Phase 2 Open-Label Extension (OLE) Study of Revusiran

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

04 July 2016 | ISA | Uppsala, Sweden

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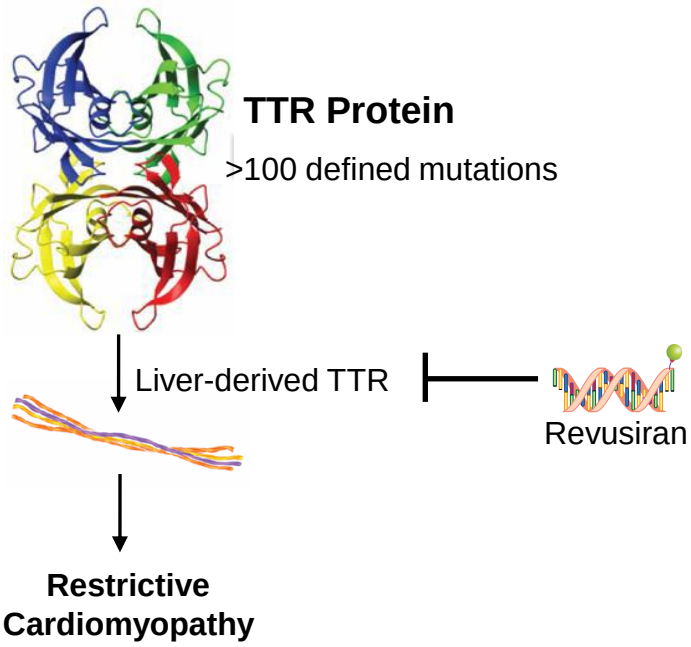
ATTR Cardiac Amyloidosis

Epidemiology

- Estimated >40,000 hereditary ATTR amyloidosis with cardiomyopathy (hATTR-CM also known as familial amyloidotic cardiomyopathy [FAC]) patients world wide
  - 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 wild type ATTR (wtATTR; also known as senile systemic amyloidosis [SSA]) worldwide

Rapidly Progressive Disease

- Onset >65 yrs
- Cardiac amyloid deposition leads to cardiac wall thickening, atrial arrhythmias, conduction disease and heart failure
- Median survival after diagnosis is poor
  - hATTR-CM: 26 months; wtATTR: 43 months[1]
  - hATTR-CM with V122I and T60A: 41 months[2,3]



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

[1] Ruberg et al. The Transthyretin Outcomes Survey *American Heart Journal* (2012)
[2] Connors et al. *Amyloid* (2011)
[3] Sattiannayagam PT, et al. *European Heart Journal* (2012)

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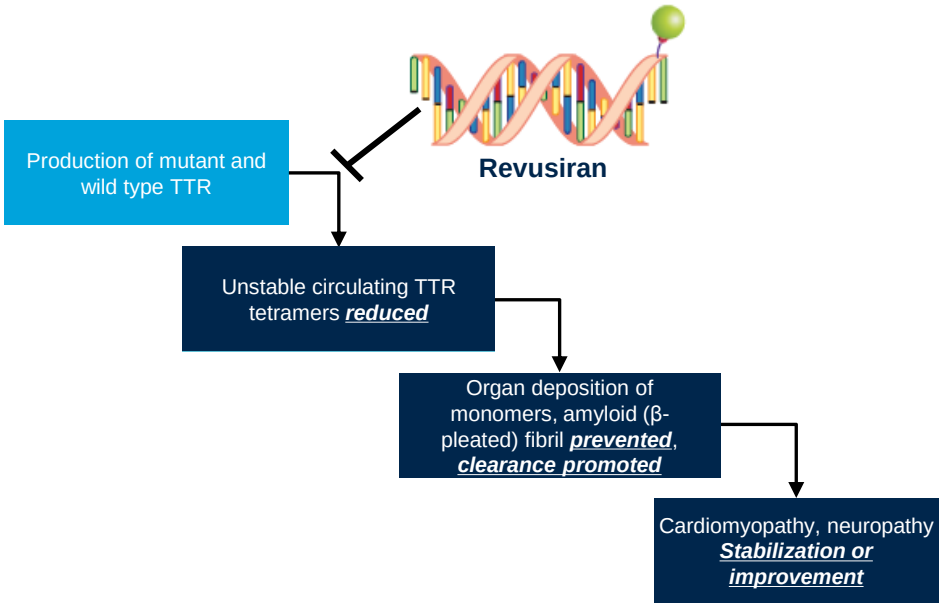
Revusiran
Clinical Development Overview

- International Nonproprietary Name designation for ALN-TTRsc = Revusiran (re-VOO-si-ran)
- First generation GalNAc-siRNA targeting TTR
- Subcutaneous delivery
- Positive Phase 1 study results[1]
  - Normal healthy volunteer study in UK
- Positive initial Phase 2 study results[2]
  - Patients with ATTR cardiac amyloidosis
- Phase 2 Open-Label Extension (OLE) ongoing
  - Preliminary 6-month data reported at EC ATTR, Nov 2015
- DISCOVERY study completed
  - Screening study examining prevalence of TTR mutations in patients suspected of having cardiac amyloidosis
    - Interim data reported at EC ATTR, Nov 2015
- ENDEAVOUR Phase 3 trial ongoing

Revusiran Therapeutic Hypothesis



[1]Zimmermann T, et al. *Heart Failure Society of America (HFSA) Annual Scientific Meeting* (2013)
[2]Gillmore J, et al. *American College of Cardiology (ACC) Annual Scientific Session* (2015)

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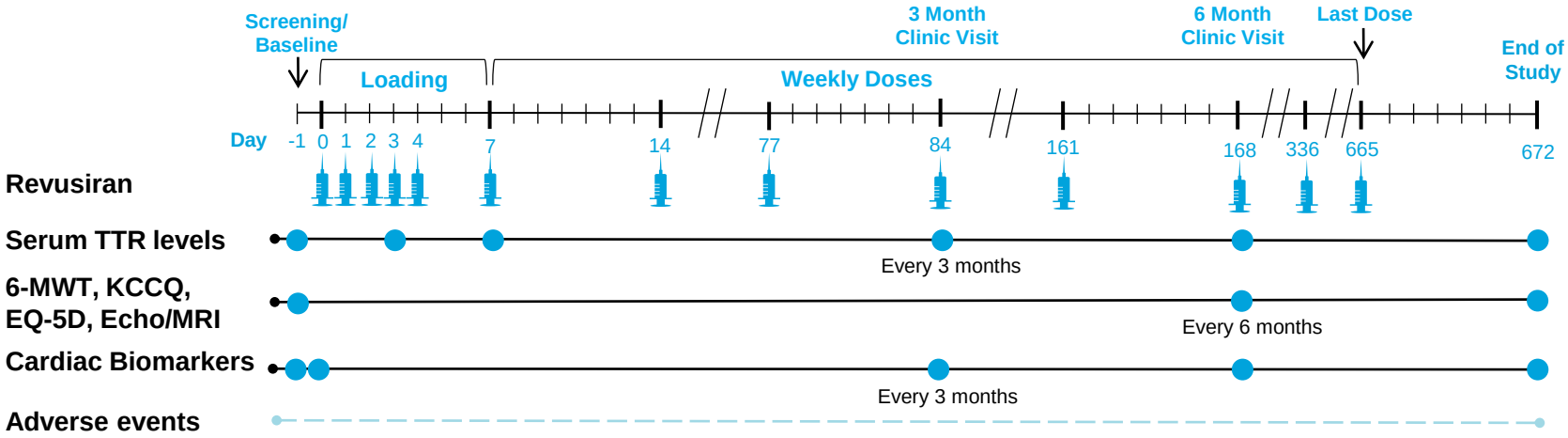
Revusiran Phase 2 OLE Study Design



hATTR-CM and wtATTR patients previously enrolled in Phase 2 study eligible to enter Phase 2 OLE study

- Chronic 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

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Revusiran Phase 2 OLE Preliminary Results*

Demographics and Exposure

This presentation highlights 12 month data from the study

Characteristics		hATTR-CM (N=14)	wtATTR (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 time from diagnosis to first dose (range)		34 months (5,94)	35 months (15,57)	35 months (5,94)
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		788	524	1312
Mean number of doses (range)		56 (14-80)	48 (9-67)	53 (9-80)
Mean treatment duration (range)		12 months (2-18)	10 months (1-15)	11 months (1-18)

AA: African American
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Revusiran Phase 2 OLE Preliminary Results*

Baseline Characteristics

Characteristics	Mean (range)					
	N	hATTR-CM	N	wtATTR	N	Total
mBMI (kg/m^2 x albumin [g/dL])	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 (1.7–2.5)	11	2.0 (1.5–2.9)	25	2.0 (1.5–2.9)
LVEF (%)	14	51 (28–69)	11	48 (27–64)	25	49 (27–69)
Longitudinal Strain (%)	14	-12.0 (-20.8 to -6.3)	11	-10.4 (-17.3 to -6.4)	25	-11.3 (-20.8 to -6.3)
Cardiac MRI						
LV Mass (g)	12	200 (135–338)	9	229 (156–387)	21	212.7 (135-387)
Stroke Volume (mL)	12	67.6 (44.6–97.2)	9	90.6 (61.9–123.4)	21	77.5 (44.6–123.4)
Global ECV	12	0.55 (0.4–0.7)	9	0.55 (0.4–0.8)	21	0.55 (0.4–0.8)

mBMI: Modified Body Mass Index; 6-MWD: 6-Minute Walk Distance; KCCQ: Kansas City Cardiomyopathy Questionnaire; EQ-5D score uses US references; IVS: Interventricular Septum; LVEF: Left Ventricular Ejection Fraction; LV: Left Ventricular; ECV: Extracellular Volume Fraction; H/CL: heart to collateral lung; 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 g (M), 103 g (F), Stroke Volume 78.6 mL (M), 59.3 mL (F), ECV <0.3

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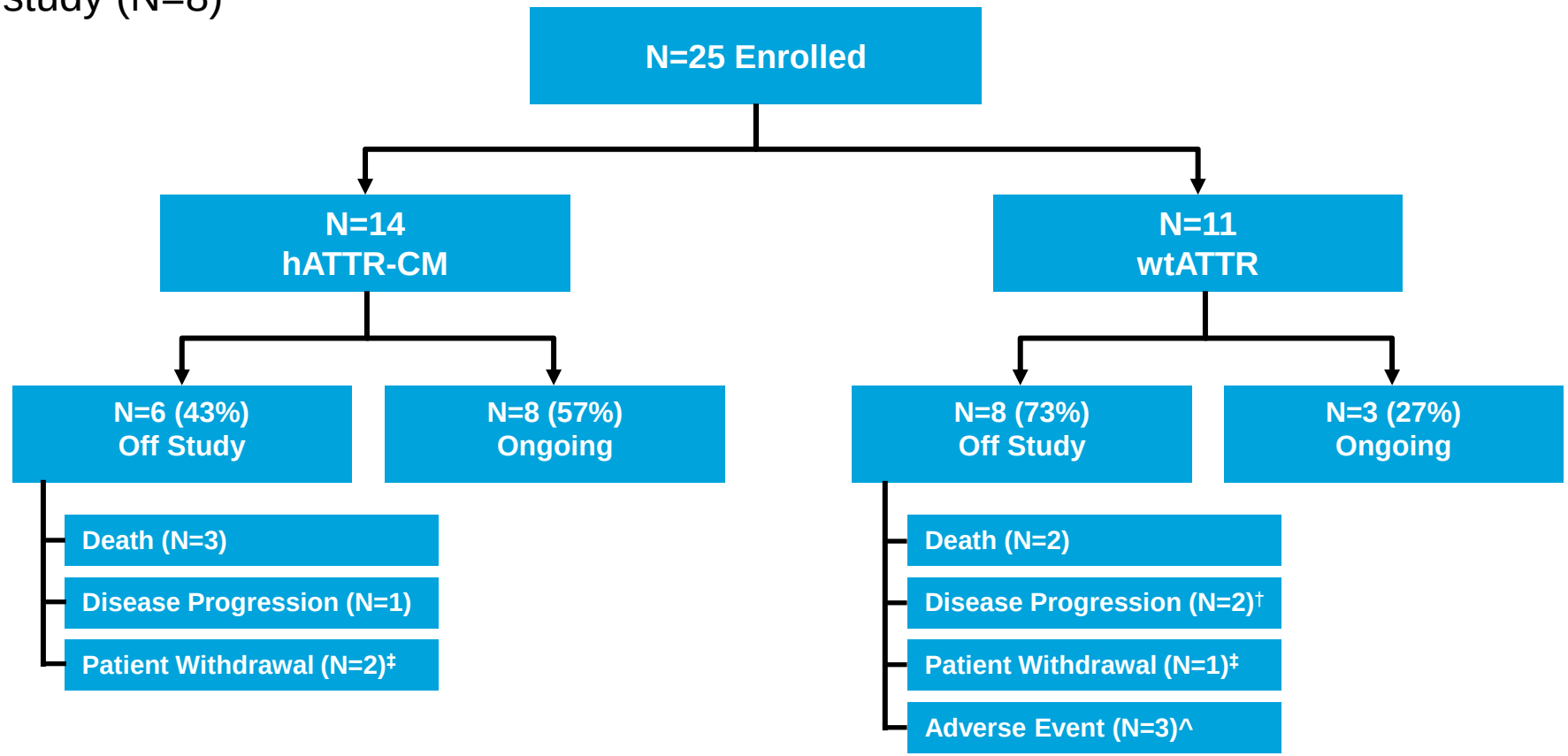
Revusiran Phase 2 OLE Preliminary Results*
Patient Disposition

- Disease progression and death, occurring after median time of 12 months (range 2-14 months) on study, are the most common reasons for discontinuation from the study (N=8)



† Both patients died during follow-up period
‡ Reason for withdrawals: 1 patient for end of life planning due to underlying disease progression, 1 patient with worsening peripheral neuropathy, 1 patient with stable cardiac disease unable to attend clinic visits (descriptions based on verbal investigator communication)
^ AEs due to ISRs or diffuse rashes as previously reported at EC-ATTR, November 2015
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Revusiran Phase 2 OLE Preliminary Results*

Patients who discontinued due to death or disease progression had longer time from diagnosis to first dose

Characteristics		Ongoing n=11	Off Study† n=8	P-value
Median Age (range)		68 years (53-73)	73 years (62-75)	p=0.07
Male Gender		9 (82%)	7 (88%)	p=1.00
TTR Type	**V122I**	3 (27%)	-	p=0.35
	T60A	3 (27%)	4 (50%)	
	I84S	1 (9%)	-	
	S77Y	1(9%)	-	
	Wild-Type	3 (27%)	4 (50%)	
NYHA Class	**I**	2 (18%)	0	p=0.14
	II	8 (74%)	4 (50%)	
	III	1 (9%)	4 (50%)	
Time from ATTR Diagnosis to First Dose on Ph2 OLE	**Mean (range)**	25 months (6-48)	48 months (26-94)	p < 0.05
Baseline 6MWD	**Mean (range)**	468 meters (316-617)	359 meters (73-444)	p=0.08

† Patients who discontinued for reasons of death or disease progression
P-value based upon non-parametric test to determine if there were differences between Ongoing versus Off study (t-test for continuous parameters and fisher's exact test for categorical)
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Summary of Safety

Common Adverse Events (AEs) reported in ≥ 20% of patients

AE by Preferred Term	Revusiran (N=25)
Patients with an AE, n (%)	25 (100%)
Cough	10 (40%)
Dizziness	10 (40%)
Injection site erythema	8 (32%)
Dyspnea	7 (28%)
Fatigue	7 (28%)
Edema peripheral	7 (28%)
Hypotension	6 (24%)
Injection site pruritus	6 (24%)
Neuropathy peripheral	6 (24%)
Atrial fibrillation	5 (20%)
Cardiac failure	5 (20%)
Constipation	5 (20%)
Fall	5 (20%)
Muscle spasms	5 (20%)
Weight decreased	5 (20%)

- 14 patients (56%) with serious adverse events (SAEs)
  - Only 1 deemed possibly related to study drug: patient with lactic acidosis, discontinued treatment; patient also had myopathy, neuropathy, hypotension, and vasoplegic shock resulting in death (all considered not related)
- 7 deaths (28%); all considered not related to study drug†
- 4 patients (16%) discontinued treatment due to drug-related AE
  - 3 patients due to recurrent localized reactions at the injection site or diffuse rash (previously reported at EC ATTR, 2015)
  - 1 patient due to lactic acidosis and other events as noted above
- Injection site reactions (ISR) reported in 12 patients (48%)
  - Majority of symptoms were mild in severity
    - Most common symptoms were erythema, pruritus, pain or swelling at the injection site
- 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, including platelets

† Deaths reported as: anoxic encephalopathy due to cardiac arrest; cardiac failure aggravated (disease progression); congestive heart failure; amyloid disease progression; heart failure, hypotension, lower respiratory tract infection; vasoplegic shock (lactic acidosis, myopathy, neuropathy, hypotension); Suicide

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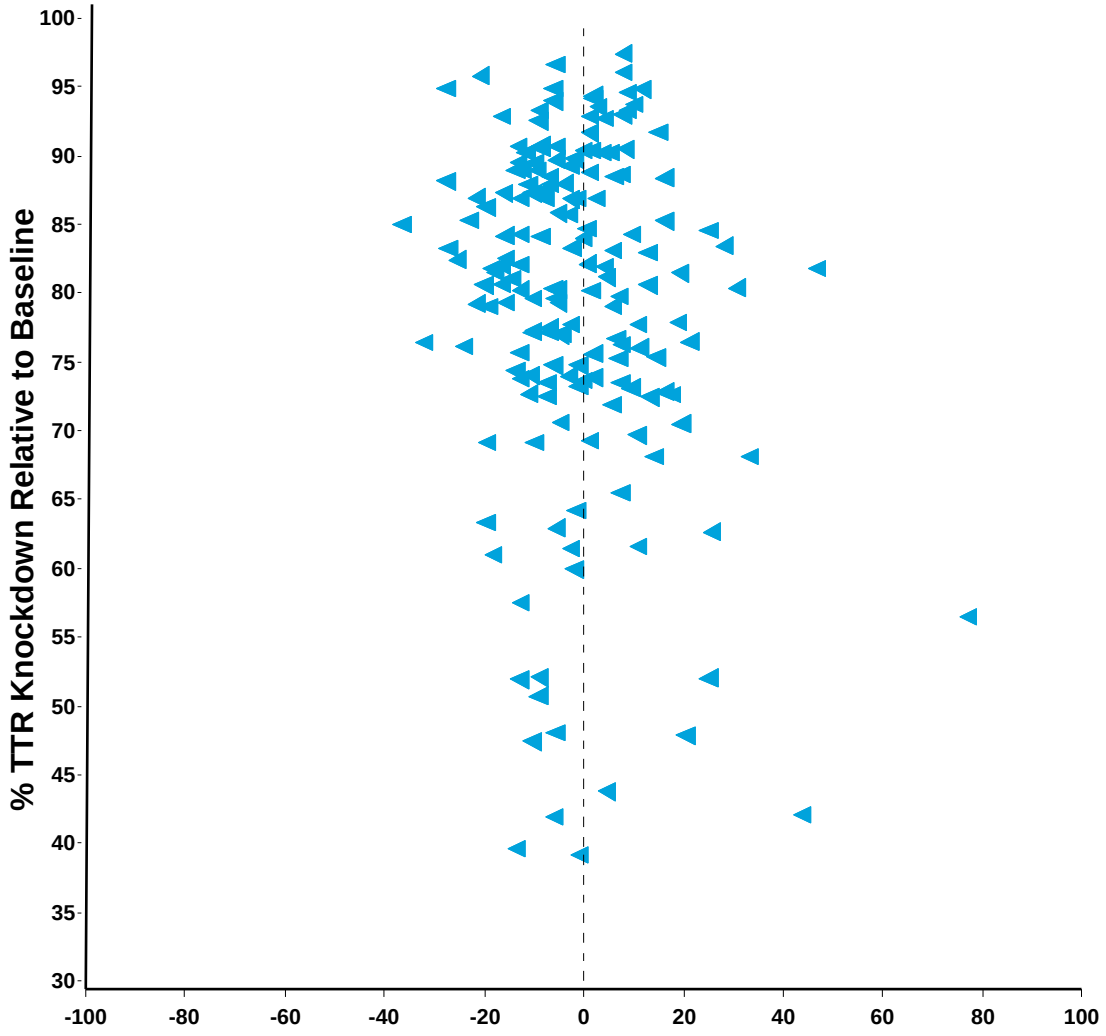
TTR KD Effect versus Platelets for All Visits

No correlation between TTR KD and change in platelets



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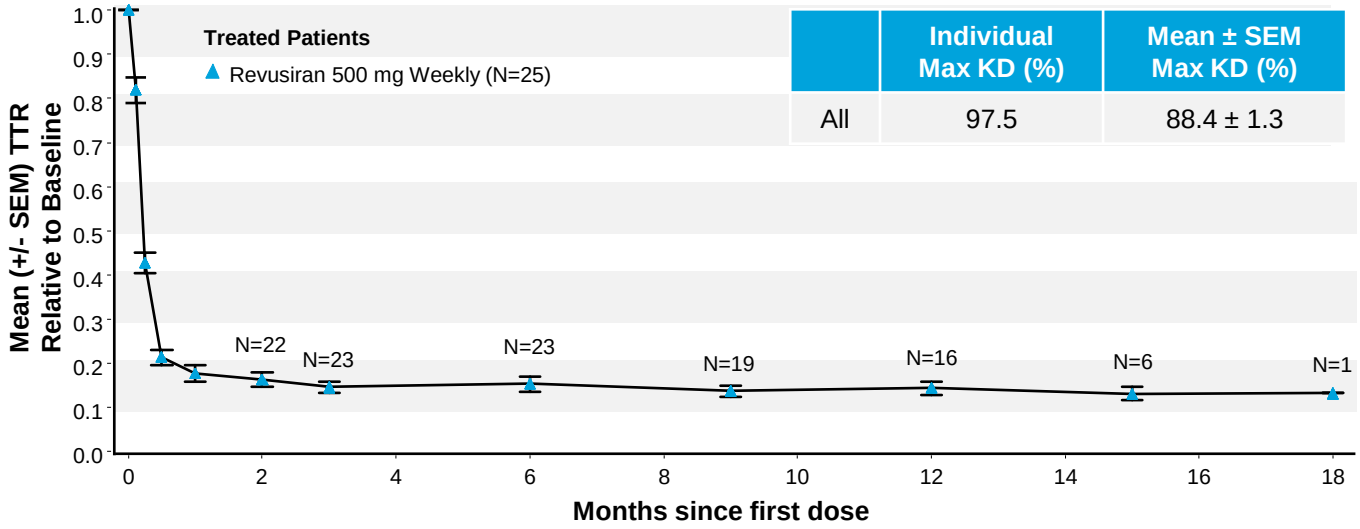
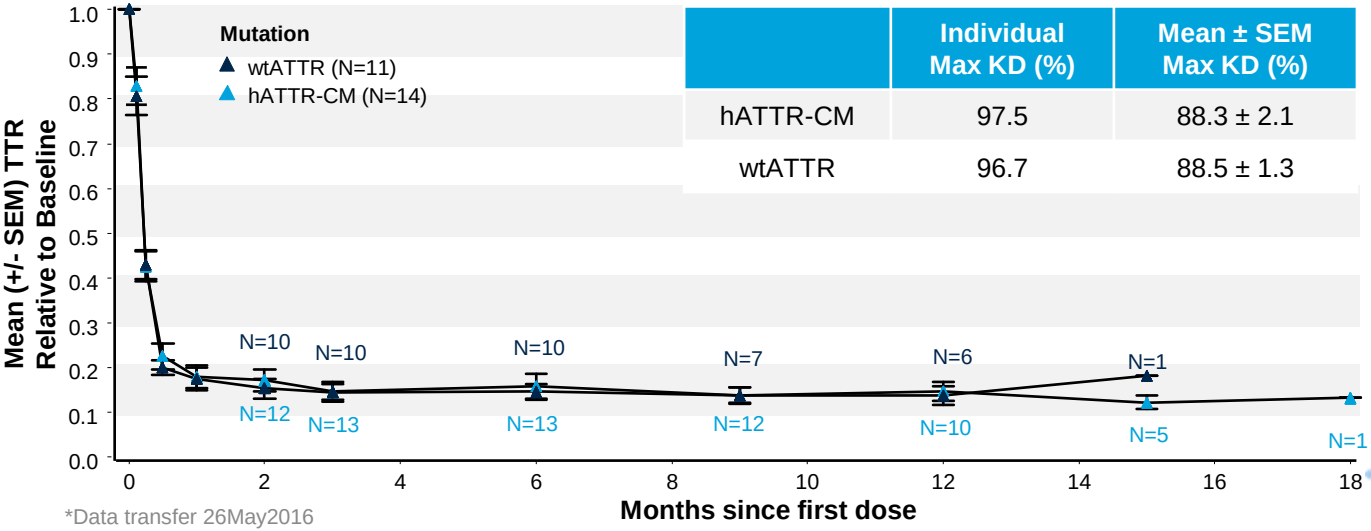
Revusiran Phase 2 OLE Preliminary Results*

Durable TTR Knockdown through 18 Months

- Longest first generation GalNAc-siRNA conjugate experience in humans to-date, low inter-patient variability and no diminished PD effect over time



	Individual Max KD (%)	Mean ± SEM Max KD (%)
All	97.5	88.4 ± 1.3



	Individual Max KD (%)	Mean ± SEM Max KD (%)
hATTR-CM	97.5	88.3 ± 2.1
wtATTR	96.7	88.5 ± 1.3

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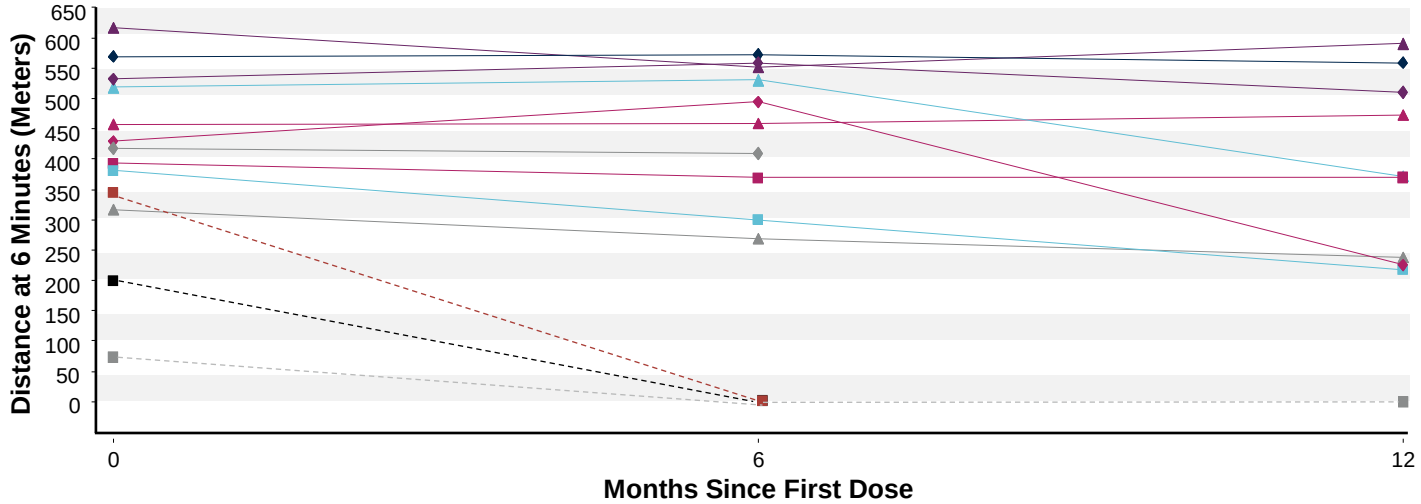
Revusiran Phase 2 OLE Preliminary Results*

Change in 6-MWD in hATTR-CM Patients

- 5 of 9 evaluable hATTR-CM patients have generally stable 6-MWD at 12 month compared to baseline with a mean change of -14 ± 8 meters



No Imputation			
	Baseline [meters]	**Δ Month 6 [meters]**	**Δ Month 12 [meters]**
Ph2 OLE	N=14	N=10	N=9
Mean ±SEM	400 ±39	-12 ±14	-73 ±26
Median (Min, Max)	406 (73, 617)	-4 (-81, 65)	-27 (-204, 15)
Natural History	N=37	N=30	N=24
Mean ±SEM	283 ±19	-23 ±21	-69 ±14
Median (Min, Max)	276 (46, 485)	-14 (-311, 209)	-57 (-188, 32)

With Imputation†			
	Baseline [meters]	**Δ Month 6 [meters]**	**Δ Month 12 [meters]**
Ph2 OLE	N=14	N=13	N=10
Mean ±SEM	400 ±39	-57 ±30	-73 ±23
Median (Min, Max)	406 (73, 617)	-24 (-345, 65)	-50 (-204, 15)
Natural History	N=39	N=32	N=27
Mean ±SEM	281 ±20	-36 ±23	-106 ±24
Median (Min, Max)	276 (46, 485)	-19 (-426, 209)	-79 (-499, 32)

† Patients too unwell to perform test at planned visit were imputed as 0 meters
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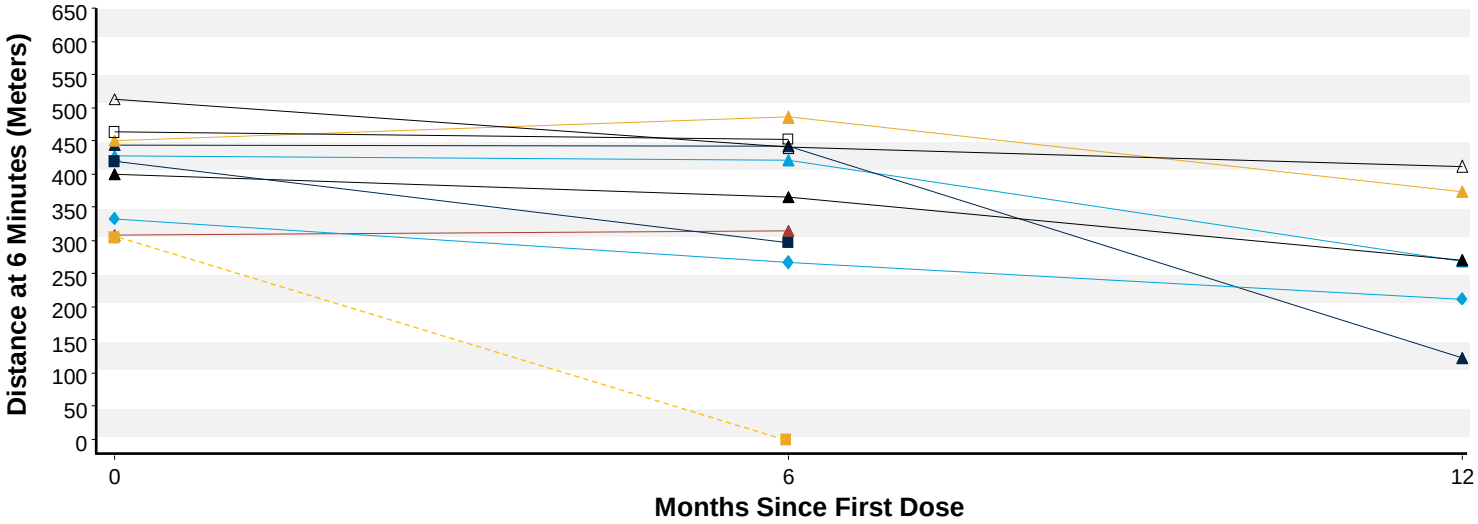
Revusiran Phase 2 OLE Preliminary Results*

Change in 6-MWD in wtATTR Patients



No Imputation				With Imputation†			
	Baseline [meters]	Δ Month 6 [meters]	Δ Month 12 [meters]		Baseline [meters]	Δ Month 6 [meters]	Δ Month 12 [meters]
Ph2 OLE	N=11	N=9	N=6	**Ph2 OLE**	11	N=10	N=6
Mean ±SEM	403 ±20	-30 ±16	-152 ±36	Mean ±SEM	403 ±20	-58 ±31	-152 ±36
Median (Min, Max)	419 (305, 513)	-11 (-122, 35)	-126 (-322, -78)	Median (Min, Max)	419 (305, 513)	-23 (-305, 35)	-126 (-322, -78)
Natural History	N=145	N=119	N=79	**Natural History**	N=153	N=125	N=88
Mean ±SEM	320 ± 9	-25 ± 7	-29 ± 10	Mean ±SEM	313 ±10	-30 ±7	-59 ±13
Median (Min, Max)	334 (16, 570)	-17 (-240, 136)	-11 (-259, 152)	Median (Min, Max)	333 (16, 570)	-22 (-345, 136)	-30(-506, 152)

† Patients too unwell to perform test at planned visit were imputed as 0 meters

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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	12 Month	Δ Month 6	Δ Month 12
mBMI (kg/m^2 x albumin [g/L])	16	1139 (58.6)	1061 (60.3)	977 (45.0)	-78 (16.8)	-162 (26.5)
KCCQ Overall Summary Score	15	79.3 (4.1)	74.5 (5.5)	63.4 (5.9)	-4.8 (2.2)	-15.9 (3.7)
EQ-5D (max impairment=0)	15	0.83 (0.04)	0.84 (0.04)	0.78 (0.04)	0.010 (0.03)	-0.055 (0.03)
Cardiac Biomarkers						
NT-proBNP (ng/L)	15	2188 (358)	2412 (401)	3136 (721)	224 (181)	949 (511)
Troponin I (ng/mL)	15	0.11 (0.02)	0.11 (0.02)	0.13 (0.02)	0.00 (0.01)	0.02 (0.02)
Echocardiogram						
IVS Thickness (cm)	16	2.1 (0.1)	2.1 (0.1)	2.1 (0.1)	0.01 (0.03)	-0.02 (0.05)
LVEF (%)	16	51.8 (2.8)	54.1 (3.5)	55.3 (3.5)	2.4 (1.9)	3.5 (2.3)
Longitudinal Strain (%)	16	-11.9 (0.9)	-12.4 (0.8)	-12.6 (0.8)	-0.5 (0.6)	-0.7 (0.7)
Cardiac MRI						
LV Mass (g)	10	240.1 (29.1)	249.2 (26.9)	251.7 (25.7)	8.5 (13.3)	10.9 (17.1)
Stroke Volume (mL)	9	86.1 (6.7)	88.0 (4.8)	92.9 (5.7)	1.9 (5.0)	6.9 (7.5)
Global ECV	9	0.51 (0.02)	0.48 (0.03)	0.54 (0.03)	-0.03 (0.02)	0.02 (0.03)

KCCQ: Kansas City Cardiomyopathy Questionnaire; EQ-5D score uses US references; mBMI: Modified Body Mass Index; IVS: Interventricular Septum; ECV: Extracellular Volume Fraction; H/CL: heart to collateral lung

† Includes results for pooled hATTR-CM and wtATTR patients with available data at baseline and 12 months

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Revusiran Phase 2 OLE Preliminary Results*
Summary

Phase 2 OLE study includes patient population with advanced ATTR cardiac amyloidosis

- Mean time from diagnosis to first dose of 35 months
- Disease progression and death were primary reason for study discontinuation
- Longer time from diagnosis identified as risk factor for discontinuation due to disease progression and death
- Preliminary data from ENDEAVOUR suggest that patients have shorter time to first dose of study drug compared to Phase 2 OLE

Safety and tolerability of revusiran out to 18 months exposure

- 7 deaths occurred; none considered related to study drug
- 4 patients discontinued treatment due to drug-related AE; no new discontinuations due to ISRs

Revusiran achieves durable TTR lowering of >85%

- Maximum knockdown of serum TTR up to 98%; mean maximum knockdown of 88%
- Comparable degree of TTR knockdown in hATTR-CM and wtATTR patients

6-MWD results generally in line with natural history data

- Majority of evaluable hATTR-CM patients (5 of 9) showed stable 6-MWD at 12 months
  - Mean change in 6-MWD of -14 ± 8 meters at 12 months

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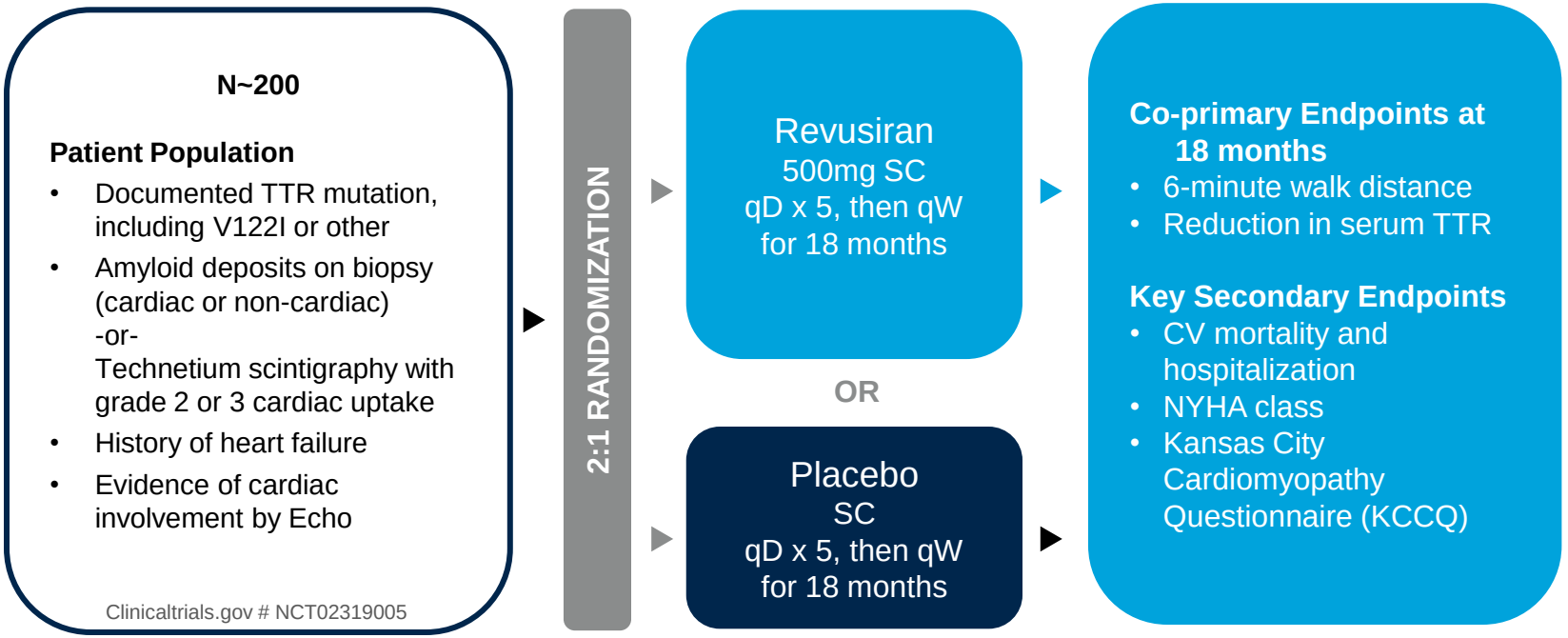
ENDEAVOUR Phase 3 Study Design

Expect to complete enrollment by end summer and report data in early 2018



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 FAC patients (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 months

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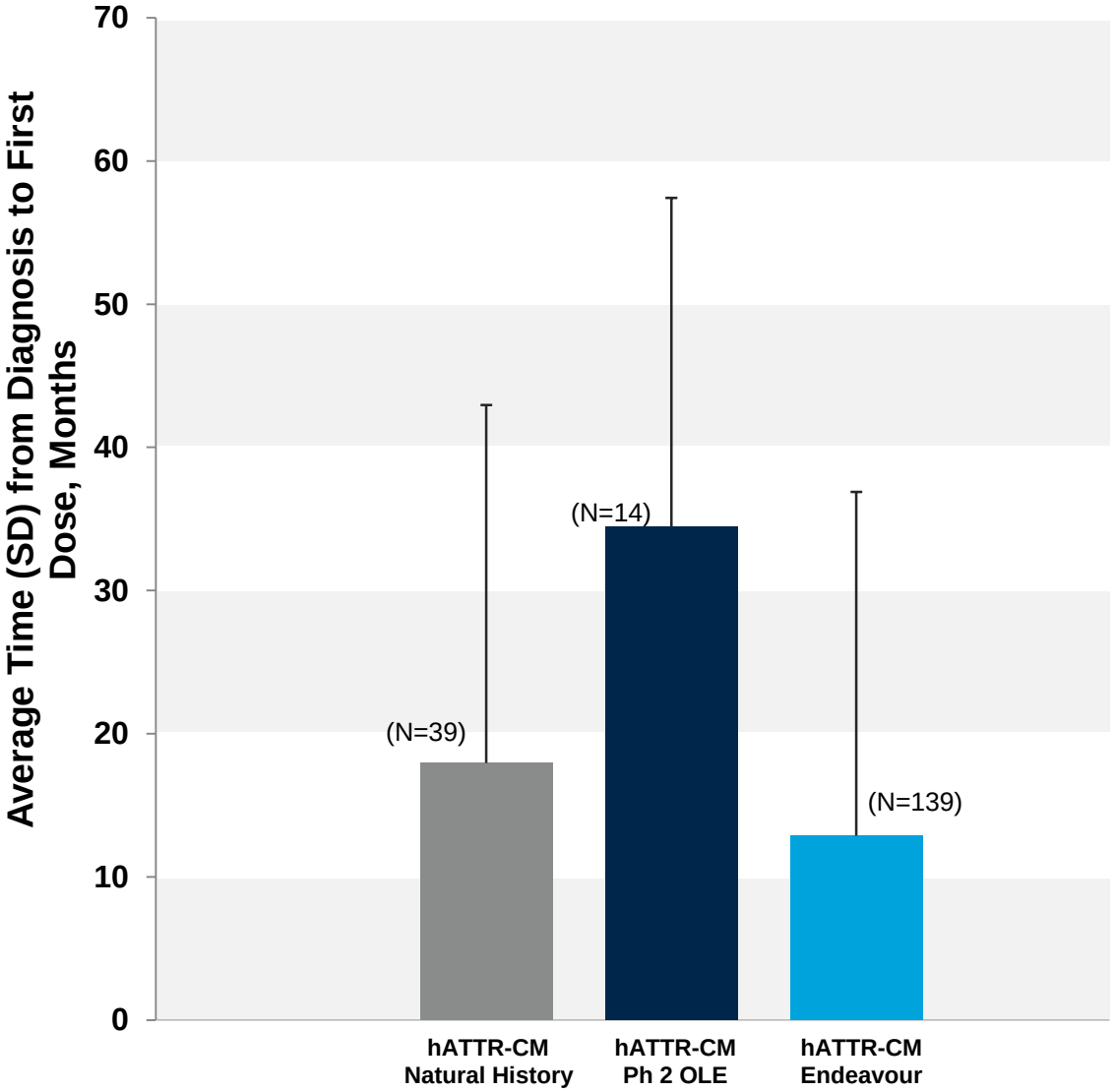
Time from Diagnosis Across hATTR-CM Studies



SD: standard deviation bars
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Thank You!

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