Infusion Related Reactions in Patients with hATTR Amyloidosis Treated with Patisiran

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Background and Rationale

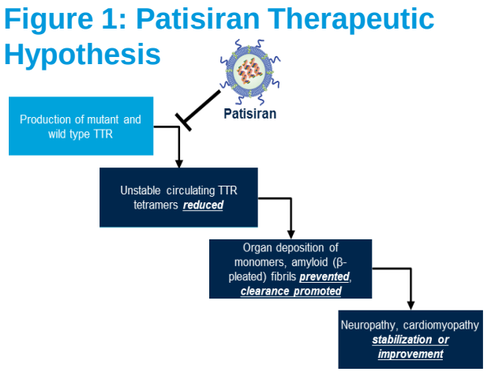
Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- Rare, inherited, rapidly progressive, life-threatening disease caused by a mutation in 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]
- Limited treatment options are available
- Continued high unmet medical need for novel therapeutic options

Patisiran

- Lipid nanoparticle formulation of siRNA targeting hepatic production of mutant and wild-type TTR (wtTTR) (Figure 1)
- Patisiran demonstrated rapid and sustained reduction of mutant and wtTTR by inhibiting the synthesis of disease-causing protein
- Phase 3, APOLLO: patisiran demonstrated significant improvement in neuropathy (measured by mNIS+7) and Quality of Life (QoL) compared to placebo among patients with hATTR amyloidosis and was generally well-tolerated[12]

Figure 1: Patisiran Therapeutic Hypothesis



Objective

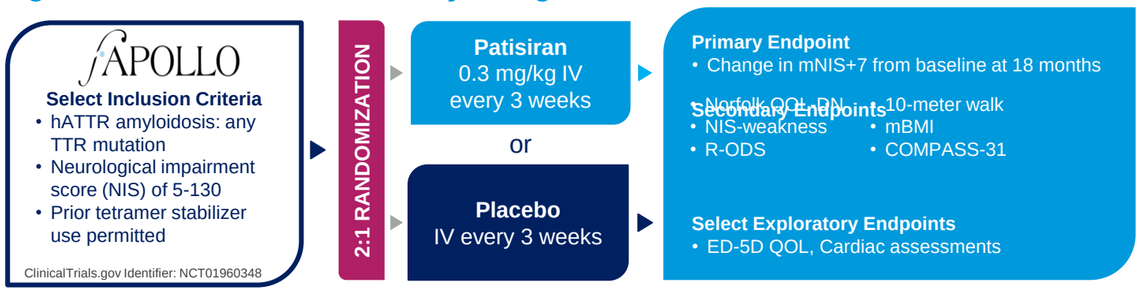
- Here we present a detailed summary of the infusion-related reactions (IRRs) observed in the APOLLO study

Methods

APOLLO Phase 3 Study Design

- Multi-center, international, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of patisiran in patients with hATTR amyloidosis with polyneuropathy[11,12] (Figure 2)

Figure 2: Phase 3 APOLLO Study Design



Dosing Regimen

- Blinded study drug was administered every three weeks intravenously at an initial infusion rate of 1 mL/min for the first 15 minutes and then to 3 mL/min for the remainder of the fusion amounting to an 80 minute infusion[11]

Premedications

- In order to reduce the potential for an IRR, all patients received premedication with corticosteroids, antihistamines (H1 and H2 blockers), and acetaminophen or equivalents at least 60 minutes prior to the start of the infusion[11]
- For premedications not available or not tolerated intravenously, equivalents could be administered orally

Categorization of IRRs

- Severity of an IRR was categorized as mild, moderate, or severe depending on the actions taken to manage the IRR[11] (Table 1)

Table 1: Categorization of Infusion-Related Reactions in Phase 3 APOLLO Study

Categorization	Description
Mild	Infusion may be continued; if intervention is indicated it is minimal and additional treatment (other than paracetamol for delayed reactions) is not required
Moderate	Requires treatment including more intensive therapy (e.g., IV fluids, nonsteroidal anti-inflammatory [NSAIDs]) in addition to infusion interruption but responds promptly to medication. Treatment is indicated for ≤24 hours
Severe	Not rapidly responsive to medication or to interruption of infusion; and/ or prolonged (treatment is indicated for >24 hours); recurrence of severe symptoms following initial improvement

Results

APOLLO Baseline Demographics

- APOLLO enrolled 225 patients: mean age 61 years, 43% V30M mutation; mean NIS 59.3 (6.0, 141.6), 75% PND>1 (walking difficulties) and 56% with cardiac involvement per pre-specified criteria
- Patients were enrolled globally from 44 sites in 19 countries: 21% in North America, 44% in Western Europe and 36% in Rest of World

Exposure to Study Drug

- 148 patients were administered a cumulative total of 3,740 infusions of patisiran with 77 patients received a cumulative total of 1,637 infusions of placebo

Results (continued)

Safety in the mITT Population

- Adverse events (AEs) were balanced between arms; majority of AEs were mild or moderate in severity
- Causes of deaths (7.8% placebo, 4.7% patisiran) were consistent with natural history
- Common AEs that occurred more frequently with patisiran than placebo were peripheral edema (22.1% placebo, 29.7% patisiran) and infusion-related reactions (described below)
  - Peripheral edema decreased over time; no events led to discontinuation

Infusion Related Reactions (IRRs)

- IRRs were observed in 18.9% of patients in the patisiran arm and 9.1% of patients in the placebo arm

Infusion Interruptions Due to IRRs

- In the patisiran group, 8 patients (5%) had a total of 17 infusion interruptions due to IRRs
  - 5 patients resumed the infusions with no change in the rate of the infusion
  - 2 patients resumed the infusions at a slower rate and received their subsequent infusions at a slower rate
  - 1 patient (0.7%) discontinued treatment and withdrew from the study due to flushing of the face (moderate in severity) that began at the start of the first infusion; the patient received a partial dose
- In 15 of the 17 infusion interruptions due to IRRs, the patients resumed the infusion and received their complete dose of patisiran
- Of the 8 patients with infusion interruptions, all had their first IRR within the first 2 infusions and their first interruption of an infusion within the first 4 infusions
- The majority (approximately 80%) of the interruptions occurred within a half hour of the start of the infusion

IRR Signs and Symptoms

- Symptoms reported during infusion of patisiran in ≥2% of patients were nausea, arthralgia, back pain, headache, dyspnea, flushing (Table 2)
- Flushing occurred in both treatment groups and was most likely due to premedication or other causes

Table 2: IRR Signs and Symptoms in ≥1% of Patients the Patisiran Group

Symptom, n (%)	Placebo (N=77)	Patisiran (N=148)
Number of patients with any IRRs, n (%) / Number of events	7 (9.1) / 79	28 (18.9) / 145
Back pain	0	9 (6.1)
Flushing	6 (7.8)	6 (4.1)
Nausea	0	5 (3.4)
Headache	1 (1.3)	4 (2.7)
Arthralgia	0	3 (2.0)
Dyspnea	0	3 (2.0)
Abdominal pain	0	2 (1.4)
Chest discomfort	0	2 (1.4)
Chest pain	0	2 (1.4)
Chills	1 (1.3)	2 (1.4)
Fatigue	0	2 (1.4)
Infusion site erythema	0	2 (1.4)
Injection site swelling	0	2 (1.4)
Pain	0	2 (1.4)
Cough	0	2 (1.4)
Skin warm	0	2 (1.4)
Hypotension	0	2 (1.4)

IRRs Over Time

- The proportion of patients with IRRs and the number of IRRs decreased over time
- Among patients with IRRs, the median number of IRRs was 11.0 (range 1-15) in the placebo group and 2.5 (range 1-24) in the patisiran group
- In patisiran patients with IRRs, 78.6% of patients had their first IRR within the first 2 doses
- Symptoms were more common earlier in the course of treatment and did not increase in frequency or severity with repeated doses

Severity of IRRs

- In the patisiran treated patients, all IRRs were either mild (95.2%) or moderate (4.8%) in severity (Table 3)
- The majority of patients who experienced IRRs had IRRs that were managed without the need for additional medications
- If IRRs occurred, they were managed, depending on the severity, by slowing or temporarily stopping the infusion

Table 3: Severity of IRRs

Number of patients with at least 1 IRR/ Number of IRRs	Placebo (N=77)		Patisiran (N=148)	
	Patients, n (%)	IRRs, n (%)	Patients, n (%)	IRRs, n (%)
At least 1 Mild IRR	7 (9.1)	78 (98.7)	25 (16.9)	138 (95.2)
Medication received	1 (1.3)	18 (22.8)	5 (3.4)	10 (6.9)
No medication received	7 (9.1)	60 (75.9)	23 (15.5)	128 (88.3)
At least 1 Moderate IRR	1 (1.3)	1 (1.3)	6 (4.1)	7 (4.8)
Medication received	1 (1.3)	1 (1.3)	3 (2.0)	3 (2.1)
No medication received	0	0	3 (2.0)	4 (2.8)
At least 1 Severe IRR	0	0	0	0

Conclusion

- IRRs associated with patisiran were generally mild or moderate, manageable and rarely led to treatment discontinuation
- Patisiran was generally well tolerated

Abbreviations: AE, Adverse Events, hATTR amyloidosis, hereditary transthyretin-mediated amyloidosis; COMPASS-31, Composite Autonomic Symptom Score-31; EQ-5D, European Quality of Life-5 Dimensions; IV, intra-venous; IRR, Infusion Related Reaction; mBMI, modified Body Mass Index; Norfolk QOL-DN, Norfolk Quality of Life Questionnaire-Diabetic Polyneuropathy; 10-MWT, 10-Meter Walk Test; mNIS+7, Modified Neuropathy Impairment Score + 7; NSAID, Nonsteroidal Anti-inflammatory Drugs; PND, Polyneuropathy Disability; R-ODS, Rasch-built overall disability scale; RNAi, RNA interference; siRNA, small interfering ribonucleic acid; TTR, Transthyretin; QOL, Quality of Life; WT, wild-type:

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