Outcomes of Patients with Hereditary Transthyretin-Mediated Amyloidosis with Early Onset V30M versus All Other Mutations in APOLLO, a Phase 3 Study of Patisiran

***T Coelho*[1]**, *D Adams*[2], *A Gonzalez-Duarte*[3], *W O'Riordan*[4], *CC Yang*[5], *T Yamashita*[6], *A Kristen*[7], *I Tournev*[8], *H Schmidt*[9], *J Berk*[10], *KP Lin*[11], *PJ Gandhi*[12], *M Sweetser*[12], *M White*[12], *S Goyal*[12], *J Gollob*[12], *and O B Suhr*[13]

[1]Hospital de Santo António, Porto, Portugal, [2]National Reference Center for FAP (NNERF)/ APHP/ INSERM U 1195/ CHU Bicêtre, Le Kremlin-Bicêtre, France; [3]National Institute of Medical Sciences and Nutrition, Salvador Zubirán (INCMNSZ), Mexico City, Mexico; [4]eStudy Site, La Mesa, USA; [5]National Taiwan University Hospital, Taipei, Taiwan; [6]Kumamoto University Hospital, Kumamoto, Japan; [7]Heidelberg University Hospital, Heidelberg, Germany; [8]University Multiprofile Hospital for Active Treatment, Sofia, Bulgaria; [9]University Hospital Muenster, Muenster, Germany; [10]Amyloid Treatment and Research Program, Boston University, Boston; USA;[11]Taipei Veterans General Hospital, Taipei, Taiwan; [12]Alnylam Pharmaceuticals, Cambridge, USA; [13]Department of Public Health and Clinical Medicine, Umeå University Hospital, Umeå, Sweden

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APOLLO

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

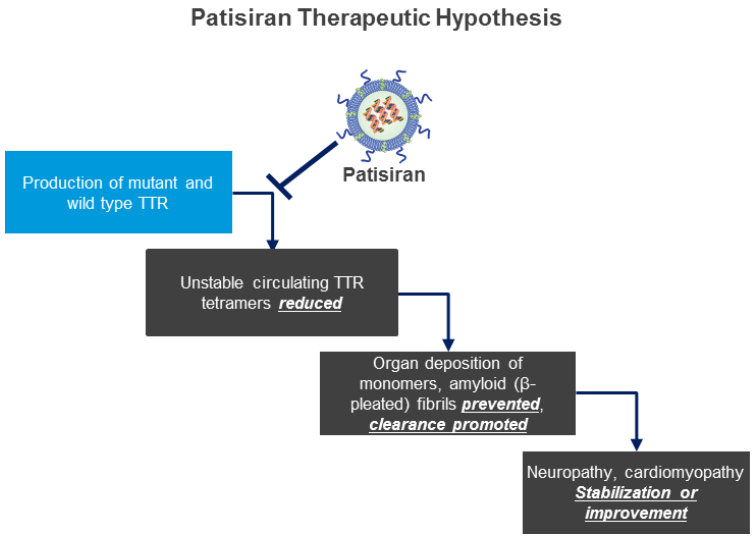
Disease Overview and Introduction to Patisiran, an Investigational RNAi Therapeutic

- **hATTR Amyloidosis**
  - Rare, inherited, rapidly progressive, debilitating, life-threatening disease caused by mutations in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and gastrointestinal tract[1-5]
    - V30M is most common mutation worldwide, with early age of symptom onset (< 50 years) seen in regions where the mutation is endemic[6,7]
  - Median survival 4.7 years following diagnosis[6]; reduced survival (3.4 years) for patients presenting with cardiomyopathy[8-10]

- Limited treatment options
  - Liver transplant for early-stage disease and TTR tetramer stabilizers
    - Tafamidis approved in EU for Stage 1 hATTR amyloidosis[11] and certain other countries outside U.S.
    - Diflunisal (generic NSAID) showed positive Phase 3 data in NIH-sponsored study[12]

- Continued high unmet medical need for novel therapeutics

- **Patisiran, an Investigational RNAi Therapeutic**
  - Lipid nanoparticle formulated RNAi, administered by IV infusion, targeting hepatic production of mutant and wild-type TTR



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Patisiran Phase 3 APOLLO Study Results

Study Design, Baseline Demographics and Characteristics

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Patient Population
- hATTR amyloidosis diagnosis with documented TTR mutation
- Neurological impairment score (NIS) of 5-130
- Prior tetramer stabilizer use permitted

ClinicalTrials.gov Identifier: NCT01960348

2:1 RANDOMIZATION†

Patisiran
0.3 mg/kg IV q3w*

or

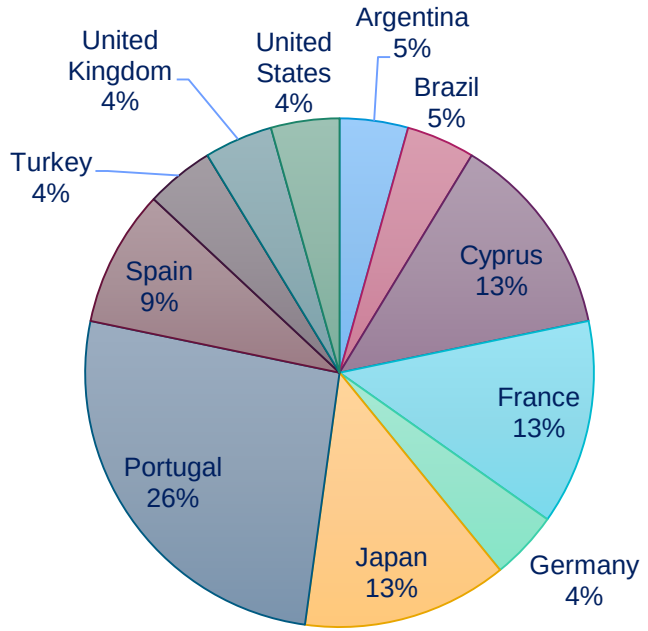
Placebo
IV q3W*

Primary Endpoint
- Change in mNIS+7 from baseline at 18 months

Secondary Endpoints
- Norfolk QOL-DN (quality of life)
- NIS-W (muscle weakness)
- R-ODS (disability)
- 10-MWT (gait speed)
- mBMI (nutritional status)
- COMPASS-31 (autonomic symptoms)

	APOLLO Population (N=225)	
	Placebo (N=77)	**Patisiran (N=148)**
Median Age, years (range)	63 (34-80)	62 (24-83)
Gender, male, n (%)	58 (75.3)	109 (73.6)
TTR Genotype, n (%)	**V30M:** 40 (51.9) **Non-V30M:** 37 (48.1)	**V30M:** 56 (37.8) **Non-V30M:** 92 (62.2)
Genotype Class, n (%) Early Onset V30M (<50 years of age at onset): All Other Mutations (including late onset V30M and non-V30M):	 10 (13.0) 67 (87.0)	 13 (8.8) 135 (91.2)
NIS, mean (min, max)	57 (7, 125.5)	60.5 (6, 141.6)
FAP Stage, n (%)	**1:** 37 (48.1); **2:** 39 (50.6); **3:** 1 (1.3)	**1:** 67 (45.3); **2:** 81 (54.7)

Early Onset V30M By Country



†Stratification factors for randomization include: neuropathy impairment score (NIS: < 50 vs. ≥ 50), early onset V30M (< 50 years of age at onset) vs. all other mutations (including late onset V30M), and previous tetramer stabilizer use (tafamidis or diflunisal) vs. no previous use.
*To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min before each study drug infusion: dexamethasone; oral acetaminophen/paracetamol; H2 blocker (e.g., ranitidine or famotidine); and H1 blocker (e.g., diphenhydramine).
10-MWT, 10 meter walk test; COMPASS-31, composite autonomic symptom score-31; FAP, familial amyloid polyneuropathy; mBMI, modified body mass index; mNIS+7, modified neuropathy impairment scale +7; NIS-W, neuropathy impairment score weakness; Norfolk QOL-DN, Norfolk quality of life-diabetic neuropathy questionnaire; q3W, every 3 weeks; PND, polyneuropathy disability; R-ODS; Rasch-built overall disability scale;

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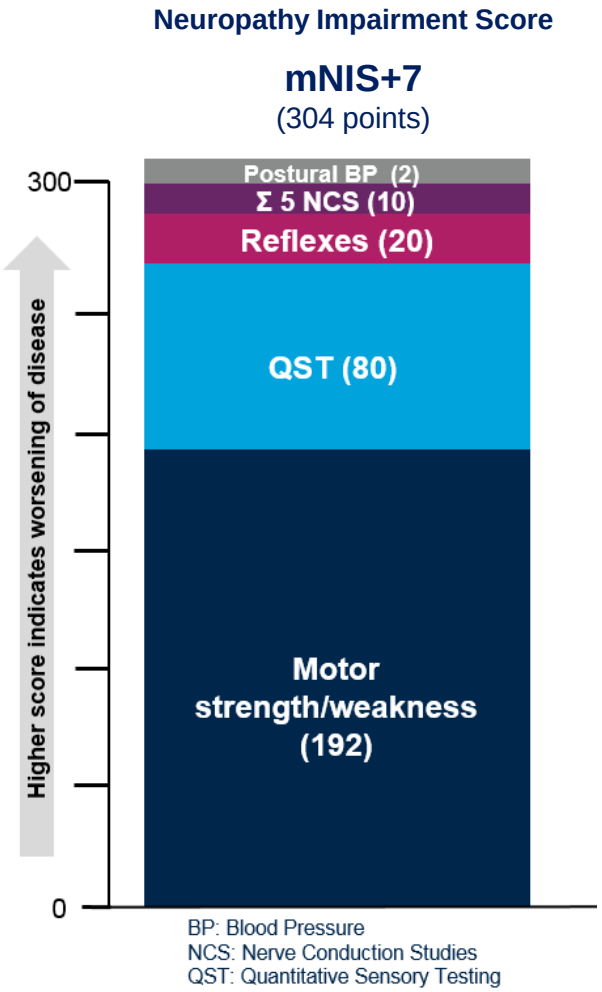
Patisiran Phase 3 APOLLO Study Endpoints

Primary Endpoint

- **mNIS+7:** a composite measure of neurological impairment
  - Higher score indicates worsening of neuropathy

Secondary Endpoints

- **Norfolk QOL-DN:** 35-item QOL questionnaire that is sensitive to small fiber, large fiber, and autonomic nerve function
  - Higher score indicates worsening of QOL
- **NIS-W:** motor function/strength assessment
  - Higher score indicates worsening of strength
- **R-ODS:** 24-item questionnaire used to capture activity and social participation (disability)
  - Lower score indicates worsening disability
- **10-meter walk test (m/sec):** assessment of ambulation that measures gait speed
  - Lower score indicates worsening
- **mBMI (kg/m^2 x albumin [g/mL]): nutritional status**
  - Lower score indicates worsening of nutritional status
- **COMPASS 31:** 31-item questionnaire used to evaluate patient reported autonomic neuropathy symptoms
  - Higher score indicates worsening of autonomic neuropathy symptoms

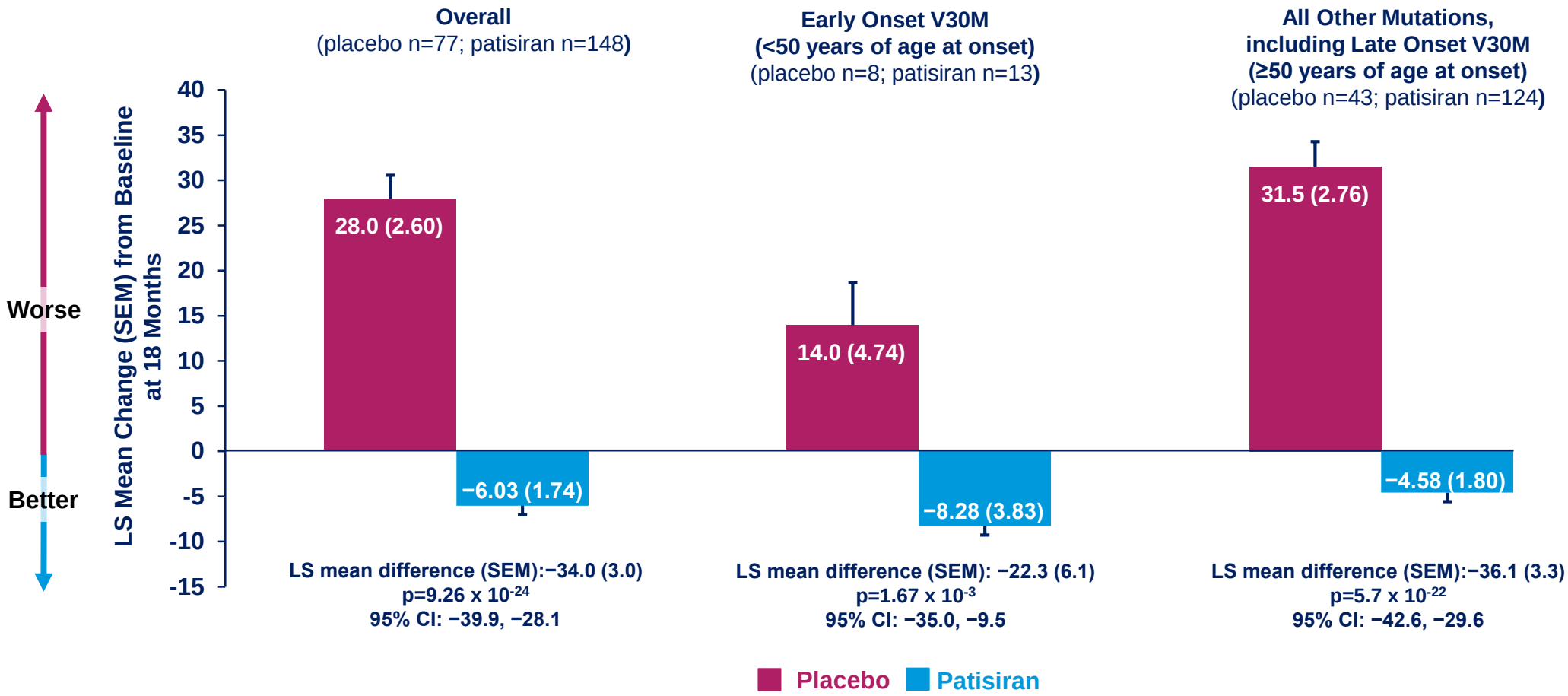


All primary and secondary endpoints achieved statistical significant difference in favor of patisiran at 18 months
Nominal statistical significance was achieved as early as month 9 for mNIS+7, Norfolk QOL-DN, NIS-W, R-ODS, 10-MWT and mBMI

10-MWT, 10 meter walk test; COMPASS-31, composite autonomic symptom score-31; mBMI, modified body mass index; mNIS+7, modified neuropathy impairment scale +7; NIS-W, neuropathy impairment score weakness; Norfolk QOL-DN, Norfolk quality of life-diabetic neuropathy questionnaire; QOL, quality of life; R-ODS; Rasch-built overall disability scale;

Patisiran Phase 3 APOLLO Study Results

mNIS+7: Early Onset V30M Subgroup Analysis

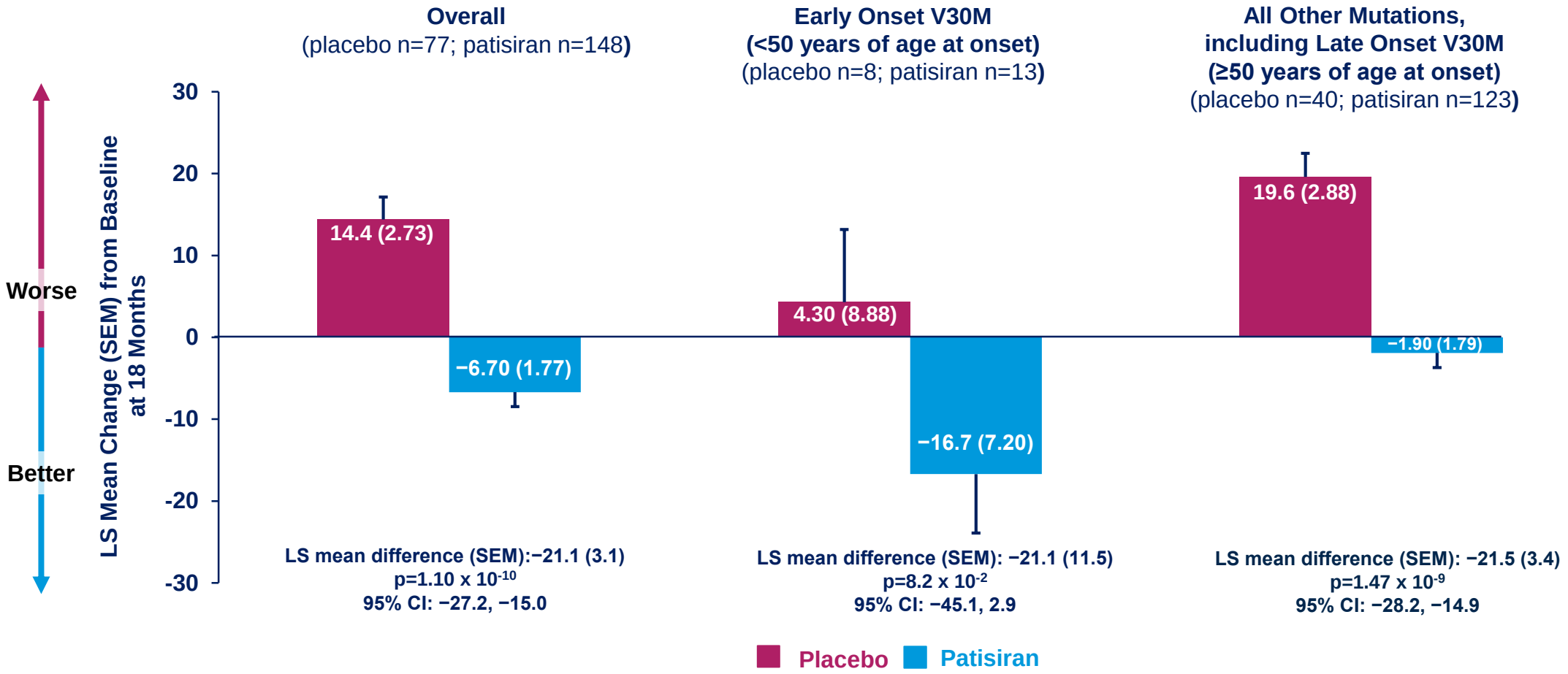


Improvement in polyneuropathy with patisiran versus placebo was seen for all TTR mutation types, including early/late onset V30M and a range of non-V30M mutations

CI, confidence interval; LS, least squares; mNIS, modified neurological impairment score; SEM, standard error of the mean

Patisiran Phase 3 APOLLO Study Results

Norfolk QOL-DN: Early Onset V30M Subgroup Analysis



Improvement in QOL with patisiran versus placebo was seen across all TTR mutation types, including early/late onset V30M and a range of non-V30M mutations

CI, confidence interval; QoL-DN, quality of life-diabetic neuropathy; SEM, standard error of the mean

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Patisiran Phase 3 APOLLO Study Results

Safety and Tolerability

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)

No deaths considered related to study drug

- Causes of death consistent with natural history

Majority of AEs were mild or moderate in severity

- Peripheral edema
  - Decreased over time
  - Did not result in any treatment discontinuations
- Infusion-related reactions (IRRs)
  - Majority mild in severity
  - Decreased over time
  - 1 patient discontinued treatment

The safety profile of patisiran was similar in V30M and nonV30M patients

No safety signals regarding liver function tests, hematology including thrombocytopenia, or renal dysfunction related to patisiran

Adverse Events Occurring in ≥ 10% in Either Group

Preferred AE Term, number of patients (%)	Placebo (N=77)	Patisiran (N=148)
Diarrhea	29 (37.7)	55 (37.2)
Edema, peripheral	17 (22.1)	**44 (29.7)**
Infusion related reaction (IRR)	7 (9.1)	**28 (18.9)**
Fall	**22 (28.6)**	25 (16.9)
Constipation	13 (16.9)	22 (14.9)
Nausea	**16 (20.8)**	22 (14.9)
Dizziness	11 (14.3)	19 (12.8)
Urinary tract infection	**14 (18.2)**	19 (12.8)
Fatigue	8 (10.4)	18 (12.2)
Headache	9 (11.7)	16 (10.8)
Cough	9 (11.7)	15 (10.1)
Insomnia	7 (9.1)	15 (10.1)
Nasopharyngitis	6 (7.8)	15 (10.1)
Vomiting	8 (10.4)	15 (10.1)
Asthenia	9 (11.7)	14 (9.5)
Pain in Extremity	8 (10.4)	10 (6.8)
Muscular Weakness	**11 (14.3)**	5 (3.4)
Anemia	**8 (10.4)**	3 (2.0)
Syncope	**8 (10.4)**	3 (2.0)

Blue, bolded text: Indicates ≥5 percentage point difference in either group

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Patisiran Phase 3 APOLLO Study

Summary

- hATTR amyloidosis is a multisystem, progressive, debilitating, life-threatening, often fatal disease with high morbidity and mortality and limited therapeutic options
- Patisiran treatment improved neuropathy and QOL at 18 months
  - In the prespecified early onset V30M subgroup, consistent efficacy was observed compared to patients with other mutations, including late onset V30M and non-V30M genotypes combined
- Patisiran showed an encouraging safety and tolerability profile
  - Frequency of deaths trended lower in the patisiran group versus placebo arm
  - Key patisiran safety findings include mild to moderate peripheral edema and IRRs with only one treatment discontinuation due to these events
  - No safety signals with regard to thrombocytopenia, hepatic or renal dysfunction
- 99% of eligible APOLLO patients enrolled into Global OLE study

QOL, quality of life; OLE, open label extension

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Study Investigators

- Adams, David: CHU Bicêtre, France
- Ajroud-Driss, Senda: Northwestern University, USA
- Attarian, Shahram: Hôpital de La Timone, France
- Barroso, Fabio: Instituto FLENI Montaneses, Argentina
- Berk, John: Boston University, USA
- Brannagan, Thomas: Columbia University Medical Center, USA
- Buades Reines, Juan: Hospital Son Llatzer, Spain
- Campistol, Joseph: Hospital Clinic, ICNU, Spain
- Coelho, Teresa: Hospital de Santo António, Portugal
- Conceicao, Isabel: Hospital de Santa Maria, Portugal
- Marques Junior, Wilson: Hospital das Clinicas da USP de Ribeirao, Brazil
- Dispenzieri, Angela: Mayo Clinic, USA
- Galan Davila, Lucia: Hospital Clinic San Carlos, Spain
- Gonzalez-Duarte, Alejandra: National Institute of Med Sciences, Mexico
- Gorevic, Peter: Mount Sinai Medical Center, USA
- Hazenberg, Bouke: UMC, Netherlands
- Ito, Mizuki: Nagoya University Hospital, Japan
- Kim, Byoung-Joon: Samsung Medical Center, South Korea
- Kristen, Arnt: Heidelberg University Hospital, Germany
- Kyriakides, Theodoros: CING, Cyprus
- Lin, Kon-Ping: Taipei Veterans General Hospital, Taiwan
- Lopate, Glenn: Washington University School of Medicine Center, USA
- Mezei, Michelle: Vancouver General Hospital, Canada
- Munoz Beamud, Francisco: Juan Ramon Jimenez Hospital, Spain
- Obici, Laura: Fondazione IRCCS Policlinico San Matte, Italy
- Oh, Jeeyoung: Konkuk University Hospital, South Korea
- O'Riordan, William: eStudy Site, USA
- Parman, Yesim: Istanbul University, Turkey
- Plante-Bordeneuve, Violaine: CHU Henri, France
- Polydefkis, Michael: Johns Hopkins Bayview Medical Center, USA
- Quan, Dianna: University of Colorado, Aurora, USA
- Sabatelli, Mario: Universita Cattolica del Sacro Cuore Institute of Neurology, Italy
- Schmidt, Hartmut: University Hospital of Muenster, Germany
- Sekijima, Yoshiki: Shinshu University Hospital, Japan
- Suhr, Ole: Umeå University Hospital, Sweden
- Tard, Celine: CHRU de Lille, France
- Taubel, Jorg: St George's University of London, UK
- Tournev, Ivaylo: UMHAT Aleksandrovska, Bulgaria
- Tuchman, Sascha: Duke University Medical Center, USA
- Vita, Giuseppe: Policlinico Universitario, Italy
- Waddington-Cruz, Marcia: Hospital Universitario Clementino Fraga Filho, Brazil
- Yamashita, Taro: Kumamoto University Hospital, Japan
- Yang, Chih-Chao: National Taiwan University Hospital, Taiwan
- Zonder, Jeffrey: Karmanos Cancer Institute, USA

Study Collaborators

- Peter Dyck: Mayo Clinic, USA

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