 (88%)
Race		10 White, 4 AA	11 White	21 White, 4 AA
TTR Type	**WT**		11 (100%)	11 (44%)
	T60A	7 (50%)		7 (28%)
	V122I	5 (36%)		5 (20%)
	S77Y	1 (7%)		1 (4%)
	I84S	1 (7%)		1 (4%)
NYHA Class	**I**	1 (7%)	1 (9%)	2 (8%)
	II	11 (79%)	6 (55%)	17 (68%)
	III	2 (14%)	4 (36%)	6 (24%)
Mean eGFR (mL/min/1.73m^2)		79.8 (42–131)	60.4 (27–101)	71.2 (27–131)
Karnofsky (60/70/80/90/100)		2/2/5/4/1	1/4/4/2/0	3/6/9/6/1
Concurrent Diflunisal use		3	1	4
Exposure				
Total doses administered		419	319	738
Mean number of doses (range)		30 (14–48)	29 (9–44)	30 (9–48)
Mean treatment duration (range)		6.2 months (2–10)	5.9 months (1–9)	6 months (1–10)

AA: African American
*Data transfer 12Oct2015

Alnylam PHARMACEUTICALS

Revusiran Ph2 OLE Preliminary Results*

Baseline Characteristics

Characteristics	Mean (range)					
	N	FAC	N	SSA	N	Total
mBMI (kg/m^2 x albumin [g/L])	14	1093 (859–1812)	11	1133 (963–1287)	25	1111 (859–1812)
6-MWD (meters)	14	400 (73–617)	11	403 (305–513)	25	401 (73–617)
KCCQ Overall Summary Score	14	71.1 (22.8–98.4)	11	68.4 (43.5–88.0)	25	69.9 (22.8–98.4)
EQ-5D (max impairment=0)	14	0.83 (0.48–1.00)	11	0.78 (0.68–0.85)	25	0.81 (0.48–1.00)
Cardiac Biomarkers						
NT-proBNP (ng/L)	14	3949 (349–21310)	11	3054 (419–5652)	25	3555 (349–21310)
Troponin I (ng/mL)	14	0.15 (0.1–0.4)	11	0.13 (0.1–0.4)	25	0.14 (0.1–0.4)
Echocardiogram						
IVS Thickness (cm)	14	2.1 (1.6–2.7)	11	1.84 (1.5–2.9)	25	2.0 (1.5–2.9)
LVEF (%)	14	51 (28–69)	11	50 (27–64)	25	50 (27–69)
Longitudinal Strain (%)	14	-12.0 (-20.8 to -6.3)	11	-11.6 (-17.3 to -8.3)	25	-11.8 (-20.8 to -6.3)
Cardiac MRI						
LV Mass (g)	12	197 (114–338)	9	219 (156–363)	21	206 (114–363)
Stroke Volume (mL)	12	66.8 (44.6–97.7)	9	77.6 (60.1–109.1)	21	71.4 (44.6–109.1)
Global ECV	12	0.56 (0.5–0.7)	9	0.53 (0.4–0.6)	21	0.55 (0.4–0.7)

6-MWD: 6-Minute Walk Distance; KCCQ: Kansas City Cardiomyopathy Questionnaire; EQ-5D score uses US references; IVS: Interventricular Septum; LV: Left Ventricular; ECV: Extracellular Volume Fraction; LVEF: Left Ventricular Ejection Fraction; mBMI: Modified Body Mass Index
Reference Ranges: IVS 0.6-1.0 cm (M), 0.6-0.9 cm (F), LVEF >50%, Longitudinal strain: -15.9% to -21.1%
Normal Average Values: LV Mass 155.1 g (M), 103.0 g (F), Stroke Volume 78.6 mL (M), 59.3 mL (F), ECV <0.3
*Data transfer 12Oct2015

Alnylam® PHARMACEUTICALS

Revusiran Ph2 OLE Preliminary Results*

Summary of Safety

Most common adverse events ≥10%†	All subjects (n=25)
Number of subjects with an adverse event, n (%)	22 (88%)
Injection site erythema	8 (32%)
Cough	7 (28%)
Dizziness	5 (20%)
Dyspnea	4 (16%)
Injection site pain	4 (16%)
Injection site pruritus	4 (16%)
Injection site swelling	4 (16%)
Edema peripheral	4 (16%)
Atrial fibrillation	3 (12%)
Cardiac failure	3 (12%)
Contusion	3 (12%)
Diarrhea	3 (12%)
Hypotension	3 (12%)
Joint swelling	3 (12%)
Nausea	3 (12%)
Urinary tract infection	3 (12%)

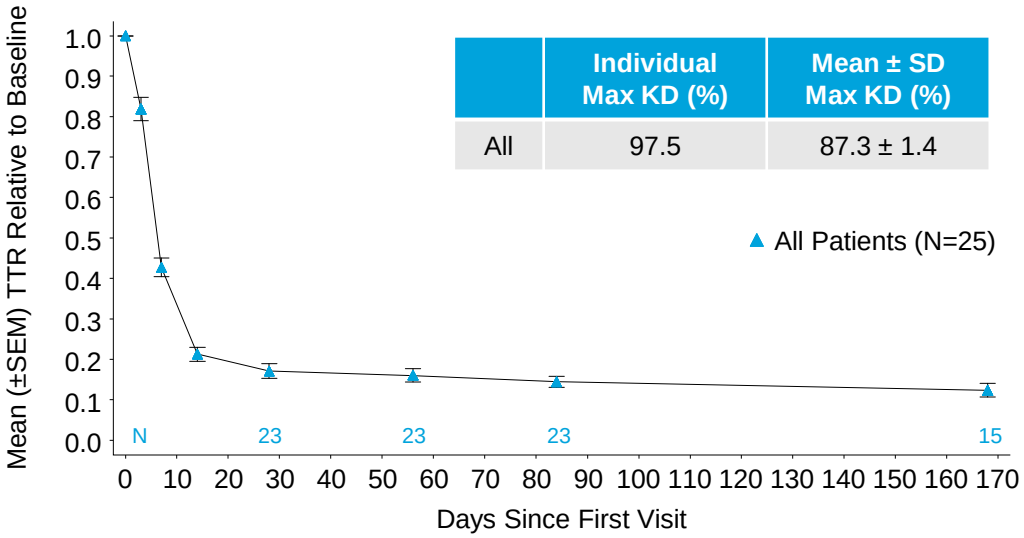
- 8 (32%) patients with serious adverse events (SAEs) – all unrelated
  - 1 death due to infiltrative cardiomyopathy (not related)
- Majority of patients had AEs that were mild or moderate in severity
  - 5 (20%) patients with severe AEs
- Injection site reactions‡ were reported in 11 (44%) patients
  - Most common symptoms were erythema, pruritus, pain or swelling at the injection site
  - Majority of symptoms were mild in severity
  - ISRs were the most common reported related AEs
- 3 patients discontinued study drug due to recurrent localized reactions at the injection site or diffuse rash
- 2 dose reductions to 250 mg weekly
  - 1 patient for recurrent injection site reactions and 1 patient for LFT elevation which resolved with continued dosing
- No other notable changes in liver function tests, renal function or hematologic parameters

†By preferred term in MedDRA
‡By High Level Term in MedDRA
*Data transfer 12Oct2015

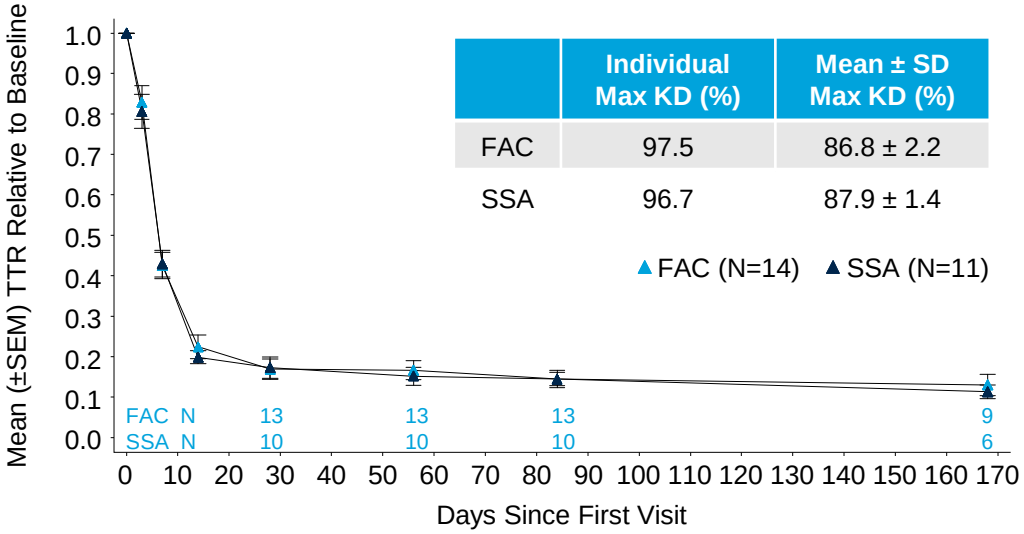
Alnylam PHARMACEUTICALS

Revusiran Ph2 OLE Preliminary Results*

Durable TTR Knockdown (KD) through 6 Months



	Individual Max KD (%)	Mean ± SD Max KD (%)
All	97.5	87.3 ± 1.4



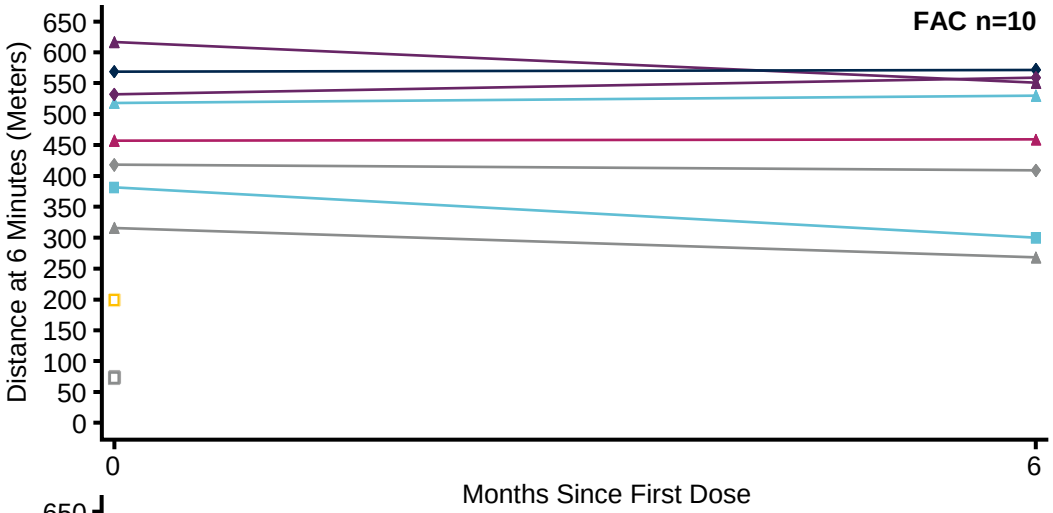
	Individual Max KD (%)	Mean ± SD Max KD (%)
FAC	97.5	86.8 ± 2.2
SSA	96.7	87.9 ± 1.4

*Data transfer 12Oct2015

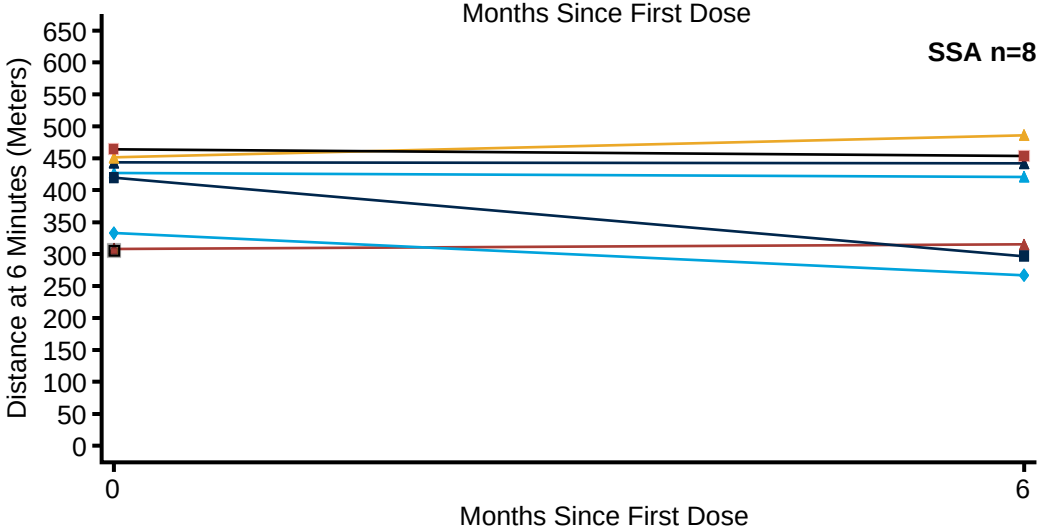
Alnylam PHARMACEUTICALS

Revusiran Ph2 OLE Preliminary Results*

6-MWD in Individual Patients



FAC	No Imputation	With Imputation
Baseline N Mean (±SEM) Median (Min, Max)	8 476 (36) 488 (316,617)	10 408 (54) 438 (73,617)
Δ 6 Months [meters] N Mean (±SEM) Median (Min, Max)	8 -20 (14) -3 (-81, 27)	10* -43 (21) -29 (-199, 27)



SSA	No Imputation	With Imputation
Baseline N Mean (±SEM) Median (Min, Max)	7 407 (23) 427 (308, 464)	8 394 (24) 423 (305, 464)
Δ 6 Months [meters] N Mean (±SEM) Median (Min, Max)	7 -24 (20) -6 (-122, 35)	8* -59 (39) -9 (-305, 35)

*2 FAC (□□) and 1 SSA (□) patients imputed 6-MWD (6-Minute Walk Distance) as 0 meters at 6 months (Patients were unable to perform test at planned visit)
NH: Natural History
*Data transfer 12Oct2015

Alnylam® PHARMACEUTICALS

Revusiran Ph2 OLE Preliminary Results*

Comparison of 6-MWD in Ph2 OLE to Natural History

	FAC Natural History		FAC Ph2 OLE	
	No Imputation	With Imputation	No Imputation	With Imputation
Baseline, N Mean (±SEM) Median (Min, Max)	37 283 (19) 276 (46, 485)	39 281 (20) 276 (46, 485)	8 476 (36) 488 (316,617)	10 408 (54) 438 (73,617)
Δ 6 Months [meters] N Mean (±SEM) Median (Min, Max)	30 -23 (21) - 14 (-311, 209	32† -36 (23) -19 (-426, 209)	8 -20 (14) -3 (-81, 27)	10† -43 (21) -29 (-199, 27)

	SSA Natural History		SSA Ph2 OLE	
	No Imputation	With Imputation	No Imputation	With Imputation
Baseline N Mean (±SEM) Median (Min, Max)	145 320 (9) 334 (16, 570)	153 313 (10) 333 (16, 570)	7 407 (23) 427 (308, 464)	8 394 (24) 423 (305, 464)
Δ 6 Months [meters] N Mean (±SEM) Median (Min, Max)	119 -25 (7) -17 (-240, 136)	125‡ -30 (7) -22 (-345, 136)	7 -24 (20) -6 (-122, 35)	8‡ -59 (39) -9 (-305, 35)

† Includes 2 FAC OLE and 2 FAC-NH patients imputed 6-MWD as 0 meters at 6 months (Patients were unable to perform test at planned visit)
‡Includes 1 SSA OLE and 6 SSA-NH patients imputed 6-MWD as 0 meters at 6 months (Patients were unable to perform test at planned visit)
6-MWD natural history data collected retrospectively from National Amyloidosis Center, UK. Full dataset reported separately.
*Data transfer 12Oct2015

Alnylam® PHARMACEUTICALS

Revusiran Phase 2 OLE Preliminary Results*

Clinical Measurements

Characteristics	Actual Results at Each Visit Mean (SEM)			Changes From Baseline Mean (SEM)
	N**	Baseline	6 Month	Δ Month 6
mBMI (kg/m^2 x albumin [g/L])	17	1162 (52.3)	1065 (56.1)	-97 (15.6)
KCCQ Overall Summary Score	17	68.8 (4.7)	61.2 (5.7)	-7.5 (3.5)
EQ-5D (max impairment=0)	17	0.80 (0.03)	0.75 (0.04)	-0.05 (0.03)
Cardiac Biomarkers				
NT-proBNP (ng/L)	17	3454 (1173)	3853 (979)	399 (321)
Troponin I (ng/mL)	17	0.12 (0.02)	0.14 (0.03)	0.02 (0.02)
Echocardiogram				
IVS Thickness (cm)	15	2.00 (0.10)	2.03 (0.10)	0.03 (0.03)
LVEF (%)	15	46.9 (3.3)	47.9 (3.9)	1.1 (2.3)
Longitudinal Strain (%)	15	-12.0 (1.1)	-12.7 (0.9)	-0.8 (0.5)
Cardiac MRI				
LV Mass (g)	11	215.1 (24.7)	231.9 (21.4)	16.8 (14.4)
Stroke Volume (mL)	11	71.9 (6.6)	76.9 (3.9)	4.9 (5.0)
Global ECV	10	0.53 (0.02)	0.51 (0.03)	-0.01 (0.02)

KCCQ: Kansas City Cardiomyopathy Questionnaire; EQ-5D score uses US references; mBMI: Modified Body Mass Index; IVS: Interventricular Septum; ECV: Extracellular Volume Fraction

**Includes results for pooled FAC and SSA patients with available data at baseline and 6 months

*Data transfer 12Oct2015

Alnylam PHARMACEUTICALS

Revusiran Phase 2 OLE Preliminary Results*
Summary

- Weekly dosing with revusiran generally well tolerated in ATTR cardiac amyloidosis patients
  - Longest first generation GalNAc-siRNA conjugate experience in humans to-date with dosing up to 10 months
  - Most common related adverse events were ISRs which were generally mild
    - ISR or diffuse rashes led to study discontinuation in 3 patients
- Revusiran administration resulted in durable TTR lowering of >85%
  - Maximum knockdown of serum TTR up to 98%; mean maximum knockdown of 87%
  - Comparable degree of TTR knockdown in FAC vs SSA patients
- At the early timepoint of 6 months, the majority of evaluable patients showed stable 6-MWD
- No clinically meaningful changes observed in additional cardiac parameters at 6 months

*Data transfer 12Oct2015

Alnylam® PHARMACEUTICALS

ENDEAVOUR Phase 3 Study Design

Patient population

(n≈200)

- Documented TTR mutation, including V122I or other
- Amyloid deposits on biopsy (cardiac or non cardiac)
- Medical history of heart failure
- Evidence of cardiac amyloid involvement by echocardiogram
- New York Heart Association (NYHA) classification I-III

2:1 Randomization

Double-blind

Revusiran
500mg SC qD x 5,
then qW for 18 mos

Placebo
SC qD x 5,
then qW for 18 mos

Co-primary endpoints (at 18 months)

- Change in 6-MWD
- Percent reduction in serum TTR

Secondary endpoints

- Composite CV mortality and CV hospitalization
- Change in NYHA class
- Change KCCQ

Statistical Considerations

- Placebo-estimated decline in 6-MWD of ~140 meters over 18 months in natural history study of 137 FAC patients (N=39 for 6-MWD data)5
- 90% Power to detect as little as 39% difference in 18 mo change from baseline 6-MWD between treatment groups with significance level of $p < 0.05$

6-MWD: 6 minute walk distance; KCCQ: **in Kansas City Cardiomyopathy Questionnaire**
ClinicalTrials.gov: NCT02319005

Alnylam® PHARMACEUTICALS

Acknowledgements

Patients Participating in Phase 2 Study

Phase 2 Investigators and Site Staff

- Julian Gillmore, Lisa Rannigan, Helen McPhilips, Thirusha Lane
  - National Amyloidosis Centre, London, UK
- Mat Maurer, Stephen Helmke, Julissa Alvarez-Munoz, Sergio Teruya
  - Columbia University, New York, NY
- Rodney Falk, Tara Mirto
  - Brigham and Women's Hospital, Boston, MA
- Mazen Hanna, Patricia Bouscher, Barb Gus, Lauren Ives
  - Cleveland Clinic, Cleveland, OH
- Nowell Fine, Kimberley Ronak, Leslie Jackson
  - Libin Institute, Calgary, Alberta, Canada

Alnylam® PHARMACEUTICALS

Thank You

Alnylam®
PHARMACEUTICALS