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RIMS

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

#P918

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INTRODUCTION

- Acute optic neuritis (AON) involves inflammation of the optic nerve, which can lead to visual impairment through axonal loss and retinal ganglion cell degeneration[1]
- Although corticosteroids may manage symptoms, there is a need for long-term neuroprotective treatments[2,3]
- Privosegtor (OCS-05), a peptoid small molecule, has shown neuroprotective activity in several experimental animal models and is being studied as a treatment for individuals with AON[4]
- AON serves as a predictive model for evaluating neuroprotective therapies; AON is often the earliest manifestation of neurological disorders such as multiple sclerosis (MS) and neuromyelitis optica[5,6]
- A phase 1, randomized, double-masked, placebo-controlled, single- and multiple-ascending-dose study demonstrated safety and tolerability with privosegtor in healthy participants (N=48; privosegtor, n=36; placebo, n=12)[4]
- The phase 2 ACUITY trial (NCT04762017) investigated the safety and efficacy of privosegtor plus steroid versus placebo plus steroid in individuals with AON

METHODS

Study design

- ACUITY was a phase 2, randomized, double-masked, placebo-controlled, multicenter trial in France that evaluated outcomes following privosegtor plus steroid compared with placebo plus steroid administered via 2-hour intravenous (IV) infusion once daily for 5 days (**Figure 1**)
- The primary analysis focused on safety and evaluated incidence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs), along with shifts in electrocardiogram (ECG)-based events (heart rate, PR interval, QRS duration, QTcB interval, QTcF interval)
- Key efficacy secondary endpoints evaluated structural preservation of neurons and were defined as changes from baseline in ganglion cell-inner plexiform layer (GCIPL) thickness and retinal nerve fiber layer (RNFL) thickness
- Another secondary endpoint was visual function as evaluated through change from baseline in low contrast visual acuity (LCVA), assessed with a 2.5% contrast Early Treatment Diabetic Retinopathy Study (ETDRS) letter chart
- Participants were randomly assigned (1:1:1) to receive IV privosegtor (either 2 mg/kg/day or 3 mg/kg/day) plus steroid or IV placebo plus steroid
  - The 2-mg/kg/day treatment group (n=5) was discontinued after a protocol amendment
- Randomization was stratified by visual acuity (i.e., baseline high contrast visual acuity [HCVA])

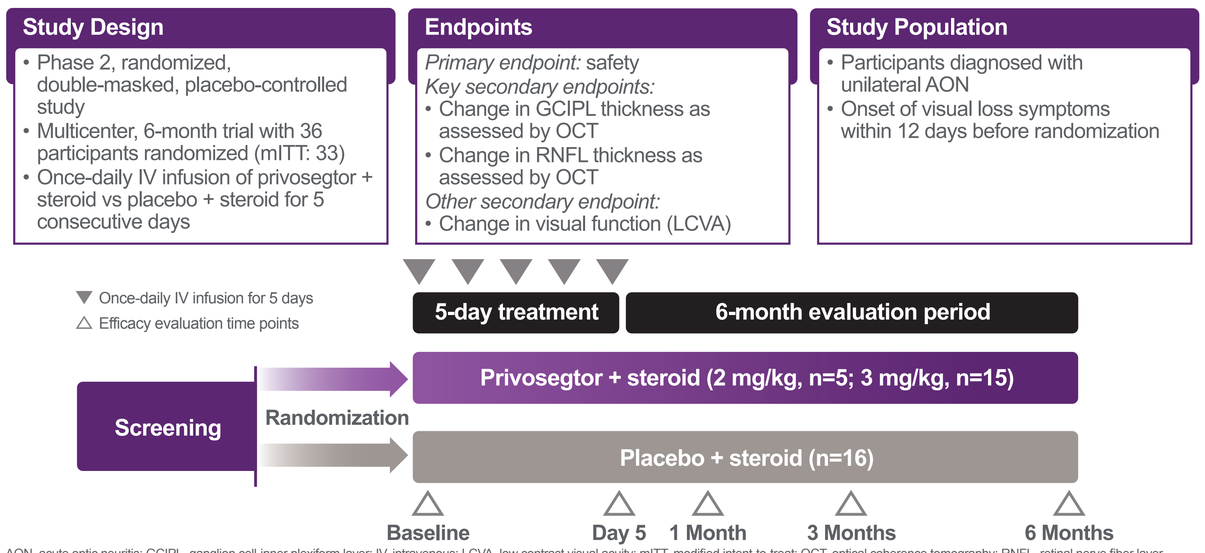
Participants

- Participants were 18 to 60 years of age and diagnosed with unilateral AON, with onset of visual loss symptoms within 12 days of randomization. Those with positive aquaporin-4 (AQP4) antibodies were excluded.

Data analysis

- Safety and efficacy analyses were based on all randomized participants who received at least one dose of study treatment (i.e., safety population and modified intent-to-treat [mITT] population were the same)
- Safety data were summarized and presented using descriptive statistics; risk differences were presented for cardiac safety between groups using the Wilson method, including continuity correction
- Efficacy analyses used mixed model for repeated measures and least-squares mean change from baseline (SE) of the affected eye

Figure 1. ACUITY study design



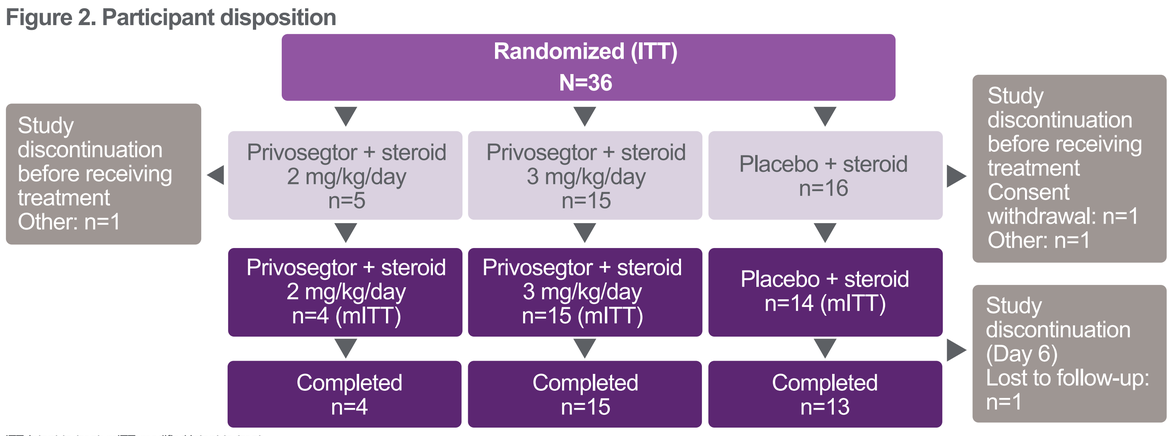
AON, acute optic neuritis; GCIPL, ganglion cell-inner plexiform layer; IV, intravenous; LCVA, low contrast visual acuity; mITT, modified intent-to-treat; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer.

RESULTS

Participants

- Of 36 participants randomized, 33 were available for the mITT analysis (**Figure 2**)
- Demographics and clinical characteristics were balanced at baseline between pooled privosegtor and placebo groups; overall, mean (SD) disease duration was 9.8 ± 2.5 days, and 61% of participants had MS (**Table 1**)

Figure 2. Participant disposition



ITT, intent-to-treat; mITT, modified intent-to-treat.

Table 1. Participant demographics and baseline characteristics

Characteristic	Privosegtor + steroid			Placebo + steroid
	2 mg/kg/ (n=4)	3 mg/kg/d (n=15)	Pooled (n=19)	1 g/d (n=14)
Age, mean (SD), years	44.0 (9.8)	33.7 (9.8)	35.9 (10.5)	32.7 (10.3)
Female, n (%)	4 (100)	9 (60.0)	13 (68.4)	10 (71.4)
GCIPL thickness, mean (SD), µm	85.9 (17.5)	89.3 (8.3)	88.6 (10.3)	84.3 (13.8)
RNFL thickness, mean (SD), µm	174.3 (134.1)	104.6 (13.1)	119.3 (63.1)	115.5 (54.1)
HCVA, mean (SD), ETDRS	28.5 (28.8)	54.1 (34.5)	48.7 (34.4)	42.6 (34.5)
LCVA, mean (SD), ETDRS	1.5 (3.0)	19.4 (22.3)	15.6 (21.1)	17.8 (24.3)
Time since first visual loss symptoms at date of first dose, mean (SD), days	11.3 (1.7)	9.5 (2.7)	9.8 (2.6)	9.6 (2.5)
MS at baseline, n (%)	1 (25.0)	10 (66.7)	11 (57.9)	9 (64.3)

ETDRS, Early Treatment Diabetic Retinopathy Study; GCIPL, ganglion cell-inner plexiform layer; HCVA, high contrast visual acuity; LCVA, low contrast visual acuity; MS, multiple sclerosis; RNFL, retinal nerve fiber layer.

Safety

- There were no adverse events (AEs) leading to drug withdrawal or study discontinuation (**Table 2**)
- The most frequently reported drug-related TEAEs as assessed by the investigator (>10% of participants) in the pooled privosegtor treatment group (2 or 3 mg/kg/day) were headache and acne, each reported in two participants (10.5%)
- There were no privosegtor-related SAEs; two unrelated SAEs were reported, including hospitalization due to MS relapse (3 mg/kg/day privosegtor + steroid), and hospitalization due to myelitis (placebo + steroid)
- Cardiac safety (shifts in ECG parameters) demonstrated no differences between groups
  - Overall events: privosegtor 2 mg or 3 mg/kg/day + steroid (n=2 [12.5%]) versus placebo + steroid (n=1 [12.5%])
  - Risk difference (90% CI): 0.0% (−34.4% to 25.1%)

Table 2. Safety

Event, n (%)	Privosegtor + steroid			Placebo + steroid
	2 mg/kg/d (n=4)	3 mg/kg/d (n=15)	Pooled (n=19)	1 g/d (n=14)
At least one TEAE	4 (100)	12 (80.0)	16 (84.2)	14 (100)
Related to study drug	4 (100)	6 (40.0)	10 (52.6)	6 (42.9)
Leading to drug withdrawal, or dose reduction or interruption	0	0	0	0
Leading to study discontinuation	0	0	0	0
At least one 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
At least one serious TEAE	0	1 (6.7)	1 (5.3)	1 (7.1)
Related to study drug	0	0	0	0
At least one SAE leading to death	0	0	0	0

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

Efficacy

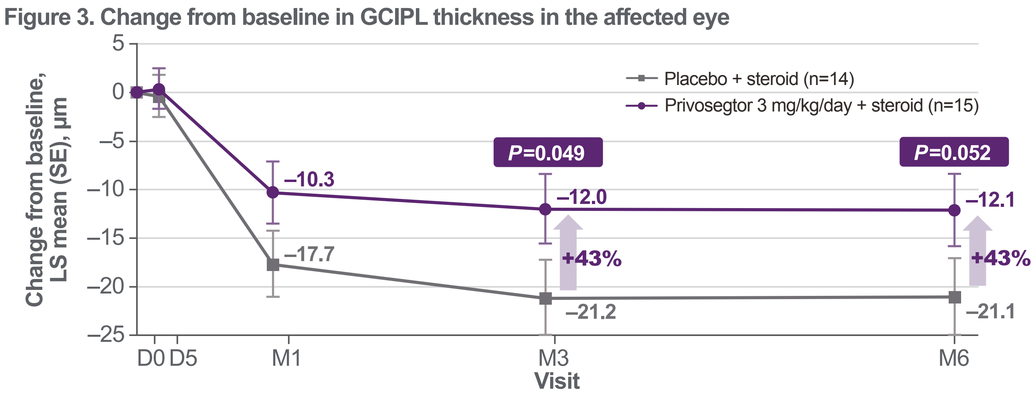
Structural changes

- At Month 3, the privosegtor 3-mg/kg/day group showed an approximately 43% relative preservation in mean GCIPL thickness, a biomarker of retinal ganglion cell integrity, compared with placebo, with the effect maintained through Month 6 (**Figure 3**)
- Similarly, an approximately 28% relative preservation in mean RNFL thickness, a biomarker of axonal integrity, was observed at Month 3 and maintained through Month 6 (**Figure 4**)

Functional benefit

- A numerically greater improvement in LCVA was observed in the privosegtor 3-mg/kg/day group, with a mean gain of approximately 18 ETDRS letters at Month 3 versus placebo; this treatment effect was sustained through Month 6 (**Figure 5**)

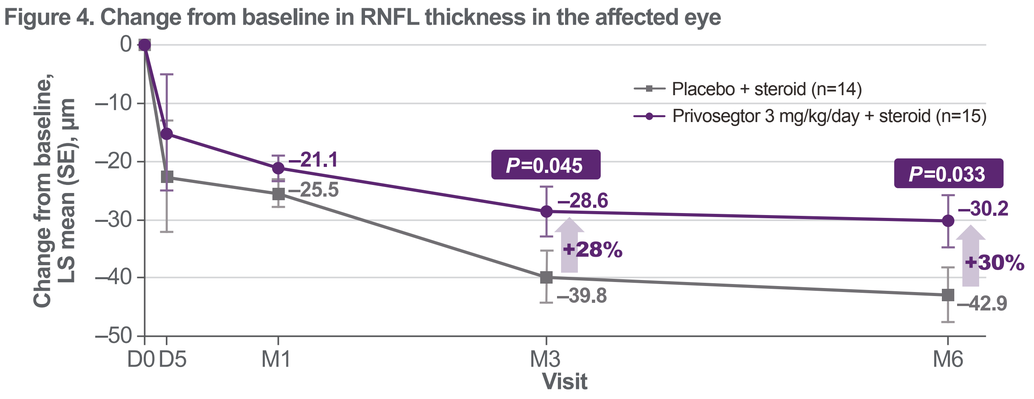
Figure 3. Change from baseline in GCIPL thickness in the affected eye



LS mean (SE) (90% CI) difference	D5	M1	M3	M6
3 mg/kg/day privosegtor vs placebo	0.8 (2.5) (–3.6, 5.3)	7.4 (4.6) (–0.5, 15.4)	9.2 (5.4) (0.0, 18.3) , *P*=0.049	9.1 (5.4) (–0.1, 18.2) , *P*=0.052

Analysis conducted for MMRM for the LS mean change from baseline with a 1-sided directional nominal *P* value for the mITT population (affected eye).
CI, confidence interval; D, Day; GCIPL, ganglion cell-inner plexiform layer; LS, least squares; M, Month; MMRM, mixed model for repeated measures; mITT, modified intent-to-treat.

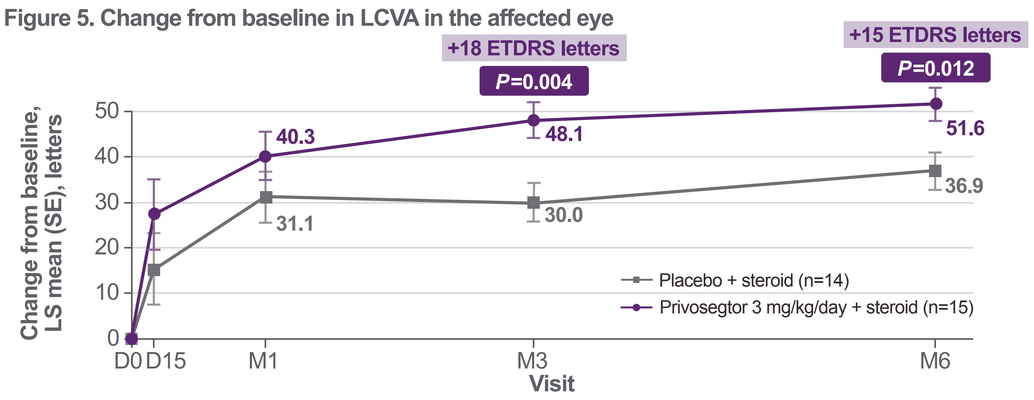
Figure 4. Change from baseline in RNFL thickness in the affected eye



LS mean (SE) (90% CI) difference	D5	M1	M3	M6
3 mg/kg/day privosegtor vs placebo	7.5 (13.8) (–16.8, 31.9)	4.4 (3.1) (–0.9, 9.8)	11.1 (6.2) (0.4, 21.9) , *P*=0.045	12.7 (6.4) (1.5, 23.9) , *P*=0.033

Analysis conducted for MMRM for the LS mean change from baseline with a 1-sided directional nominal *P* value for the mITT population (affected eye).
CI, confidence interval; D, Day; LS, least squares; M, Month; MMRM, mixed model for repeated measures; mITT, modified intent-to-treat; RNFL, retinal nerve fiber layer.

Figure 5. Change from baseline in LCVA in the affected eye



LS mean (SE) (90% CI) difference	D15	M1	M3	M6
3 mg/kg/day privosegtor vs placebo	10.1 (11.1) (–9.0, 29.2)	9.1 (7.8) (–4.1, 22.3)	18.2 (5.7) (8.4, 27.9); *P*=0.004	14.8 (5.5) (5.4, 24.1); *P*=0.012

MMRM analysis conducted for the LS mean change from baseline with a 2-sided nominal *P* value for the mITT population (affected eye).
CI, confidence interval; D, Day; ETDRS, Early Treatment Diabetic Retinopathy Study; LCVA, low contrast visual acuity; LS, least squares; M, Month; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures.

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LIMITATIONS

- While encouraging, the findings of this phase 2 study should be interpreted in context of the limited sample size and absence of statistical controls typical of later stage confirmatory studies

CONCLUSIONS

- In this phase 2 study, privosegtor at 3 mg/kg/day demonstrated a tolerable safety profile with preservation of retinal structure and improvement in visual function for participants with AON
- These consistent findings across structural and functional outcomes support further clinical development of privosegtor in future larger adequate and well-controlled studies for the treatment of individuals with AON
- Given the observed neuroprotective effects, privosegtor may also have therapeutic potential for other neurological disorders such as MS, where axonal preservation is a key determinant of long-term disability

Disclosures: CL and **SB** contributed equally. **CL** has received speaker or consultancy fees from Biogen, Sanofi, Novartis, and Merck, not related to the present study, and is a consultant for Oculis SA. **SB** is a consultant for Oculis SA. **LLM** received research support grants from the CNES, INSERM, JNLF, The L'Oreal Foundation, the French Parkinson Association, Fondation de France, the Paris Brain Institute, and the Axa Foundation; received honoraria for scientific advice or lectures for Digital Medical Hub, Elivie, Sanofi-Genzyme, Accure Therapeutics, Owkin, Emeis, and the Paris Brain Institute; and received travel funding from the Movement Disorders Society, ANAINF, Merck, Merz, Medtronic, Teva, and AbbVie, outside of the submitted work. **MC** and **CF** report no conflicts of interest. **MK** is a consultant to Oculis SA. **LAL** has served as a consultant to Annexon, Dompe, Eyevensys, Genentech, Janssen Pharmaceuticals, Neuroptika, Oculis SA, Perfuse, Perceive, Prilenia, Roche, Santen, and UNITY. **SM** is a consultant to Oculis SA. **CP** has been an advisory board member or conference speaker for Roche, Biogen, Novartis, Amgen, and Alexion. **VT** is a consultant for Institut du Cerveau for the Acuity study and for Chiesi Laboratory. **SW** is a consultant for Celltrion Healthcare, Novartis Pharma, Oculis SA, and Priothera SAS. **PV** holds several patents covering privosegtor composition of matter and its use for the treatment of central nervous system and ophthalmologic diseases. He holds stocks or stock options and has received consultancy fees from Oculis SA, Bionure Therapeutics, and Accure Therapeutics as part of the development of this program.