Patisiran: Dose Ranging Studies

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SUMMARY

- The only dose of patisiran studied in phase 3 clinical studies and approved by regulatory authorities is 0.3 mg/kg IV once every 3 weeks.[1]
- In the clinical development program for patisiran, a phase 1 dose ranging study and a phase 2 trial exploring different dosing regimens were conducted.

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PHASE 1 TRIAL

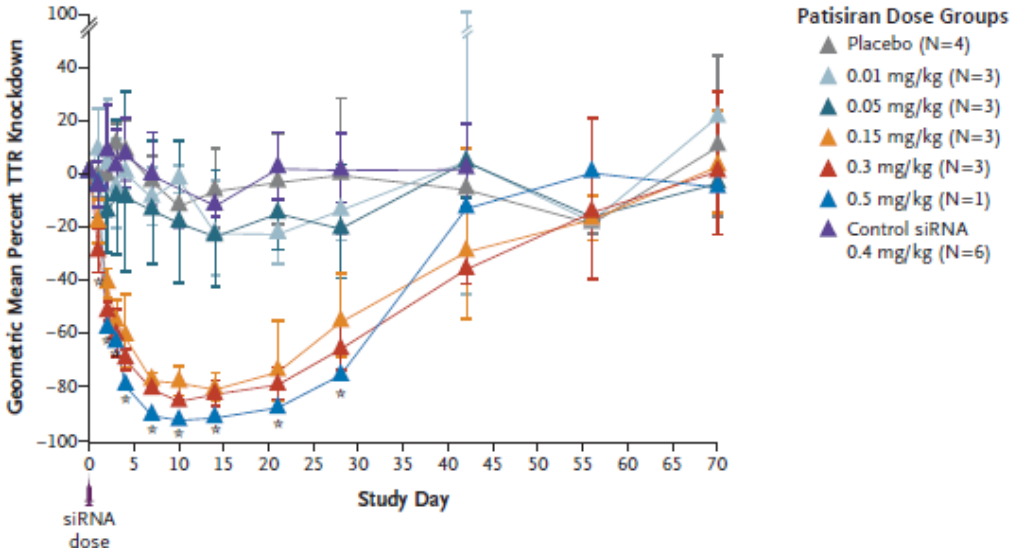
Study Methods

A phase 1 trial was conducted to evaluate the safety and efficacy of a single dose of patisiran. The trial was a multicenter, randomized, single-blind, placebo-controlled, dose-ranging study conducted in healthy adult volunteers. Individuals were randomly assigned to receive a single dose of IV patisiran (at doses of 0.01 mg/kg, 0.05 mg/kg, 0.15 mg/kg, 0.3 mg/kg, and 0.5 mg/kg) or placebo (normal saline).[2]

Efficacy Results

Figure 1 shows the geometric mean percent serum TTR knockdown, as compared to baseline, at the indicated time points over a 70-day period in groups of patients receiving placebo, increasing doses of patisiran, or the control siRNA (siRNA targeting *PCSK9* formulated in the same type of lipid nanoparticles as were used in patisiran). No significant changes in TTR levels compared with placebo were observed at the two lowest doses administered or control siRNA. Individuals receiving doses of 0.15 mg/kg, 0.3 mg/kg, and 0.5 mg/kg demonstrated significant changes, as compared with placebo ($p<0.001$), through day 28.[2]

Figure 1. Efficacy of Patisiran in Healthy Volunteers in the Phase 1 Trial.[2]



Abbreviations: siRNA = small interfering ribonucleic acid; TTR = transthyretin.
*Denotes P<0.001 for the comparison between the group receiving a dose of 0.3 mg/kg and the placebo group, according to repeated-measures analysis of variance and post hoc tests. The I bars indicate 95% confidence intervals.
From Coelho et al[22]

Safety Results

Table 1 shows the AEs reported in the trial. The use of patisiran did not result in any significant changes in hematologic, liver, or renal parameters or in thyroid function, and there were no drug-related serious adverse events or any study drug discontinuations because of adverse events.[2]

Table 1. AEs in Patisiran Phase 1 Trial, According to Study Group.[2]

Preferred Term[a], n (%)	0.01 mg/kg (n=3)	0.05 mg/kg (n=3)	0.15 mg/kg (n=3)	0.3 mg/kg (n=3)	0.5 mg/kg (n=1)	Across All Doses (n=13)	Placebo (n=4)
Skin erythema	1 (33.3)	2 (66.7)	0	2 (66.7)	1 (100.0)	6 (46.0)	2 (50.0)
Infusion reaction	0	0	0	0	1 (100.0)	1 (7.7)	0
Headache	0	1 (33.3)	0	0	0	1 (7.7)	0
Backache	0	0	0	0	0	0	1 (25.0)
Nausea	0	0	0	0	0	0	1 (25.0)
Sore throat	0	0	1 (33.3)	0	0	1 (7.7)	0
Chest pain	0	0	0	0	0	0	1 (25.0)
Lightheadedness	1 (33.3)	0	0	0	0	1 (7.7)	0
Sleepiness	1 (33.3)	0	0	0	0	1 (7.7)	0

[a]Includes adverse events probably or possibly related to study drug, all mild to moderate in severity.

PHASE 2 TRIAL

The phase 2 study was a multicenter, international, open-label, multiple-dose escalation study in patients with hATTR-PN. Cohorts of 3 patients received 2 doses of patisiran, with each dose administered as an IV infusion.

- Cohorts 1–3 (n=10) received 2 doses of patisiran 0.01 mg/kg (n=4), 0.05 mg/kg (n=3), and 0.15 mg/kg (n=3) every 4 weeks (Q4W), respectively.
- Cohorts 4 and 5 (n=7) both received 2 doses of patisiran 0.3 mg/kg Q4W.
- Cohorts 6–9 (n=12) all received 2 doses of patisiran 0.3 mg/kg Q3W.

All patients received premedication prior to each patisiran infusion to reduce the risk of IRRs. The primary objective was to evaluate the safety and tolerability of multiple ascending doses of patisiran.[3]

Efficacy Results

Serum TTR knockdown by dose group is shown in **Table 2**. In comparison with the 0.01 mg/kg dose cohort, a significant reduction ($p<0.001$) in nadir TTR levels was observed after the first and second doses of patisiran in the 0.3 mg/kg Q4W and Q3W cohorts.[3]

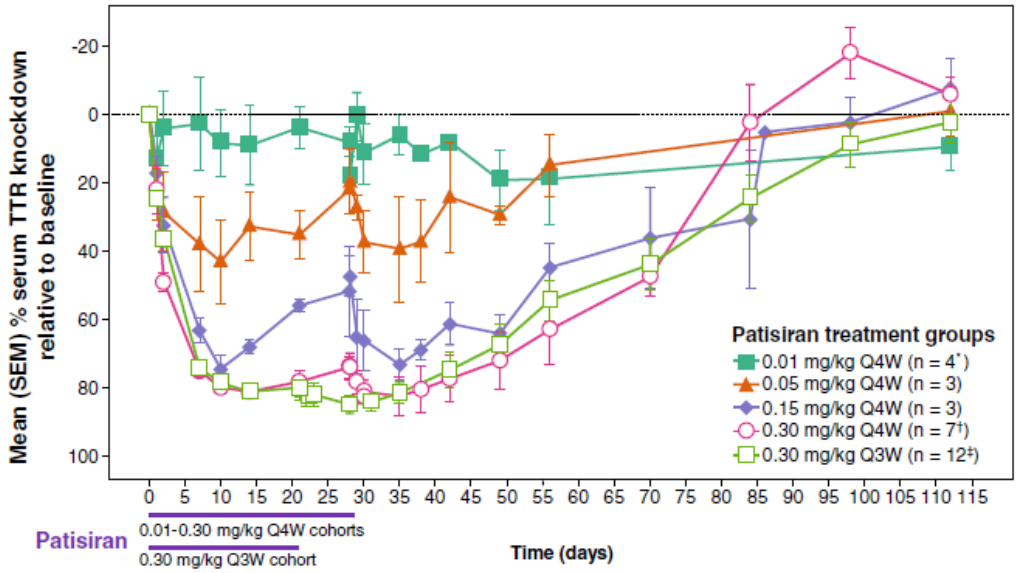
Table 2. Serum TTR Knockdown by Dose Group.[3]

Dose Group (mg/kg)	Dose 1		Dose 2	
	Maximum TTR KD (%)	TTR KD at Nadir (Mean % ± SD)	Maximum TTR KD (%)	TTR KD at Nadir (Mean % ± SD)
0.01 Q4W (n=4[a])	37.8	22.1 ± 12.5	34.4	32.9 ± 2.3
0.05 Q4W (n=3)	58.0	48.4 ±16.2	58.5	46.9 ±15.0
0.15 Q4W (n=3)	81.7	74.5 ± 6.8[d]	86.0	77.0 ±7.8
0.3 Q4W (n=7[b])	87.5	82.9 ± 5.4[d]	90.8	85.7 ± 9.6[d]
0.3 Q3W (n=12[c])	94.2	83.8 ± 5.1[d]	96.0	86.7 ± 7.0[d]

Abbreviations: ANCOVA = analysis of variance; KD = knockdown; SD = standard deviation; TTR = transthyretin.
Footnotes: p values from ANCOVA models including baseline TTR as covariate and dose groups as factor; models significant at $p<0.001$ for dose 1, $p<0.001$ for dose 2.
[a]Includes first-dose data from additional patient prior to protocol amendment.
[b]Excludes post-day 28 data from patient who experienced drug extravasation during second infusion.
[c]One patient discontinued the study before second dose of patisiran.
[d]$p<0.001$ vs 0.01 mg/kg group.

Mean percentage serum TTR knockdown relative to baseline is shown in **Figure 2**. As shown in the figure, a mean TTR knockdown from baseline of ≥80% was maintained between doses in the Q3W cohort, yet TTR levels recovered to <80% knockdown between doses with the Q4W regimen. Based on the data obtained from this trial, the 0.3 mg/kg Q3W was the dose selected for evaluation in the phase 3 trial and the dose that was ultimately approved by the FDA to treat patients.[3]

Figure 2. Mean Percentage Serum TTR Knockdown Relative to Baseline.[3]



Abbreviations: SEM = standard error of the mean; TTR = transthyretin.
Footnotes: Dose response and duration of TTR knockdown. Mean (±SEM) percentage of baseline serum concentration–time profile.
*Includes first dose data from additional patient prior to protocol amendment.
†Excludes post-day 28 data from patient who experienced drug extravasation during second infusion.
‡One patient discontinued before the second dose of patisiran.
From Suhr et al[3]

Safety Results

TEAEs related or possibly related to patisiran are shown in **Table 3**. The most common TEAE related to study drug was mild-to-moderate IRR, which occurred in 3 out of 29 patients overall (10.3%), all in the 0.3 mg/kg Q4W group. None of these TEAEs led to discontinuation of treatment. There were no dose-limiting toxicities or deaths due to TEAEs reported during the study. The use of patisiran did not result in any significant changes in hematologic, liver, or renal parameters.[3]

Table 3. TEAEs Related or Possibly Related to Patisiran (ITT [safety] population).[3]

Preferred Term, n (%)	0.01 mg/kg Q4W(n=4)	0.05 mg/kg Q4W(n=3)	0.15 mg/kg Q4W(n=3)	0.3 mg/kg Q4W(n=7)	0.3 mg/kg Q3W(n=12)	Across All Doses (n=29)
Infusion Related Reaction	0	0	0	3 (42.9)	0	3 (10.3)
Back Pain	0	0	0	2 (28.6)	0	2 (6.9)
Asthenia	0	0	0	1 (14.3)	1 (8.3)	2 (6.9)
Leukocytosis	0	0	0	0	1 (8.3)	1 (3.4)
Neutrophilia	0	0	0	0	1 (8.3)	1 (3.4)
Cellulitis[a]	0	0	0	1 (14.3)	0	1 (3.4)
Lymphangitis	0	0	0	1 (14.3)	0	1 (3.4)
Polyuria	0	0	0	1 (14.3)	0	1 (3.4)
Nausea/Vomiting	0	0	0	0	1 (8.3)	1 (3.4)
Facial Erythema	0	0	0	0	1 (8.3)	1 (3.4)
Dry Mouth	0	0	0	0	1 (8.3)	1 (3.4)
Pyrexia	0	0	0	0	1 (8.3)	1 (3.4)
Dysphagia	0	0	0	0	1 (8.3)	1 (3.4)

Abbreviations: ITT = intent-to-treat; TEAE = treatment emergent adverse event.
[a]Due to drug extravasation.

ONPATTRO PRESCRIBING INFORMATION – RELEVANT CONTENT

The DOSAGE AND ADMINISTRATION section provides the following information[1]:

Dosing Information

ONPATTRO should be administered by a healthcare professional.

ONPATTRO is administered via intravenous (IV) infusion. Dosing is based on actual body weight.

For patients weighing less than 100 kg, the recommended dosage is 0.3 mg/kg once every 3 weeks.

For patients weighing 100 kg or more, the recommended dosage is 30 mg once every 3 weeks.

ABBREVIATIONS

AE = adverse event; ANCOVA = analysis of variance; FDA = Food and Drug Administration; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IRR = infusion-related reaction; ITT = intent-to-treat; IV = intravenous; KD = knockdown; PCSK9 = proprotein convertase subtilisin/kexin type 9; Q3W = every 3 weeks; Q4W = every 4 weeks; SD = standard deviation; SEM = standard error of the mean; siRNA = small interfering ribonucleic acid; TEAE = treatment emergent adverse event; TTR = transthyretin.

Updated 13 September 2024

REFERENCES

1. ONPATTRO (patisiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.
2. Coelho T, Adams D, Silva A, et al. Safety and Efficacy of RNAi Therapy for Transthyretin Amyloidosis. *N Engl J Med*. 2013;369(9):819-829. doi:10.1056/NEJMoa1208760
3. Suhr OB, Coelho T, Buades J, et al. Efficacy and safety of patisiran for familial amyloidotic polyneuropathy: a phase II multi-dose study. *Orphanet J Rare Dis*. 2015;10:109. doi:10.1186/s13023-015-0326-6