Improved Low Contrast Visual Acuity, Reduction in Retinal Ganglion Cell Loss, and Neurofilament-light with Privosegtor in Acute Optic Neuritis: Results from a Multicenter, Randomized, Placebo-Controlled, Double Masked Trial

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Background

- Acute optic neuritis (ON) is an inflammatory demyelinating disorder of the optic nerve that can result in permanent visual impairment.[1]
- Privosegtor is a novel neuroprotective candidate with broad potential for neuro-axonal diseases.[2]
- In vivo data show neuro-axonal survival in models of ON and multiple sclerosis.[2]

Objective

- To evaluate the safety and efficacy of privosegtor in acute ON.

Methods

1 Design
Randomized, double-masked, placebo-controlled trial (NCT04762017; **Figure 1**).
Multi-center, 6-month trial with 36 patients randomized (modified intent-to-treat [mITT]: 33).

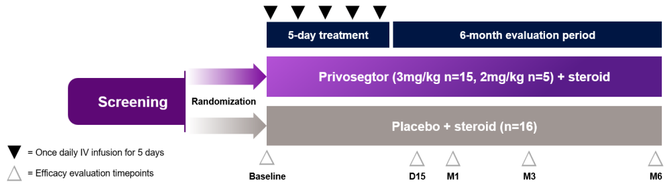
2 Intervention & comparator
Once-daily IV infusion of privosegtor + steroid vs. placebo + steroid for 5 days.

3 Participants
Patients diagnosed with a unilateral acute ON.
Onset of visual loss symptoms in the last 12 days before randomization.

4 Key endpoints
Primary endpoint: Safety
Secondary endpoints: Visual function and retinal structural anatomy
- 2.5% ETDRS low-contrast visual acuity (LCVA)
- Ganglion cell and inner plexiform layer (GCIPL) thickness as assessed by OCT
- Retinal nerve fiber layer (RNFL) thickness as assessed by OCT

Exploratory endpoint: Plasma neurofilament-light chain (NfL) levels, measured centrally using Single Molecule Array technology

Figure 1. Trial design



Statistical Analysis: The mITT population was analyzed using a mixed model for repeated measures (MMRM) to estimate the least-squares (LS) mean change from baseline. One placebo subject was excluded from the mITT population in the LCVA analysis due to missing LCVA post-baseline assessments. Analyses focused on privosegtor 3 mg/kg/day because only four participants received 2 mg/kg/day.

Ethics: The trial was approved by the French Regulatory Authority and French Independent Ethics Committee, in accordance with the Declaration of Helsinki and ICH Good Clinical Practice guidelines. All participants provided written informed consent.

Results

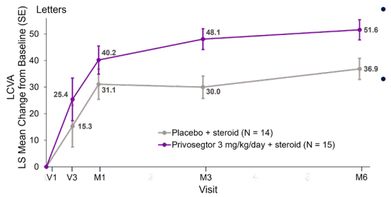
Demographic and Baseline characteristics

Characteristic	Privosegtor + steroid 3 mg/kg/day (N = 15)	Placebo + steroid (N = 14)
Age, years	33.7 (9.8)	32.7 (10.3)
Female	9 (60.0%)	10 (71.4%)
GCIPL thickness, µm	89.3 (8.3)	84.3 (13.8)
RNFL thickness, µm	104.6 (13.1)	115.5 (54.1)
HCVA, ETDRS	54.1 (34.5)	42.6 (34.5)
LCVA, ETDRS	19.4 (22.3)	17.8 (24.3)
Visual field mean deviation, dB	-14.1 (11.9)	-14.5 (12.5)
Time since first visual loss symptoms at date of first dose, days	9.5 (2.7)	9.6 (2.5)
Multiple sclerosis at baseline	10 (66.7%)	9 (64.3%)
Disease Modifying Therapies	10 (66.7%)	9 (64.3%)

Results are mean (SD) or n (%). ETDRS, Early Treatment Diabetic Retinopathy Study

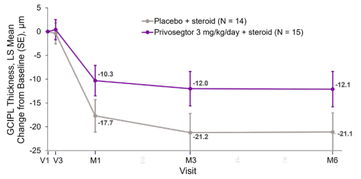
Visual function, retinal structure, and serum-based biomarkers

Figure 2. Change from baseline in 2.5% ETDRS LCVA in the affected eye



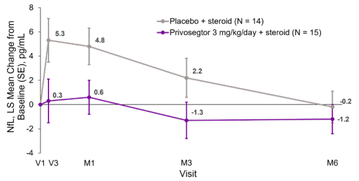
- Patients in the privosegtor 3 mg/kg/day arm achieved clinically meaningful improvement in LCVA vs. placebo.
- Improvement in LCVA with privosegtor vs. placebo was 18.2 letters at Month 3 and 14.8 letters at Month 6 (Figure 2).

Figure 3. Change from baseline in GCIPL thickness in the affected eye



- Patients in the privosegtor 3 mg/kg/day arm showed less GCIPL and RNFL thinning vs. placebo.
- There was a 43% reduction in GCIPL thinning at Month 3 and 6 with privosegtor vs. placebo (Figure 3), and a 28% and 30% reduction in RNFL thinning at the respective timepoints.

Figure 4. Change from baseline in plasma NfL levels



- Mean plasma NfL concentrations remained stable from baseline through Month 6 with privosegtor; with placebo, levels increased from baseline to Month 1, before returning to baseline by Month 6 (Figure 4).

Safety

- Adverse event (AE) rates were similar between groups (Table 2).
- No AEs leading to drug withdrawal or study discontinuation.
- No drug-related serious adverse events (SAEs).

Table 2: Safety

Event, n (%)	Privosegtor + steroid			Placebo + steroid (N=14)
	2 mg/kg/day (N = 4)	3 mg/kg/day (N = 14)	Pooled (N = 19)	
≥1 TEAE	4 (100.0%)	12 (80.0%)	16 (84.2%)	14 (100.0%)
Related to study treatment	*4 (100.0%)*	*6 (40.0%)*	*10 (52.6%)*	*6 (42.9%)*
≥1 grade ≥2 TEAE	2 (50.0%)	9 (60.0%)	11 (57.9%)	6 (42.9%)
Related to study drug	*0*	*2 (13.3%)*	*2 (10.5%)*	*0*
≥1 serious TEAE	0	1 (6.7%)	1 (5.3%)	1 (7.1%)
Related to study drug	*0*	*0*	*0*	*0*
≥1 SAE leading to death	0	0	0	0
≥1 TEAE leading:				
Dose reduction	0	0	0	0
Dose interruption	0	0	0	0
Drug withdrawal	0	0	0	0
Premature study discontinuation	0	0	0	0

SAE, serious adverse event; TEAE, treatment-emergent adverse event

Conclusions

1. **Safety:** Well tolerated, with no treatment-related SAEs.
2. **Visual Function:** Clinically meaningful and sustained improvements in visual function, with an 18-letter mean difference vs. placebo.
3. **Retinal Structure:** Greater preservation of GCIPL and RNFL.
4. **Disease Biology:** Increases in plasma NfL were smaller with privosegtor, particularly at early timepoints close to acute ON onset.

PIONEER-1 (NCT07623668) **will further evaluate privosegtor as a potential neuroprotective therapy for ON.**

References. 1. Bennett J, et al. Lancet Neurol. 2023; 22:89-100; 2. Villoslada P, et al. Neurotherapeutics. 2019;16(3):808-827

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