Analysis of NT-proBNP Baseline Levels in APOLLO as a Predictor of Survival in Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

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Background and Rationale

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- Rare, inherited, rapidly progressive, life-threatening disease caused by a mutation in the transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and gastrointestinal tract[1-5]
  - Affecting approximately 50,000 people worldwide[5,6]; median survival of 4.7 years following diagnosis with a reduced survival of 3.4 years for patients presenting with cardiomyopathy[6-8]
- Multisystem disease with heterogenous clinical presentation; amyloid accumulation often leads to dysfunction in multiple organs, including the peripheral nervous system, heart, gastrointestinal tract, and kidneys[2,9,10]
- Accumulation of amyloidosis fibrils in nerves can lead to manifestations of polyneuropathy, including peripheral neuropathy, autonomic dysfunction, and motor weakness causing fine and gross motor impairments whereas accumulation in the heart can lead to cardiomyopathy
- Disease penetrance and rate of progression may be influenced by TTR genotype[11]
- Limited treatment options are available. Continued high unmet medical need for novel therapeutic options

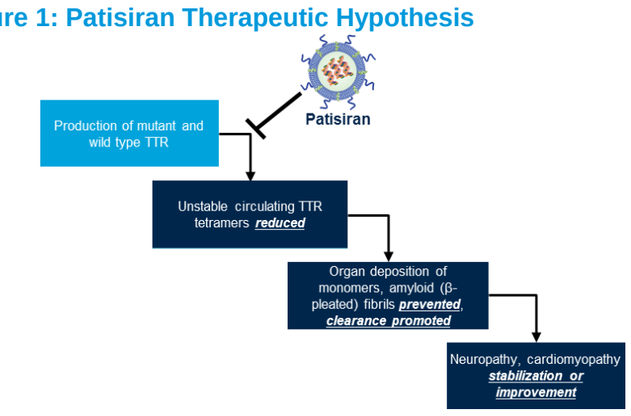
N-terminal Pro B-type Natriuretic Peptide (NT-proBNP)

- NT-proBNP is a serum biomarker released into circulation from the heart because of increased myocardial wall tension and stress
- Clinical studies in patients with light chain (AL) amyloidosis have shown NT-proBNP to be predictive of clinical outcome and survival in patients with cardiac involvement; thus suggesting its use as a potential surrogate endpoint for treatment efficacy in a hATTR amyloidosis population[12]
- A recent analysis demonstrated that NT-proBNP levels had prognostic utility for outcomes, not only in AL amyloidosis, but also in ATTR amyloidosis[12]
  - Survival in ATTR cardiac amyloidosis patients with serum NT-proBNP levels of >3000 ng/L was associated with poorer survival compared to patients with NT-proBNP < 3000 ng/L[12]

Patisiran, an investigational RNAi Therapeutic

- Lipid nanoparticle formulation of siRNA targeting hepatic production of mutant and wild type TTR (Figure 1)
- Phase 2 and Phase 2 Open-Label Extension (OLE): positive multi-dose results in patients with hATTR amyloidosis, patisiran generally well tolerated[13,14]
- Phase 3, APOLLO: study met primary efficacy endpoint (mNIS+7) and all secondary endpoints with a favorable safety profile[15,16]
- Global-OLE: ongoing[17]

Figure 1: Patisiran Therapeutic Hypothesis



Objective

- Evaluate the predictive value of baseline NT-proBNP on survival in patients enrolled in the APOLLO study

Methods

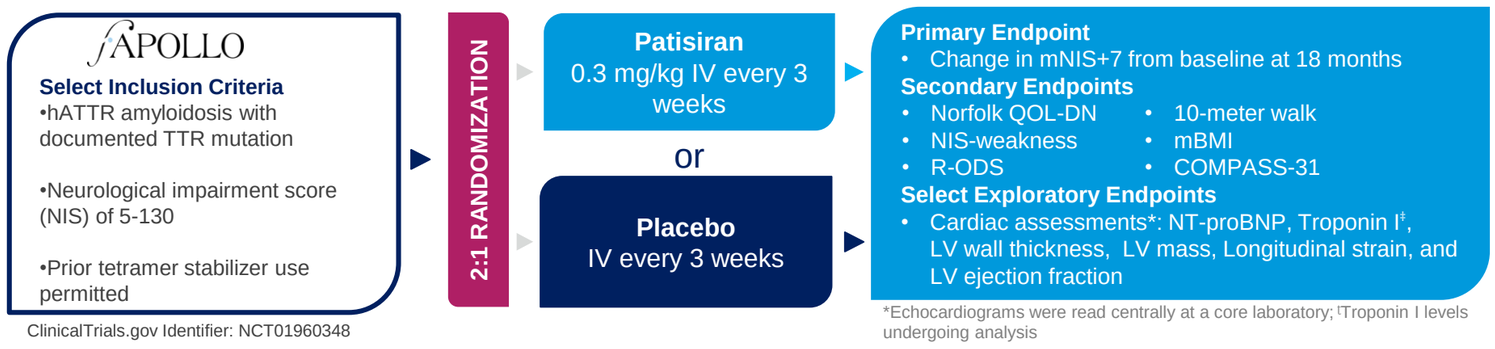
APOLLO Study Design

- Phase 3, randomized (2:1), double-blind study of patisiran 0.3mg/kg or placebo IV every 3 weeks in patients with hATTR amyloidosis patients with polyneuropathy (Figure 2)
- 126 (56%) patients had cardiac involvement on the basis of prespecified criteria: left ventricular (LV) wall thickness ≥ 13mm and absence of aortic valve disease or hypertension

Statistical Methods

- Post-hoc analyses were conducted to assess the prognostic factors for survival using univariate and multivariate Cox regression models. The potential risk for mortality assessed included baseline NT-proBNP, genotype, FAP stage, cardiac subpopulation, and age of disease onset
- NT-proBNP was evaluated as a continuous variable following logarithmic transformation as well as a binary variable using a cut off value of 3000 ng/mL
- The outcome variable is overall survival (months) and the model includes baseline NT-proBNP as a categorical covariate (≤3000 ng/L vs. >3000 ng/L)

Figure 2: APOLLO Study Design



ClinicalTrials.gov Identifier: NCT01960348

*Echocardiograms were read centrally at a core laboratory; ‡Troponin I levels undergoing analysis

Results

APOLLO Baseline Demographics

- Overall, 225 patients with 39 different genotypes were enrolled in the APOLLO study (Table 1), of which the baseline NT-proBNP was ≤3000 ng/L for 196 patients and >3000 for 29 patients (Table 2)

Table 1: APOLLO Baseline Demographics and Disease Characteristics

Demographic, n (%)	Placebo (N=77)	Patisiran (N=148)
Median Age, years (range)	63 (34, 80)	62 (24, 83)
Gender, males	58 (75.3)	109 (73.6)
hATTR Diagnosis		
Years since hATTR diagnosis, mean (min, max)	2.60 (0.0, 16.5)	2.39 (0.0, 21.0)
TTR Genotype		
V30M	40 (51.9)	56 (37.8)
nonV30M‡	37 (48.1)	92 (62.2)
Previous tetramer stabilizer use	41 (53.2)	78 (52.7)
NIS, Mean (min, max)	57.0 (7.0, 125.5)	60.5 (6.0, 141.6)
<50	35 (45.5)	62 (41.9)
≥50 - <100	33 (42.9)	63 (42.6)
≥100	9 (11.7)	23 (15.5)
NT-proBNP, pg/mL		
Median	845.7	756.4
Geometric Mean (CV%)	711.1 (151.1)	726.9 (103.0)
Cardiac Subpopulation#	36 (46.8)	90 (60.8)

‡Represents 38 different TTR mutations
♯Pre-specified cardiac subpopulation: patients with evidence of pre-existing cardiac amyloid involvement at baseline without confounding medical conditions (i.e., patients with baseline left ventricular [LV] wall thickness ≥ 13 mm and no aortic valve disease or hypertension in medical history)

Table 2: APOLLO Baseline Demographics by Baseline NT-proBNP Threshold

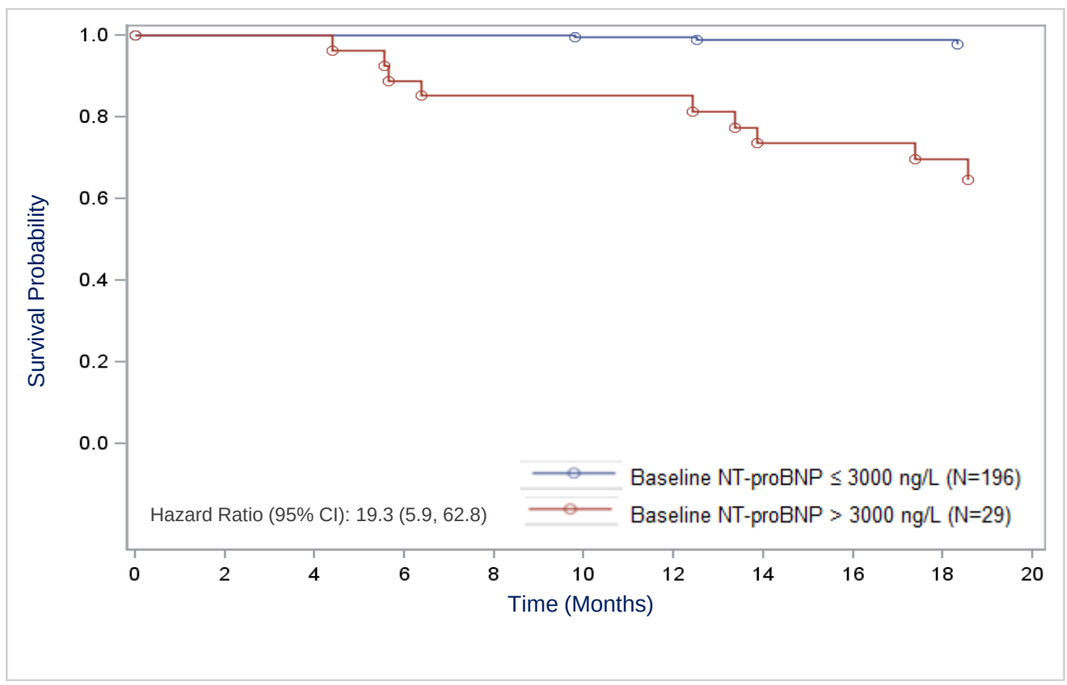
Characteristic, n (%)	NT-proBNP ≤3000 ng/L (N=196)	NT-proBNP >3000 ng/L (N=29)
Median Age, years (IQR)	62 (52.5 , 69.0)	65 (59.0 , 70.0)
Gender, male	146 (74.5)	21 (72.4)
Genotype		
Non-V30M	108 (55.1)	21 (72.4)
V30M	88 (44.9)	8 (27.6)
NYHA Class		
NYHA Class I*	101 (51.5)	9 (31.0)
NYHA Class II*	93 (47.4)	20 (69.0)
NT-proBNP, pg/mL		
Median (IQR)	400.1 (166.65 , 924.10)	4257.2 (3667.38 , 5949.67)
Geometric Mean (CV%)	385.6 (164.84)	4900.0 (40.38)

IQR, interquartile range; CV, Coefficient of variation;*NYHA class missing for two patients

Impact of Baseline NT-proBNP on Survival

- NT-proBNP was the key significant factor predictive of survival based on univariate and multivariate analyses
- Risk of death increased with higher baseline NT-proBNP (hazard ratio =2.9 [95% CI: 1.8, 4.8, p-value=$8.7x10^{-7}$] per unit increment in log (NT- proBNP))
- Patients with NT-proBNP above 3000 ng/L (n=29) had a 19.3-fold [95% CI 5.9, 62.8, p-value=8.7x10- 7] increased risk for mortality compared with those below 3000 ng/L (n=196) (Figure 3)

Figure 3: Survival by Baseline NT-proBNP Threshold



Safety

- Majority of adverse events were mild or moderate in severity (Table 3); causes of deaths were consistent with natural history

Table 3: Safety and Tolerability Over 18 Months of Treatment in the mITT Population

Type of Adverse Event, number of patients (%)	Placebo (N=77)	Patisiran (N=148)
Adverse event (AE)	75 (97.4)	143 (96.6)
Severe AE	28 (36.4)	42 (28.4)
Serious adverse event (SAE)	31 (40.3)	54 (36.5)
AE leading to treatment discontinuation	11 (14.3)	7 (4.7)
AE leading to study withdrawal	9 (11.7)	7 (4.7)
Death	6 (7.8)	7 (4.7)

- Overall, 13 deaths in APOLLO study; no deaths considered related to study drug
  - Causes of death (e.g., cardiovascular, infection) consistent with natural history; frequency of death trended lower in the patisiran group compared with placebo group
- Majority of AEs were mild or moderate in severity
  - Peripheral edema
    - Did not result in any treatment discontinuations and decreased over time
  - Infusion-related reactions (IRRs)
    - Majority mild in severity that decreased over time; led to treatment discontinuation in 1 patient
    - No severe, life-threatening or serious IRRs
- No safety signals regarding cataracts, hyperglycemia, infection, or osteopenia/osteoporosis
- No safety signals regarding liver function tests, hematology including thrombocytopenia, or renal dysfunction related to patisiran
- Safety in cardiac subpopulation comparable to overall study population

Summary

- A post-hoc exploratory analysis of data from the APOLLO study showed that baseline NT-proBNP serum levels were predictive of survival in hATTR amyloidosis patients. These findings underscore the value of early evaluation for cardiac involvement in hATTR amyloidosis patients, and potentially treating patients early in the course of the disease

AE, adverse events; COMPASS-31, Composite Autonomic Symptom Score-31; LS mean, Least Squares Mean; mBMI, modified Body Mass Index; GI, Gastrointestinal; mNIS+7, Modified Neuropathy Impairment Score + 7; NIS; Neuropathy Impairments Score; NIS-W; Neuropathy Impairment Score – Weakness; Norfolk QOL-DN, Norfolk Quality of Life Questionnaire-Diabetic Polyneuropathy; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; PND, polyneuropathy disability; R-ODS, Rasch-built Overall Disability Scale; RNAi, RNA interference; SAE, serious adverse events; WT, wild-type.; 10-MWT, 10-Meter Walk Test; 95% CI, 95% Confidence Interval. References: 1. Hanna M. Curr Heart Fail Rep. 2014;11(1):50-57; 2. Mohty D et al. Arch Cardiovasc Dis. 2013;106(10):528-540; 3. Adams D et al. Neurology. 2015;85(8):675-682; 4. Damy T et al. J Cardiovasc Transl Res. 2015;8(2):117-127; 5. Hawkins PN, et al. Ann Med. 2015;47(8):625-638; 6. Swiecicki PL, et al. Amyloid 2015;22(2):123-31; 7. Sattianayagam AJ, et al. Eur Heart J 2012;33;1120; 8. Gertz MA, et al. Mayo Clin Proc 1992;67(5):428-40; 9. Conceição I et al. J Peripher Nerv Syst. 2016;21(1):5-9; 10. Shin SC et al. Mt Sinai J Med. 2012;79(6):733-748; 11. Mariani LL et al. Ann Neurol. 2015;78(6):901-16; 12. Gillmore JD, et al. European Heart Journal. 2017, ehx589; 13. Suhr OB et al. Orphanet J Rare Dis. 2015;10:109; 14. Adams et al. Neurology. 2017;88:15 Supplement S27.004 (NCT01961921); 15. Adams D et al. BMC Neurology. 2017;17:181; 16. Adams, D. Orphanet J Rare Dis 2017, 12(Suppl 1):O9 – oral presentation EU ATTR ; 02 Nov; 17; 17. Clinicaltrials.gov: NCT02510261;
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