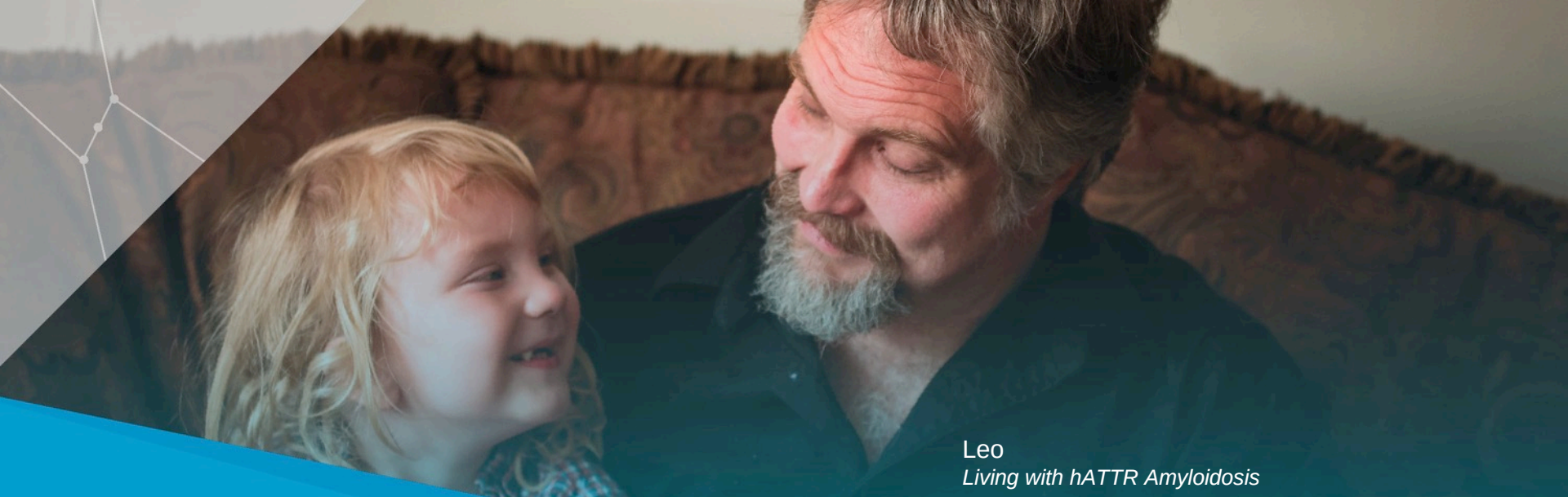

Leo
Living with hATTR Amyloidosis

Investigation of Mortality Imbalance in Revusiran Phase 3 Study, ENDEAVOUR

August 9, 2017

RNAi ROUNDTABLE 2017

Alnylam® PHARMACEUTICALS

Agenda

Welcome

- Josh Brodsky, Associate Director, Investor Relations & Corporate Communications

Executive Summary

- John Maraganore, Ph.D., Chief Executive Officer

Revusiran Investigation Results

- Akshay Vaishnaw, M.D., Ph.D., Executive Vice President of R&D

Q&A Session

Reminders

Event will run for approximately 60 minutes

Q&A Session at end of presentation

- Submit questions at top of webcast screen
- Questions may be submitted at any time

Replay, slides and transcript available at www.alnylam.com/capella

Alnylam Forward Looking Statements

This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies; delays, interruptions or failures in the manufacture and supply of our product candidates; our ability to obtain, maintain and protect intellectual property, enforce our intellectual property rights and defend our patent portfolio; our ability to obtain and maintain regulatory approval, pricing and reimbursement for products; our progress in establishing a commercial and ex-United States infrastructure; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses, obtain additional funding to support our business activities and establish and maintain business alliances; the outcome of litigation; and the risk of government investigations; as well as those risks more fully discussed in our most recent quarterly report on Form 10-Q under the caption “Risk Factors.” If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements

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Q&A Session

Executive Summary

Background

- Following reports of peripheral neuropathy and elevated blood lactate levels in revusiran Phase 2 Open Label Extension study (OLE), Alnylam requested *ad-hoc* ENDEAVOUR Data Monitoring Committee (DMC) meeting
  - DMC met October 4, 2016 to conduct unblinded safety review of ENDEAVOUR data
    - Imbalance in mortality on revusiran arm compared to placebo (16:2, revusiran:placebo)
    - No imbalance in peripheral neuropathy or lactic acidosis observed at the time
  - Dosing stopped in all revusiran studies Oct 5, 2016
- ENDEAVOUR patients followed until ≥3 mo after last dose
  - Extensive investigational plan and data reviewed with FDA and ex-US regulatory authorities, investigators, and independent academic cardiologists and neurologists

Executive Summary

Key Findings

- Mortality imbalance observed in revusiran vs. placebo arm in ENDEAVOUR phase 3 trial in hATTR amyloidosis with cardiomyopathy
- Extensive investigational plan and data reviewed with regulatory authorities, investigators and cardiac expert panel. Key findings include:
  - No significant baseline imbalance, although greater % >75 yrs of age in revusiran arm
  - No clinical evidence for revusiran-related cardiotoxicity
  - No evidence for PK/PD related mortality
  - Some evidence to suggest lower than expected mortality in placebo group at time of discontinuation
  - However, investigation cannot exclude possibility of drug-related effect
- Further to initial Phase 2 OLE reports, peripheral neuropathy adverse events observed in 20% of revusiran and 12% of placebo patients in ENDEAVOUR
  - Consistent with underlying disease, but potential role for revusiran cannot be excluded

Results will inform future studies with patisiran/ALN-TTRsc02 in hATTR amyloidosis with cardiomyopathy

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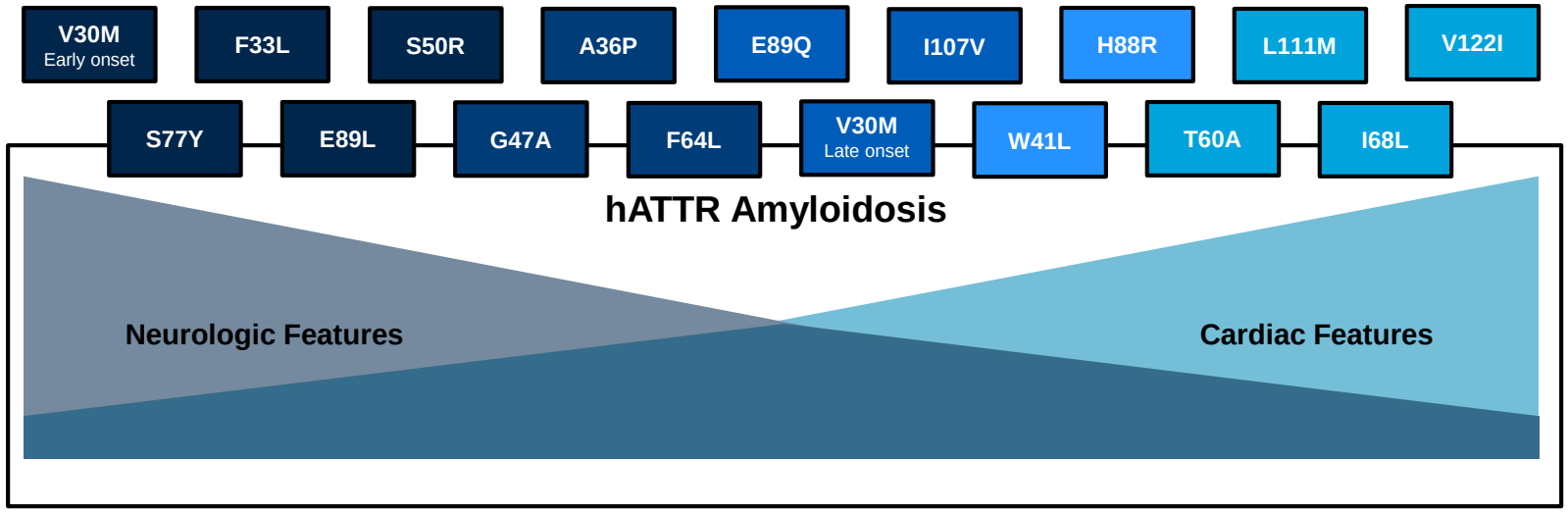
Revusiran Investigation Results
Agenda

- hATTR Amyloidosis and Revusiran Background
- Investigation of ENDEAVOUR Mortality Imbalance
- Implications of Revusiran Findings for TTR Programs and Platform

Hereditary ATTR (hATTR) Amyloidosis

- Orphan, multi-system disease caused by mutant transthyretin (TTR) amyloid deposits in nerves, heart, GI tract, and other tissues
- Range of clinical presentations including neuropathy and cardiomyopathy, with most patients having a mixed presentation of symptoms



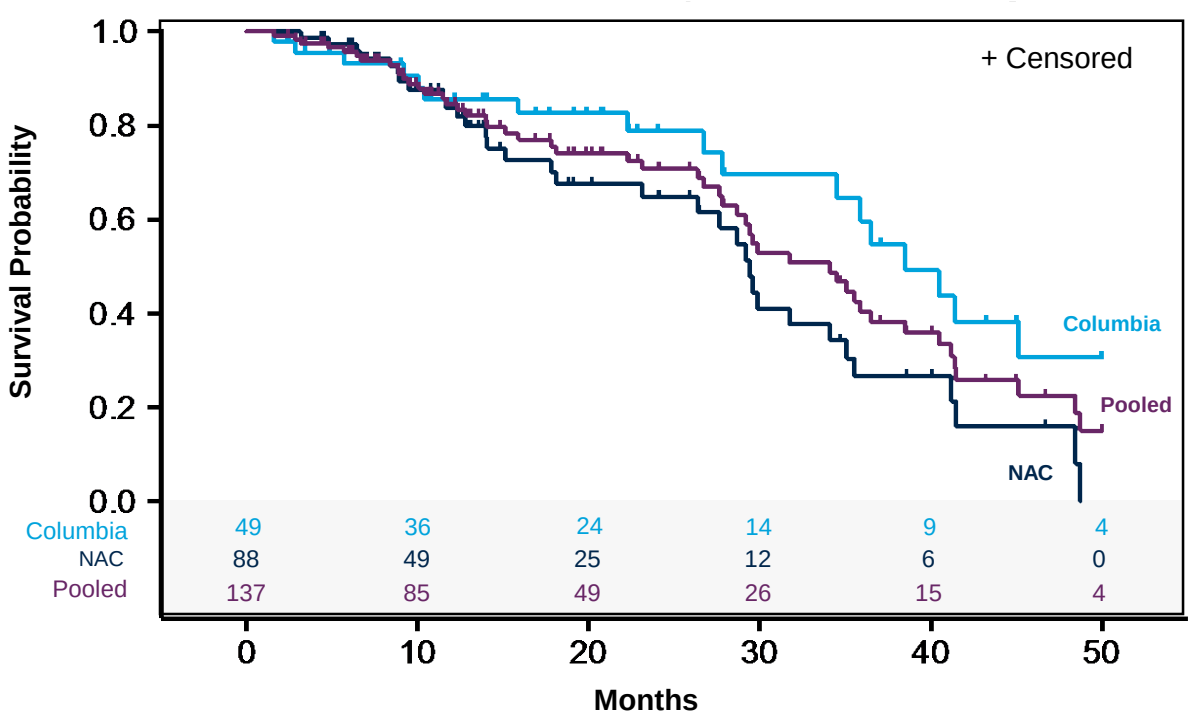
1. Based on Rapezzi et al. *EHJ* 2013;34:520–8; Semigran et al. *JACC* 2016;68:173–75

Natural History of hATTR Amyloidosis with Cardiomyopathy

Rare, complex disease with high morbidity and mortality

- Fatal within 2.5 - 5 years of diagnosis[1-3]

Survival in hATTR amyloidosis with cardiomyopathy at the National Amyloidosis Center (NAC, UK) and Columbia University



[1] Hawkins et al, *Ann Med*, 2015
[2] Maurer et al, *JACC*, 2016
[3] Gilmore et al. presented at *EU ATTR* Nov 2015

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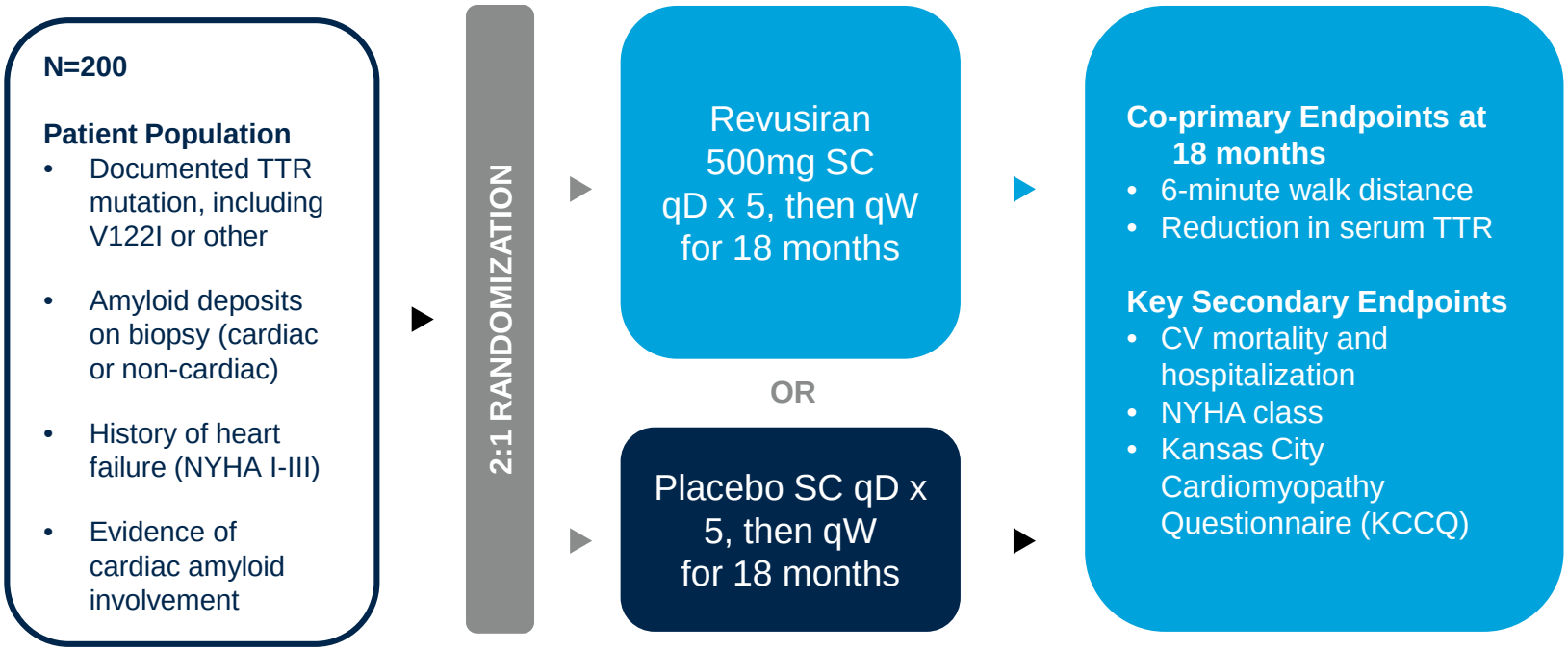
ENDEAVOUR Phase 3 in hATTR Amyloidosis with Cardiomyopathy



- Median follow-up at time of dosing cessation ~6 mo; precludes assessment of primary efficacy endpoint and therapeutic hypothesis

Clinicaltrials.gov # NCT02319005

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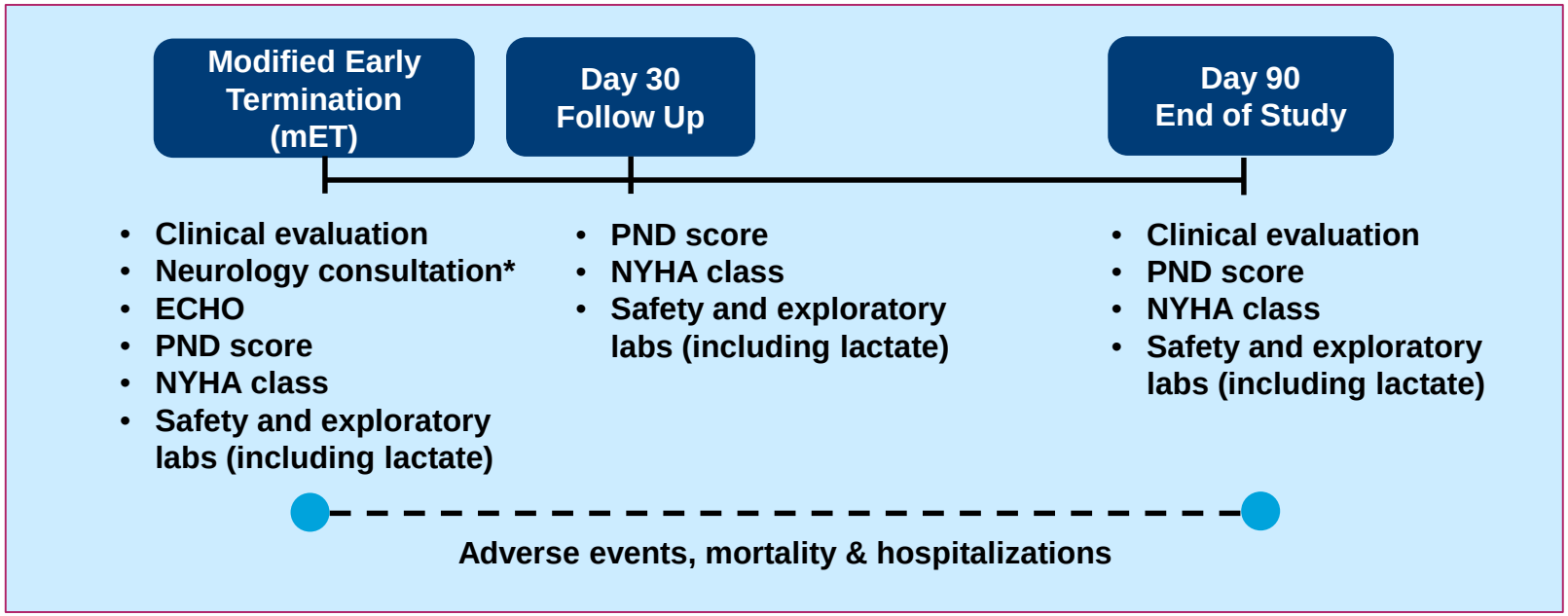
ENDEAVOUR Protocol Amendment Post Discontinuation

Amendment incorporated additional safety monitoring



* For patients with new onset or worsening peripheral neuropathy

ENDEAVOUR Study Population (1/2)

ENDEAVOUR enrolled older patients with advanced heart failure and multiple other cardiovascular risk factors

Characteristics		Placebo N=66	Revusiran N=140
Median Age (Q1,Q3)		68 (62,73)	69 (64,76)
Age ≥ 75		12 (18%)	43 (31%)
Male Gender, n (%)		53 (80%)	105 (75%)
TTR Genotype, n (%)	**V122I**	37 (56%)	80 (57%)
	T60A	12 (18%)	21 (15%)
	E89Q	2 (3%)	3 (2%)
	Other	15 (23%)	36 (26%)
NYHA Class, n (%)	**I**	4 (6%)	13 (9%)
	II	42 (64%)	83 (59%)
	III	20 (30%)	44 (31%)
Polyneuropathy Disability Score (PND), n (%)	**0**	35 (53%)	62 (44%)
	1	20 (30%)	55 (39%)
	2	11 (17%)	23 (16%)
eGFR (mL/min/1.73m^2), n (%)	**≥90**	7 (11%)	15 (11%)
	>60 to <90	28 (42%)	63 (45%)
	>30 to ≤60	31 (47%)	62 (44%)
Median mBMI (kg/m^2 x albumin [g/dL]) (Q1,Q3)		1067 (944,1222)	1071 (974,1239)
Median Baseline 6-MWD (m) (Q1, Q3)		404 (300,488)	385 (309,456)

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ENDEAVOUR Study Population (2/2)

ENDEAVOUR enrolled older patients with advanced heart failure and multiple other cardiovascular risk factors

Characteristics Median (Q1,Q3)	Placebo N=66	Revusiran N=140
NT-proBNP (ng/L)	2719 (1396,4846)	2371 (1363,3711)
Troponin T (ug/L)*	0.035 (0.05)	0.043 (0.06)
Troponin I (ug/L)^	0.13 (0.07, 0.20)	0.12 (0.07,0.22)
LV Mass (g)	329 (285-362)	323 (269-384)
LVEF (%)	53 (45-60)	56 (45-63)
Longitudinal Strain (%)	-9.7 (-12.2, -7.8)	-10.7 (-13, -8.5)
IVS Thickness (cm)	1.9 (1.7-2.0)	1.8 (1.7-2.0)
Cardiac Output (l/min)	3.0 (2.6, 3.7)	3.2 (2.6, 4.1)

* Mean (Standard Deviation)
^Troponin I LLOQ < 0.016 ug/L

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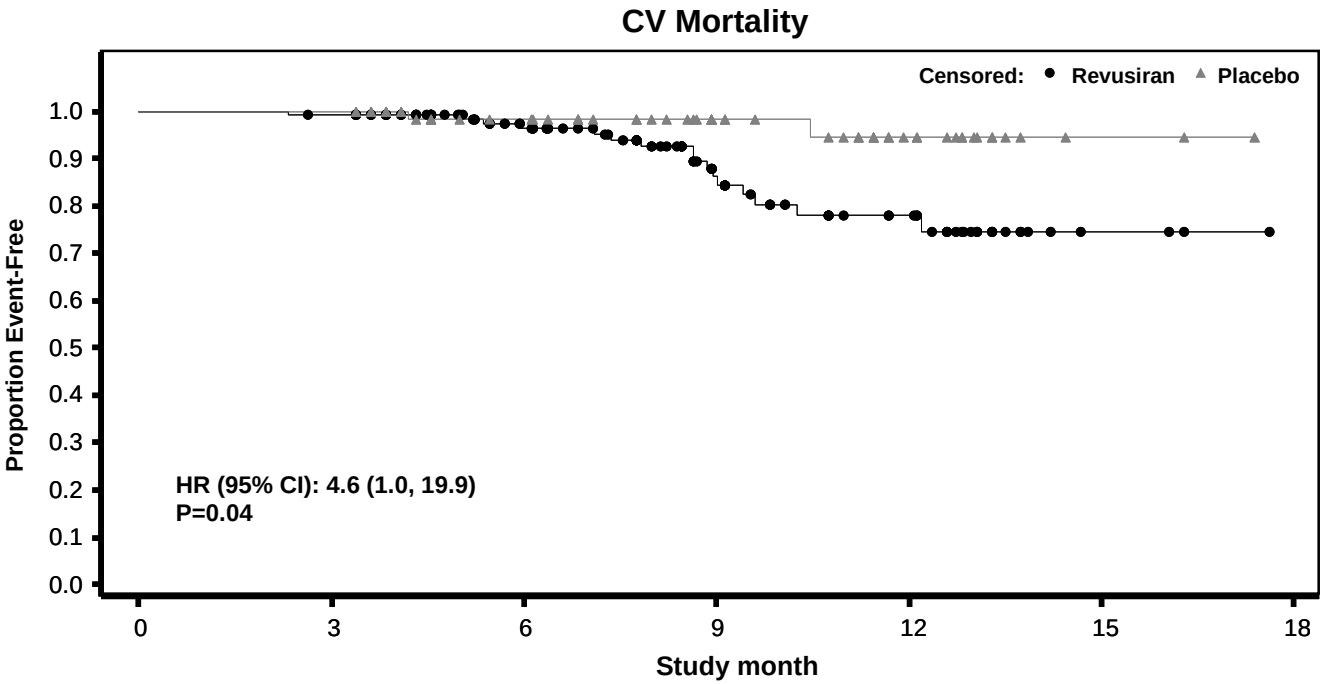
Observed Mortality Imbalance in ENDEAVOUR

Imbalance in cardiovascular (CV) mortality in revusiran versus placebo

- Majority of deaths CV, primarily heart failure, as expected in study population

	Placebo N=66	Revusiran N=140
All Deaths	2 (3%)	18 (13%)
CV Deaths	2 (3%)	16 (11%)



Number of Patients at Risk							
Revusiran	140	138	93	49	26	3	0
Placebo	66	66	47	29	15	2	0

All mortality and hospitalization events were adjudicated by independent committee
Follow-up through 4 Nov 2016

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Baseline Characteristics in Revusiran Patients by Outcome

Mortality on revusiran occurred in older patients with advanced disease

Characteristics Median (Q1, Q3)		Revusiran Alive N=122	Revusiran Dead N=18
Median Age		68 (63,75)	77 (71,78)
Age ≥ 75, n (%)		33 (27%)	10 (56%)
Male Gender, n (%)		96 (79%)	9 (50%)
TTR Genotype, n (%)	**V122I**	67 (55%)	13 (72%)
	T60A	19 (16%)	2 (11%)
	E89Q	3 (3%)	0 (0%)
	Other	33 (27%)	3 (17%)
NYHA Class, n (%)	**I**	13 (11%)	0 (0%)
	II	77 (63%)	6 (33%)
	III	32 (26%)	12 (67%)
eGFR (mL/min/1.73m^2)		67 (52,79)	52 (40,65)
6-MWD (m)		386 (320,464)	317 (228,408)
NT-proBNP (ng/L)		2254 (1262,3520)	3547 (2699,8973)
Troponin T (ug/L)*		0.039 (0.06)	0.072 (0.06)
Troponin I (ug/L)^		0.11 (0.06,0.21)	0.20 (0.16,0.29)
LVEF (%)		56 (45,63)	49 (44,60)
IVS (cm)		1.8 (1.7,2.0)	1.8 (1.7,2.0)
Global Longitudinal Strain (%)		-11.1 (-13.3, -9.3)	-9.5 (-10.7, -6.8)
Cardiac Output (l/min)		3.4 (2.8,4.1)	2.5 (2.0,3.0)

* Mean (Standard Deviation)
^ Troponin I LLOQ < 0.016 ug/L

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Revusiran Investigation Results
Agenda

- hATTR Amyloidosis and Revusiran Background
- Investigation of ENDEAVOUR Mortality Imbalance
- Implications of Revusiran Findings for TTR Programs and Platform

Revusiran Safety Investigation

Comprehensive evaluation of ENDEAVOUR Phase 3 results

- Two key time points analyzed
  - November 4, 2016, approximately 30 days after dosing discontinuation to evaluate for potential direct drug toxicity
  - March 30, 2017, includes safety follow-up to explore any carry-over effects
- Regulatory and expert input sought on final ENDEAVOUR safety analysis
  - Expert panel with extensive cardiovascular clinical trial experience and/or ATTR amyloidosis expertise
  - ATTR amyloidosis neuropathy expert reviewed patients referred for neurology consult
  - Investigational plan submitted to FDA
  - Multiple interactions with regulatory agencies to share interim and final data
- Assessed a number of potential hypotheses on mortality imbalance

Investigation of ENDEAVOUR Mortality Imbalance

- Hypothesis 1: Mortality related to baseline imbalance
- Hypothesis 2: Mortality resulting from cardiotoxicity
- Hypothesis 3: Mortality resulting from PK or PD related toxicity
- Hypothesis 4: Mortality imbalance related to lower than expected mortality in placebo group at time of discontinuation

Hypothesis 1: Mortality Related to Baseline Imbalance

Treatment arms generally balanced for baseline characteristics

- Of note, greater proportion of patients age ≥75 on revusiran
  - However, adjusting for age in multivariate model did not explain mortality imbalance
- Medical history and concomitant medications balanced

Characteristics Median (Q1,Q3)	Placebo N=66	Revusiran N=140
Median Age	68 (62,73)	69 (64, 76)
Age ≥ 75 years, n (%)	12 (18%)	43 (31%)
NYHA Class, n (%) I	4 (6%)	13 (9%)
II	42 (64%)	83 (59%)
III	20 (30%)	44 (31%)
eGFR (mL/min/1.73m^2)	61 (46,78)	65 (49,78)
6-MWD (meters)	404 (300,488)	385 (309,456)
NT-proBNP (ng/L)	2719 (1396,4846)	2371 (1363,3711)
Troponin T (ug/L)*	0.035 (0.05)	0.043 (0.06)
Troponin I (ug/L)^	0.13 (0.07,0.20)	0.12 (0.07,0.22)
Longitudinal Strain	-9.7 (-12.2, -7.8)	-10.7 (-13.0, -8.5)
LVEF (%)	52.5 (45,60)	56 (45,63)

* Mean (Standard Deviation)
^Troponin I LLOQ < 0.016 ug/L

Investigation of ENDEAVOUR Mortality Imbalance

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Hypothesis 2: Mortality Resulting from Cardiotoxicity

- No clinical evidence of direct revusiran-related cardiotoxicity
- Findings consistent with similar progression of heart failure in both treatment arms
  - Similar change over time in key echocardiographic parameters and cardiac biomarkers
  - Similar time to first and recurrent CV and HF hospitalization
- Analyses of lactate and electron microscopy of biopsy samples do not suggest evidence for revusiran-related mitochondrial toxicity

Analysis of Cardiac Biomarkers and Functional Parameters
Matched Pairs*

No difference in change over time to suggest revusiran-related cardiotoxicity

Parameter Median (Q1, Q3)		Placebo N=66		Revusiran N=140
LVEF (%)	**N**		**N**	
Baseline	38	51 (42,59)	73	57 (45,64)
6 months	38	48 (43,57)	73	58 (46,63)
Longitudinal Strain (%)				
Baseline	38	-9.3 (-12.2, -7.5)	72	-11.0 (-12.9, -8.4)
6 months	38	-9.2 (-10.8, -6.6)	72	-10.8 (-13.2, -8.4)
NT-proBNP (ng/L)				
Baseline	40	2698 (1421,4869)	70	2426 (1262,3678)
3 months	40	3124 (1736,4398)	70	2444 (1059,4057)
6 months	40	3514 (1519,5223)	70	2812 (1489,4867)
Troponin I (ug/L)^				
Baseline	40	0.14 (0.08,0.22)	75	0.11 (0.06,0.21)
3 months	40	0.15 (0.07,0.21)	75	0.11 (0.06,0.15)
6 months	40	0.15 (0.08,0.32)	75	0.11 (0.06,0.19)

*Includes patients with data available at all indicated time points; similar findings when all available data are considered
Normal Ranges: LVEF > 55%, Longitudinal Strain < -17 (less negative = more abnormal), NT-proBNP < 285ng/L, Troponin I < 0.03ug/L

^Troponin I LLOQ < 0.016 ug/L

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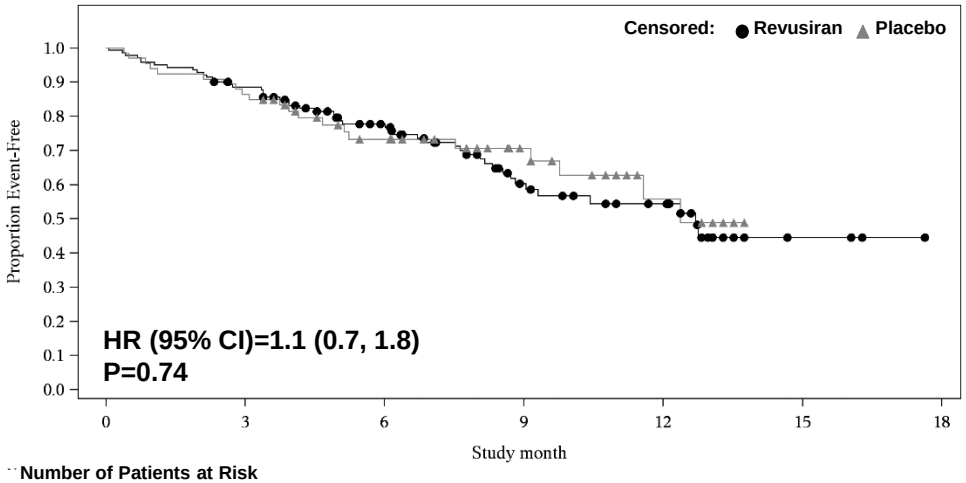
Time to first CV and HF Hospitalizations Similar Between Arms

Cardiovascular and heart failure hospitalizations do not mirror observed imbalance in mortality

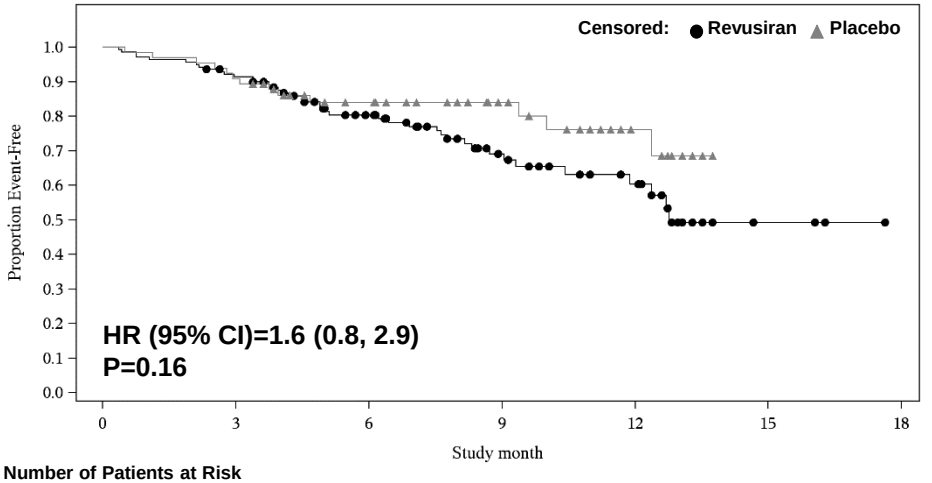
	Placebo N=66	Revusiran N=140
No. (%) of Patients with at least one CV Hospitalization	21 (32%)	49 (35%)
No. (%) of Patients with at least one HF Hospitalization	13 (20%)	41 (29%)

Time to First CV Hospitalization



Number of Patients at Risk							
Revusiran	140	122	77	36	21	3	0
Placebo	66	57	34	19	8	0	0

Time to First HF Hospitalization



Number of Patients at Risk							
Revusiran	140	126	79	40	22	3	0
Placebo	66	60	39	24	10	0	0

All mortality and hospitalization events were adjudicated by independent committee
Follow-up through 4 Nov 2016

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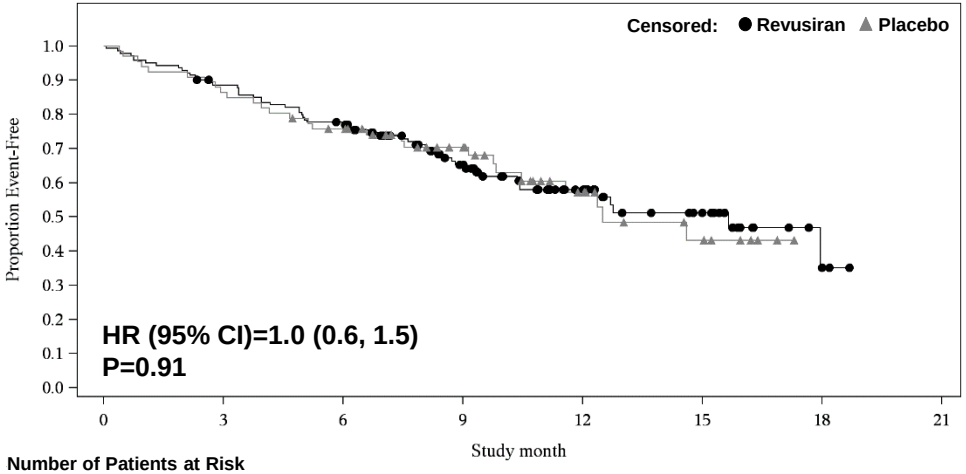
Time to first CV and HF Hospitalizations Through End of Study

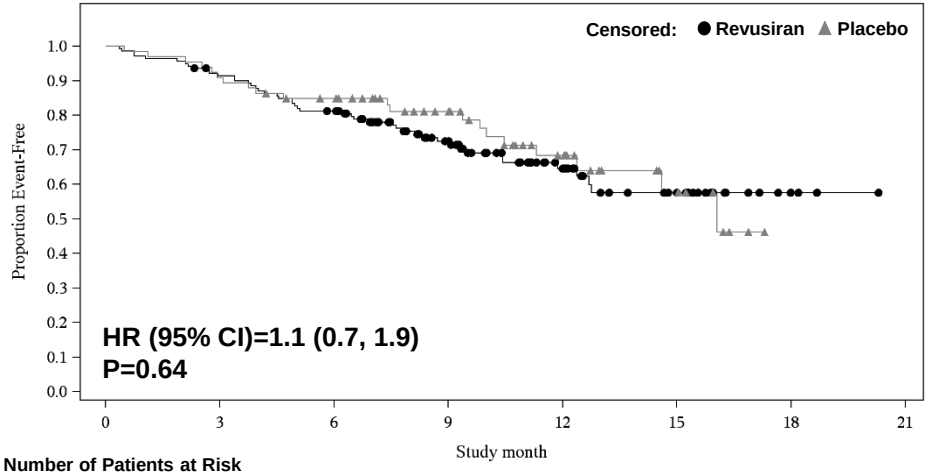
	Placebo N=66	Revusiran N=140
No. (%) of Patients with at least one CV Hospitalization	27 (41%)	56 (40%)
No. (%) of Patients with at least one HF Hospitalization	20 (30%)	45 (32%)

Time to First CV Hospitalization
(End of Study Including Safety Follow Up*)



Number of Patients at Risk								
Revusiran	140	122	103	63	33	16	2	0
Placebo	66	57	48	33	17	8	0	0

Time to First HF Hospitalization
(End of Study Including Safety Follow Up*)

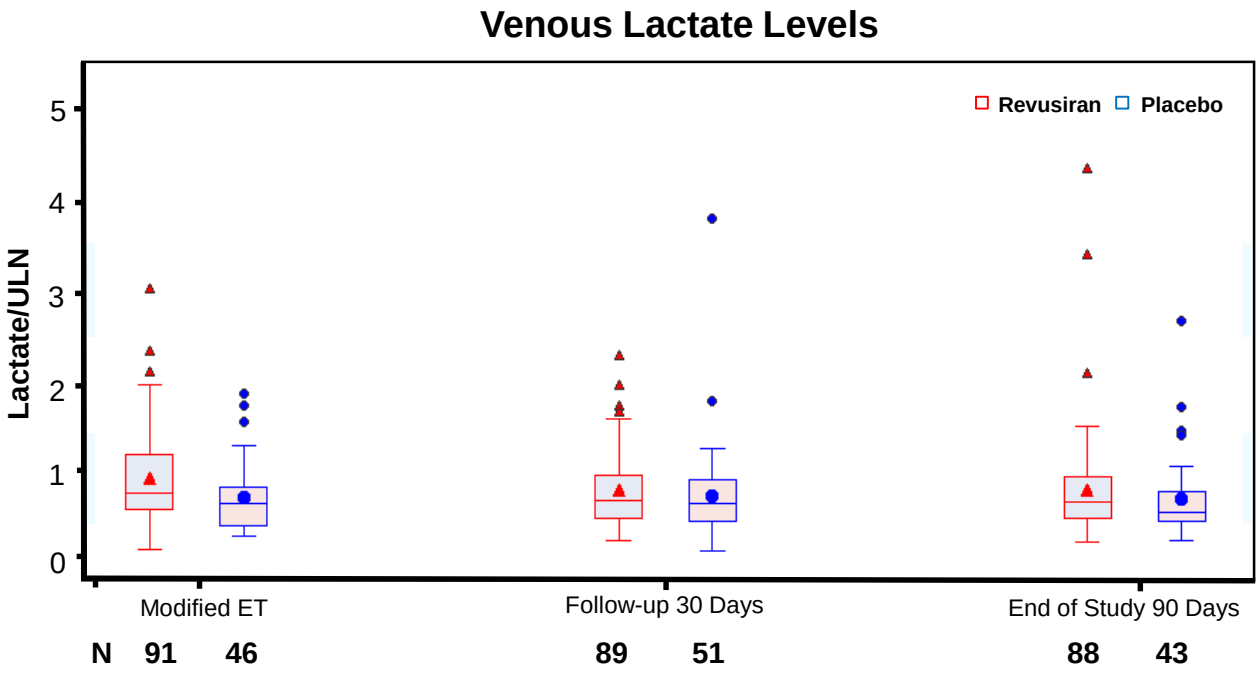


Number of Patients at Risk								
Revusiran	140	126	108	70	36	17	3	0
Placebo	66	60	53	38	22	9	0	0

All mortality and hospitalization events were adjudicated by independent committee
* Follow-up through 30 Mar 2017

Evaluation of Lactate During Safety Follow Up Period

- Overall distribution of lactate values similar in revusiran and placebo arms
- Placebo data suggests lactate elevations occur as part of natural history
- 3% of revusiran patients had lactate results >2x ULN at mET visit
  - Lactate not adjusted for severity of heart failure; potentially confounding results
- During treatment, no difference in anion gap (revusiran vs. placebo) to suggest any potential revusiran-related lactic acidosis

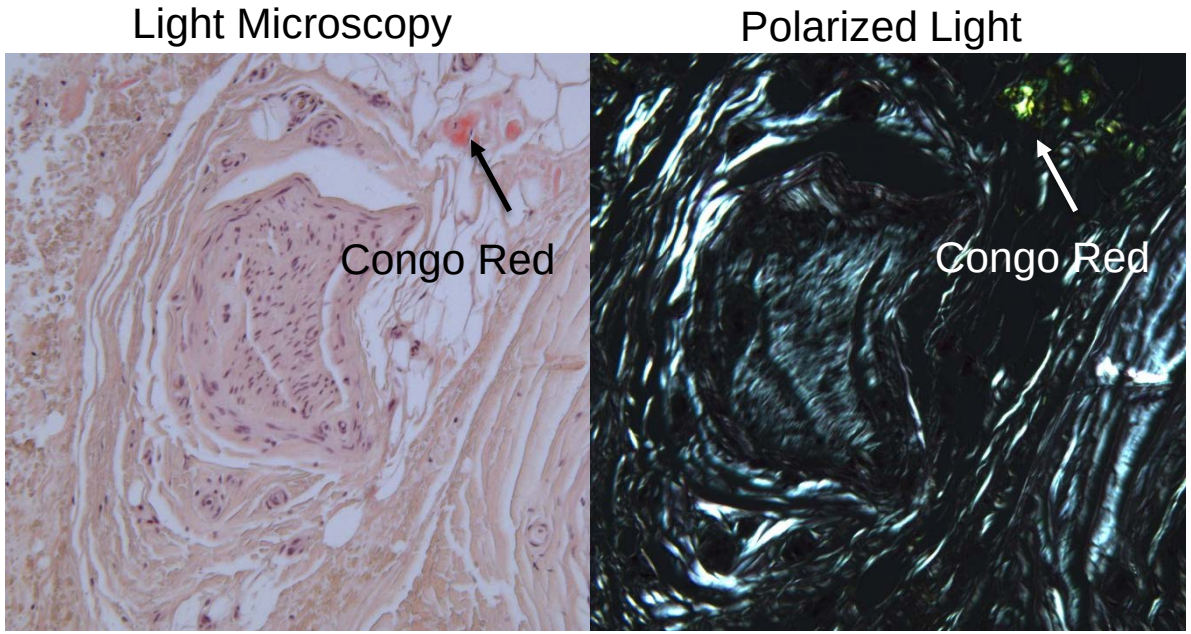


Tissue Biopsy Results

Findings generally consistent with amyloid neuropathy and amyloid myopathy

- 14 patients had skin, nerve and/or muscle biopsies*
  - 6 included histochemical and ultrastructural evaluation of mitochondria in tissue
- No evidence drug related mitochondrial toxicity on electron microscopy

Representative nerve biopsy from patient on revusiran arm on ENDEAVOUR



*Includes patients from ENDEAVOUR and Ph2 OLE

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Investigation of ENDEAVOUR Mortality Imbalance

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- Hypothesis 3: Mortality resulting from PK or PD related toxicity
- Hypothesis 4: Mortality imbalance related to lower than expected mortality in placebo group at time of discontinuation

Hypothesis 3: Mortality Resulting from PK or PD Related Toxicity

- No difference in revusiran plasma concentration or TTR knockdown* in patients dead vs. alive to suggest exposure or pharmacodynamic (PD) effect contributed to mortality

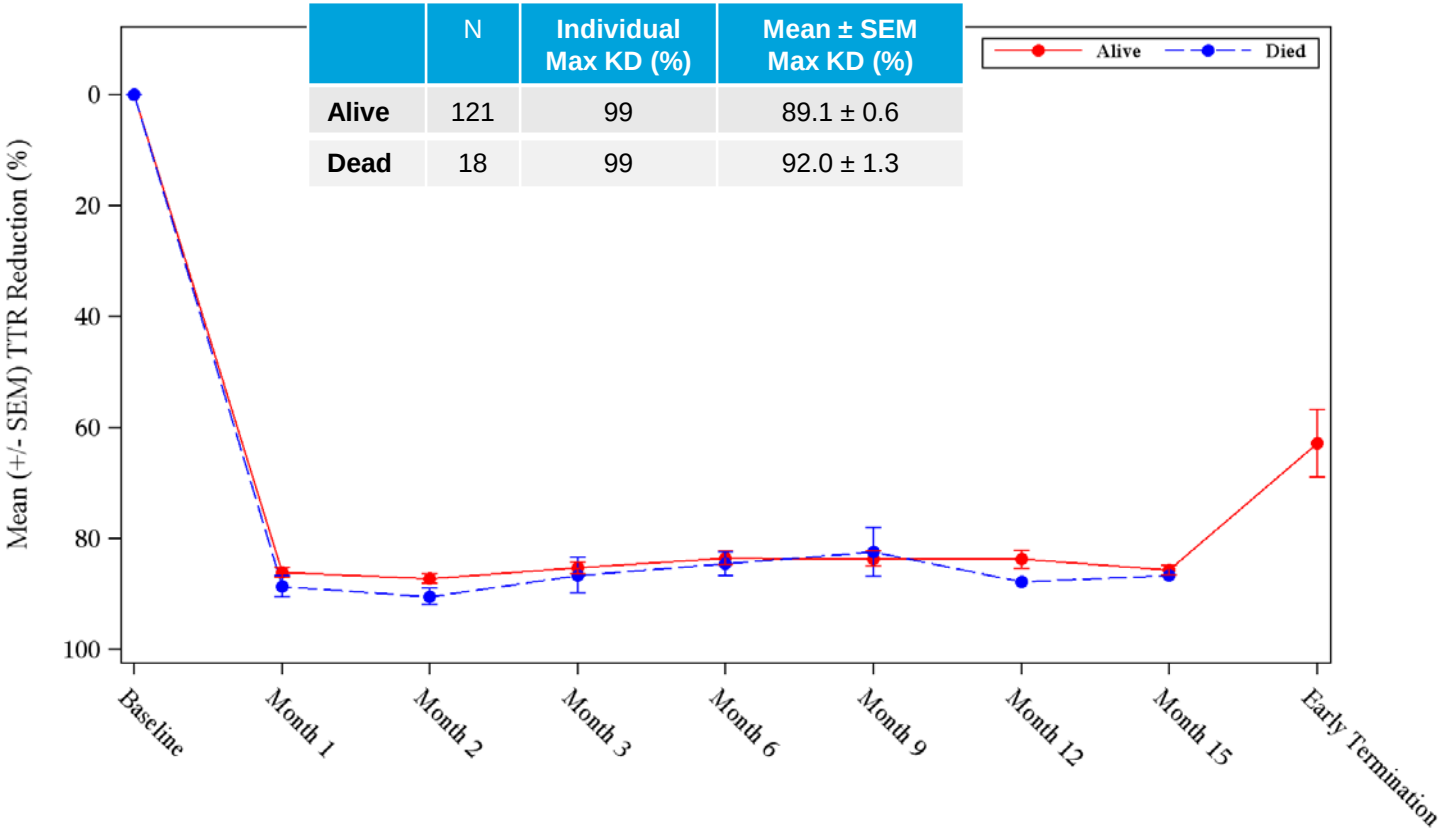
- No findings on exploratory imaging (technetium scanning and cardiac MRI**) to suggest PD related resorption/redistribution of amyloid in myocardium contributed to mortality

*Percentage and absolute levels
** Technetium scanning (Heart to Collateral Lung Ratio) and cardiac MRI (extracellular volume fraction); exploratory parameters potentially reflecting myocardial TTR deposition; small N's precludes definitive conclusions

TTR Knockdown in Revusiran Arm by Outcome

No evidence that TTR knockdown contributed to mortality imbalance

	N	Individual Max KD (%)	Mean ± SEM Max KD (%)
Alive	121	99	89.1 ± 0.6
Dead	18	99	92.0 ± 1.3

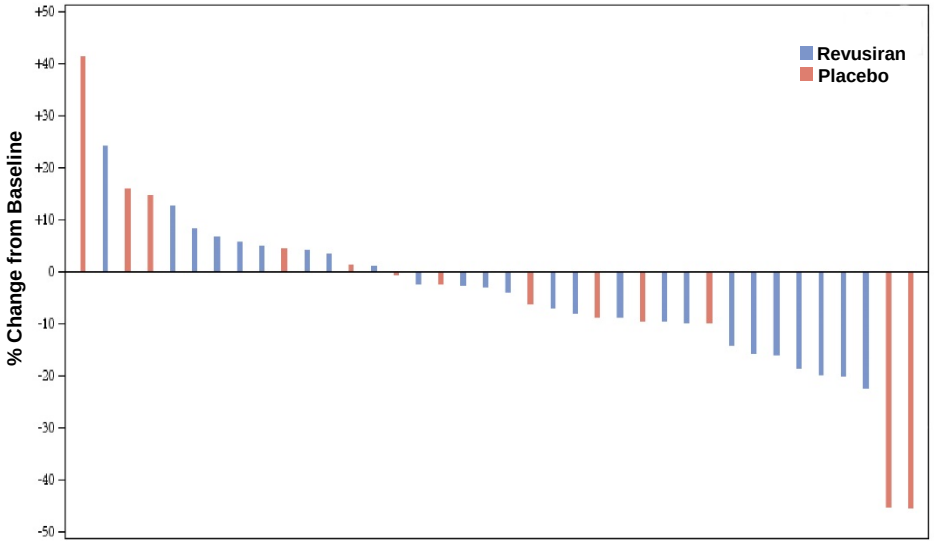


Follow-up through 4 Nov 2016

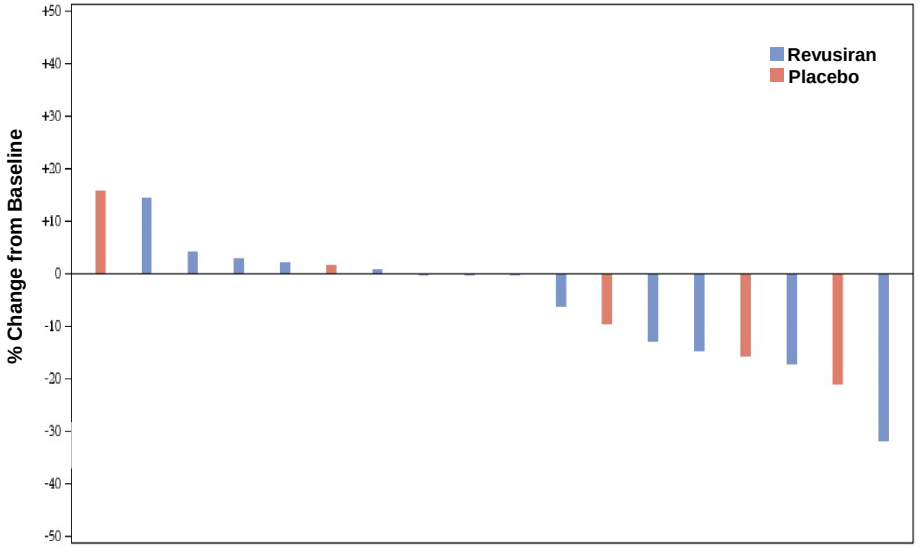
Exploratory Cardiac Imaging Results

No findings on exploratory imaging (technetium and cardiac MRI) to suggest PD related resorption/redistribution of amyloid contributed to mortality

Percent Change from Baseline in H/CL Ratio (Technetium)



Percent Change from Baseline in ECV (MRI)



	Median H/CL Ratio (Q1,Q3)		Median ECV (Q1,Q3)	
	Placebo N=13	Revusiran N=25	Placebo N=5	Revusiran N=13
Baseline	1.9 (1.7,2.3)	1.7 (1.6,1.8)	0.59 (0.58,0.65)	0.60 (0.58,0.62)
Month 6	1.7 (1.7,2.1)	1.5 (1.4,1.8)	0.54 (0.45,0.58)	0.58 (0.50,0.66)

ECV: Extracellular Volume Fraction; H/CL: heart to contra-lateral lung
Reference Ranges: H/CL < 1.5, ECV <0.3 (Bokhari, *Circulation*, 2013)

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Investigation of ENDEAVOUR Mortality Imbalance

- Hypothesis 1: Mortality related to baseline imbalance
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- Hypothesis 3: Mortality resulting from PK or PD related toxicity
- Hypothesis 4: Mortality imbalance related to lower than expected mortality in placebo group at time of discontinuation

Hypothesis 4: Mortality imbalance related to lower than expected mortality in placebo group at time of discontinuation

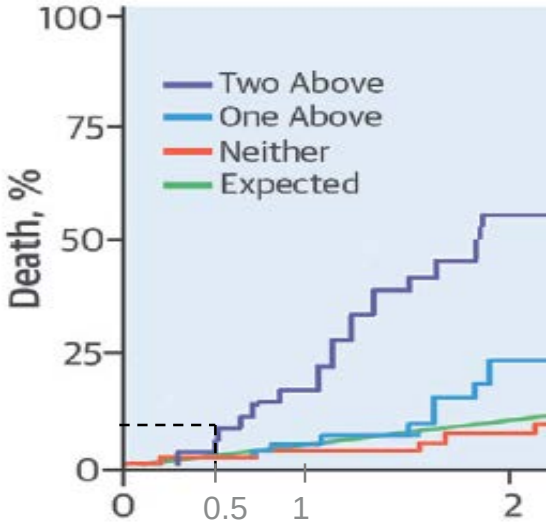
- Mortality in placebo arm may have been lower than expected based on:
  - Comparison to natural history
  - Subgroup analysis of patients age ≥ 75 years vs. age < 75 years
- CV and HF hospitalizations (time to first and cumulative) similar between treatment arms
  - Imbalance in CV/HF hospitalizations would also have been expected if there were drug-related CV deaths
- Small study with small placebo group, increases risk of chance imbalance

*Adjudication performed by an independent committee

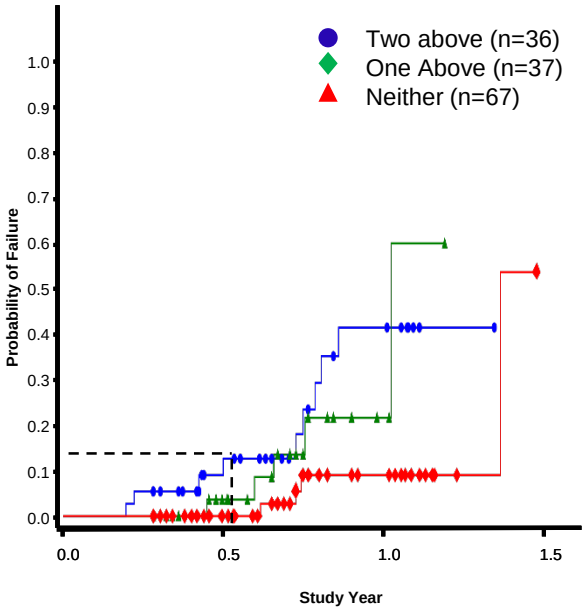
Risk Stratified Mortality in ENDEAVOUR vs Natural History

Revusiran mortality consistent with natural history; no placebo deaths in patients predicted to be at highest risk

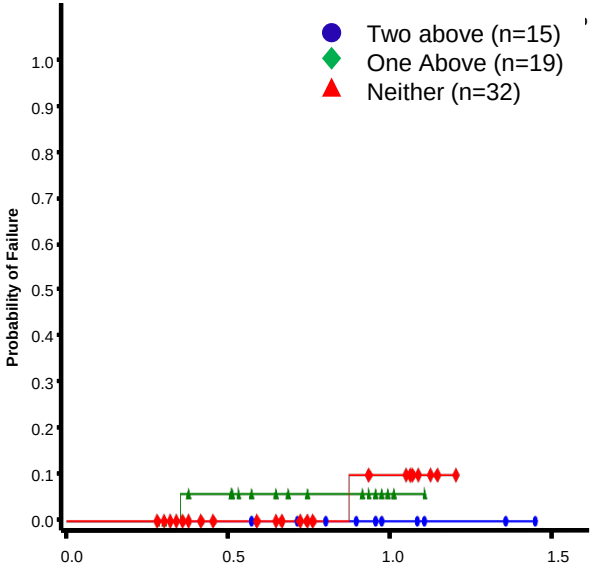
- Acknowledging limitations of cross-study comparisons, ENDEAVOUR data compared to available natural history data for additional context
- Data permit risk stratification based upon cardiac biomarkers prognostic of mortality in wtATTR and hATTR amyloidosis[1, 2]
  - **Biomarker thresholds**: Troponin T > 0.05 ng/mL, NT-proBNP > 3000 pg/mL
  - **Risk Groups**: High Risk - Both biomarkers above threshold; Intermediate - One above; Low Risk – Neither above



wtATTR (Mayo Clinic)[1]



Revusiran



Placebo

ENDEAVOUR

[1]Grogan et al. *JACC*, 2016, [2]Kristen et al. *PLOS One*, 2017

Follow-up through 4 Nov 2016

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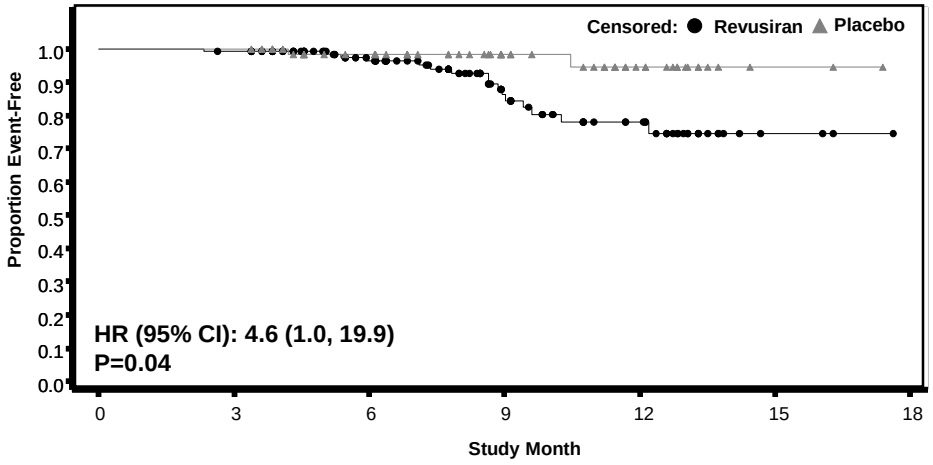
Observed Mortality Events

With additional post treatment follow-up, increasing deaths in placebo arm narrowed mortality imbalance

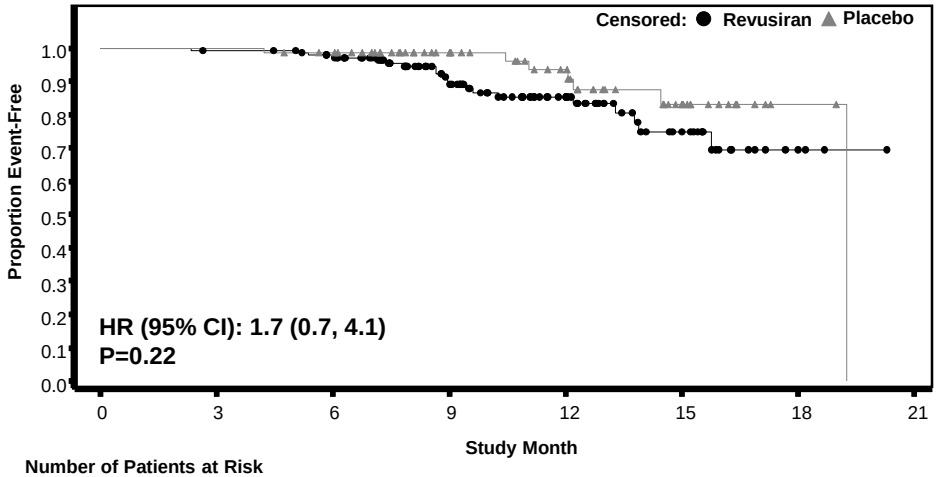
	30 Days Post Discontinuation (04 Nov 2016)		End Of Study (30 Mar 2017)	
	Placebo N=66	Revusiran N=140	Placebo N=66	Revusiran N=140
All Deaths	2 (3%)	18 (13%)	7 (11%)	23 (16%)
CV Deaths	2 (3%)	16 (11%)	7 (11%)	20 (14%)

CV Mortality
(30 Days Post Discontinuation*)



Number of Patients at Risk							
Revusiran	140	138	93	49	26	3	0
Placebo	66	66	47	29	15	2	0

CV Mortality
(End of Study Including Safety Follow Up^)



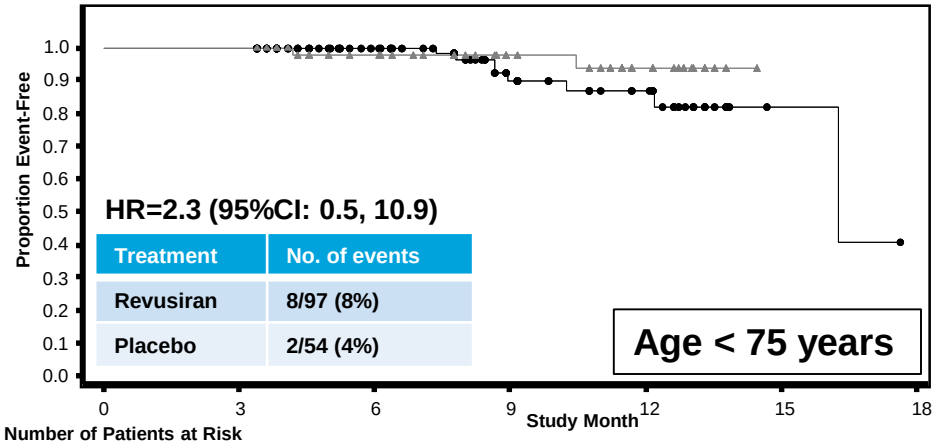
Number of Patients at Risk								
Revusiran	140	138	128	83	49	20	3	0
Placebo	66	66	63	46	33	14	2	0

All mortality and hospitalization events were adjudicated by independent committee
* Follow-up through 4 Nov 2016, ^ Follow up through 30 Mar 2017

Mortality and CV Hospitalization by Age Subgroups

No deaths in placebo age ≥ 75 despite increased CV hospitalizations in older subgroup

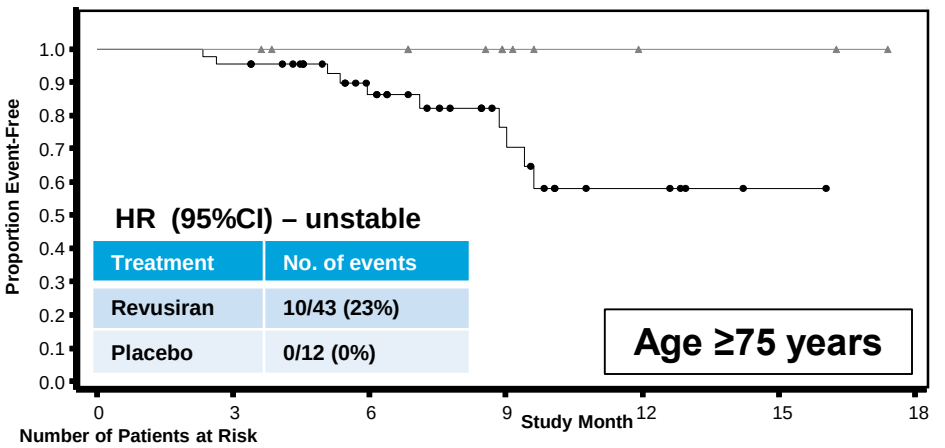
All Cause Mortality



Number of Patients at Risk

Revusiran	97	97	67	36	21	2	0
Placebo	54	54	37	24	13	0	0

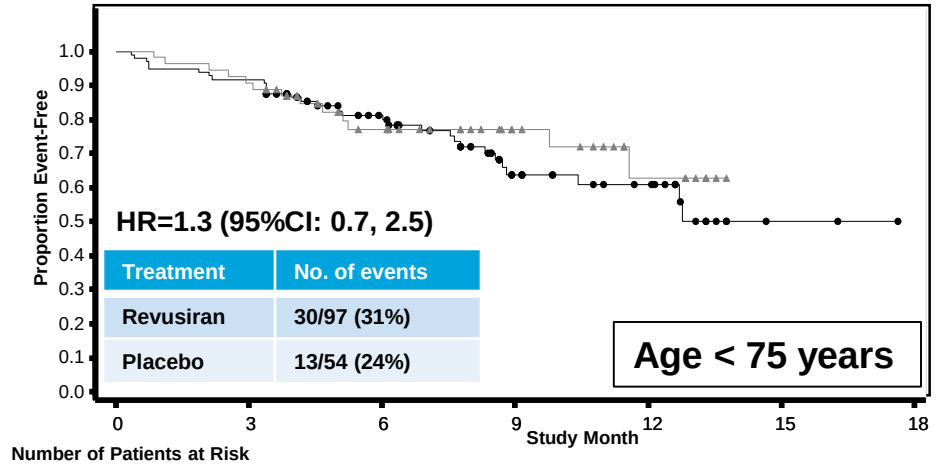
Revusiran Placebo



Number of Patients at Risk

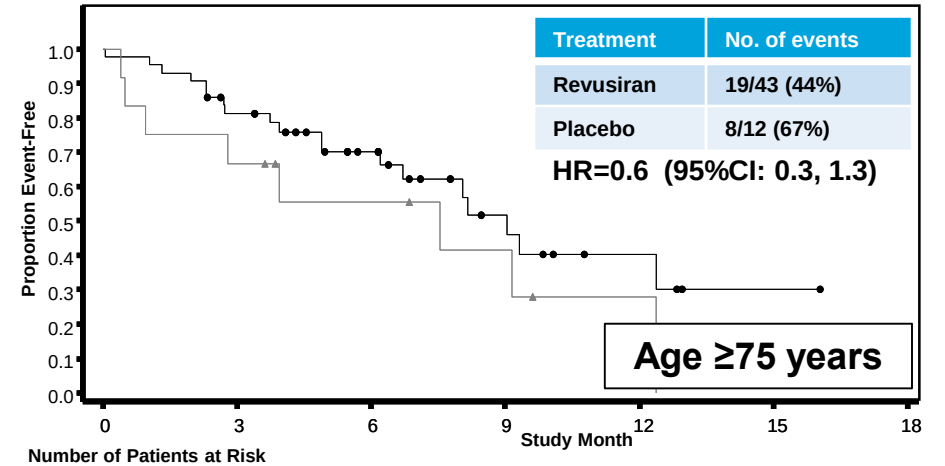
Revusiran	43	41	26	13	5	1	0
Placebo	12	12	10	5	2	2	0

CV Hospitalization



Number of Patients at Risk

Revusiran	97	89	57	27	17	2	0
Placebo	54	49	29	16	7	0	0



Number of Patients at Risk

Revusiran	43	33	20	9	4	1	0
Placebo	12	8	5	3	1	0	0

Follow-up through 4 Nov 2016

Results from ENDEAVOUR Mortality Investigation

- Hypothesis 1: Mortality related to baseline imbalance
  - Baseline characteristics generally balanced
  - Greater number of patients >75 years in revusiran arm, with impact uncertain
- Hypothesis 2: Mortality resulting from cardiotoxicity
  - No clinical evidence of revusiran-related cardiotoxicity
- Hypothesis 3: Mortality resulting from PK or PD related toxicity
  - No evidence of PK or PD based toxicity from TTR knockdown or mobilization
- Hypothesis 4: Mortality imbalance related to lower than expected mortality in placebo group at time of discontinuation
  - Some evidence of lower than expected mortality rate in placebo arm

Implications for Future Studies in hATTR Amyloidosis with Cardiomyopathy

- Data from ENDEAVOUR will inform appropriate design of subsequent studies
  - Entry criteria, including baseline disease severity and age
  - Sample size & randomization
  - Neuropathy assessments
  - Study duration

- Patisiran APOLLO Phase 3 hATTR polyneuropathy study will provide additional insights
  - ~50% patients have cardiac involvement
  - DMC has met on multiple occasions since Oct 2016; study continued without modification
  - Topline results on schedule for Sept 2017

- ALN-TTRsc02 transition to Phase 3 anticipated in 2018
  - Early profile encouraging
  - Overall program to include hATTR amyloidosis with cardiomyopathy study

Revusiran Investigation Results
Agenda

- hATTR Amyloidosis and Revusiran Background
- Investigation of ENDEAVOUR Mortality Imbalance
- Implications of Revusiran Findings for TTR Programs and Platform

Alnylam Clinical Development Pipeline

Focused in 3 Strategic Therapeutic Areas (STArs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Hepatic Infectious Diseases

		HUMAN POC*	EARLY STAGE *(IND or CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL	COMMERCIAL RIGHTS
Patisiran	*Hereditary ATTR Amyloidosis*	✓		●		US, Canada, Western Europe
Fitusiran	*Hemophilia and Rare Bleeding Disorders*	✓		●		50% US, Canada, Western Europe
Inclisiran	*Hypercholesterolemia*	✓		●		Milestones & Royalties
Givosiran	*Acute Hepatic Porphyrias*	✓		●		Global
ALN-CC5	*Complement-Mediated Diseases*	✓	●			Global
ALN-GO1	*Primary Hyperoxaluria Type 1*	✓	●			Subject to partner option rights
ALN-TTRsc02	*Hereditary ATTR Amyloidosis*	✓	●			Subject to partner option rights
ALN-HBV	*Hepatitis B Virus Infection*		●			Global

*Proof of concept defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies

Alnylam Investigational RNAi Therapeutics Platform
Extensive Human Safety Experience

Number of Programs	Number of Clinical Studies	Total Patients or Volunteers Dosed	Greatest Duration of Exposure
>10	>20	>1000	~36 months

Platform related findings*

- Low incidence (15.2%) of generally mild, transient injection site reactions
- Low incidence (2.2%) of generally mild, asymptomatic, reversible LFT increases >3x ULN
- No evidence of safety signals similar to revusiran program

Favorable emerging profile for ESC-GalNAc platform compared with competing oligo platforms†

- No evidence of thrombocytopenia, renal toxicity, or systemic inflammatory effects

*All reported data as of December 2016
† Based on reported study data - not based on direct comparative studies

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Inclisiran ORION-1 Phase 2 Final Study Results*

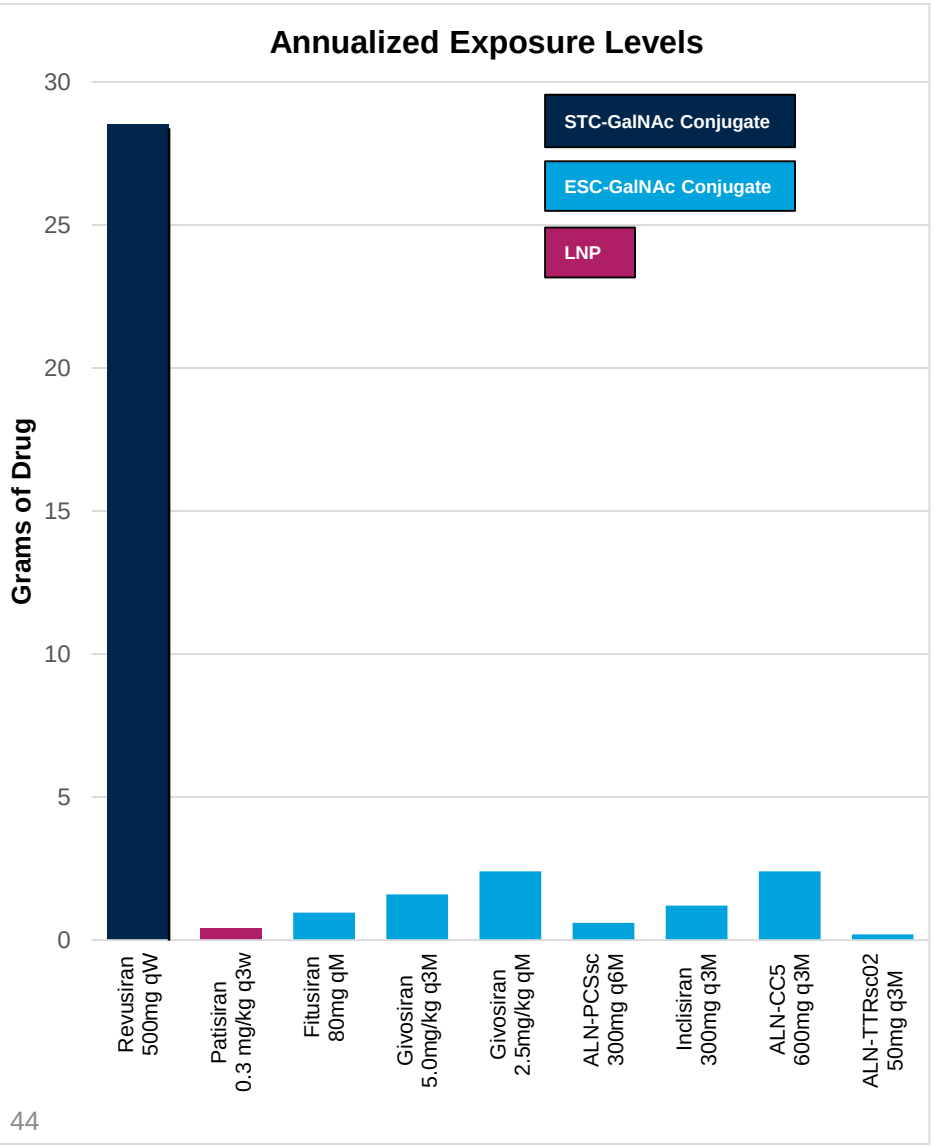
Largest Randomized, Placebo-Controlled Study of Investigational RNAi Therapeutic

	Single Dose Regimen				Two Dose Regimen			
	Placebo	Inclisiran			Placebo	Inclisiran		
		200 mg	300 mg	500 mg		100 mg	200 mg	300 mg
	N=65	N=60	N=61	N=65	N=62	N=61	N=62	N=61
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	46 (71)	47 (78)	44 (72)	49 (75)	50 (81)	48 (79)	47 (76)	47 (77)
SAE	3 (5)	6 (10)	5 (8)	6 (9)	6 (10)	11 (18)	6 (10)	7 (11)
Severe AE	2 (3)	2 (3)	4 (7)	5 (8)	7 (11)	5 (8)	6 (10)	8 (13)
Deaths	0	0	0	1 (2)	0	0	1 (2)	0

- SAEs: placebo (8%), inclisiran (11%)
- Two deaths: 500 mg (cardiac arrest in man with vasculopathy/angina) and 200 mg two dose (fistula/sepsis s/p aortic aneurysm repair)
- Two discontinuations: placebo (Herpes zoster, n=1) and 100 mg two dose inclisiran (influenza, n=1)
- Most common adverse events (incidence >2%) myalgia, headache, fatigue, nasopharyngitis, back pain, hypertension, diarrhea, and dizziness
  - Well balanced between placebo and inclisiran
  - ISRs in 5% of inclisiran patients
  - No drug-related LFT changes

*Ray et al., *NEJM*, 2017; Treatment emergent safety results to day 210 by dose group

Exposure Levels with Revusiran Significantly Higher than Other GalNAc Conjugate Programs

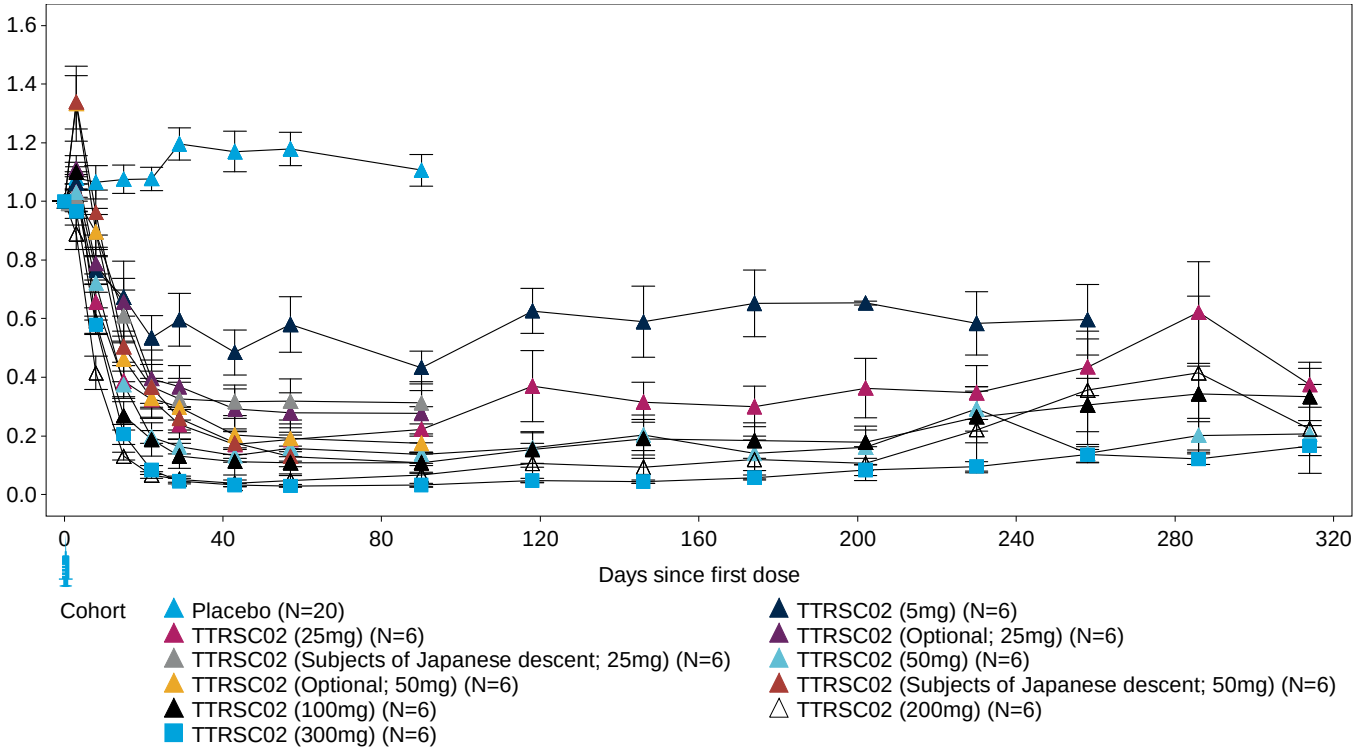


Exposure Year Equivalents Relative to Revusiran

Program	Years
Revusiran 500mg qW	**1**
Patisiran 0.3mg/kg q3W	**70**
Fitusiran 80mg qM	**30**
Givosiran 5.0mg/kg q3M	**18**
Givosiran 2.5mg/kg qM	**12**
Inclisiran 300mg q6M	**48**
Inclisiran 300mg q3M	**24**
ALN-CC5 600mg q3M	**12**
ALN-TTRsc02 50mg q3M	**140**

ALN-TTRsc02 Phase 1 Preliminary Study Results

Single Ascending Dose Study in Healthy Volunteers



- No SAEs and no discontinuations due to AEs
- All AEs mild or moderate in severity
  - 14 AEs in 8 subjects considered possibly related to treatment; majority mild
  - Events included injection site erythema, injection site pain, injection site bruising, rhinorrhea, pruritus, cough, nausea, fatigue, genital rash and abdominal pain
  - No clinically significant changes in lab parameters, EKG or physical exam

PD results as of data cutoff on 31 May 2017; safety through 14 Jun 2017

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Summary and Next Steps

Summary

- Mortality imbalance observed in revusiran vs. placebo arm in ENDEAVOUR phase 3 trial in hATTR amyloidosis with cardiomyopathy
- Extensive investigational plan and data reviewed with regulatory authorities, investigators and cardiac expert panel. Key findings include:
  - No significant baseline imbalance, greater % >75 yrs of age in revusiran arm
  - No clinical evidence for revusiran-related cardiotoxicity
  - No evidence for PK/PD related mortality
  - Some evidence to suggest lower than expected mortality in placebo group at time of discontinuation
  - However, investigation cannot exclude possibility of drug-related effect

Next Steps

- Plan to present and/or publish full revusiran results in peer-reviewed meetings/publications
- Continue advancement of patisiran and ESC-GalNAc conjugate programs, including ALN-TTRsc02, where safety remains encouraging

We want to thank all the patients, caregivers, investigators and trial site staff who participated in the revusiran studies

Alnylam remains committed to developing novel, effective medicines for all patients with ATTR amyloidosis and to advancing knowledge of the disease

Agenda

Welcome

- Josh Brodsky, Associate Director, Investor Relations & Corporate Communications

Executive Summary

- John Maraganore, Ph.D., Chief Executive Officer

Revusiran Investigation Results

- Akshay Vaishnaw, M.D., Ph.D., Executive Vice President of R&D

Q&A Session

Upcoming RNAi Roundtables

Platform advances in RNAi therapeutics

- Wednesday, August 23, 3:30 pm ET

Givosiran, in development for the treatment of acute hepatic porphyrias

- Thursday, September 7, 10:30 am ET

Fitusiran, in development for the treatment of hemophilia and rare bleeding disorders

- Tuesday, September 12, 10:30 am ET

Additional details for upcoming RNAi Roundtables, including speakers, dates and times, will be provided on the Capella section of the Company's website, www.alnylam.com/capella.

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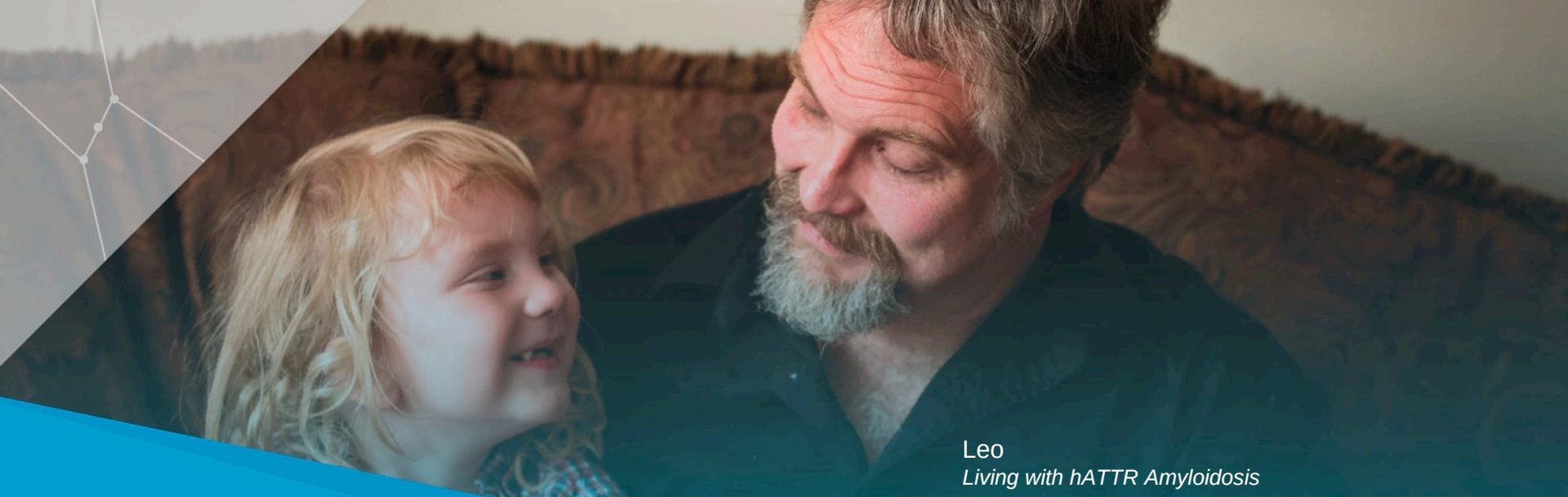

Leo
Living with hATTR Amyloidosis

Thank you

RNAi
ROUNDTABLE 2017

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