Home Infusion Administration of Patisiran, an Investigational RNAi Therapeutic in Patients with Hereditary Transthyretin-Mediated Amyloidosis: An Analysis of Safety and Adherence

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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 GI tract[1-5]
  - Affecting approximately 50,000 people worldwide[5,6]; median survival of 4.7 years following diagnosis with a reduced survival (3.4 years) for patients presenting with cardiomyopathy[6-8]
- Multi-systemic amyloid accumulation often leads to dysfunction in multiple organs, including the peripheral nervous system, heart, gastrointestinal tract, and kidneys[2,9,10]
- Accumulation of 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 heart can lead to cardiomyopathy
  - Disease penetrance and rate of progression may be influenced by TTR genotype which can vary by geographical region[11]
- Limited treatment options are available
- Continued high unmet medical need for novel therapeutic options

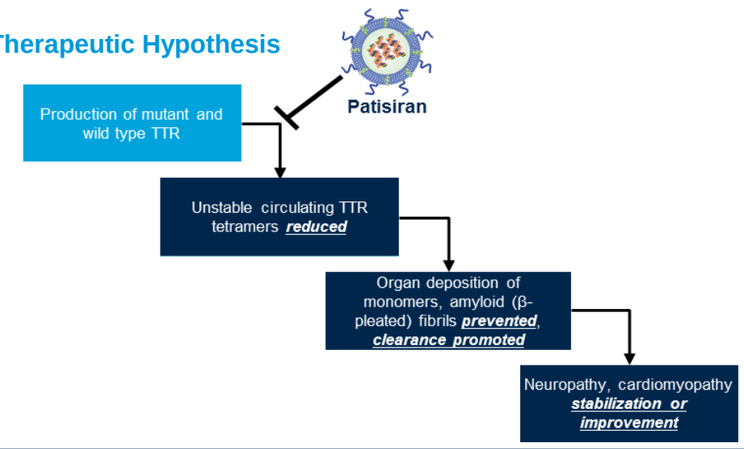
Patisiran

- Lipid nanoparticle formulation of siRNA targeting hepatic production of WT and mutant TTR (Figure 1)
- Phase 2: positive multi-dose results in patients with hATTR amyloidosis with polyneuropathy[12]
- Phase 2 Open-Label Extension (OLE): trial completed with sustained mean serum TTR knockdown of 80%, patisiran generally well tolerated, and mean 7.0-point decrease in mNIS+7 at 24 months[13]
- Phase 3, APOLLO: study met primary efficacy endpoint (mNIS+7) and all secondary endpoints with favorable safety profile[14,15]
- Global-OLE: ongoing[16]

Objective

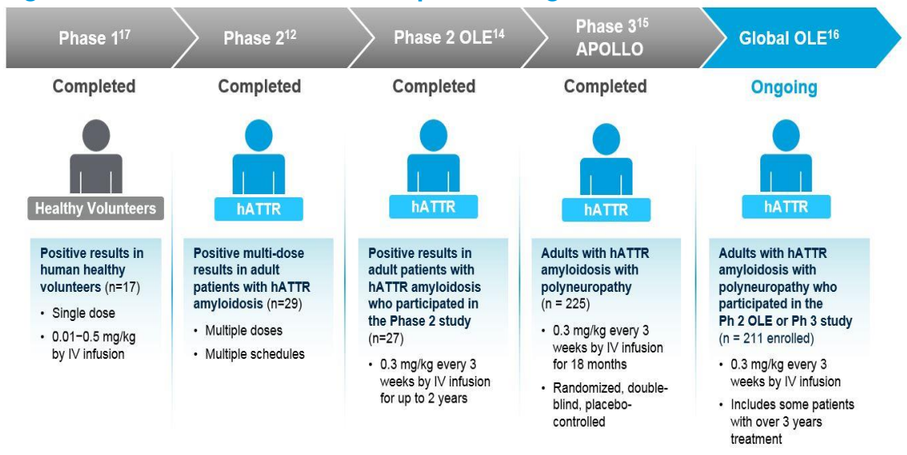
- Evaluate patients who have received patisiran by means of a home infusion in the Global OLE

Figure 1: Patisiran Therapeutic Hypothesis



Methods

Figure 2: Patisiran Clinical Development Program



Global OLE Study Design

- Multicenter, international, OLE study to evaluate the long-term safety and efficacy of patisiran in patients with hATTR amyloidosis with polyneuropathy (Figure 2)
- Patients with hATTR amyloidosis who completed the Phase 2 OLE and Phase 3 APOLLO patisiran studies and met eligibility criteria were able to roll over and continue receiving patisiran 0.3mg/kg IV q3W for up to 5 years
- Safety assessments include monitoring for adverse events (AEs) (including serious AEs [SAEs]), clinical laboratory tests such as: hematology, clinical chemistry, urinalysis; measurement of anti-drug antibodies (if clinically indicated); vital signs; physical examinations; and ophthalmology examinations
- Complete set of efficacy assessments will be done at 52 weeks, followed by more limited assessments yearly until study completion
  - Assessments include: effects on neurologic impairment (mNIS+7), Quality of Life (Norfolk QOL-DN), disability, ambulation, mBMI, grip strength, autonomic symptoms, cardiac endpoints and serum TTR levels
- Patients in selected regions, where local and country regulations allowed, received home infusions by a health care professional; home infusions were allowed following 3 completed doses at a clinical site with no evidence of Infusion Related Reactions (IRRs) or other adverse events

Results

Global OLE: Enrollment and Baseline Demographics

- 186 of 187 (99%) patients who completed the APOLLO study and were eligible for the Global OLE study, and 25 patients from the Phase 2 OLE study, enrolled in the Global OLE study
  - Male 74% , V30M 46%, Mean baseline NIS and mNIS+7 were 64 (range: 0-162) and 77 (range: 3-199), respectively and PND I: 0.5%, PND II: 28%, PND IIIA: 20%, PND IIIB: 21%, and PND IV: 8%

IRRs in Global OLE Study

- IRRs were observed in 22 patients (10.4%) in the Global OLE study (APOLLO placebo 12 [24.5%], APOLLO patisiran 8 [5.8%], Phase 2 OLE 2 [8.0%])
- IRRs were mild or moderate in severity, and decreased in frequency over time
- No patients withdrew from study due to IRRs

Home Infusions were an Option where Local/Country Regulations Allowed

- As of the December 1, 2017, 25 patients were administered over 269 home infusions with 100% of patients receiving the full dose (Figure 3,Tables 1 and 2)
- Patients received home infusions administered by a health care professional in select locations in Europe and the United States, including Spain, Canada, Sweden, Netherlands, and Chicago (Figure 4)
- Patients have received 1-27 infusions at home, with mean of 10.72 doses (median of 9 doses) (Table 2)

Figure 3: Global OLE Patients Receiving Home Infusions

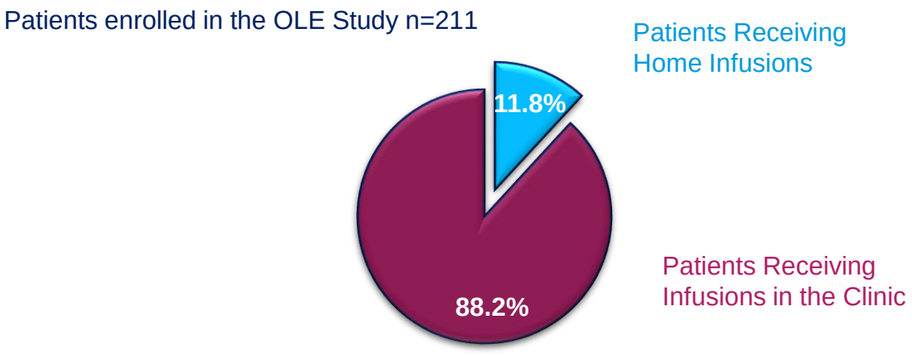
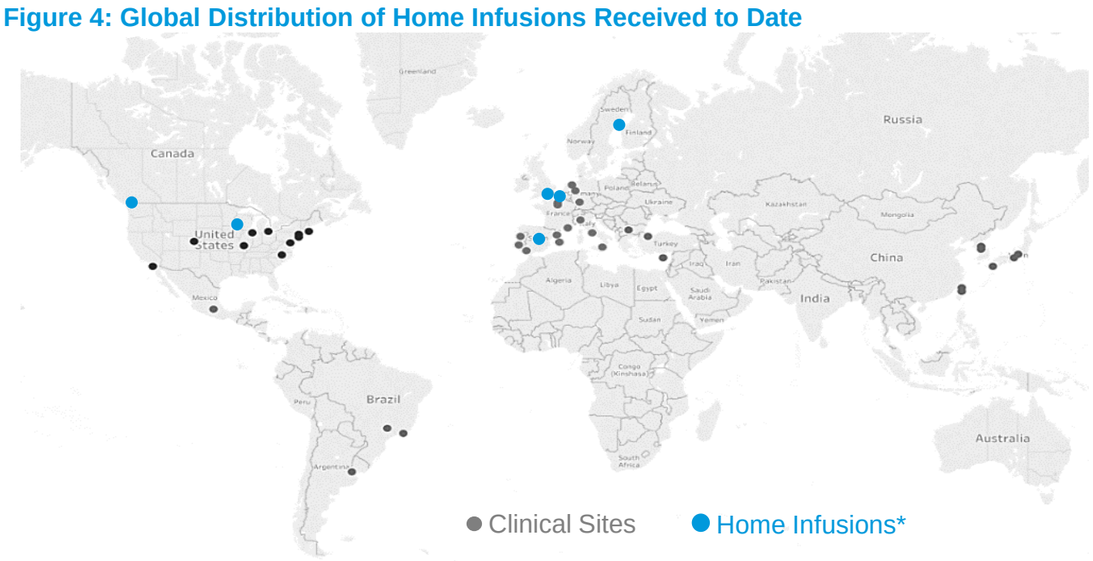


Figure 4: Global Distribution of Home Infusions Received to Date



*Home infusion and clinical sites

Table 1: Drug Exposure for Patients with at Least 1 Home Infusion*

	APOLLO Placebo (N=49)	APOLLO Patisiran (N=137)	Phase 2 OLE Patisiran (N=25)	Total (N=211)
Number of patients who received ≥1 dose of patisiran at home, n (%)	7 (14.3)	15 (10.9)	3 (12.0)	25 (11.8)
Total number of doses of patisiran administered at home, n	88	133	48	269
Number of patients with infusion interruptions due to IRRs during home infusion, n	0	0	0	0
Number of infusion interruptions due to IRRs during home infusions, n	0	0	0	0

*Patients who received home infusions as of December 1, 2017 interim data analysis

Table 2: Home Infusions Received* (Individual Patient Breakdown)

Patient	Total Patisiran Infusions, n	Home Patisiran Infusions, n (%)
1	37	27 (73)
2	34	27 (21)
3	33	19 (58)
4	31	9 (29)
5	31	26 (84)
6	31	19 (61)
7	30	19 (63)
8	29	18 (62)
9	28	18 (64)
10	27	18 (67)
11	20	7 (35)
12	18	11 (61)
13	17	11 (65)
14	15	9 (60)
15	15	6 (40)
16	10	4 (40)
17	10	4 (40)
18	9	4 (44)
19	8	4 (50)
20	7	2 (29)
21	7	1 (14)
22	6	2 (33)
23	6	1 (17)
24	6	1 (17)
25	6	1 (17)

*Patients who received home infusions as of December 1, 2017 interim data analysis

Safety Summary of Patients Receiving Patisiran via Home Infusion:

- Among patients receiving infusions at home, all patients received complete doses and no patients had interruptions of their infusions due to IRRs
- One of the 25 patients had mild symptoms (primarily flushing) that occurred after several infusions, and no specific medical treatment was required.

Summary

- Patients receiving patisiran by home infusion were compliant with each patient completing all scheduled doses with 25 patients receiving 269 cumulative doses as of the interim data analysis
- One patient had several IRRs after home infusion, which were mild and required no treatment or change to the infusion regimen
- These data suggest that home infusion may be a viable option for patients with hATTR amyloidosis receive treatment with patisiran

AE, adverse events; COMPASS-31, Composite Autonomic Symptom Score-31; LS mean, least squares mean; mBMI, modified body mass index; mNIS+7, Modified Neuropathy Impairment Score + 7; NIS; Neuropathy Impariments Score; NIS-W; Neuropathy Impairment Score – Weakness; Norfolk QOL-DN, Norfolk Quality of Life Questionnaire-Diabetic Polyneuropathy; NYHA, New York Heart Association; PND, polyneuropathy disability; R-ODS, Rasch-built Overall Disabiity Scale; RNAi, RNA interference; SAE, serious adverse events; WT, wild type; 10-MWT, 10-Minute 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. Suhr OB et al. Orphanet J Rare Dis. 2015;10:109; 13. Adams et al. Neurology. 2017;88:15 Supplement S27.004 (NCT01961921); 14. Adams D et al. BMC Neurology. 2017;17:181; 15. Adams, D. Orphanet J Rare Dis 2017, 12(Suppl 1):O9 – oral presentation EU ATTR ; 02 Nov; 17; 16. Clinicaltrials.gov: NCT02510261; 17. Coelho T et al. N Engl J Med. 2013;369:819-29. Disclosures: Pritesh J Gandhi, Marianne Sweetser, Jihong Chen, Sunita Goyal and Jared Gollob are employees of Alnylam Pharmaceuticals. Study sponsored by Alnylam.

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