A Phase 2 Multi-Center, Open-Label Trial to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics and Exploratory Clinical Activity of Revusiran (ALN-TTRsc), an RNAi Therapeutic for the Treatment of Patients with Transthyretin Cardiac Amyloidosis

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Abstract

Background: Transthyretin (TTR) cardiac amyloidosis is an under-recognized form of cardiomyopathy caused by the deposition of liver-derived mutant and/or wild-type (WT) TTR in the myocardium resulting in heart failure and death. The hereditary form, known as familial amyloidotic cardiomyopathy (FAC), is most frequently associated with the V122I TTR genotype, which is present in ~4% of African-Americans. There are currently no approved therapies. Revusiran (ALN-TTRsc) is a subcutaneously administered investigational RNA interference therapeutic comprised of a small interfering RNA targeting both mutant and wild-type TTR mRNA. The therapeutic hypothesis is that lowering of serum TTR protein may prevent cardiac amyloid deposition and result in clinical benefit.

Methods: This open-label study was undertaken to evaluate revusiran in patients with TTR cardiac amyloidosis. Eligible patients must have biopsy-proven mutant or WT TTR cardiac amyloidosis, stable heart failure, NYHA class ≤3, 6-MWD ≥150 m. Patients received revusiran 5.0 or 7.5 mg/kg SC daily x 5, followed by 5 weekly doses (through Day 35). The purpose of the study is to evaluate safety, PD, and explore clinical activity of revusiran through 6-MWD; NYHA class; cardiac magnetic resonance imaging (CMR) and echocardiography; cardiac biomarkers; KCCQ; modified BMI; and EQ-5D QOL in patients with TTR cardiac amyloidosis.

Results: 26 patients have been enrolled. Baseline characteristics include: 12 patients with senile systemic amyloidosis (SSA) and 14 patients with FAC (including 7 T60A, 5 V122I); median age 68 years; mean 6-MWD 408 m; mean NT-proBNP 3435 pg/mL; mean interventricular septum thickness 19 mm (range 15 – 29) and preserved LVEF (50%). Two, 21 and 3 patients were NYHA class I, II and III, respectively. Serum TTR lowering was > 85% and comparable between dose groups and between SSA and FAC. The most common adverse events were mild LFT elevations. Cardiac biomarkers and imaging parameters showed disease stability at Days 42 and 90.

Revusiran Program in TTR Cardiac Amyloidosis

Epidemiology

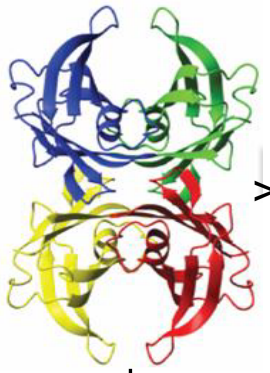
- Orphan disease
- Estimated >40,000 FAC patients WW
  - Currently underdiagnosed
- Cardiac-predominant TTR genotypes in US/EU
  - V122I is most common mutation; occurs in ~4% of African-Americans
  - T60A most common mutation in UK/Irish population
- Growing recognition of WT TTR (SSA) worldwide

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

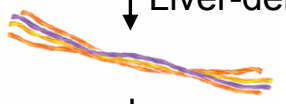


TTR Protein

>100 defined mutations

Revusiran

Liver-derived TTR



Restrictive Cardiomyopathy

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

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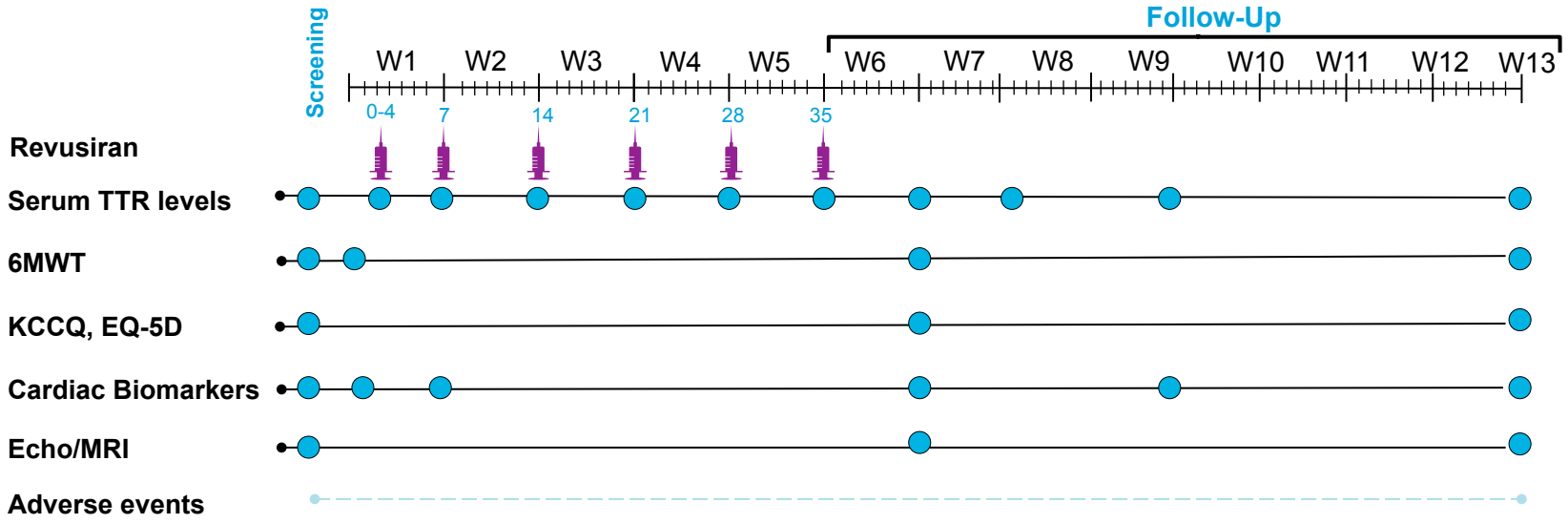
Revusiran Phase 2 Study Design



Study Design

- Open-label, multi-dose study in patients with TTR cardiac amyloidosis
  - NYHA class ≤ 3 (stable CHF)
  - Concomitant tafamidis, diflunisal, doxycycline/TUDCA allowed
  - Dose/regimen: 5.0 or 7.5 mg/kg, daily x 5, followed by weekly x 5

Primary Objective

- Evaluate safety and tolerability of multiple doses of revusiran

Secondary Objectives

- Assess PK of revusiran in patients with TTR cardiac amyloidosis
- Assess PD effect on serum TTR

Exploratory Clinical Measurements

- NT-proBNP and troponin T and I, Echo, CMR, 6-MWT, NYHA class, mBMI, KCCQ, Quality of Life (EQ-5D-5L)

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Revusiran Phase 2 Study Results
Demographics

Characteristics	FAC (n=14)	SSA (n=12)	Total (n=26)
Mean Age	65.0	71.8	68.1
Gender (M/F)	11/3	12/0	23/3
Race	10 White, 4 African American	12 White	22 White, 4 African American
Mean Weight [kg]	77.8	83.1	80.3
TTR Type	T60A (7) V122I (5) S77Y (1) I84S (1)	WT (12)	T60A (7) V122I (5) S77Y (1) I84S (1) WT (12)
NYHA Class: **1** **2** **3**	 1 (7.1%) 12 (85.7%) 1 (7.1%)	 1 (8.3%) 9 (75%) 2 (16.7)	 2 (7.7%) 21 (80.8%) 3 (11.5%)
Karnofsky 60/70/80/90	4/0/5/5	0/1/8/3	4/1/13/8
Concurrent Stabilizer Use*	3	1	4

* Diflunisal 250 mg BID

Results as of February 4, 2015

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Revusiran Phase 2 Study Results
Baseline Characteristics

	FAC (n=14)	SSA (n=12)	Total (n=26)
Characteristics	Mean (Range)		
Serum TTR (ug/ml)	211.8 (94.3-415.7)	240.9 (167.6-332.4)	225.2 (94.3-415.7)
eGFR (mL/min/1.73m^2)	62.9 (43-89)	60.8 (37-90)	61.9 (37-90)
mBMI (kg/m^2 x albumin [g/L])	1112.0 (934.4-1621.5)	1110.9 (706.1-1393.3)	1111.5 (706.1-1621.5)
6-MWD (meters)	419.5 (212.8-610.0)	393.9 (289.0-487.0)	407.7 (212.8-610.0)
KCCQ Overall Summary Score	73.9 (42-96)	71.3 (42.96)	72.7 (42-96)
EQ-5D (max impairment=0)	0.84 (0.59-1.0)	0.85 (0.66-1.0)	0.84 (0.59-1.0)
Cardiac Biomarkers			
NT-proBNP (ng/L)	4386.0 (322-20199)	2325.5 (421-4815)	3435.0 (322-20199)
Troponin I (ng/mL)	0.16 (0.05-0.34)	0.10 (0.05-0.27)	0.13 (0.05-0.34)

KCCQ: Kansas City Cardiomyopathy Questionnaire; EQ-5D score uses US references

Reference Ranges:
- NT-proBNP <124 ng/L
- Troponin I < 0.10 ng/mL

Results as of February 4, 2015

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Revusiran Phase 2 Study Results
Baseline Characteristics

	FAC (n=14)	SSA (n=12)	Total (n=26)
Characteristics	Mean (Range)		
Echocardiogram			
IVS Thickness (cm)	2.0 (1.5-2.9)	1.8 (1.6-2.0)	1.9 (1.5-2.9)
LVEF (%)	48.8 (30.5-67.6)	50.6 (28.1-64.1)	49.6 (28.1-67.6)
Longitudinal Strain (%)	-12.8 (-21.6 to -8.8)	-11.3 (-14.6 to -9.0)	-12.1 (-21.6 to -8.8)
Cardiac MRI			
LV Mass (g)	194.5 (96.9-295.2)	208.8 (131.9-304.7)	201.0 (96.9-304.7)
Stroke Volume (ml)	73.0 (41.0-101.8)	71.8 (54.5-92.4)	72.4 (41.0-101.8)
Global ECV	0.55 (0.44-0.73)	0.53 (0.40-0.59)	0.54 (0.40-0.73)

IVS: Interventricular Septum; ECV: Extracellular Volume Fraction

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

Results as of February 4, 2015

Revusiran Phase 2 Study Results
Safety and Tolerability

Treatment Emergent Adverse Events Possibly or Definitely Related ≥10%

	5.0 mg/kg (n=23)	7.5 mg/kg (n=3)	Total (n=26)
LFT elevation^	4 (17%)	0	4 (15%)
Injection site erythema	3 (13%)	0	3 (12%)

^ Preferred Terms: LFT abnormal (1), ALT increased (2), alkaline phosphatase increased (1)

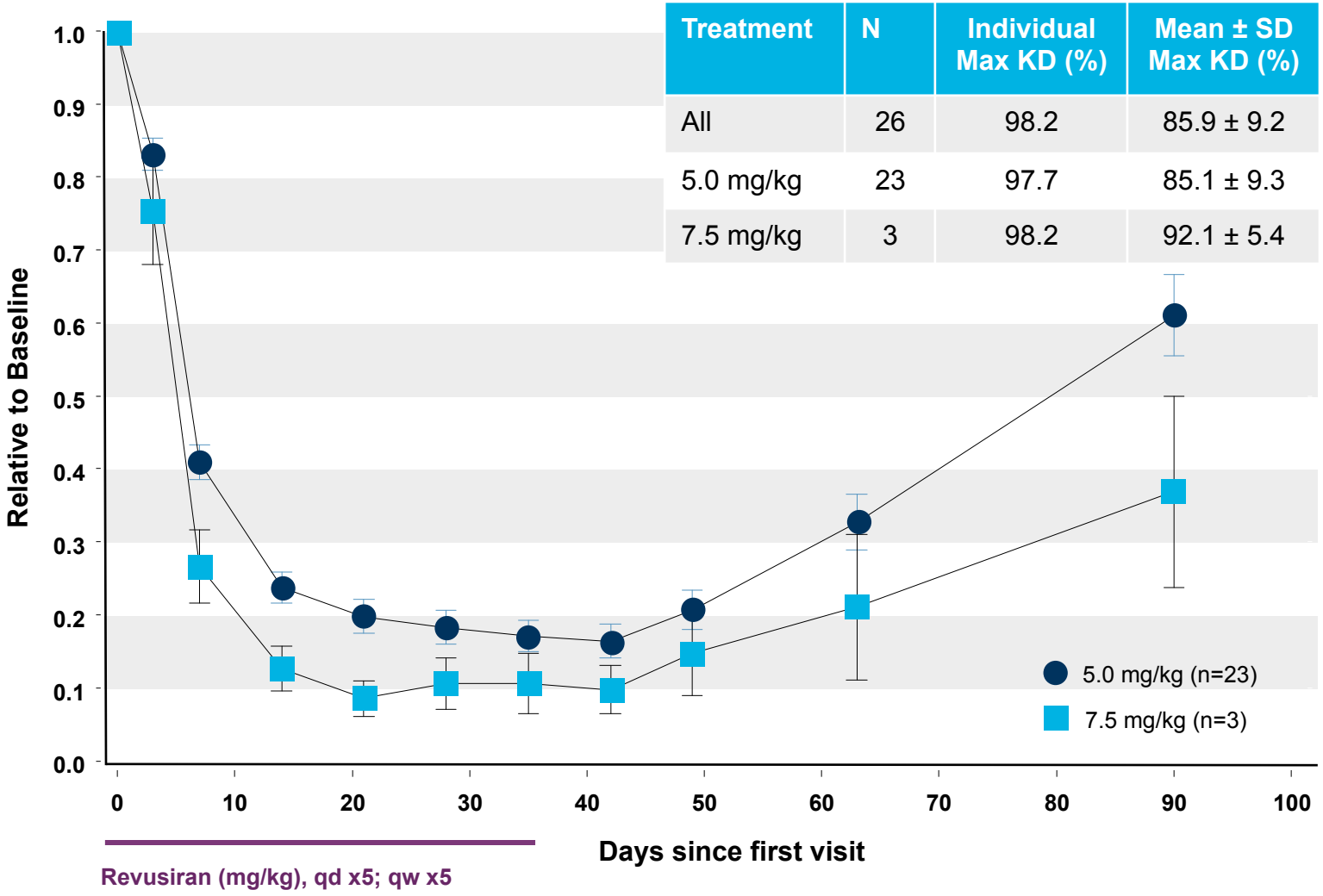
- All related TEAEs mild in severity
  - Injection site reactions occurred in 4 (15%) patients, including erythema (3) and rash (1)
  - Transient mild liver function test (LFT) changes
    - In 3 of 4 patients (<1.5 x ULN ALT) with uninterrupted dosing
    - 1 possibly related SAE for LFT changes (~4 x ULN ALT/AST), which resolved during continued dosing; graded mild in severity
  - Elevated percent monocyte counts were pre-existing at baseline and are considered medical history
- 2 unrelated SAEs (non-cardiac chest pain, AICD placement)
- No study discontinuations
- No significant changes in renal function, other laboratory chemistries, or hematologic parameters

Results as of February 4, 2015

Revusiran Phase 2 Study Results

Serum TTR Lowering by Dose Group

Treatment	N	Individual Max KD (%)	Mean ± SD Max KD (%)
All	26	98.2	85.9 ± 9.2
5.0 mg/kg	23	97.7	85.1 ± 9.3
7.5 mg/kg	3	98.2	92.1 ± 5.4



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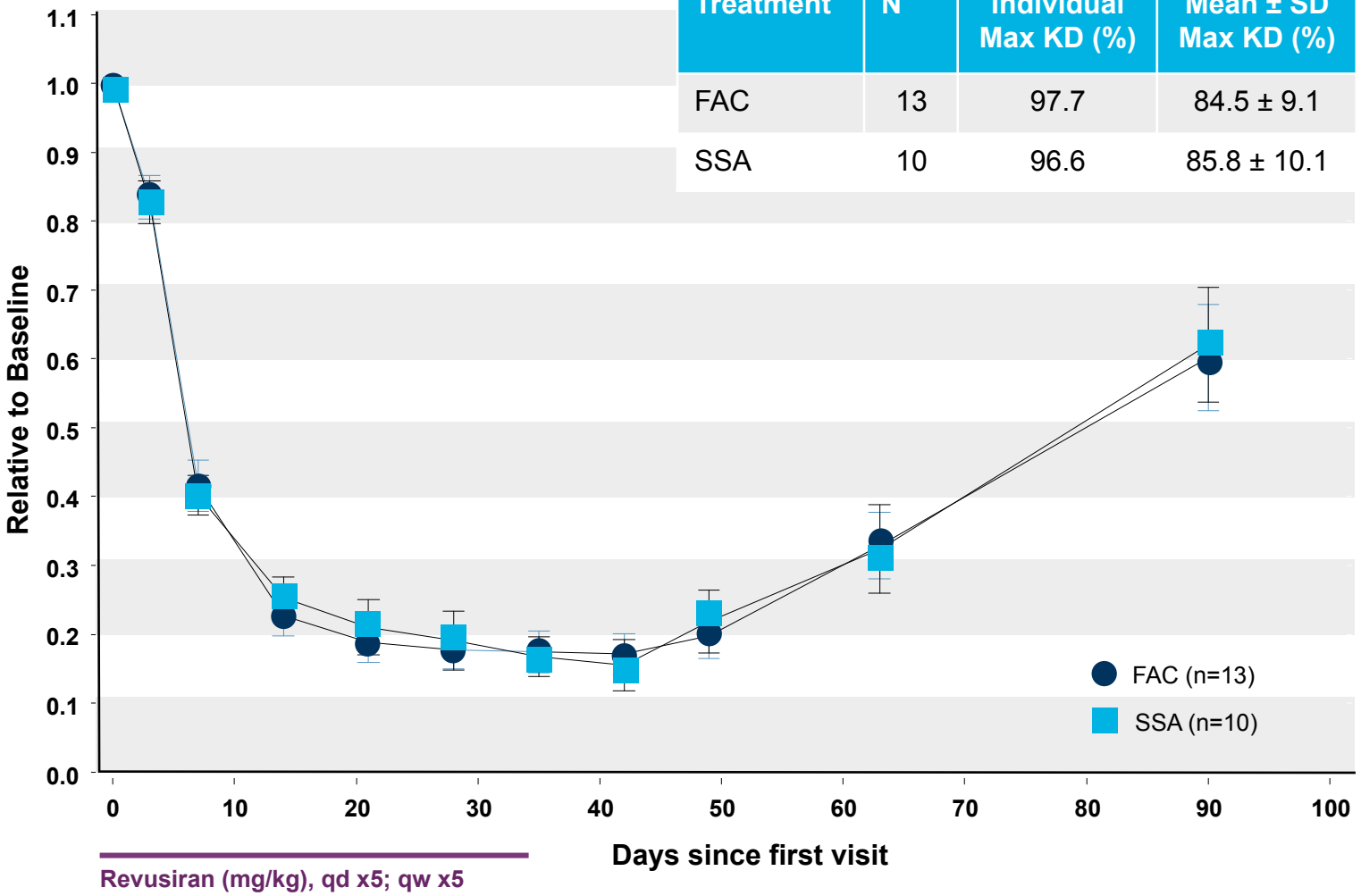
Revusiran Phase 2 Study Results

Serum TTR Lowering at 5.0 mg/kg by TTR Type

Treatment	N	Individual Max KD (%)	Mean ± SD Max KD (%)
FAC	13	97.7	84.5 ± 9.1
SSA	10	96.6	85.8 ± 10.1



Results as of February 4, 2015

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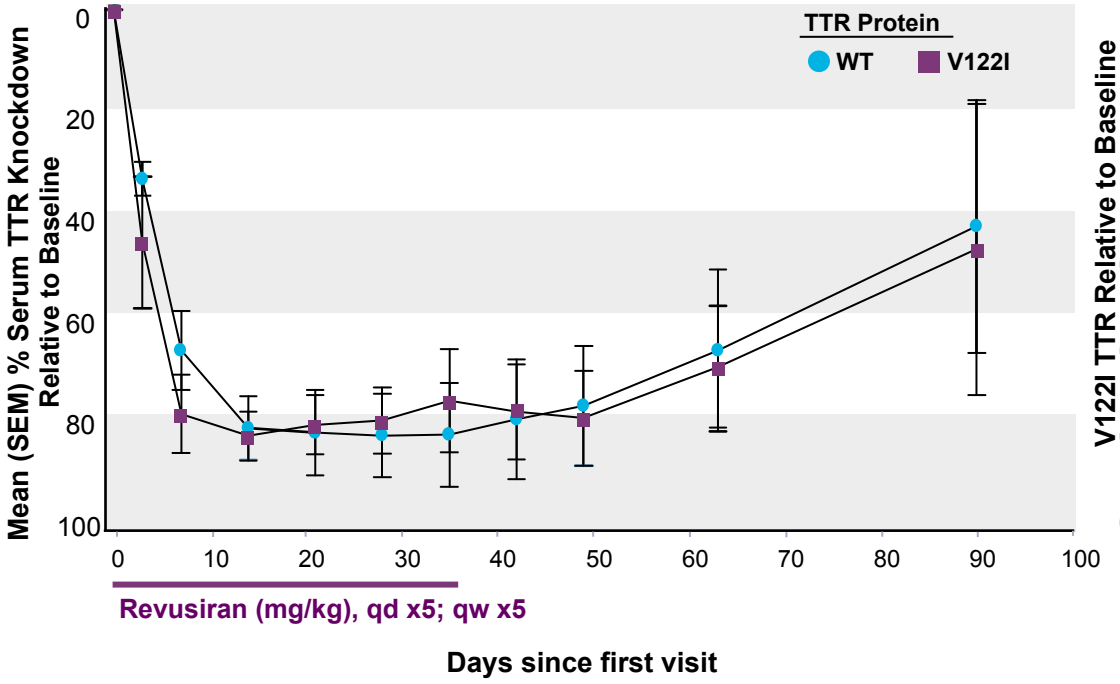
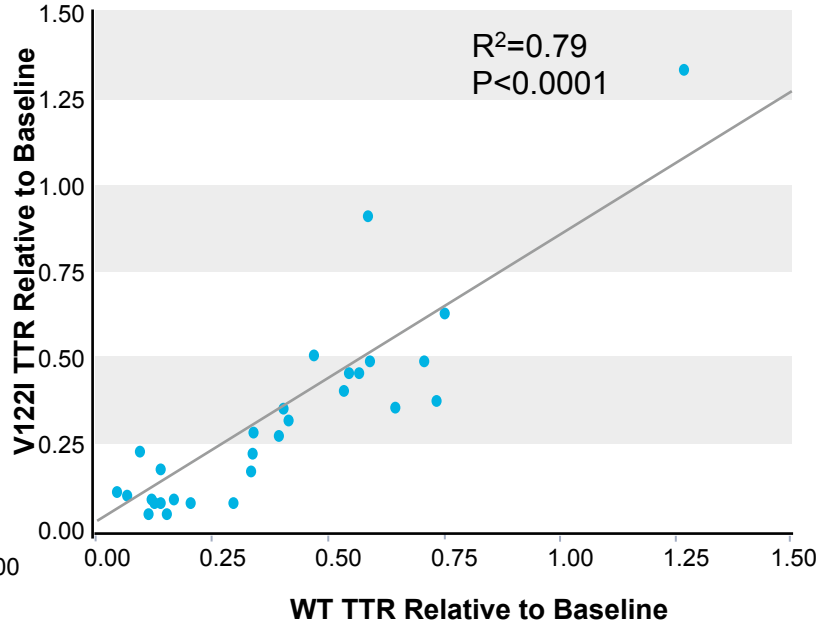
Revusiran Phase 2 Study Results

Knockdown of WT and Mutant TTR within V122I Patients

- Similar magnitude and kinetics of knockdown of WT and mutant TTR within individual V122I patients (N=4)
- Strong correlation of WT and mutant TTR knockdown in V122I patients





Results as of February 4, 2015

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Revusiran Phase 2 Study Results
Exploratory Clinical Measurements

	Actual Results at Each Visit Mean (SEM)						Changes from Baseline Mean (SEM)	
Measurements	N	Baseline	N	Day 42	N	Day 90	Δ Day 42*	Δ Day 90*
6-MWD (m)	26	407.7 (18.6)	26	426.7 (17.3)	24	409.5 (26.2)	19.0 (8.1)	2.7 (18.3)
mBMI (kg/m^2 x albumin [g/L])	26	1111.5 (39.7)	26	1119.0 (35.0)	26	1085.1 (35.5)	7.5 (18.4)	-26.4 (15.7)
KCCQ Overall Summary Score	26	72.7 (3.3)	26	70.2 (2.1)	26	70.6 (3.3)	-2.5 (1.8)	-2.1(2.9)
EQ-5D (max impairment=0)	26	0.84 (0.02)	26	0.81 (0.03)	26	0.83 (0.02)	-0.03 (0.02)	-0.01 (0.02)
Cardiac Biomarkers								
NT-proBNP (ng/L)	26	3435.0 (900.4)	26	3046.4 (571.6)	26	3274.2 (781.7)	-388.6 (380.4)	-160.9 (468.2)
Troponin I (ng/ml)	25	0.13 (0.02)	26	0.14 (0.02)	24	0.14 (0.02)	0.01 (0.01)	0.01 (0.01)

KCCQ: Kansas City Cardiomyopathy Questionnaire; EQ-5D score uses US references
* Mean [+/-SEM] changes are calculated using baseline and the corresponding follow-up visit

Results as of February 4, 2015

Revusiran Phase 2 Study Results
Exploratory Clinical Measurements

		Actual Results at Each Visit Mean (SEM)					Changes from Baseline Mean (SEM)	
Measurements	N	Baseline	N	Day 42	N	Day 90	Δ Day 42*	Δ Day 90*
Echocardiogram								
IVS Thickness (cm)	25	1.9 (0.06)	26	1.8 (0.06)	26	1.8 (0.06)	-0.01 (0.02)	-0.02 (0.02)
LVEF (%)	22	49.6 (2.3)	25	51.1 (2.4)	26	51.3 (1.8)	1.3 (1.1)	1.3 (1.4)
Longitudinal Strain (%)	23	-12.1 (0.6)	25	-11.9 (0.6)	25	-12.1 (0.5)	0.17 (0.4)	-0.08 (0.4)
Cardiac MRI								
LV Mass (g)	22	201.0 (12.4)	22	200.3 (13.0)	20	198.1 (13.8)	-0.67 (4.7)	-4.1 (4.3)
Stroke Volume (ml)	22	72.4 (3.6)	22	68.4 (3.8)	20	70.7 (3.8)	-4.1 (3.4)	-2.0 (3.4)
Global ECV	21	0.54 (0.01)	21	0.53 (0.01)	21	0.54 (0.01)	-0.01 (0.01)	0.01 (0.01)

IVS: Interventricular Septum; ECV: Extracellular Volume Fraction
* Mean [+/-SEM] changes are calculated using baseline and the corresponding follow-up visit

Results as of February 4, 2015

Revusiran Phase 2 Study Results
Summary

Multiple doses of revusiran generally well tolerated in TTR cardiac amyloidosis patients with low incidence of reported adverse events

- Transient mild injection site reactions in 15% of patients
- Transient mild LFT changes in 15% of patients, resolved with continued dosing
- No study discontinuations
- No clinically significant changes in renal function, other laboratory chemistries, or hematologic parameters

Revusiran achieved rapid, consistent, and durable knockdown of serum TTR

- Maximum knockdown of serum TTR up to 98.2%; mean maximum knockdown of 85.9%
- Comparable degree of TTR knockdown with 5.0 and 7.5 mg/kg and in FAC vs SSA patients
- Comparable knockdown of mutant and WT TTR protein within V122I patients

No significant changes observed in exploratory clinical measurements following 5-week course of revusiran treatment