Results of a Phase 1b clinical trial of KPI-012, a novel secretome therapy, in participants with Persistent Corneal Epithelial Defect (PCED)

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PURPOSE

PCEDs are defined by a failure of rapid epithelialization and closure of a corneal injury within 10-14 days, despite standard supportive treatment. KPI-012 topical ophthalmic solution is a novel human bone marrow-derived mesenchymal stem cell (MSC) secretome with a multifactorial mechanism of action that has the potential to treat PCEDs of various etiologies. In preclinical studies, KPI-012 accelerated corneal wound healing and reduced scarring, inflammation, and corneal neovascularization. The purpose of this clinical trial was to evaluate the safety and efficacy of twice daily (BID) KPI-012 topical solution for the treatment of PCED.

TRIAL DESIGN

- Phase 1b, single-arm, prospective, open-label trial conducted at two Eye Hospitals in Mexico City, Mexico
- The Efficacy Cohort[a] included 9 adult participants with a PCED (of any etiology) of at least 10 days without improvement with one or more conventional, non-surgical treatments in the study eye[b]
- KPI-012 was administered BID for up to 4 weeks with follow-up at 2, 4, and 12 weeks after last dose
- Key endpoints included: reduction in defect size (corneal fluorescein staining), pain (visual analog scale (VAS)), intraocular pressure (IOP), and adverse events (AEs)

[a]Safety and tolerability of KPI-012 ophthalmic solution (BID, 1 week) were first established in a Lead-In Safety Cohort, consisting of 3 healthy volunteers with pre-existing permanent vision loss in their study eye (data not shown)
[b]One participant was withdrawn from the Efficacy Cohort due to a non-treatment related AE

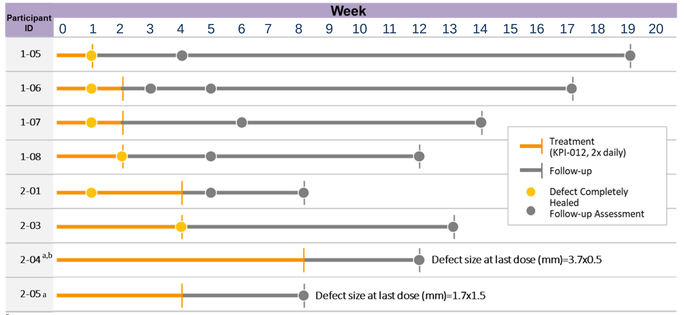
Table 1. Baseline Characteristics

Participant ID[a]	Gender	Age	Etiology	PCED Duration (Days)	Defect size (mm)
1-05	Male	52	Neurotrophic (diabetic)	17	6.0x5.5
1-06	Male	79	Neurotrophic (diabetic)	28	6.0x5.9
1-07	Male	61	Neurotrophic (diabetic)	15	5.2x2.5
1-08	Male	54	Neurotrophic (diabetic)	41	6.2x3.3
2-01	Male	52	Stevens-Johnson/ dry eye	213	4.7x2.0
2-03	Female	73	Post-infectious keratitis	37	2.2x1.5
2-04	Male	31	Neurotrophic (diabetic)	35	5.7x2.4
2-05	Female	82	Neurotrophic/ dry eye	871	3.0x2.0

[a]All participants were Hispanic/Latino

RESULTS

Figure 1. Complete healing in 6 of 8 PCED Participants by Week 4 of BID treatment



[a] Improvement in PCED was observed from baseline to end of treatment in participants without complete healing
[b] Treatment period was extended up to 8 weeks with Sponsor's agreement to increase the potential for a clinical benefit to the patient

Figure 2. Representative images of 3 participants with complete healing throughout the trial

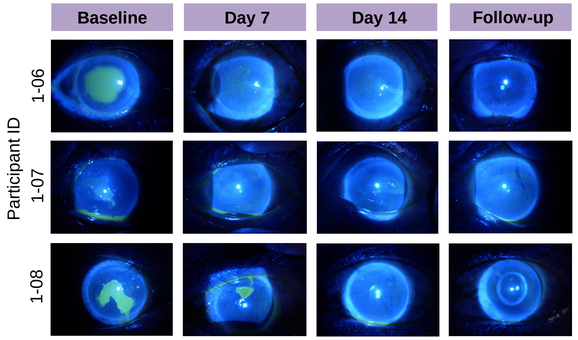


Figure 3. Distribution of lesion size in the study eye at baseline, end of treatment, and end of follow-up (n=8)

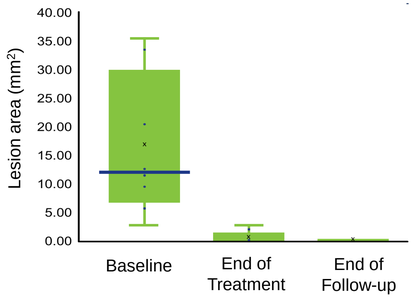


Figure 4. Diagram of the number of participants with complete healing over 4 weeks

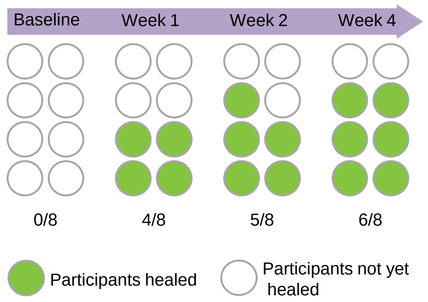
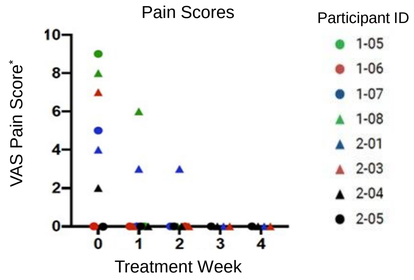


Figure 5. Scatter plot of participant pain scores during 4 weeks of treatment



*VAS Score: Pain level due to defect on scale of 0-10; 0=no pain at all, 10=worst possible pain

Table 2. Best Corrected Distance Visual Acuity

Visit Parameter[a]	logMAR
End of treatment (n=8)	
Mean (SD) of change	-0.38 (0.88)
Median change	-0.36
95% CI of mean change	-1.11, 0.36
End of follow-up (n=7)[b]	
Mean (SD) of change	-0.55 (0.78)
Median change	-0.42
95% CI of mean change	-1.27, 0.16

[a]Mean (SD) BCDVA at baseline=1.72 (0.90) logMAR; Median=1.8 logMAR
[b]Data not reported for one participant at follow-up

Table 3. Corneal Opacity

Visit Parameter	(n=8)
End of treatment	
Worsened	2 (25.0)
No change	1 (12.5)
Improved	5 (62.5)
End of follow-up	
Worsened	1 (12.5)
No change	1 (12.5)
Improved	6 (75.0)

Table 4. Treatment Emergent Adverse Events (TEAEs)

	(n=9)
Total number of participants with any TEAE	5
TEAEs considered treatment-related[a]	1
Ocular TEAEs (non treatment-related)[b]	5
Non-Ocular TEAEs	0
Participants withdrawn because of a treatment-related TEAE	0
Serious TEAEs	0
TEAEs resulting in death	0
Intraocular Pressure increase ≥10 mmHg[c]	2

[a]AE was mild and transient (itching, red eye, and blurred vision after administration of treatment)
[b]Mild=3, Moderate=0, Severe=2. [c]Both increases in IOP resolved without intervention during the trial

DISCUSSION

- KPI-012 ophthalmic solution (BID, up to 4 weeks) resulted in complete healing of PCED in 6 of 8 participants. Four of 6 healed within 1 Week of treatment; 1 of 6 healed by 2 weeks; 1 of 6 healed by 4 weeks
- Improvement in PCED lesion size was observed in those participants who did not heal completely
- All 6 healed participants remained healed through end of follow-up
- As a group, participants had a mean (SD) improvement in lesion size from baseline to end of treatment of -16.23 (12.38) mm^2
- As a group, there was a mean (SD) improvement in BCDVA from baseline to end of treatment of -0.38 (0.88) logMAR
- Most participants (5 of 8; 62.5%) improved their corneal opacity scores from baseline to end of treatment and 1 had no change in score
- Pain decreased in all participants with pain at baseline (6 of 8):
  - 100% reported pain reduction by Week 1
  - 67% reported 0 pain score by Week 1
  - 100% reported 0 pain score by Week 3
- There was only one TEAE reported, and it was mild and transient

CONCLUSIONS

- PCED is a rare condition with various underlying etiologies including mechanical or chemical injuries, limbal stem cell deficiency, neurotrophic keratopathy, and toxicity of topical medications. Risk factors and comorbid conditions such as diabetes and systemic autoimmune diseases may also negatively impact the wound healing process.
- MSCs and secretomes are known to play an important role in tissue repair and maintenance and have shown promising results in preclinical studies.
- KPI-012 is a novel ophthalmic solution of human bone marrow-derived secretome that contains a wide array of extracellular matrix components and biofactors, including growth factors, neurotrophic factors, and cytokines. These factors can potentially address corneal wound healing in PCED of various etiologies.
- In this Phase 1b clinical trial, rapid and complete wound healing was observed in 6 of 8 participants with various PCED etiologies with KPI-012 treatment (dosed BID for up to 4 weeks).
- KPI-012 also appeared safe and well-tolerated. No treatment-related serious AEs were reported.
- KPI-012 received orphan drug designation by the US FDA and is currently under development for the treatment of PCED.