ST-100 Resolves the Consequences of Dry Eye Disease

As Identified in the TFOS Dry Eye Workshop II Findings

Eric@StuartTherapeutics.com – 1.206.228.2781

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Stuart Therapeutics is Building a Leading Therapeutic Development Organization in Ophthalmology

- A **clinical stage company**, developing a **unique, patented platform technology (PolyCol™)** for a variety of ophthalmology indications
- **Successful Phase 2 clinical trial** results in Dry Eye Disease, with industry leading results… ST-100
- **Groundbreaking neuroprotection research** results, with a second drug candidate for glaucoma in development
- **Additional programs** in the pre-clinical stage, including Dry AMD, Myopia and Neurotrophic Keratitis

- **Strong management team**, with extensive collagen science and early-stage company expertise
- **Extremely capital efficient**, accomplishing these objectives for less than $16M invested

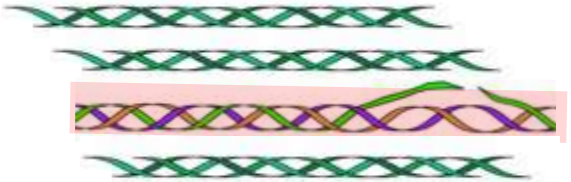
Helical Collagen is a New and Exciting Therapeutic Target - It Has a Powerful Effect on Tissue Health and Inflammation

Collagen Triple Helix

Home to cell signaling ligand binding sites that:

- Modulate inflammation
- Control cell growth and proliferation
- Found in nearly all collagen types

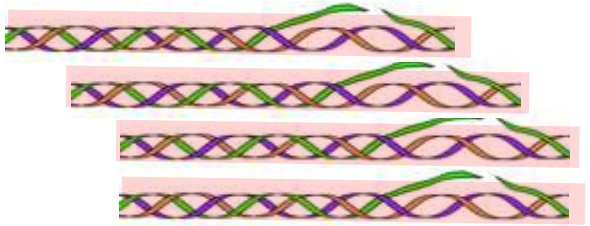
Normal Collagen Remodeling



During normal remodeling and replacement of collagen:

- Helices are disrupted (partially digested)
- Collagen is slowly *replaced* (not repaired) by mesenchymal cells and other cell types

Inflammatory Disease Remodeling

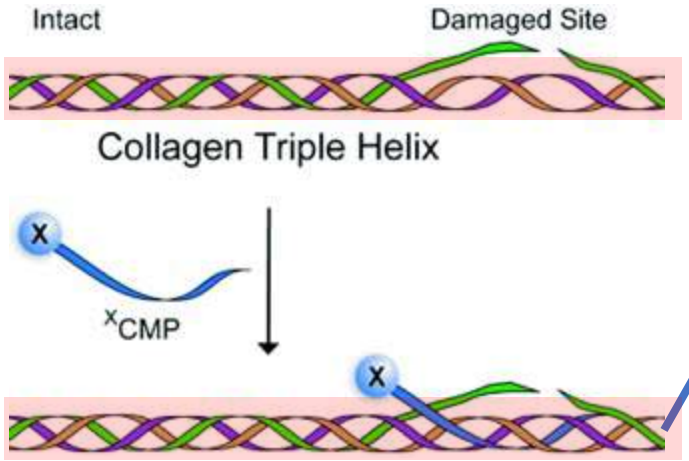


- Increased disruption
- Changes in signal modulation
- Damage to cells that replace collagen
- Leads to chronicity

Both structural and extracellular matrix (ECM) collagen play an important role in inflammatory disease; helical collagen is found in nearly all collagen types

PolyCol™ is a Collagen Mimetic Peptide (CMP) Platform That Directly *Repairs* Damaged Helical Collagen

PolyCol – Molecular View: Reducing the Remodeling Burden



Rapid and robust repair of damaged helical collagen

PolyCol intercalates with high selectivity into damaged helices

ST-100's active ingredient is a member of the* PolyCol™ *family of CMP sequences

Powerful Cell Signaling & Structural Impact

Up-Regulation:

- **Growth factors and pro-migratory cytokines**
- **Nerve and epithelial recovery**
- **Collagen production**

Down-Regulation:

- **Inflammatory cytokines**
- **Reactive oxygen species**
- **MMP[1] recruitment**

This step function improvement in both ECM and structural collagen cell signaling reduces the inflammatory and remodeling burden in the cornea… with positive benefits to epithelial and neuronal tissues

[1] MMP: Matrix Metalloproteinase

The 2017 Dry Eye Workshop II[1] Report Highlighted the Importance of Corneal Nerves in Dry Eye Disease (DED)

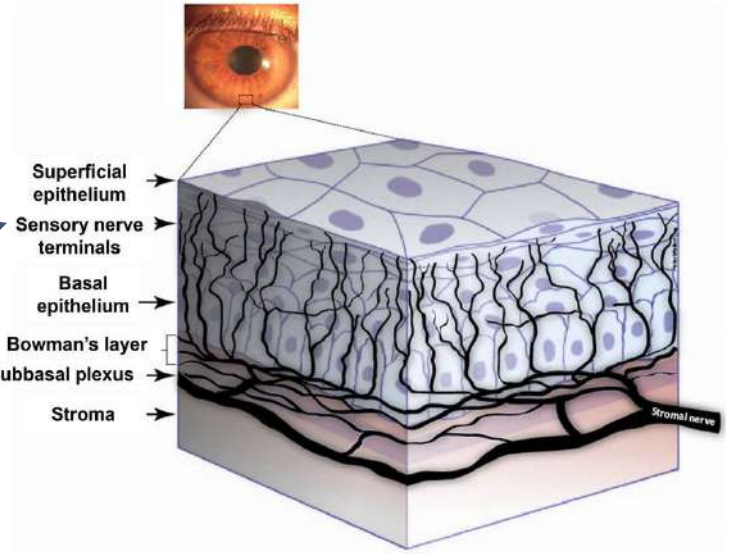
TFOS DEWS II Dry Eye Disease Consequences

- **Loss of Tear Film Homeostasis**
- **Visual Disturbance**
- **Inflammation**
- **Discomfort**
- **Ocular Surface Damage**
- **Neurosensory Abnormalities**

A healthy corneal nerve structure is a prerequisite for timely healing of damage associated with the indication. According to DEWS II:

- Lacrimal gland tearing and accessory glands are responsive to the corneal nerve.
- The corneal nerve stimulates goblet cell secretions.
- Nerves surround the meibomian glands.

These elements are involved in the production of a healthy tear film, and are restored through corneal nerve repair[2]



A therapeutic that can repair the corneal nerves and restore nerve function (and if possible, other DED consequences in parallel) is an ideal option to treat all six DEWS II consequences in the most rapid timeframe

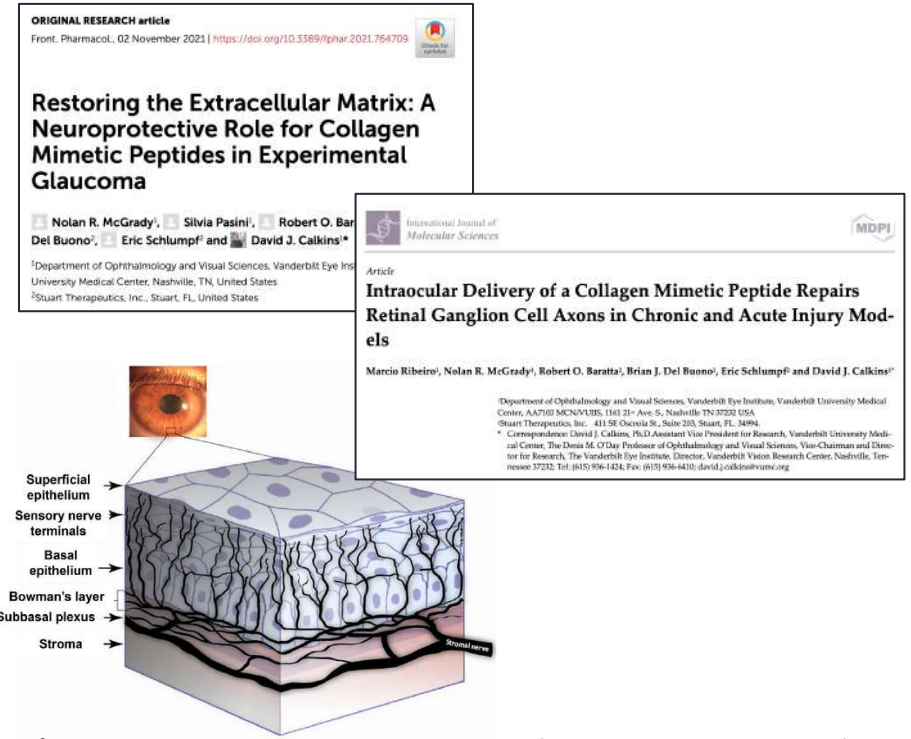
[1] Tear Film and Ocular Surface Society Dry Eye Workshop II, 2017

[2] There is limited research on the functional nerve interactions with meibomian function

Stuart Therapeutics Has Led the Way in Neuroprotection Research in Ophthalmology

Groundbreaking neuroprotection and nerve repair research in glaucoma and ocular surface disease:

- Microbead occlusion model (*in vivo)* testing demonstrating significant protection of the optic nerve (2021)[1]
- Nerve crush (*in vivo*) demonstrating nerve function recovery in the retrolaminar region of the optic nerve (2022)[2]
- Corneal atropine damage model (*in vivo*) demonstrating corneal nerve repair (2022, pending publication)



[1]McGrady NR, Pasini S, Baratta RO, Del Buono BJ, Schlumpf E, Calkins DJ. Restoring the Extracellular Matrix: A Neuroprotective Role for Collagen Mimetic Peptides in Experimental Glaucoma. Front Pharmacol. 2021 Nov 2;12:764709. doi: 10.3389/fphar.2021.764709. PMID: 34795592; PMCID: PMC8592892.

[2]Ribeiro M, McGrady NR, Baratta RO, Del Buono BJ, Schlumpf E, Calkins DJ. Intraocular Delivery of a Collagen Mimetic Peptide Repairs Retinal Ganglion Cell Axons in Chronic and Acute Injury Models. Int J Mol Sci. 2022 Mar 8;23(6):2911. doi: 10.3390/ijms23062911. PMID: 35328332; PMCID: PMC8949359.

Recent pre-clinical testing has shown that Stuart's Dry Eye Disease (DED) candidate ST-100 shows significant nerve repair capabilities in an* in vivo *atropine model of ocular surface and corneal nerve damage

Pre-Clinical and Phase 2 Trial Results Suggest a Hypothesis for ST-100's Mechanism of Action, Consistent with DEWS II

Moderate DED Patient

Two Different Patient Journeys Based on Severity

Severe DED Patient

Moderate Patient Characteristics	ST-100 Results	Severe Patient Characteristics	ST-100 Results
Corneal nerve damage: moderate	Rapid repair of corneal nerve damage	Corneal nerve damage: severe	Repair of corneal nerve damage
Visual function: moderate difficulty focusing	***Day 2 & 3***: Restoration of lacrimal function; BC logMAR & visual acuity symptom improvement; ***Day 14***: one or more Snellen lines improvement	Visual function: severe difficulty focusing	***Day 2 through 7***: Restoration of lacrimal function, BC logMAR improvement, various visual acuity symptoms
Symptoms: pain and discomfort	***Day 14***: Symptom resolution (esp. pain)	Symptoms: moderate to mild	***Day 7 through 14***: Individual and Total Symptom score resolution
Corneal staining: below median*	***Day 3 through 14***: Resolution of total eye and corneal staining	Corneal staining: above median	***Day 28 through Day 42***: Staining results conjunctiva (early) and cornea (expected by day 42 based on moderate patient results)

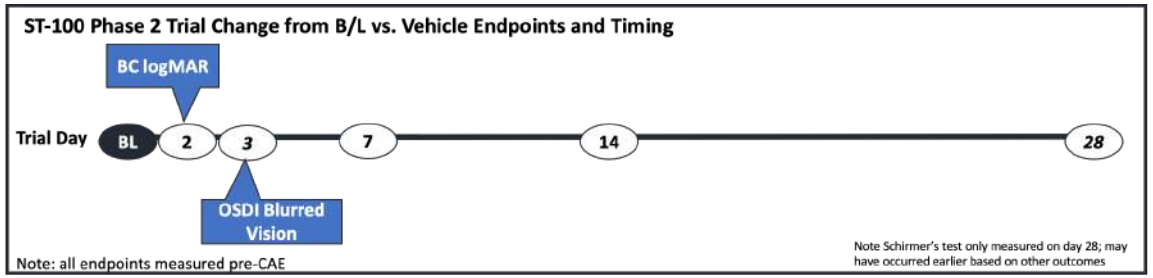
"Emerging over the last decade has been mounting evidence of the potential role of neurosensory abnormalities in the understanding and management of DED." TFOS, DEWS II Report, 2017

*Median: median baseline stain score

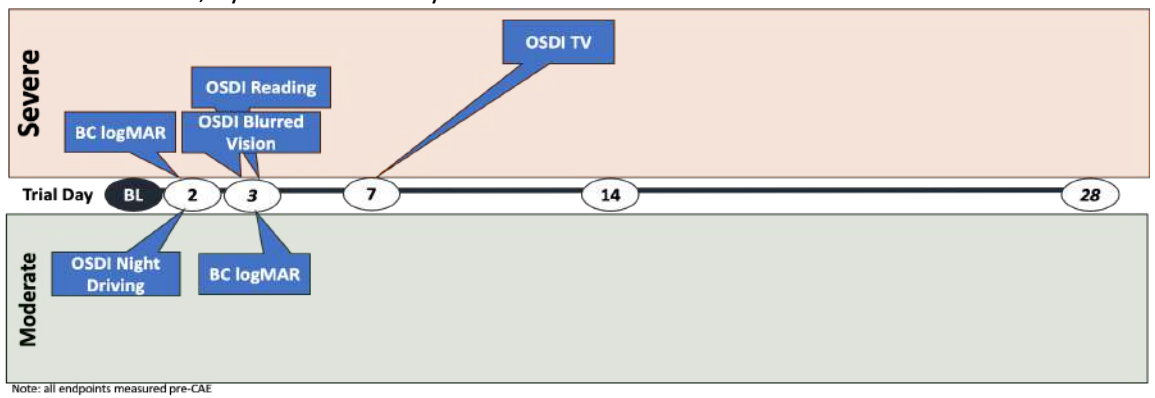
ST-100 Endpoints with Significance: Tear Film Homeostasis / Improvement in Visual Function

Loss of Tear Film Homeostasis	Visual Disturbance	Inflammation	Discomfort	Ocular Surface Damage	Neurosensory Abnormalities

Intent to Treat Population[1]



Patient Cohorts, by Disease Severity[1]



The cumulative effect of corneal nerve repair and lacrimal functional unit restoration results in:

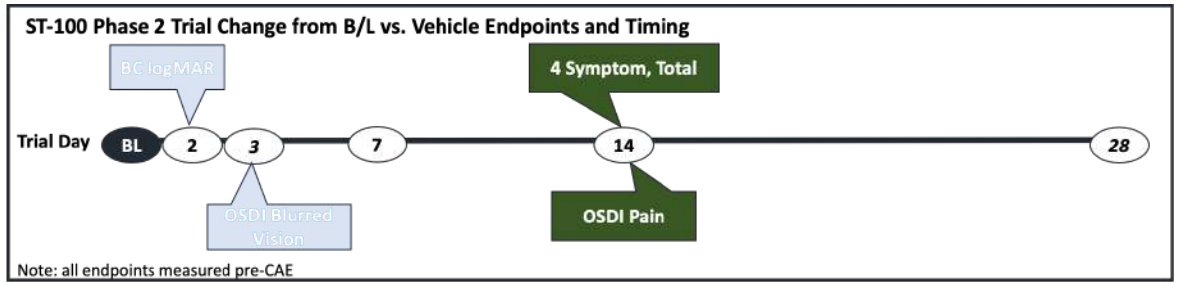
- Extremely rapid improvements in visual function (Day 2, 3 and 7)
- Consistent improvement vs. vehicle in visual function (BC logMAR) through all trial visits
- 25% of patients achieved Snellen line improvement in the trial. A subset of these patients achieved the equivalent of 2 or 3 Snellen lines of improvement in vision at various trial visits, vs. zero in the vehicle cohort

[1] All endpoints (both ITT and severity cohorts) comparison with vehicle, change from baseline, pre-CAE, p≥0.05

ST-100 Endpoints with Significance: Reduction of Inflammation / Relief of Discomfort

Loss of Tear Film Homeostasis	Visual Disturbance	**Inflammation**	**Discomfort**	Ocular Surface Damage	Neurosensory Abnormalities

Intent to Treat Population[1]



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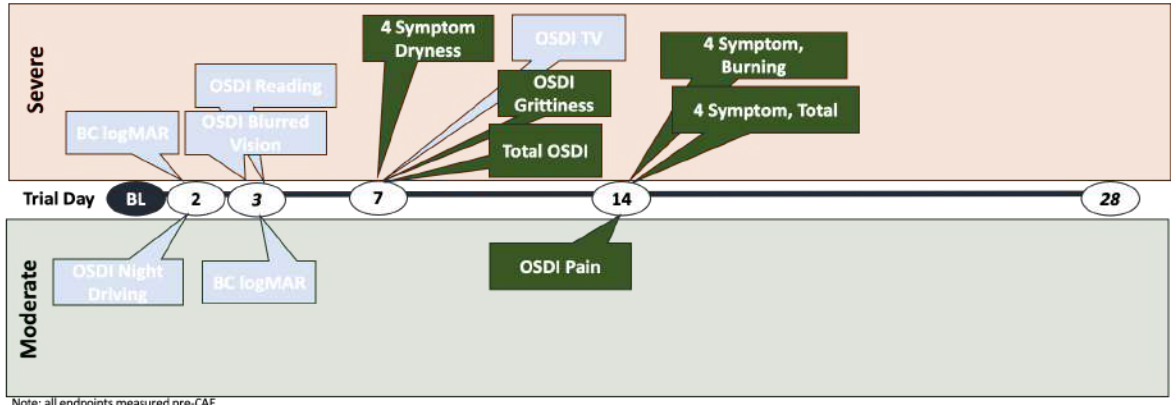


[1] All endpoints (both ITT and severity cohorts) comparison with vehicle, change from baseline, pre-CAE, p≥0.05

ST-100 has demonstrated anti-inflammatory effect in pre-clinical studies:

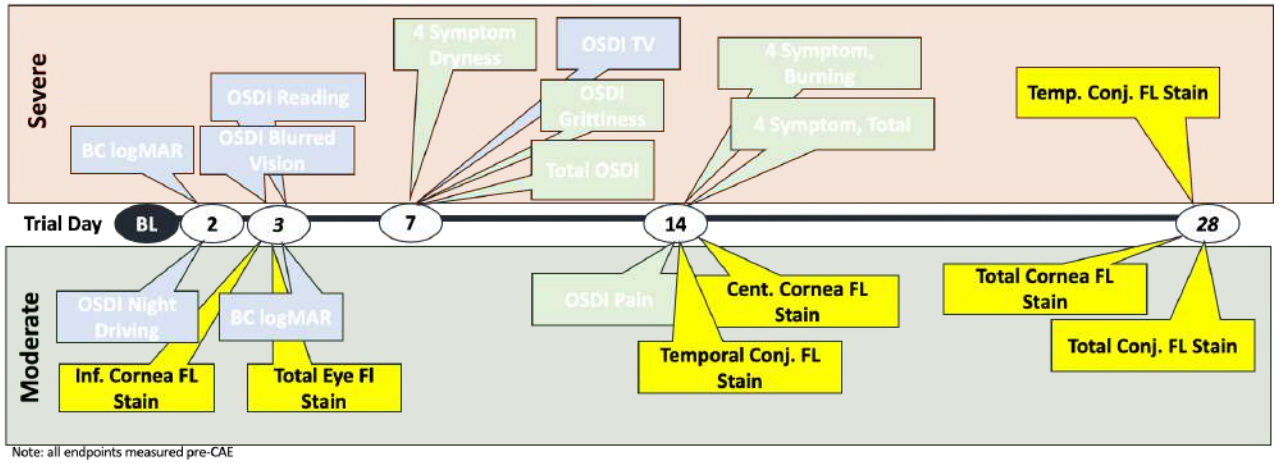
- 24-hour complete recovery in severe corneal wound rodent model; no stromal inflammation visible
- Reduction in expression of inflammatory markers – *in vitro* studies

The Phase 2 statistically significant results in pain and overall discomfort scores at Day 14 suggest ST-100 impacts inflammation early in the trial resulting in patient symptom relief

ST-100 Endpoints with Significance: Reduction of Ocular Surface Damage

Loss of Tear Film Homeostasis	Visual Disturbance	Inflammation	Discomfort	**Ocular Surface Damage**	Neurosensory Abnormalities

Patient Cohorts, by Disease Severity[1]



Consistent with the hypothesis of corneal nerve repair driving improvements in pathophysiology and signs and symptoms:

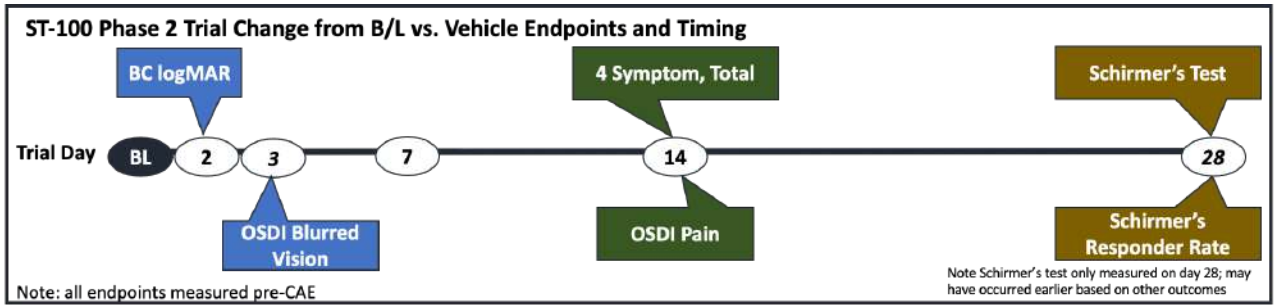
- Moderate patients saw rapid resolution of total eye, corneal and conjunctival fluorescein staining within the 28-day trial
- Resolution of Moderate patient total eye staining was seen at Day 3
- Severe patients, who likely had more significant nerve damage to repair, saw resolution of conjunctival staining beginning at Day 28

[1] All endpoints (both ITT and severity cohorts) comparison with vehicle, change from baseline, pre-CAE, p≥0.05

ST-100 Endpoints with Significance: Repair of Corneal Nerves Drives Overall Corneal Health

Loss of Tear Film Homeostasis	Visual Disturbance	Inflammation	Discomfort	Ocular Surface Damage	**Neurosensory Abnormalities**

Intent to Treat Population[1]



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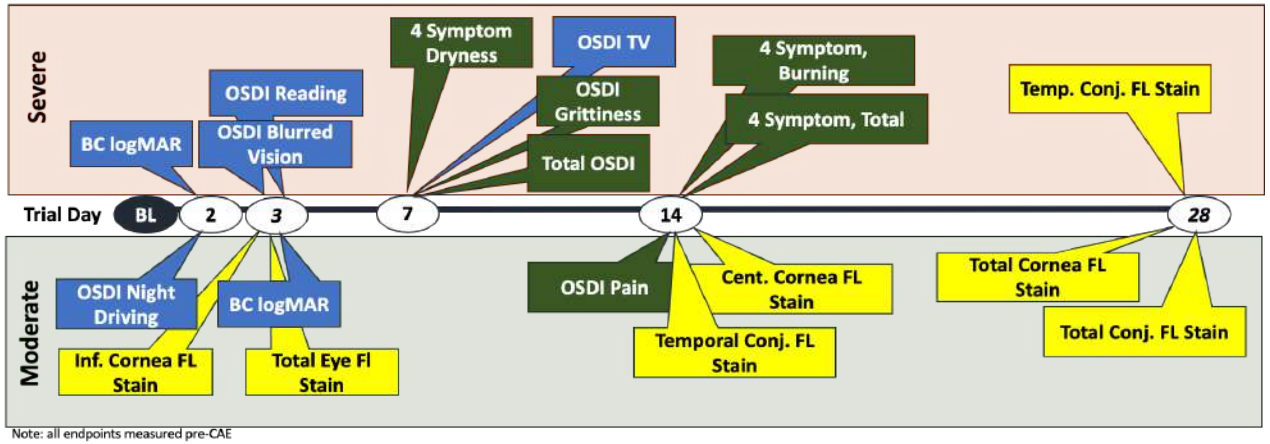


Nerve recovery results in pre-clinical studies:

- Optic nerve axon recovery and repair in chronic and acute injury models
- Corneal nerve repair in an atropine model of ocular surface damage

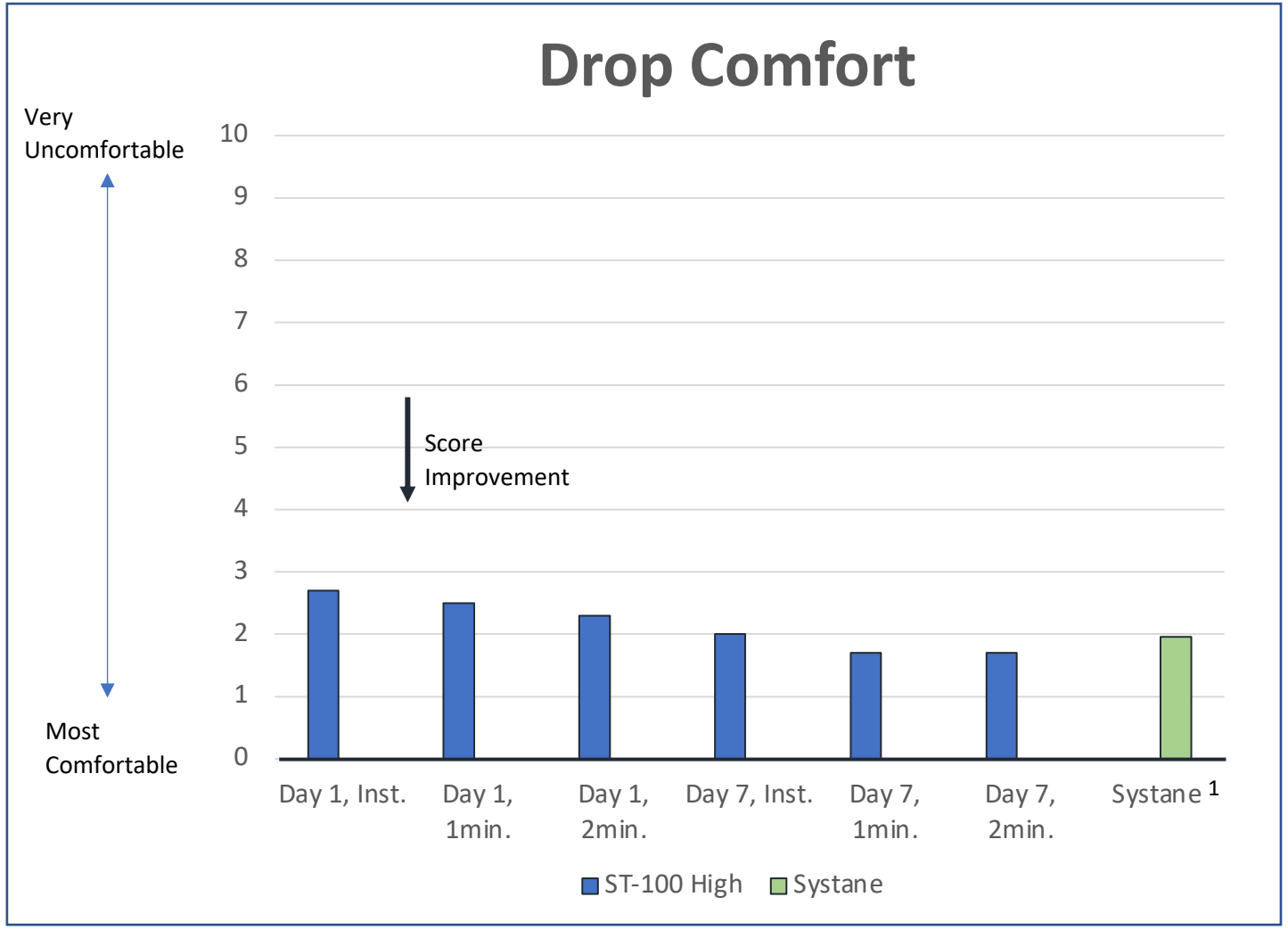
The Phase 2 results in Schirmer's Test and Schirmer's Responder Rate suggested a nerve repair induced recovery of the lacrimal functional unit.

The Schirmer's Tear Film Test was administered on Day 28 of the trial. Other effects of ST-100 suggest that the tear film impact may have been felt much earlier.

[1] All endpoints (both ITT and severity cohorts) comparison with vehicle, change from baseline, pre-CAE, p≥0.05

Patients Report that ST-100 is as Comfortable as Artificial Tears - an Important Differentiator in DED

- ST-100 high dose compares favorably with the well-known artificial tear product Systane®
- Scores in the 2.0 or less range are considered “very comfortable”[1]
- ST-100 is a comfortable eye drop, compared to competing products Restasis®, Cequa®, Eysuvis® and Xiidra® all of which have issues with site irritation [2]



[1] Torkildsen G, Brujic M, Cooper MS, Karpecki P, Majmudar P, Trattler W, Reis M, Ciolino JB. Evaluation of a new artificial tear formulation for the management of tear film stability and visual function in patients with dry eye. Clin Ophthalmol. 2017 Oct 19;11:1883-1889. doi: 10.2147/OPTH.S144369. PMID: 29089744; PMCID: PMC5656345.

[2] Restasis, Cequa, Eysuvis and Xiidra package inserts and SBA (summary bases for approval)

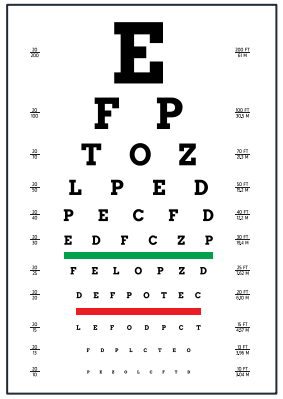
ST-100 is a Broad Acting, Etiology-Agnostic Drug Candidate That Addresses Persistent Clinical Challenges of DED

Early and Effective Relief of Discomfort

Solves a Consistently Frustrating Problem for Patients and Physicians Alike

Corneal Nerve Repair Important for Refractive Surgeons

Fast Functional Improvement



Bridges DED and NK indications; no more confusion in diagnosis

ST-100 has extremely high commercial potential because it solves persistent challenges in ocular surface indications; speed and breadth of effectiveness should lead to high patient and physician satisfaction

Change from B/L vs. Vehicle Endpoints for ITT Population, Significance at Earliest Trial Day

ITT, Day 2:

- BC logMAR; n=53 (fellow eye); p=0.0055 ANCOVA

ITT, Day 3:

- OSDI Blurred Vision; n=49; p=0.0097 ANCOVA

ITT, Day 14:

- 4 Symptom Discomfort, Total; n=49; p=0.0332 ANCOVA
- OSDI Pain; n=49; p=0.0137 ANCOVA

ITT, Day 28*

- Schirmer's Test; n=49; p=0.0094 ANCOVA
- Schirmer's Responder Rate (see elsewhere herein for description); n=49; p=0.0266, 95% Confidence Interval Treatment Arm vs. Vehicle

Change from B/L vs. Vehicle Endpoints for Severe and Moderate Patient Sub-Groups; Significance at Earliest Trial Day

Severe, Day 2:

1. BC logMAR; Stratified non-corneal clearing by D7; n=45; p=0.0047 ANCOVA; D2

Severe, Day 3:

1. OSDI Reading; Stratified >Median at B/L; n=38; p=0.0418 ANCOVA
2. OSDI Blurred Vision; Stratified >Median at B/L; n=41; p=0.0131 ANCOVA

Severe: Day 7:

1. OSDI Difficulty Watching TV; Stratified non-hyper-responders; n=25; p=0.0263 ANCOVA
2. OSDI Grittiness; Stratified <Median at B/L; n=18; p=0.0044 ANCOVA
3. OSDI Total; Stratified <Median at B/L; n=26; p=0.0342 ANCOVA
4. 4 Symptom Discomfort, Dryness; Stratified <Median at B/L; n=15; p=0.017 ANCOVA

Severe, Day 14:

1. 4 Symptom Discomfort, Total; Stratified non-hyper-responders; n=26; p=0.0299 ANCOVA
2. 4 Symptom Discomfort, Burning; Stratified non-hyper-responders; n=26; p=0.0192 ANCOVA

Severe, Day 28:

1. Temporal Conjunctival Fl Staining; Stratified > Median, Post CAE at B/L; p=0.0492 Two Sample T-Test

Moderate, Day 2:

1. OSDI Night Driving; Stratified <Median at B/L; n=13; p=0.0391 Wilcoxon; D2

Moderate, Day 3:

1. Inferior Corneal Fl Staining; Stratified <Median at B/L; n=15; p=0.0210 ANCOVA
2. Total Eye Fl Staining; Stratified <Median at B/L; n=25; p=0.0113 ANCOVA
3. BC logMAR; Stratified corneal clearing by D7; n=5 (fellow eyes); p=0.0448 ANCOVA

Moderate, Day 14:

1. Central Cornea Fl Staining; Stratified <Median at B/L; n=4; P=0.0207 ANCOVA
2. Temporal Conjunctival Fl Staining Post CAE; Stratified <Median Post CAE B/L; p=0.0358 ANCOVA
3. OSDI Pain; Stratified >Median at B/L; n=39; p=0.0088 ANCOVA; D14

Moderate, Day 28:

1. Total Corneal Fl Staining; Stratified <Median at B/L; n=16; p=0.0334 Wilcoxon (note p=0.0506 ANCOVA; D3)
2. Total Conjunctival Fl Staining; Stratified <Median at B/L; n=22; p=0.0258 ANCOVA (note p=0.0530 Wilcoxon; D3)

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