PER-001, an Endothelin Antagonist, Increased Optic Nerve Head Blood Flow and Improved Visual Function and Structure in Patients with Glaucoma

PERFUSE THERAPEUTICS

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Purpose

The PER001-201 study (NCT05822245) is a Phase 1/2a trial evaluating the safety, tolerability, and pharmacodynamic effects and exploratory efficacy of PER-001 in patients with open-angle glaucoma.

Background

Glaucoma remains a leading cause of irreversible blindness with no approved therapies. Current standard of care (SOC) focuses solely on lowering intraocular pressure (IOP), the only known modifiable risk factor. However, many patients continue to lose vision despite effective IOP control, highlighting the need for therapies that target additional disease mechanisms.

Vascular disease with impaired blood flow to the optic nerve head is implicated in glaucoma pathophysiology (Cherecheaum, 2013). Endothelin-1 (ET-1), the most potent endogenous vasoconstrictor in the human body, has been shown to be elevated in the aqueous humor and plasma of glaucoma patients (Li, 2016; Buenz et al 2025). The pathologic role of ET-1 in human vascular diseases has been studied extensively with many approved therapies. In preclinical models of glaucoma, chronic exposure to ET-1 induces a glaucoma-like optic neuropathy, and blocking ET-1 signaling has been shown to reverse ischemia, prevent retinal ganglion cell (RGC) death and dysfunction in an IOP-independent manner (Cioffi G et al, 2004; Howell GR et al, 2014).

PER-001 is a selective ET_A antagonist delivered in a bio-erodible intravitreal implant with sustained drug release over six months. PER-001 is being tested as a neuroprotective and neuro-enhancing therapy that is administered in conjunction with IOP lowering treatments.

Methods

Phase 1 was a single ascending dose study that evaluated two dose levels of PER-001 (Dose 1 and Dose 2) in participants with advanced glaucoma on SOC treatment (N=3 per dose). Phase 2a is an ongoing, randomized, sham controlled and masked study evaluating two dose levels of PER-001 (Dose 1 and Dose 2) in participants with progressive mild-moderate glaucoma on SOC treatment (N~9 per treatment group). Participants received either a sham control or a single dose of PER-001 on Day 1 and were followed for 6 months.

The primary endpoints of safety and tolerability were evaluated by adverse events (AE), BCVA, biomicroscopy, and IOP. Exploratory outcomes include optic nerve head tissue blood flow (ONH-BF) assessed by laser speckle flowgraphy (LSFG; Softcare, Co., LTD), visual field (VF) sensitivity and circumpapillary retinal nerve fiber layer (RNFL) thickness by OCT.

LSFG: ONH-BF was assessed at baseline and at Day 7, Week 2 (Phase 1 only) Weeks 4, 8, 12, 16, 20, and 24. The effect of PER-001 on ONH-BF was analyzed by % change from baseline in average mean blur rate (MBR), an arbitrary unit assigned by the manufacturer to quantify blood flow, for each dose level and both dose levels combined.

VF: Phase 1 VF testing was performed OU at Screening, Week 12 and Week 24. Phase 2a VF testing was performed in the study eye at screening, Day 1/Pre-Dose (x2), Weeks 8, 12, 16, and 24 (x2). The VF data was analyzed by mean VF MD change from baseline at Week 12 for Phase 1, at Mid-study (average of Weeks 8, 12, and 16 data) for Phase 2 and at Week 24 for both Phases.

Methods (cont'd)

Phase 2a VF data was also analyzed using a trend-based VF MD slope analysis evaluating VF MD over time (dB/year) using VF data from all visits, using a random effects mixed model, with VF MD as the response variable.

OCT RNFL: RNFL thickness was measured by OCT on Day 1/Pre-Dose and Weeks 12 and 24. OCT data was analyzed by mean RNFL change from baseline at Week 12 and Week 24.

Structure/Function Correlation: Relationship between OCT RNFL and VF MD was analyzed by least squares regression with RNFL Slope as the response variable and VF MD Slope as the explanatory variable.

Phase 1/2a Demographics

All Phase 1 (Dose 1 Cohort A, n=3 and Dose 2 Cohort B, n=3) and Phase 2a Dose 1 (Cohort C) participants (n=9 Dose 1, n=3 Control) have completed the study. Phase 2a Dose 2 (Cohort D) is ongoing.

Demographics		Phase 1 Cohort A&B		Phase 2a Dose 1 Cohort C	
		PER-001 Dose 1 Cohort A (n=3)	PER-001 Dose 2 Cohort B (n=3)	PER-001 Dose 1 Active (n=9)	Control (n=3)
Age (years)	Mean	70.7	75.0	71.8	57.0
	Minimum-Maximum	65-77	66-88	55 - 87	42 - 71
	Standard Deviation	6.03	11.53	10.93	14.53
Sex	Female	0	0	5 (55.6%)	1 (33.3%)
	Male	3 (100%)	3 (100%)	4 (44.4%)	2 (66.7%)
Race	Black or African Heritage	2 (66.7%)	1 (33.3%)	1 (11.1%)	1 (33.3%)
	White	1 (33.3%)	2 (66.7%)	8 (88.9%)	2 (66.7%)
Subject Disposition	Number of Subjects Completed	3 (100.0%)	3 (100.0%)	9 (100.0%)	3 (100.0%)
	Ongoing	0	0	0	0
Baseline Characteristics	Baseline MD, mean (SD) (dB)	-12.71 (0.55)	-25.24 (2.75)	-6.82 (4.17)	-2.34 (0.71)
	Historical Progression Slope (min, max) (dB/yr)	N/A	N/A	VF Slope: (-1.17, -0.31)	VF Slope: (-0.57, -0.30)
	Baseline IOP, mean (SD) (mmHg)	13.8 (2.0)	13.3 (4.2)	14.5 (3.9)	13.5 (3.1)

Safety Outcomes

- In Phase 1, there were no dose limiting adverse events or any adverse events related to drug product.
- In Phase 2a, there have been no serious drug related AEs or study drug related discontinuations. There was one drug related AE of a vitreous floater that was reported to be intermittent and mild and resolved on follow-up.
- There were no changes in visual acuity over time. IOP remained stable with no changes in IOP medications over the course of the study.

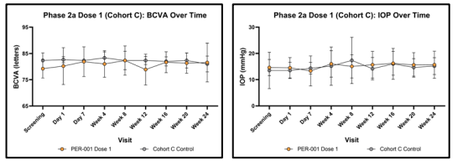

Figure 1. Phase 2a BCVA (Left) and IOP (Right) Change Over Time

Pharmacodynamic Assessment

- PER-001 treatment increased ONH-BF after a single intravitreal administration out to 6 months (**Figure 2**).
- The magnitude of ONH-BF increase induced by PER-001 treatment is above the 5% vehicle response with this device (Luft 2016).

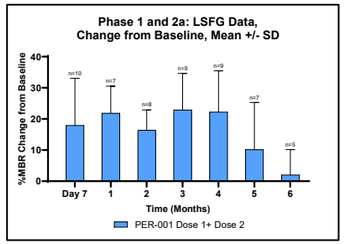

Figure 2. Phase 1/2a Dose 1 and Dose 2 (combined) LSFG % Change from Baseline in Average Mean Blur Rate (MBR)

Phase 1/2a Exploratory Efficacy Outcomes

- In Phase 1, at Week 12 (**Figure 3a**), the mean VF MD change from baseline was -1.88 dB +/- 1.73 (SD) for combined fellow eye (FE), -0.65 dB +/- 1.15 (SD) for Dose 1 (Cohort A) and -0.07 dB +/-1.50 (SD) for Dose 2 (Cohort B) and at Week 24 (**Figure 3b**), the mean VF MD change from baseline was -1.14 dB +/- 2.78 (SD) for combined FE, +0.36 dB +/- 1.36 (SD) for Dose 1 (Cohort A) and +1.58 dB for Dose 2 (Cohort B).
- In Phase 2a, at Mid-study (**Figure 3c**), the mean VF MD change from baseline was -0.13 dB +/- 1.13 (SD) for Sham Control (Cohort C) and +0.49 dB +/- 1.06 (SD) for Dose 1 (Cohort C) and at Week 24 (**Figure 3d**), the mean VF MD change from baseline was -0.50 dB +/- 0.75 (SD) for Sham Control (Cohort C) and +0.67 dB +/- 1.08 (SD) for Dose 1 (Cohort C).

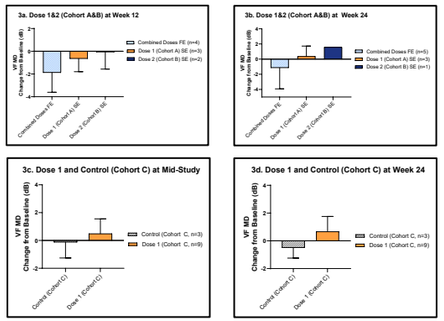

Figure 3. Phase 1/2a VF MD Change from Baseline

Phase 2a Exploratory Efficacy Outcomes

- VF MD slope was - 0.63 dB/yr (95% CI [-3.55,2.28]) for Sham Control (Cohort C) and +1.00 dB/yr (95% CI [-0.53,2.54]) for Dose 1 (Cohort C, **Figure 4**).

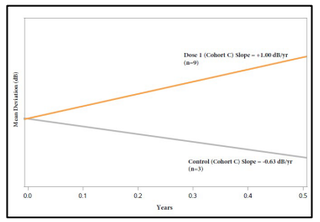

Figure 4. Phase 2a Dose 1 and Control (Cohort C) VF MD Slope

- At Week 12 (**Figure 5a**) the mean RNFL change from baseline was -0.67 µm +/- 1.53 (SD) for Sham Control (Control C) and +3.00 µm +/- 0.71 (SD) for Dose 1 (Cohort C), and at Week 24 (**Figure 5b**), the mean RNFL change from baseline was -1.33 µm +/- 3.79 (SD) for Sham Control (Control C) and +3.17 µm +/- 3.55 (SD) for Dose 1 (Cohort C).

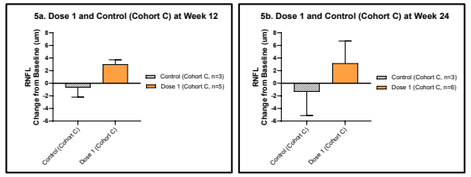

Figure 5. Phase 2a Dose 1 and Control (Cohort C) OCT RNFL Thickness (µm) Change from Baseline at Week 12 and Week 24

- VF MD slope and OCT RNFL slope were positively correlated (Pearson Correlation Coefficient: 0.685, p=0.0287) with an r^2 value of 0.470 (**Figure 6**).

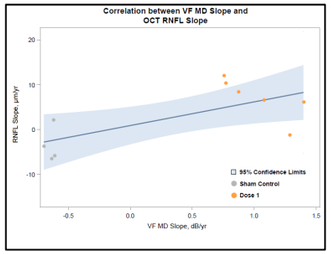

Figure 6. Phase 2a Visual Field MD (dB/yr) slope vs. OCT RNFL (µm/yr) slope Correlation Plot

Discussion

- PER-001 was found to be safe and well tolerated with stable BCVA and IOP throughout the trial.
- PER-001 showed a consistent and sustained increase in ONH-BF out to six months.
- Functional improvements in VF MD slope and VF MD change from baseline were observed in the PER-001 treated group in advanced glaucoma patients in Ph1 compared to fellow eye and in progressive mild to moderate stage glaucoma patients in Ph2a compared to control.
- The structural outcome of RNFL thickness increased in the PER-001 treated group compared to control.
- A positive correlation was observed between the VF MD slope and RNFL slope, suggesting structure/function correlation.

Conclusion

- PER-001, a selective ET_A antagonist delivered in a bio-erodible intravitreal implant with sustained drug release, demonstrated favorable safety/tolerability and improved optic nerve head blood flow out to 6 months in patients with open angle glaucoma.
- PER-001 treatment revealed promising functional and structural improvements in patients with advanced stage glaucoma and progressive, mild to moderate stage glaucoma when administered on top of IOP lowering therapies.
- PER-001 could be the first non-IOP, disease-modifying treatment with neuroprotective and neuro-enhancing benefits for patients with open angle glaucoma.

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