Eplontersen: NEURO-TTRansform Week 85 Topline Results

July 10, 2023

Nasdaq: IONS

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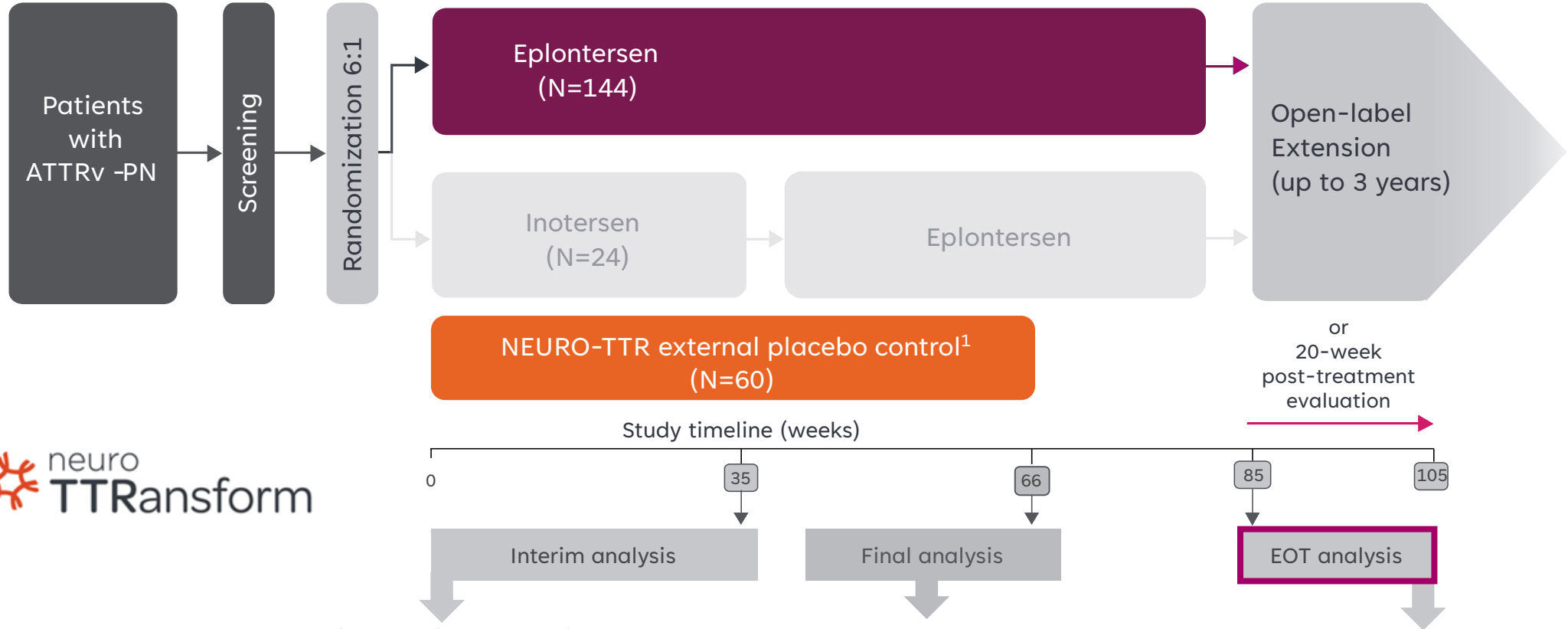
In this presentation, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

NEURO-TTRansform Study Designed to Demonstrate Benefit in Patients with ATTRv-PN

- A multicenter, open-label study in 168 patients with hereditary TTR amyloid polyneuropathy (ATTRv-PN)



neuro TTRansform

[1]Benson et al, *N Engl J Med* (2018) 379:22-3 1. Figure adapted from Coelho et al, *Neurol Ther* (2021) 10:375-89.

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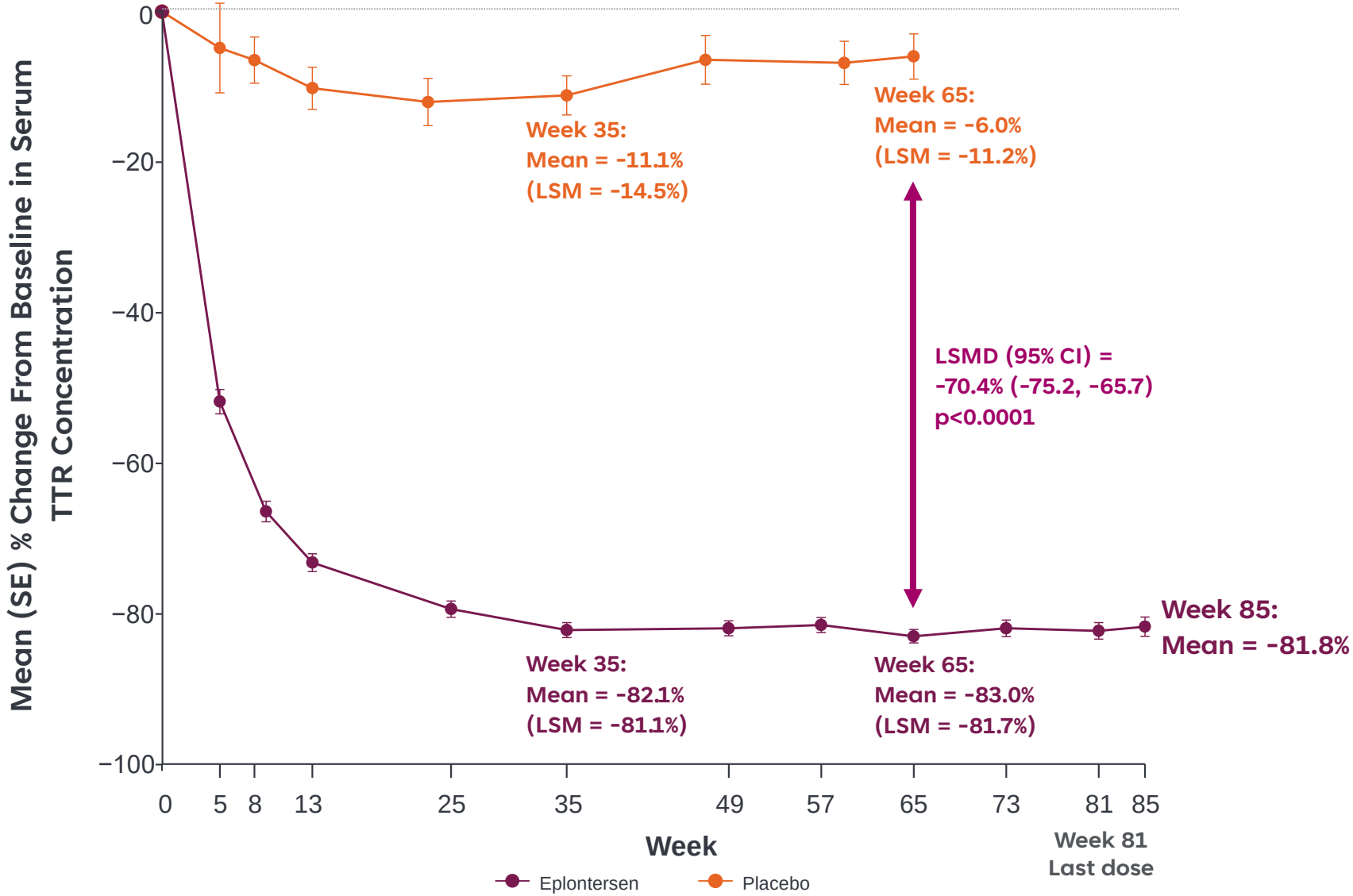
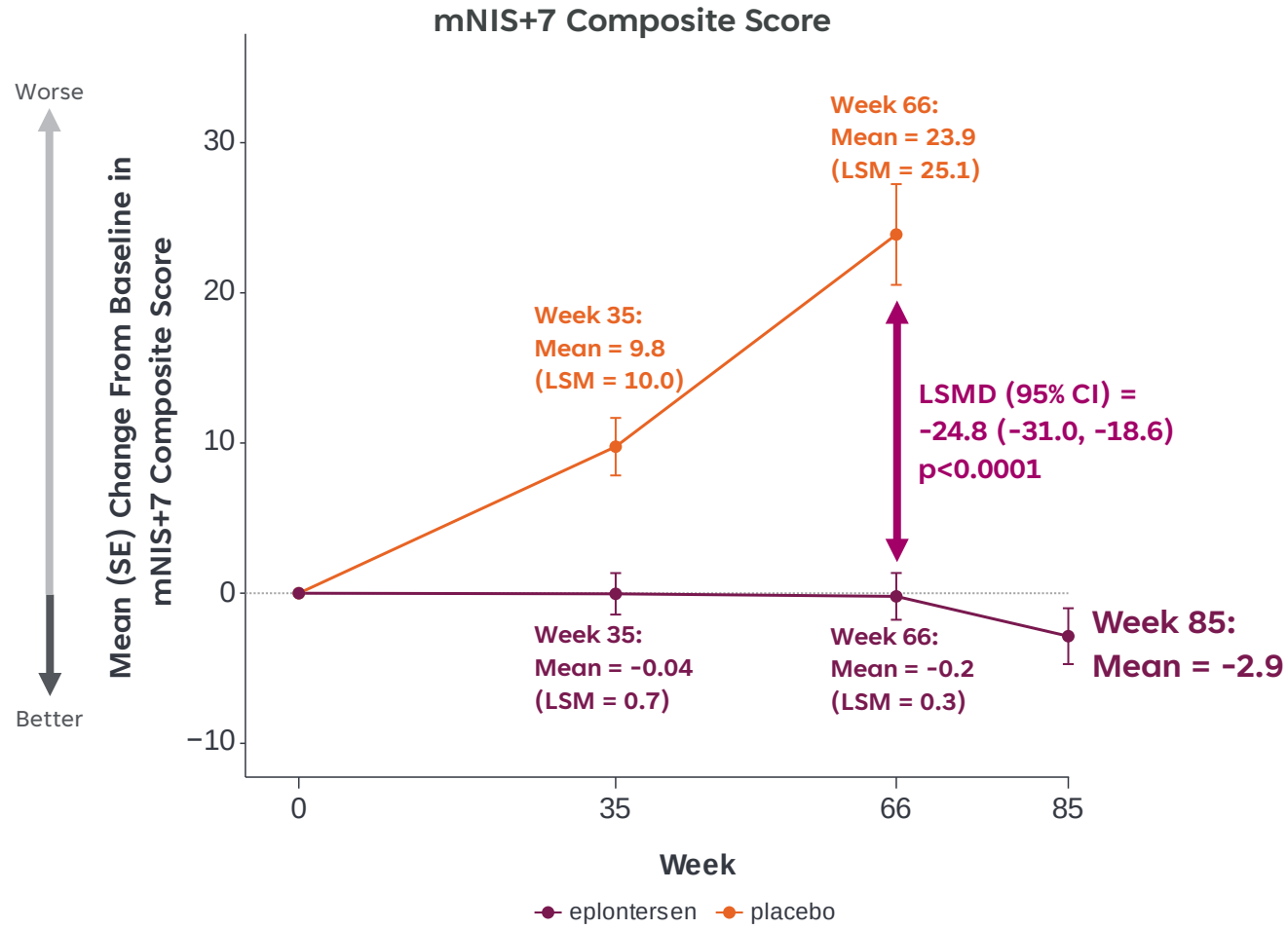
Eplontersen Treatment Resulted in Substantial and Sustained Reductions in Serum TTR Concentration Compared to Baseline



LSM: Least Square Mean; LSMD: Least Square Mean Difference

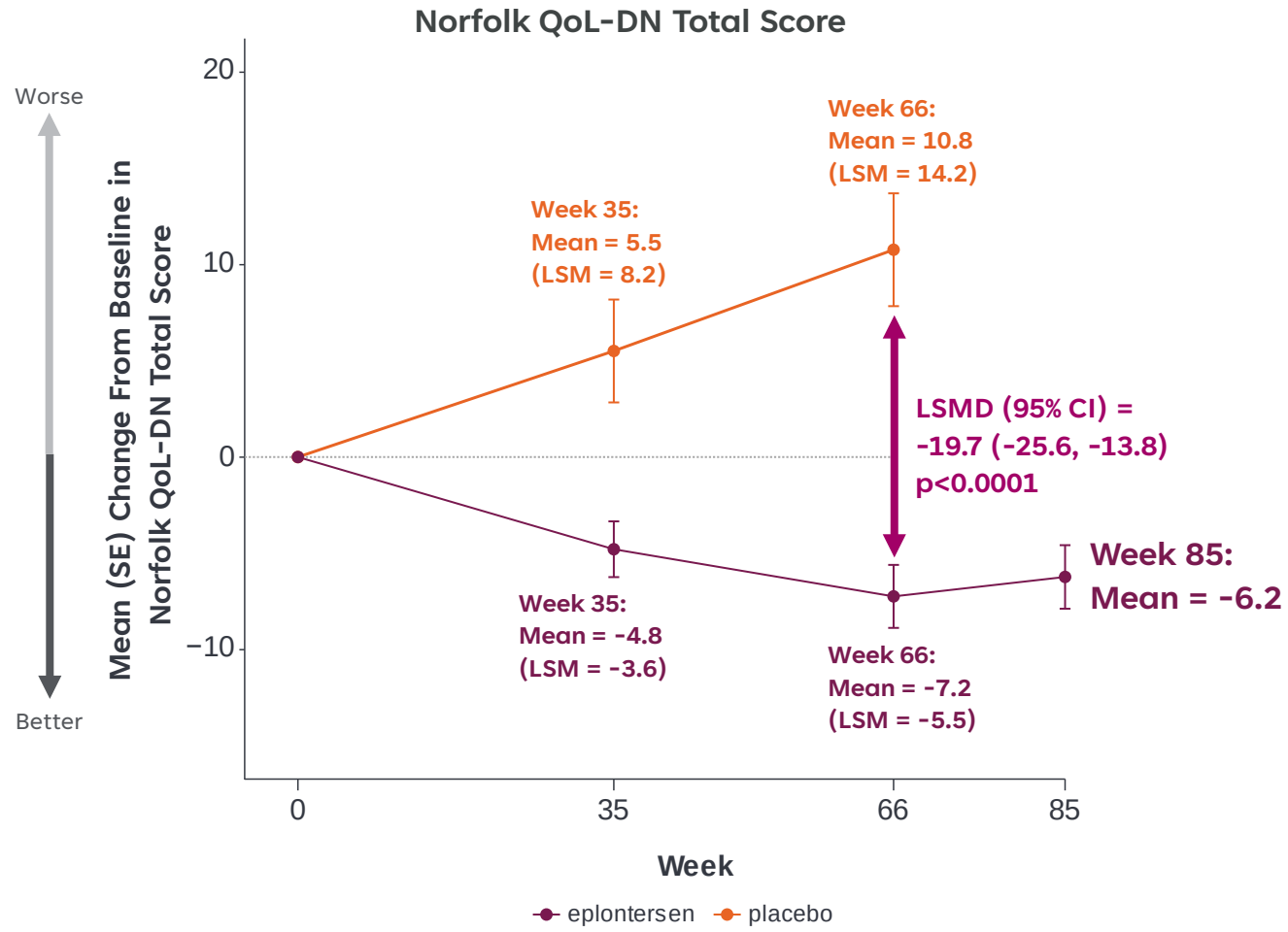
Eplontersen Continued to Halt Neuropathy Progression at Week 85



- Substantial number of patients showed improvement in neuropathy impairment through 19 months of treatment

LSM: Least Square Mean; LSMD: Least Square Mean Difference

Eplontersen Continued to Improve Quality of Life at Week 85



- Substantial number of patients showed improvement in quality of life through 19 months of treatment

LSM: Least Square Mean; LSMD: Least Square Mean Difference

Eplontersen Continued to Demonstrate a Favorable Safety and Tolerability Profile at 85 Weeks[1]

- At 85 weeks, TEAEs incidence remains consistent with week 66
- No TEAEs of special interest led to study drug discontinuation
- No imbalance of ocular events excluding vitamin A decrease or deficiency
- No SAEs were related to study drug
- 3 non-drug related deaths in the eplontersen group, all related to known sequelae of ATTR amyloidosis[2-6]

Incidence, n (%)	Placebo	Eplontersen Week 66	Eplontersen Week 85
N	60	144	144
Any TEAE	60 (100)	140 (97.2)	141 (97.9)
Related to study drug	23 (38.3)	53 (36.8)	55 (38.2)
Leading to study drug discontinuation	2 (3.3)	6 (4.2)	8 (5.6)
TEAE of special interest	14 (23.3)	41 (28.5)	43 (29.9)
Ocular events potentially related to Vit A deficiency	12 (20.0)	39 (27.1)	41 (28.5)
Ocular events excluding lab TEAEs of Vit A decrease or deficiency	9 (15.0)	24 (16.7)	26 (18.1)
Thrombocytopenia	1 (1.7)	3 (2.1)	3 (2.1)
Glomerulonephritis	2 (3.3)	0	0
Other TEAE of interest	48 (80.0)	87 (60.4)	93 (64.6)
Any serious TEAE	13 (21.7)	21 (14.6)	27 (18.8)
Related to study drug	1 (1.7)	0	0
Fatal TEAE	0	2 (1.4)	3 (2.1)
Related to study drug	0	0	0

[1]External placebo concluded at week 66 while eplontersen patients remained on treatment and could accrue additional events; [2]Cavallaro et al, *Neurology* (2016) 87:750-1; [3]Yamada et al, *Prog Mol Biol Transl Sci* (2012) 107:41-78; [4]Yamashita et al, *Neurology* (2008) 70:123-28; [5]Ellie et al, *Neurology* (2001) 57:135-7; [6]Porcari et al, *Cardiovasc Res* (2023) 118:3517-35.

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