Safety and Efficacy of a Novel Mesenchymal Stem Cell Secretome Therapy for Persistent Corneal Epithelial Defect (PCED)

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Financial Interests

- Valeria Sanchez-Huerta is a consultant for Alcon and Abbvie. She has received Research/Grant Support from Combangio, a subsidiary of Kala Pharmaceuticals.
- Hugo Quiroz-Mercado does not have any relevant financial disclosures.
- Enrique O. Graue-Hernandez does not have any relevant financial disclosures.
- Alejandro Navas does not have any relevant financial disclosures.
- Spencer Alford and Darius Kharabi are employees of Kala Pharmaceuticals and own stock and stock options in Kala Pharmaceuticals.
- Stephen Pflugfelder is a consultant to Kala Pharmaceuticals, Allergan, Novartis, Santen, Kowa, Senju, and Oyster Point.

Background

- Persistent corneal epithelial defect (PCED) is the failure of re-epithelialization and wound closure within 10-14 days after the initial corneal injury, even with standard treatment[1]. If left untreated, the PCED can lead to significant risk of stromal ulcers, corneal thinning and vision loss.
- The estimated incidence in the US is approximately 75,000 - 100,000 cases per year[2]. This includes PCEDs of several etiologies, including: neurotrophic keratitis, surgical epithelial debridement, microbial/viral keratitis, corneal transplant, limbal stem cell deficiency, and mechanical and chemical trauma.
- Normal re-epithelialization after corneal injury follows a highly coordinated process involving growth factors, cell signaling, proliferation, migration, and extracellular matrix remodeling[1]. In PCED there is an imbalance of key biomolecules (e.g., growth factors and cytokines) that can result in significant inflammation, impaired innervation and disruption of the protective corneal epithelial and stromal layers[1].
- There is a need for a treatment with a multifactorial mechanism of action to address various steps in the corneal wound healing process.
- Currently there is one approved product, which contains a single nerve growth factor (NGF) to treat PCEDs of neurotrophic keratitis etiology.

[1]Vaidyanathan U, et al. Persistent Corneal Epithelial Defects: A Review Article. Med Hypothesis Discov Innov Ophthalmol. 2019 Fall;8(3):163-176.
[2]Wirostko B, Rafii M, Sullivan DA, Morelli J, Ding J. Novel Therapy to Treat Corneal Epithelial Defects: A Hypothesis with Growth Hormone. *Ocul Surf*. 2015;13(3):204-212.e1.

Purpose

- KPI-012 is an ophthalmic solution of human bone marrow-derived mesenchymal stem cell (MSC) secretome which contains numerous biofactors needed to address the complex wound healing process involved in PCED and other ocular surface diseases. In preclinical studies, KPI-012 accelerated corneal wound healing and reduced scarring, inflammation, and corneal neovascularization in mechanical and chemical corneal injury models.
- The purpose of the current trial was to evaluate the safety and efficacy of KPI-012 in a Phase 1b, single-arm, prospective, open-label study at two high volume ophthalmology hospitals in Mexico City, Mexico.

KPI-012 Components*	Ocular Surface Wound-Healing Function
Protease Inhibitors (e.g., TIMP-1, TIMP-2, Serpin E1)	Inhibition of destructive proteases that degrade matrix in the wound bed
Matrix Proteins (e.g., Collagen)	Construction of a molecular scaffold in the wound bed for cells to migrate and adhere to
Growth Factors (e.g., HGF)	Suppression of inflammation and promotion of corneal epithelium repair
Neurotropic factors (e.g., PEDF)	Regeneration and maintenance of neurons to support corneal health

*Data on file at Kala Pharmaceuticals, Arlington, MA

Clinical Trial Design

Phase 1b, single-arm, prospective, open-label study at two eye hospitals in Mexico		
	Lead-In Safety Cohort (n=3)[a]	Efficacy Cohort (n=9)[b]
Cohort	Participants with Low Vision and No Active Corneal Disease	Participants with Various PCED Etiologies
KPI-012 Treatment	1 week, 2x Daily (Self-Administered)	Up to 4 weeks, 2x Daily (Self-Administered)
Follow-up	1 week from last dose	2, 4, 12 weeks from last dose
Inclusion Criteria	Healthy adult volunteers with pre-existing permanent vision loss in their study eye (defined as permanent visual acuity of 20/400 or worse with best conventional correction) and normal visual acuity in the fellow eye.	Adult participants with a PCED of at least 10 days without improvement from one or more conventional non-surgical treatments in the study eye and due to any etiologies.
Key Endpoints	• Adverse events, pain (visual analog scale (VAS)), and intraocular pressure (IOP)	• Adverse events, pain (VAS), and IOP • Reduction in defect size (corneal fluorescein staining)

[a]Safety and tolerability of KPI-012 ophthalmic solution, as a single drop twice daily (BID) in the study eye, were first established in the Safety Cohort prior to the initiation of the Efficacy Cohort.
[b]A total of 12 participants were enrolled (Lead-in Safety Cohort, n=3; Efficacy Cohort, n=9); 1 participant was withdrawn from the Efficacy Cohort due to a non-treatment related adverse event.

Efficacy Cohort Baseline Characteristics

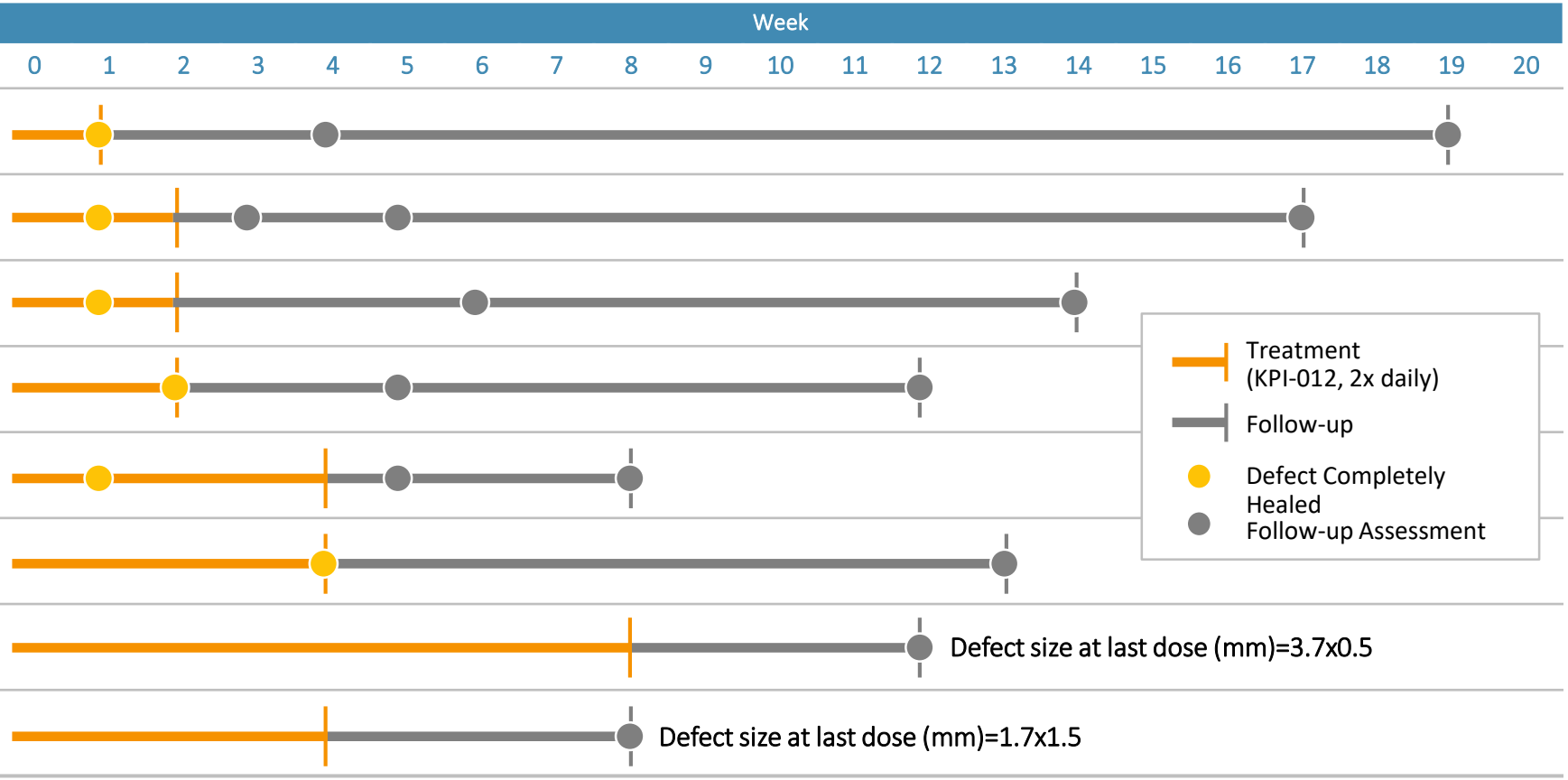
Participant ID[a]	Gender	Age	PCED Etiology	PCED Duration (Days)	Ocular (Study Eye) & Relevant Medical History
01-05	Male	52	Neurotrophic (diabetic)	17	LASIK, cataract, retinal detachment, diabetic vitrectomy, neurotrophic Systemic: Diabetes
01-06	Male	79	Neurotrophic (diabetic)	28	Vitreous hemorrhage, diabetic vitrectomy, neurotrophic Other: Diabetes, hypothyroidism
01-07	Male	61	Neurotrophic (diabetic)	15	Retinal detachment, cataract, diabetic vitrectomy, neurotrophic Other: Diabetes
01-08	Male	54	Neurotrophic (diabetic)	41	Retinal detachment, diabetic vitrectomy, neurotrophic Other: Diabetes, arterial hypertension
02-01	Male	52	Stevens-Johnson/ dry eye	213	Stevens-Johnson Syndrome, dry eye disease Other: Arterial hypertension
02-03	Female	73	Post-infectious keratitis	37	Cataract, cataract surgery, infectious keratitis Other: Arterial hypertension, hypothyroidism, orbital lymphoma, radiotherapy
02-04	Male	31	Neurotrophic (diabetic)	35	Cataract, neovascular glaucoma, neurotrophic Other: Diabetes, gender transition therapy
02-05	Female	82	Neurotrophic/dry eye	871	Herpetic endophthalmitis, dry eye disease, neurotrophic ulcer Other: Gastritis, arterial hypertension, heart valve dysfunction

[a]All participants were Hispanic/Latino

[b]Lead-In Safety Cohort (n=3): Gender=1 (33.3%) Male, 2 (66.7%) Females; Mean Age, Years (SD)= 47.7 (15.1)

Results: Overview of KPI-012 Efficacy Cohort and Treatment Outcome

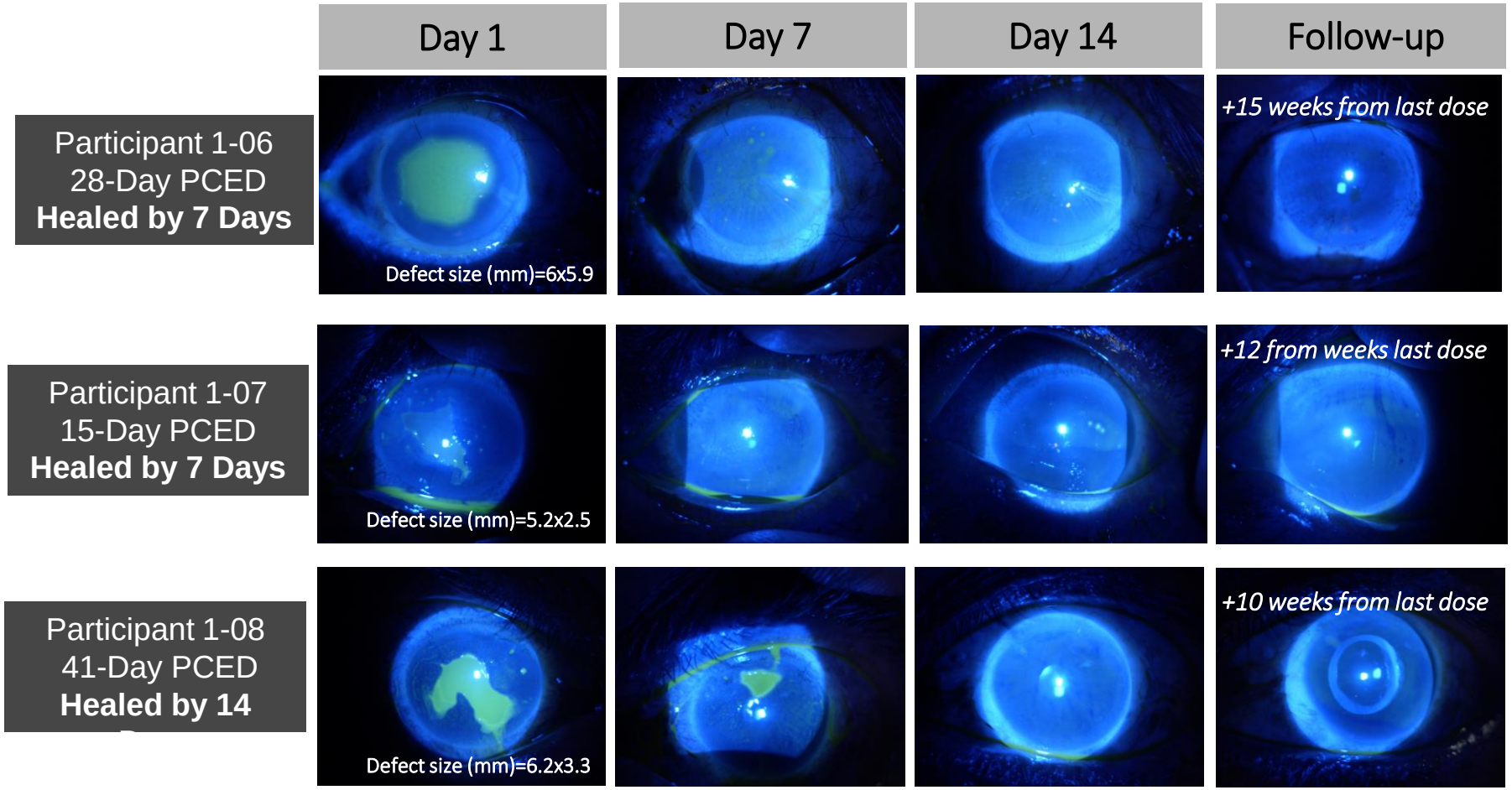
Participant ID	PCED Etiology	Baseline Defect Duration (Size, mm)[a]
1-05	Neurotrophic (Diabetic)	17 (6.5x5.5)
1-06	Neurotrophic (Diabetic)	28 (6x5.9)
1-07	Neurotrophic (Diabetic)	15 (5.2x2.5)
1-08	Neurotrophic (Diabetic)	41 (6.2x3.3)
2-01	Stevens-Johnson/ Dry Eye	213 (4.7x2)
2-03	Post-Infectious Keratitis	37 (2.2x1.5)
2-04	Neurotrophic (Diabetic)	35 (5.7x2.4)
2-05	Neurotrophic/ Dry Eye	871 (3x2)



[a]Mean PCED size at baseline (mm)=5.1x3.5; Mean PCED Duration at Baseline (Days)=58; Mean PCED Healing time with treatment (Days)=12.

- *6 of 8 of participants completely healed by Week 4 of the trial*
- *4 of 6 healed after 1 week of treatment; 1 of 6 healed by 2 weeks; 1 of 6 healed by 4 weeks*
- *All 6 healed participants remained healed through end of follow-up*
- *Improvement in PCED lesion size was observed in participants who did not heal completely*

Results: Corneal Fluorescein Staining Slit Lamp Photography*

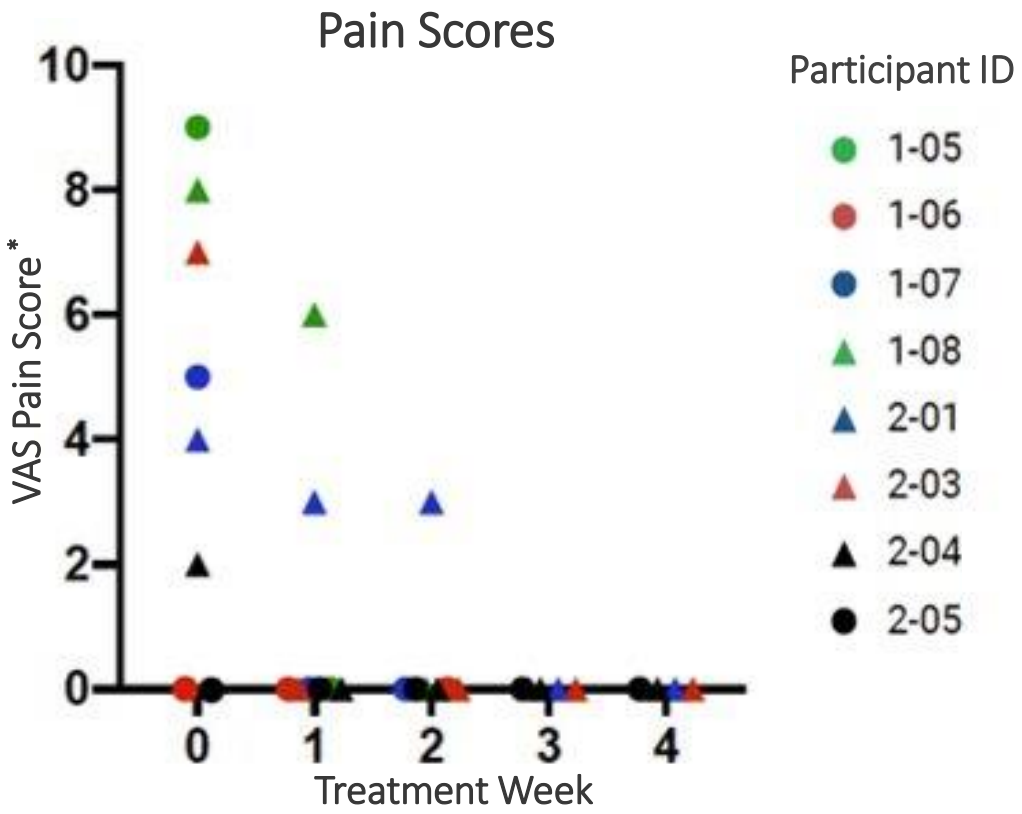


*Complete lesion healing was achieved in 6 of 8 PCED participants; 3 of these participants are shown in the images above as examples

Adverse Events and Pain Scores in Efficacy Cohort[a]

	KPI-012 (n=9)
Total number of participants with any treatment-emergent adverse event (TEAE)	5
TEAEs considered treatment related[b]	1
Ocular TEAEs	
Mild	3
Moderate	0
Severe	2
Non-Ocular TEAEs	0
Participants withdrawn because of a TEAE	0
Serious TEAEs	0
TEAEs resulting in death	0
Intraocular Pressure increase ≥10 mmHg[c]	2

[a]There was one AE reported in the safety cohort that was mild, non-ocular, and unrelated to treatment.
[b]AE was mild and transient (e.g. mild itching, mild red eye, and blurred vision in study eye after administration of study drug)
[c]Both increases in IOP resolved without intervention during the study



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

Of participants reporting PCED 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

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 an 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.

- 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 at BID for up to 4 weeks) in the efficacy cohort.

- KPI-012 also appeared safe and well-tolerated in both the efficacy and safety cohorts. No treatment-related serious adverse events were reported.

- KPI-012 received orphan drug designation by US FDA and is currently under development for the treatment of PCED of various etiologies.