Patisiran, an Investigational RNAi Therapeutic for the Treatment of Hereditary ATTR Amyloidosis with Polyneuropathy (hATTR-PN)

Baseline Demographics from the Phase 3 APOLLO Study

04 July 2016 | ISA 2016| Uppsala, Sweden

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Hereditary ATTR Amyloidosis with Polyneuropathy (hATTR-PN)

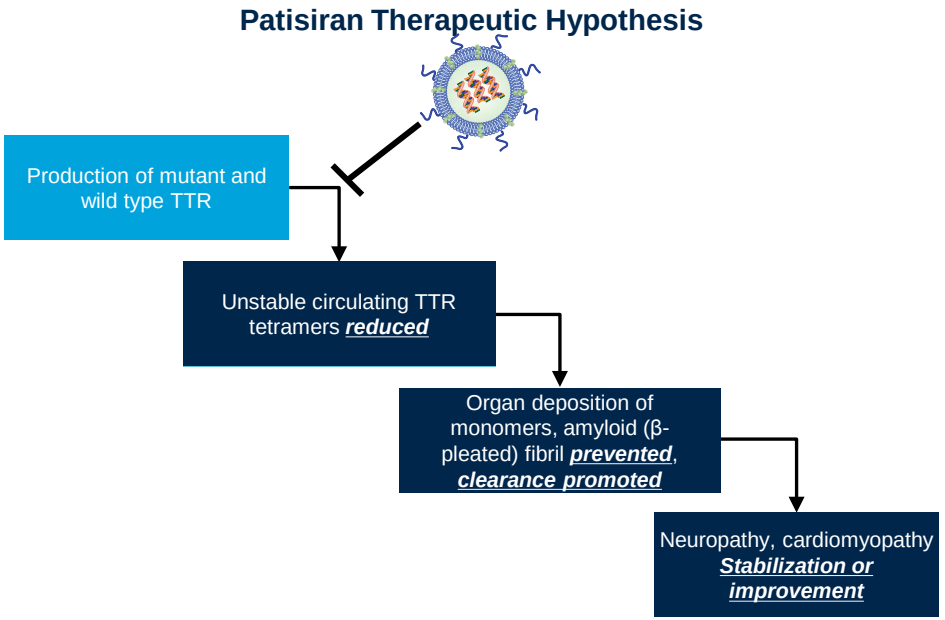
- Also known as familial amyloidotic polyneuropathy (FAP)
- Autosomal dominant hereditary amyloidosis caused by deposition of mutant and wild-type transthyretin (TTR) in nerves, gastrointestinal tract, heart, and eyes
  - Median survival 5-15 years
- Polyneuropathy is symmetrical with motor, sensory and autonomic components[1]
  - Clinical manifestations (e.g. disease penetrance and rate of progression) influenced by TTR genotype and geographical region
- Limited treatment options
  - Liver transplant for early-stage disease
  - Tetramer stabilizers
    - Tafamidis approved in the EU for Stage 1 FAP[2] and certain other countries outside the U.S.
    - Diflunisal (generic NSAID) showed positive Phase 3 data in NIH-sponsored study[3]
- Continued high unmet medical need for novel therapeutics

[1]Adams D, et al. *Neurology*. 85;675-682 (2015)
[2]Coelho T, et al. *Neurology*. 79:785-92 (2012)
[3]Berk JL, et al. *JAMA*. 310:2658-67 (2013)

Patisiran

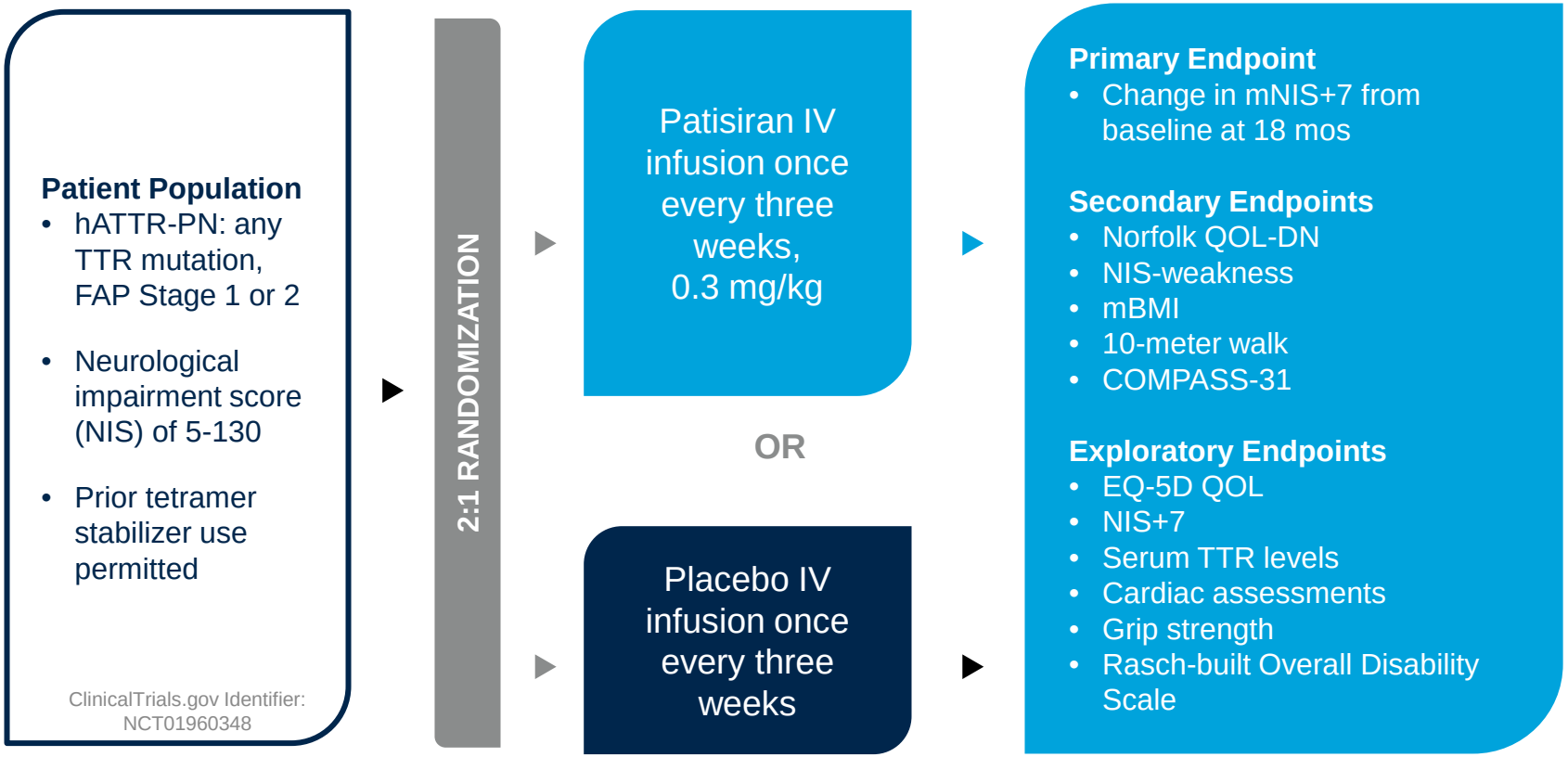
Hereditary ATTR Amyloidosis with Polyneuropathy (hATTR-PN)

- International Nonproprietary Name designation for ALN-TTR02 = Patisiran (Pa-TEE-sa-ran)
- Lipid nanoparticle formulation of siRNA targeting hepatic production of WT and mutant TTR
- Administered by IV infusion
- Positive Phase 1 results in human volunteers
  - Data published in New Engl J Med[1]
- Positive multi-dose Phase 2 results in patients with hATTR-PN
  - Data published in Orphanet J Rare Dis[2]
- Phase 2 Open-Label Extension (OLE) study ongoing
  - Includes clinical endpoints measured every 6 months
  - Positive interim data reported at ISA, April 2014; ANA, Oct. 2014; AAN, March 2015; ANA, Sept. 2015; EC-ATTR, Nov 2015; AAN, April 2016
- APOLLO Phase 3 trial: enrollment complete, trial ongoing
- APOLLO-OLE ongoing



[1]Coelho T, et al. *N Engl J Med*;369:819-29 (2013)
[2]Suhr OB, et al. *Orphanet J Rare Dis*;10:109 (2015)

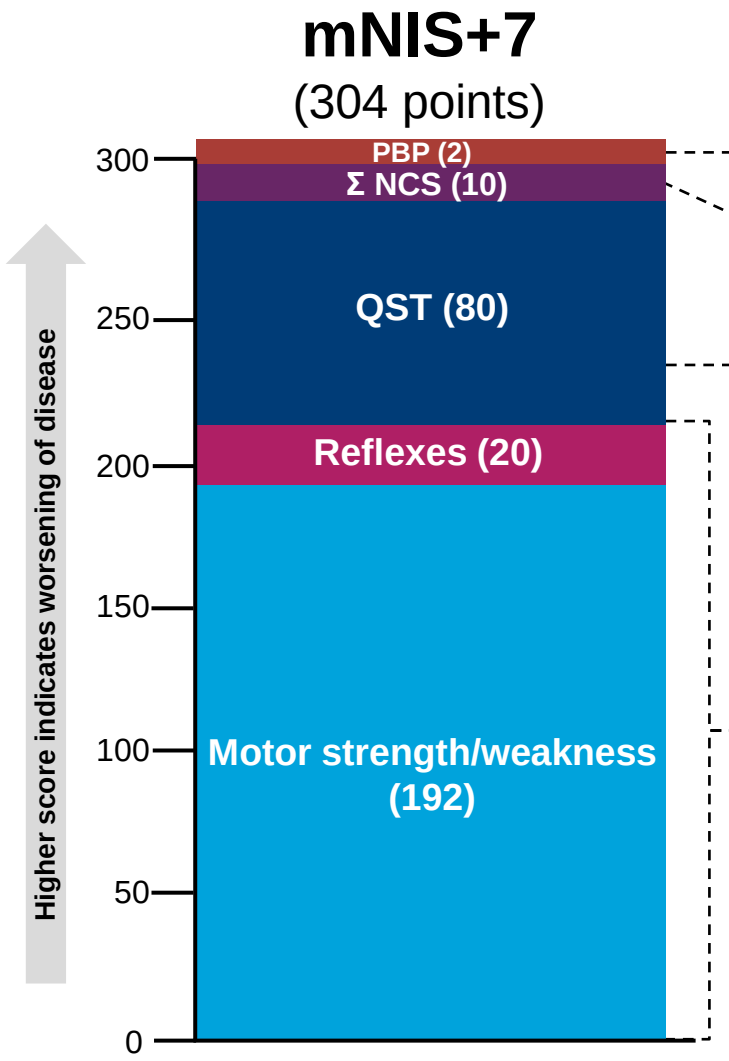
APOLLO Patisiran Phase 3 Study Design



Patients who complete the study may be eligible for patisiran treatment on Phase 3 OLE study (APOLLO-OLE), ClinicalTrials.gov Identifier: NCT02510261

APOLLO Patisiran Phase 3 Study

Primary Endpoint



Postural Blood Pressure (PBP): Measures autonomic function to address risk of orthostasis

Nerve Conduction Studies (NCS): Measures motor and sensory nerve function with focus on number of nerve fibers (action potentials)†

Quantitative Sensory Testing (QST): Measures heat pain and touch pressure at multiple sites over entire body

Neuropathy Impairment Score (NIS): Neurologic exam of lower limbs, upper limbs, and cranial nerves*

Suanprasert N, et al. *J Neurol Sci*;344:121–8 (2014)

† Points value for NCS derived for the standard deviates from the Olmsted County Normative Dataset; O'Brien PC, et al. *Neurology*, 45:17-23, (1995)

*NIS includes sensory competent; while mNIS+7 accounts for sensory within QST

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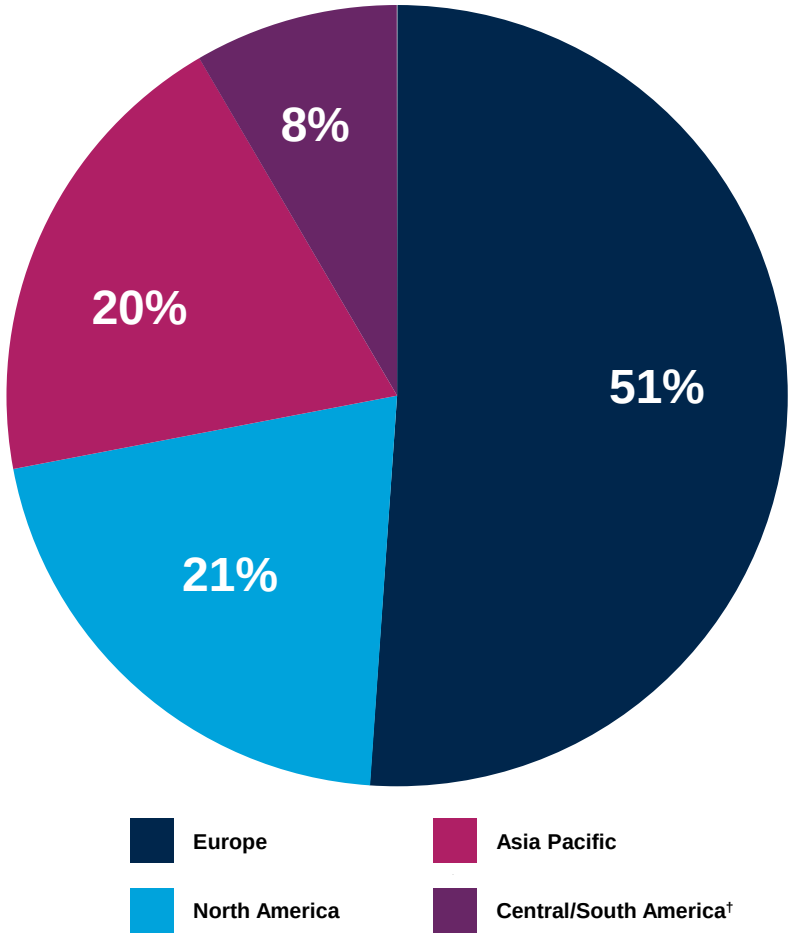
APOLLO Patisiran Phase 3 Study*

Enrollment by Geographic Region

A total of 225 patients with hATTR-PN enrolled from December 2013 – January 2016



† Including Mexico
*Data as of 01March2016

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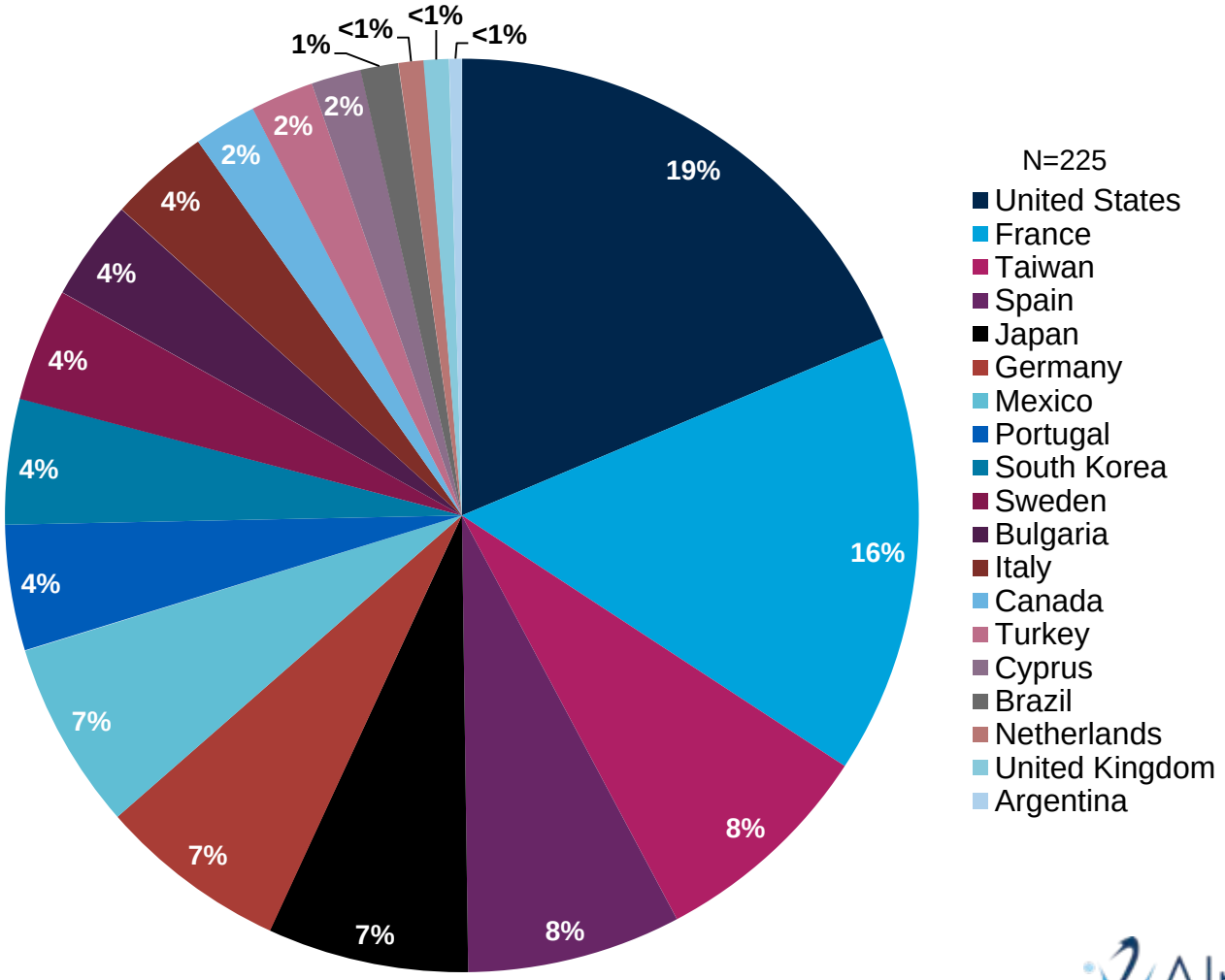
APOLLO Patisiran Phase 3 Study*

Enrollment by Country

Patients with hATTR-PN enrolled at 44 sites in 19 countries



*Data as of 01March2016

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Phase 3 Placebo-Controlled hATTR-PN Studies

Study	Enrollment, N	Study Sites, N	Enrolling Countries, N
Patisiran[1]*	225	44	19
IONIS-TTR_{Rx}[2]	172	24	10
Diflunisal[3]	130	8	5
Tafamidis[4]	128	10	9

[1]ClinicalTrials.gov Identifier: NCT01960348
[2]ClinicalTrials.gov identifier: NCT01737398
[3]Berk JL, et al. *JAMA*. 310:2658-67 (2013); ClinicalTrials.gov identifier: NCT00294671
[4]Coelho T, et al. *Neurology*. 79:785-92 (2012); ClinicalTrials.gov identifier: NCT00409175
*Data as of 01March2016

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APOLLO Patisiran Phase 3 Study*

Baseline Demographics

Characteristic	Result
Number of Patients	225
Median Age, years (range)	62 years (24-82)
Gender, n (%) males	167 (74)
Race, n (%)	
Asian	51 (23)
Black/African or African American	6 (3)
White / Caucasian	162 (72)
Other/Missing	6 (3)

*Data as of 01March2016

APOLLO Patisiran Phase 3 Study*

Baseline Demographics, continued

Characteristic	N (%)
TTR Genotype	
V30M	95 (42)
nonV30M†	130 (58)
FAP Stage	
1	104 (46)
2	119 (53)
3	2 (1)
PND Score	
I	57 (25)
II	65 (29)
IIIA	63 (28)
IIIB	38 (17)
IV	2 (1)
Previous tetramer stabilizer use	119 (53)

†Represents 57 different mutations, including GLU-89-GLN (n=13); THR-60-ALA (n=13); ALA-97-SER (n=15); SER-50-ARG (n=8), as well as numerous other mutations with ≤5 patients per group

*Data as of 01March2016

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APOLLO Patisiran Phase 3 Study*

Baseline Characteristics

Characteristic	N	Mean (Range)
Neuropathy Impairment Scores		
mNIS+7	225	78.8 (8.0-165.0)
NIS	225	59.3 (6.0-141.6)
Patients with Cardiac Involvement†	122 (54%)	
NT-proBNP, ng/L	115	1461 (40-7895)
Troponin, ng/mL	116	0.1 (0.1-1.0)
LV wall thickness, cm	122	1.67 (1.3, 2.6)
Ejection fraction	120	60.6 (31.8, 82.4)
mBMI, kg/m^2 x albumin [g/dL]	221	978.7 (522.1-1530.0)

†Definition of Cardiac Involvement: LV wall thickness ≥1.3cm; no history of hypertension or aortic valve disease
*Data as of 01March2016

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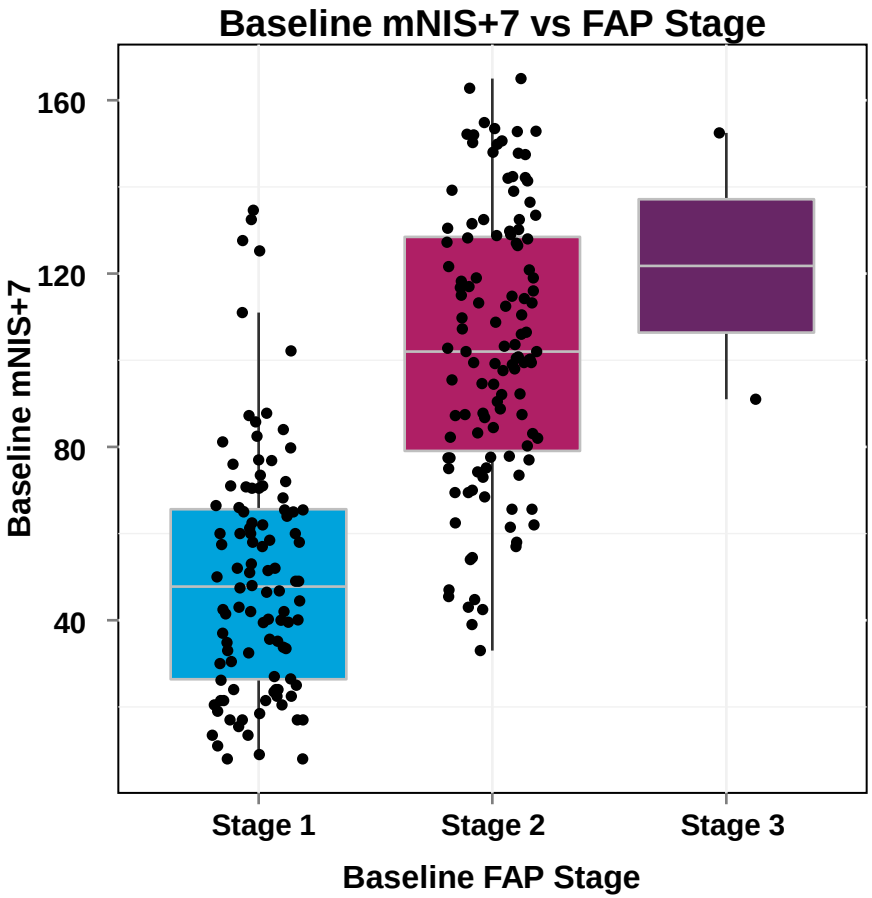
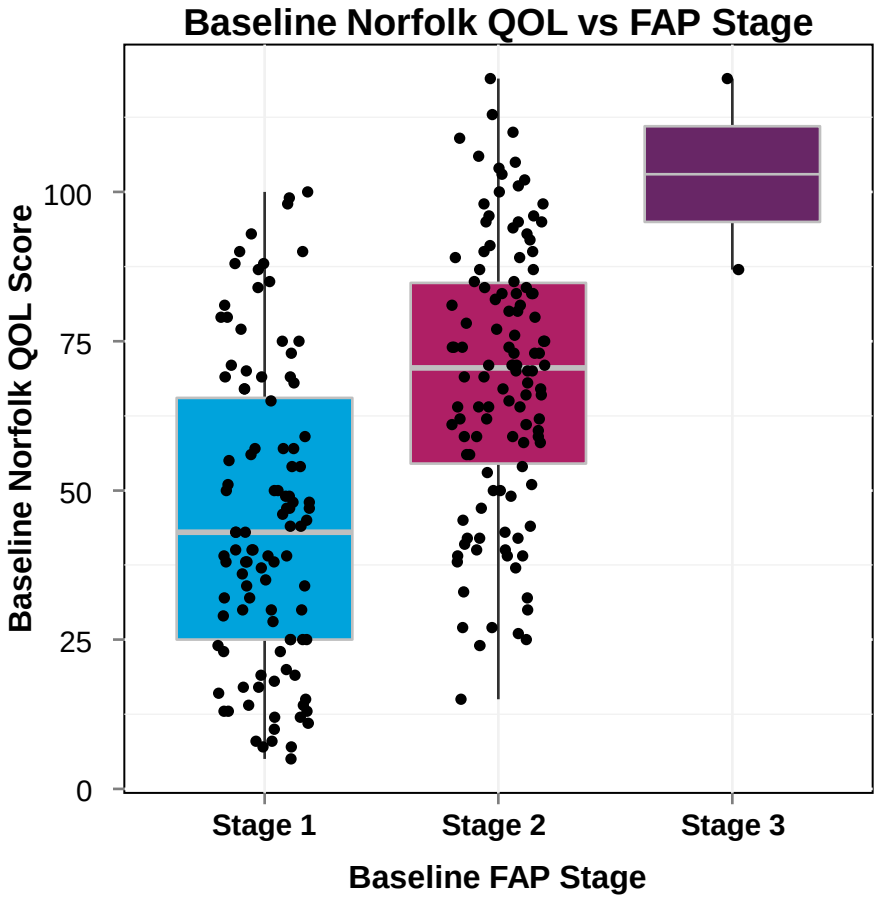
APOLLO Patisiran Phase 3 Study*

Baseline Correlation Data





*Data as of 01March2016

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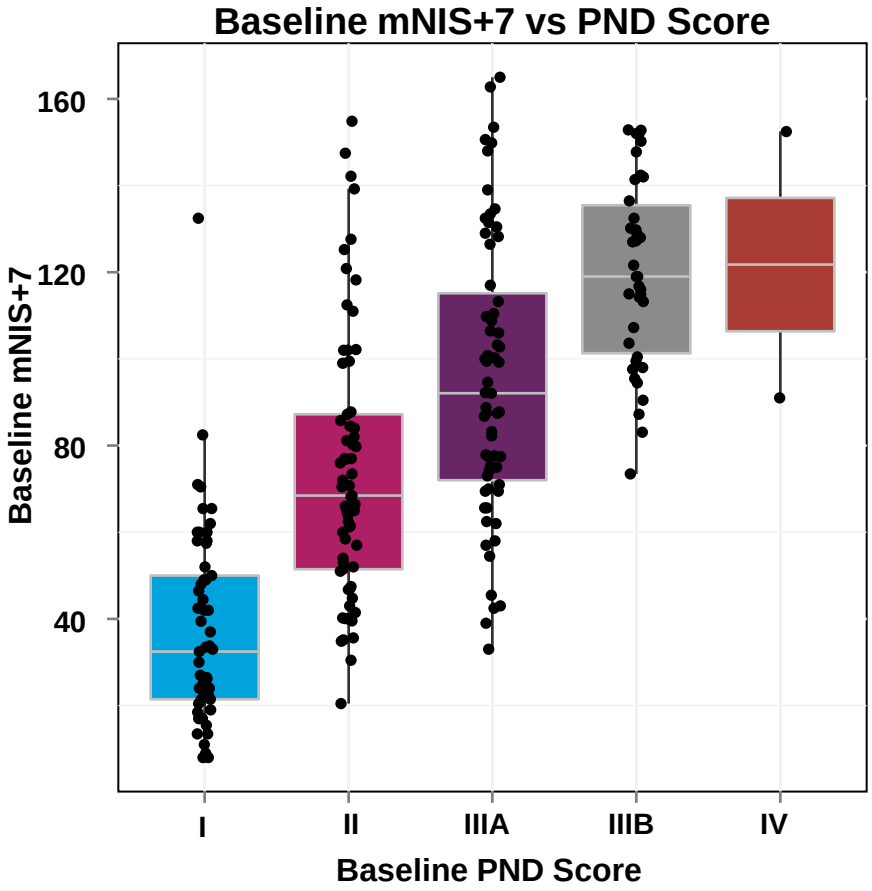
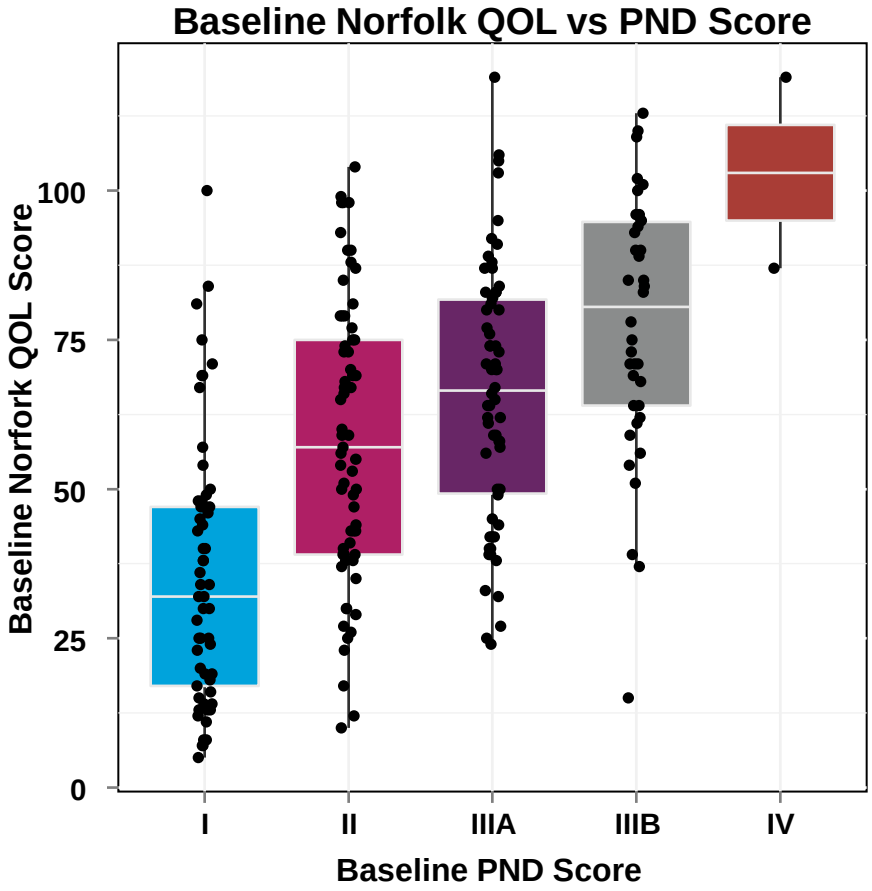
APOLLO Patisiran Phase 3 Study*

Baseline Correlation Data





*Data as of 01March2016

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APOLLO Patisiran Phase 3 Study*

Summary

APOLLO is the largest, controlled study of patients with hATTR-PN to date (N=225)

- Globally representative patient population (19 countries; 44 sites)

Patients with hATTR-PN enrolled represent a wide range of TTR mutations and disease severity

- Study includes a substantial proportion of patients with cardiac involvement (54%), enabling assessment of patisiran effects on other disease manifestations, including cardiac

Results expected in mid-2017

*Data as of 01March2016

Acknowledgments

Thank you to the patients, investigators, study staff and collaborators participating in the Phase 3 APOLLO study

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Thank You!

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