FOCAL POINT

Cannabinoids and the Eye

OTCQB: SKYE
May 2023

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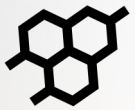
INVESTMENT SUMMARY

Innovation in ophthalmology to unlock the potential of novel cannabinoid derivatives



Phase 1: dosing started for CB1R agonist program in Dec-22
Phase 2: Received FDA okay to proceed for its Investigational New Drug application; aim to start in USA mid-2023

Transformative new class of therapeutics may play a role in multiple ocular indications

Preclinical foundation for glaucoma with strong ocular R&D capability and pipeline

Multiple academic collaborations to expand pipeline of novel cannabinoid derivatives

Pursuing collaboration and partnership opportunities for programs

STRATEGY FOR GROWTH AND VALUE CREATION

Advance distinct new class of therapeutics to positively impact health of patients with ocular and other diseases

Seeking to affect the endocannabinoid system (ECS) for therapeutic outcomes via the development of cannabinoid derivatives and small molecule drugs

Expand ophthalmology-focused pipeline with new target indications/products in 2023

Clinical plan designed for relevant outcomes with optimized time and cost

TARGETING GLAUCOMA: LARGE MARKET, UNMET NEEDS

World's leading cause of irreversible blindness

$7B drug market

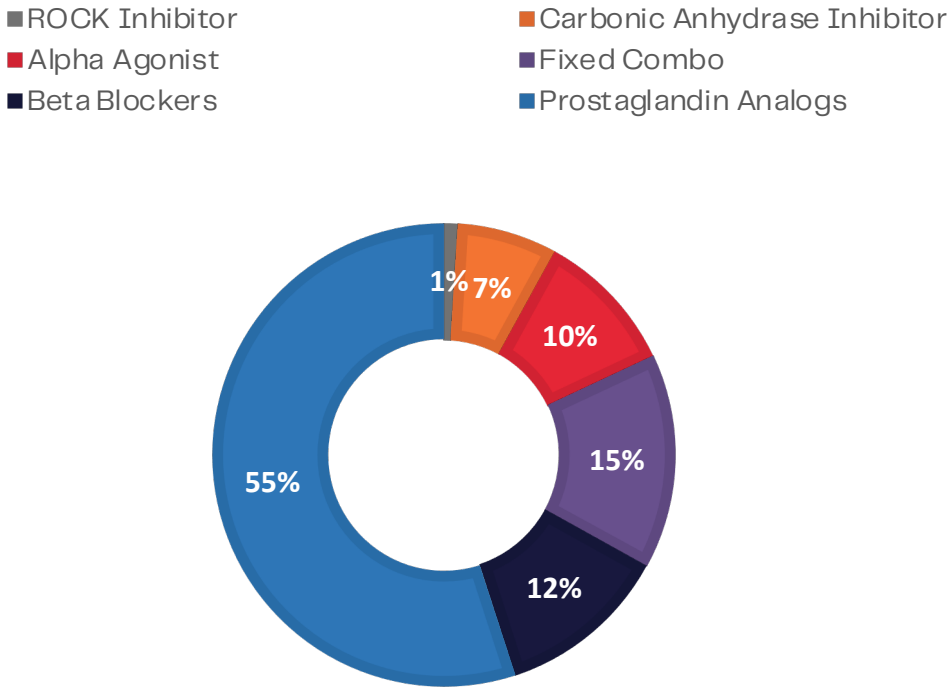
~60M patients worldwide

~110M patients by 2026

40% fail 1st line therapy[1]

50% require 2 therapies[1,2]

MARKET PREDOMINATLY LEGACY CLASSES OF DRUGS AND GENERIC COMPOUNDS



1 Kass et al, Delaying treatment of ocular hypertension: the ocular hypertension treatment study. Arch Ophthalmolgy, 2010; 128:276–287
2 Lichter et al. Interim clinical outcomes in The Collaborative Initial Glaucoma Treatment Study Comparing initial treatment randomized to medications or surgery. Ophthalmology. 2001;108:1943–1953

LEADING CAUSE OF BLINDNESS: GLAUCOMA

Causes progressive damage to the optic nerve resulting in irreversible vison loss

Open Angle Glaucoma (OAG)

- Chronic, progressive optic neuropathy characterized by acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons; associated with an open anterior chamber angle[1,2]

Etiology & Classification

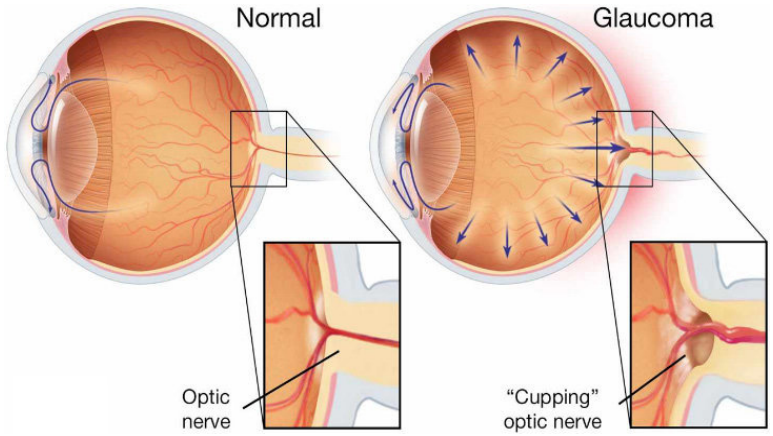
- Primary open-angle glaucoma (POAG) primary subtype of glaucoma; **increased resistance to drainage of the aqueous humor in the trabecular meshwork**, and the angle between the cornea and the iris remain open
- Secondary open-angle glaucoma (less common subtype) is a result of other secondary causes (i.e. eye injury, side effects of medication, diabetes, etc.)

Symptoms & Patient Outcomes

- Blurred vision, eye pain, high intraocular pressure (IOP), haloed vision, nausea, and blind spots in vision[3]
- 6 – 12% of patients with POAG progress to blindness at an incidence rate of ~1% per year[4]

Patient Characteristics

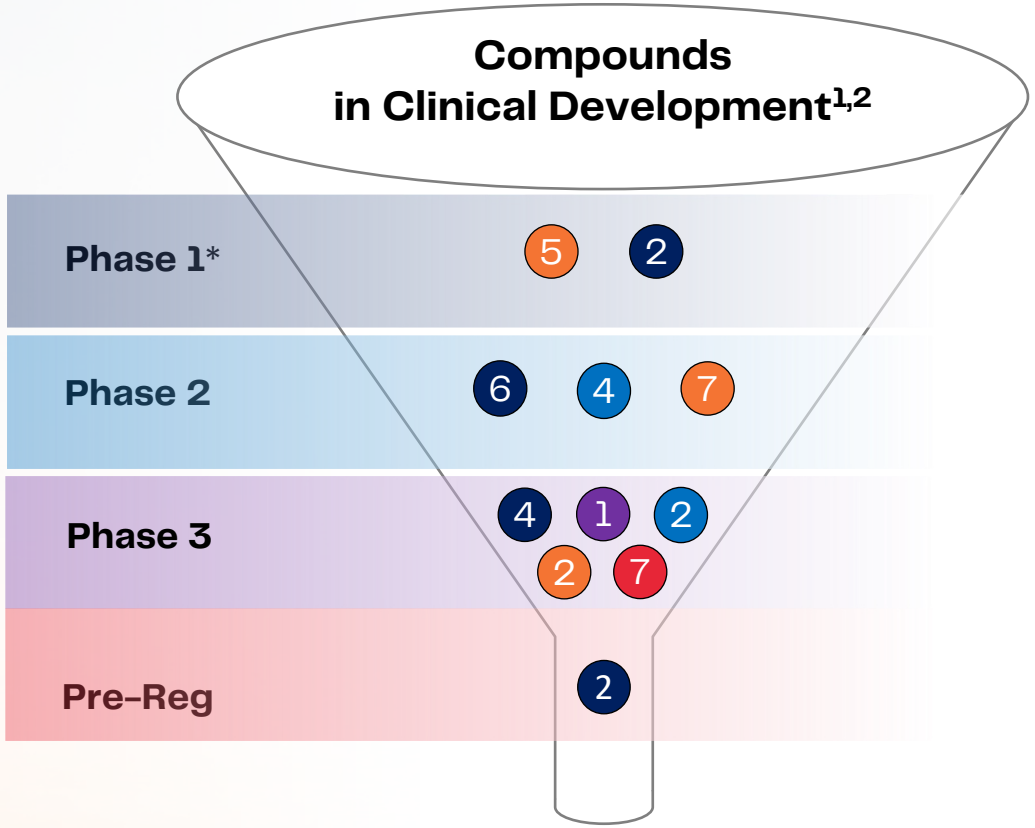
- Major risk factors: age (>60 yrs.), family history, ethnicity, certain medical conditions, and eye injury[3]
- Often undiagnosed in patients as symptoms often do not appear until advanced stages[5]



1 Gupta. Am Fam Physician. 2016;93(8):668; 2 Prum. Ophthalmol. 2016; 123(1):41 3 Glaucoma Research Foundation;
4 Rossetti. PLoS One. 2015 Aug 24;10(8):e0136632; 5 UpToDate; 6 Weinreb. JAMA. 2014; 311(18):1901.

INDUSTRY GLAUCOMA PIPELINE LACKS INNOVATION

Late-stage assets dominated by legacy mechanisms of action



- Prostaglandins
- Adrenergic
- Rho Kinase
- Combinations
- Other**

**Carbonic Anhydrase 2 Inhibitor, Receptor Type Tyrosine Protein Phosphatase Beta Inhibitor, Cholinergic Muscarinic Receptor Agonist, Sulfonamide Protein Kinase Inhibitor, C1q Inhibitor, Potent Corticosteroid Agent, Ciliary Neurotrophic Factor (CNTF), KATP Channel Vessel Relaxer

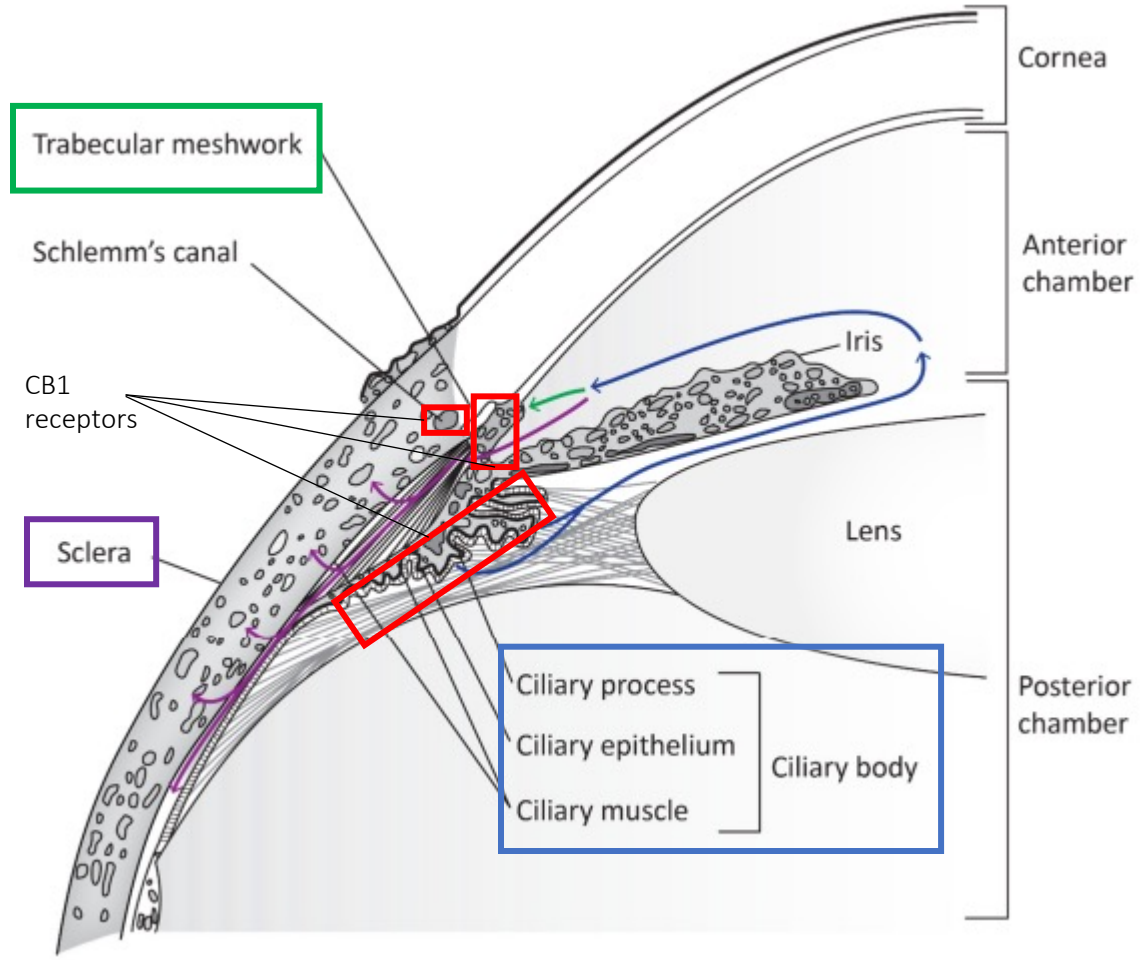
SIGNIFICANT OPPORTUNITY FOR NEW AND IMPROVED CLASSES OF THERAPY

[1] GlobalData; [2] Clinicaltrials.gov
* Compounds listed based on the most recent trial completed or initiated

ABNORMAL AQUEOUS HUMOR DYNAMICS: KEY ROLE

Increased intraocular pressure due to reduced aqueous humor outflow is key issue

- Aqueous humor **(blue)**, produced from the ciliary body, provides nourishment and maintains shape of the eye
- Flows from posterior chamber to anterior chamber. Filtered and drained out of the eye through two outflow pathways: trabecular meshwork **(green)** and uveoscleral pathway **(purple)**
- In a healthy eye, production and drainage are balanced to maintain optimal intraocular pressure or IOP
- Inflammation and fibrosis in trabecular meshwork can diminish outflow of aqueous humor, resulting in increased IOP
- **CB1 receptors** in tissues involved in aqueous humor production and drainage play a role in modulating flow of aqueous humor and health of eye tissue
- CB1R represents a new therapeutic target



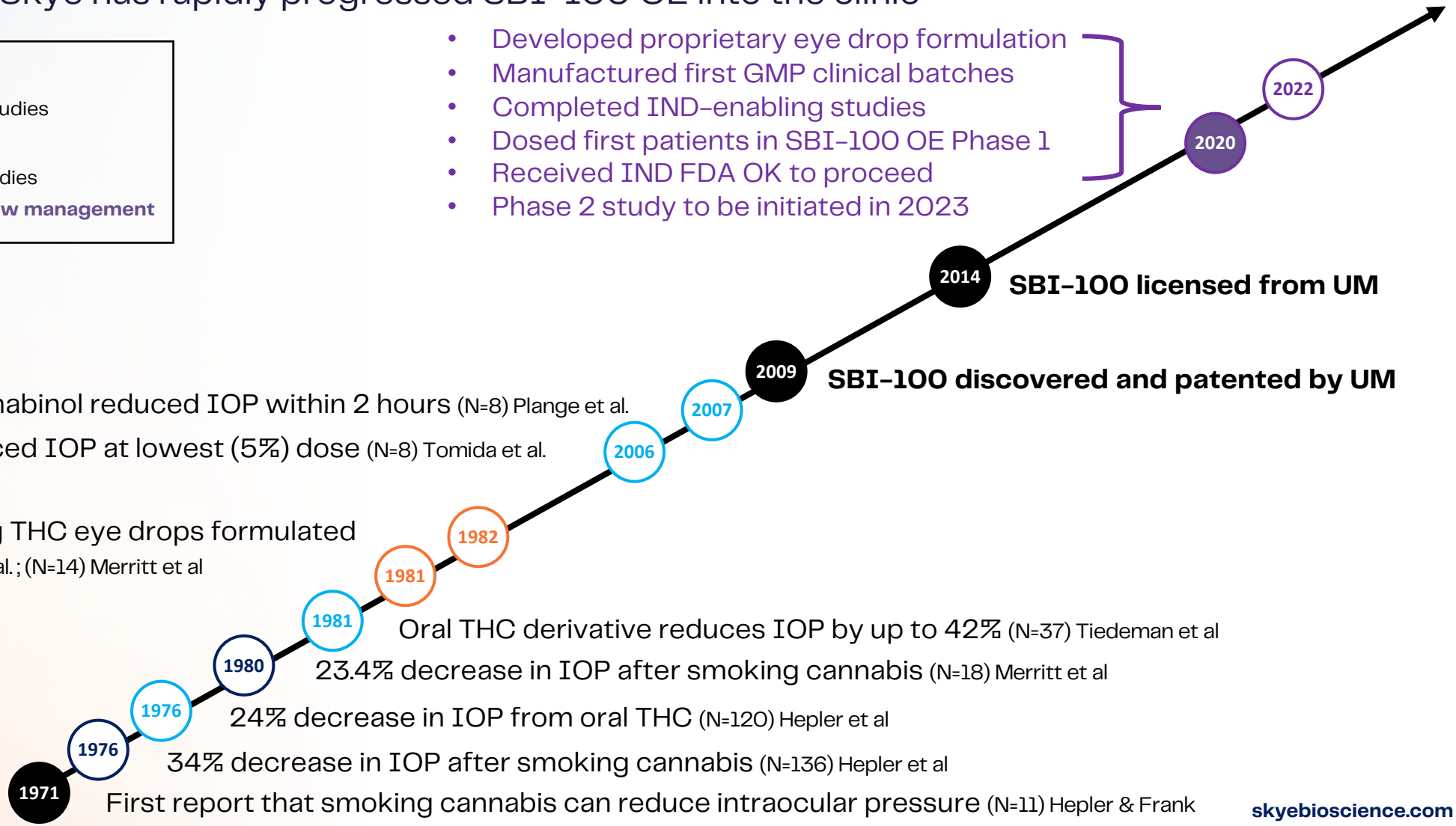
Adapted from: Cairns et al, The Endocannabinoid System as a Therapeutic Target in Glaucoma. Neural Plasticity, 2016; Article ID 9364091

THE LONG HISTORY OF GLAUCOMA AND CANNABINOIDS

Since 2020 Skye has rapidly progressed SBI-100 OE into the clinic

LEGEND
- Inhalation studies
- Oral studies
- Eye drop studies
- **Skye and new management**

- Developed proprietary eye drop formulation
- Manufactured first GMP clinical batches
- Completed IND-enabling studies
- Dosed first patients in SBI-100 OE Phase 1
- Received IND FDA OK to proceed
- Phase 2 study to be initiated in 2023



UNLOCKING CANNABINOID THERAPEUTIC POTENTIAL

Rationally designed drugs to prove potential of cannabinoids as therapeutic agents

Mechanistic Rationale

- Cannabinoid receptors are highly expressed in the eye
- CB1 receptor known to have impact on multiple eye diseases
- Previous trials show clear benefit of cannabis/ cannabinoids in glaucoma

Shortcomings of Previous Research

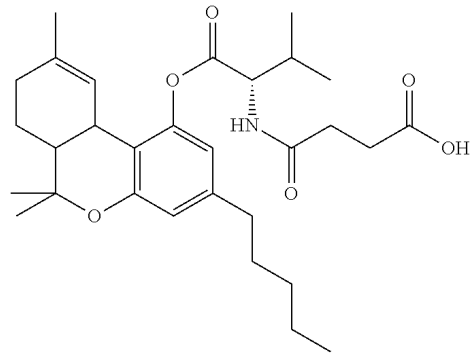
- Natural THC is insoluble and poorly bioavailable when delivered topically
- Oral/inhaled THC results in unwanted side effects
- Limited to no IP on natural THC

Novel Cannabinoids

- Prodrug approach and proprietary formulation ensures improved delivery and reduced toxicity
- Strong IP
- Proof of concept for other indications

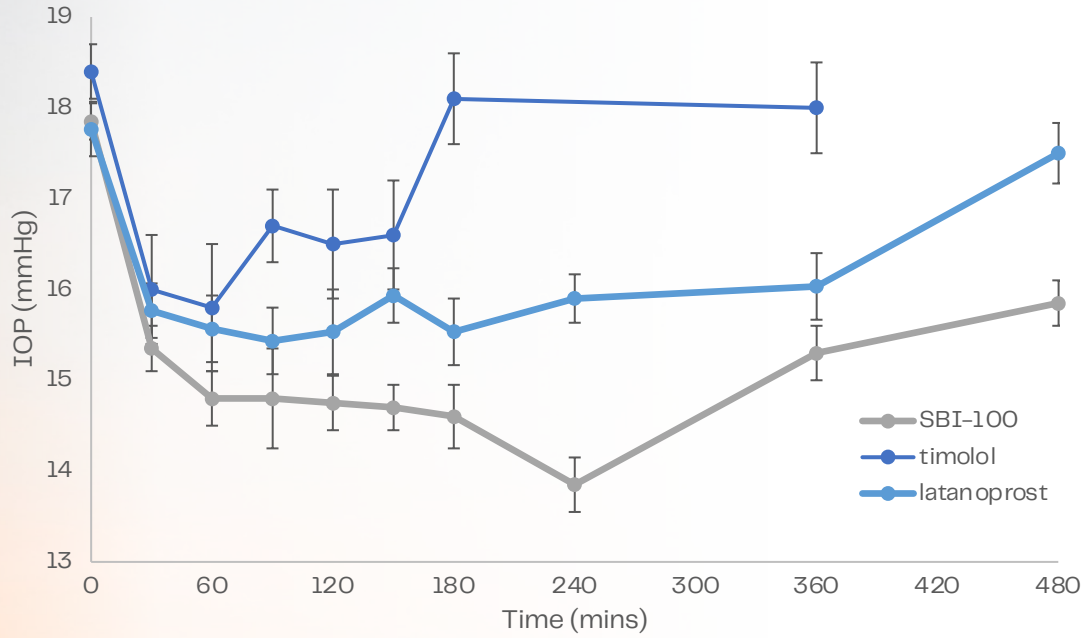
LEAD CLINICAL ASSET: SBI-100 OPHTHALMIC EMULSION

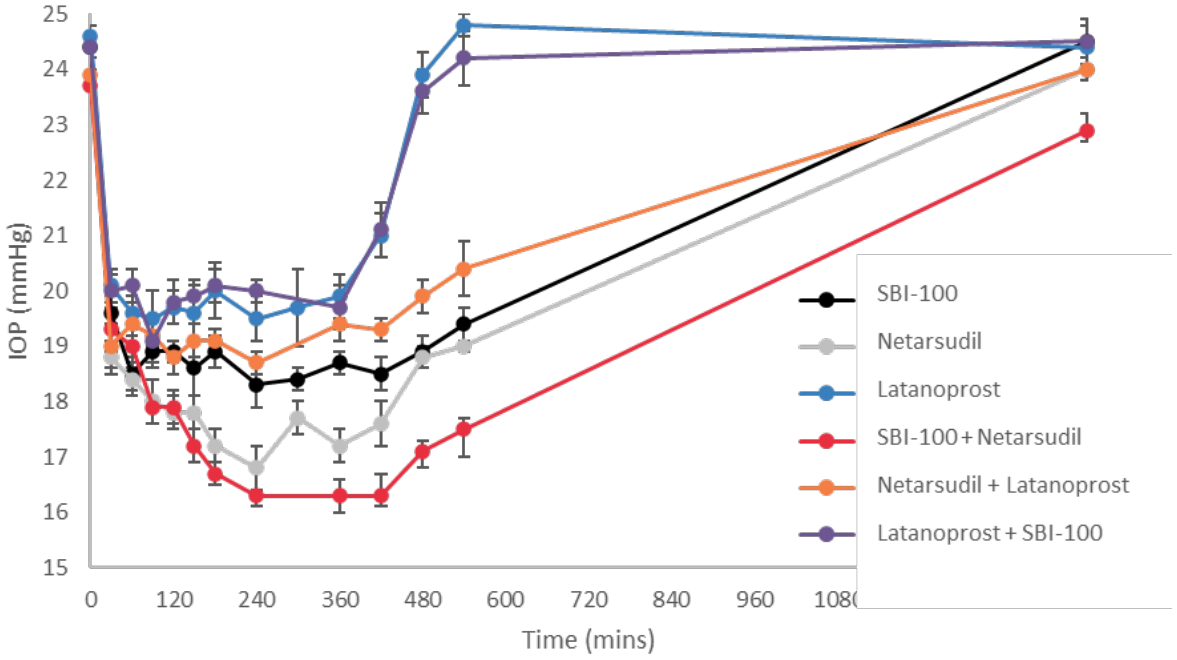
Novel proprietary cannabinoid-derived eye drop formulation

DESIGN FACTOR	RATIONALE	SBI-100 STRUCTURE
Tetrahydrocannabinol (THC)	SBI-100 is a prodrug of THC. The active drug is not water soluble and has poor bioavailability.	 Chemical Formula: $C_{30}H_{43}NO_6$ Molecular Weight: 513.6655 THC-valinate-hemisuccinate (15)
Prodrug design	Overcomes weaknesses of THC by improving solubility, stability and bioavailability. Prodrug is rapidly cleaved once delivered into the eye.	
Prodrug moiety (valine-hemisuccinate)	Valine-hemisuccinate added to THC using a scalable and proprietary synthetic method under GMP control.	
Nanoemulsion formulation (ophthalmic emulsion)	Improves delivery of SBI-100 into multiple structures of the eye.	

SBI-100 DEMONSTRATES SUPERIOR IOP LOWERING

Nonclinical comparison with standard of care drugs shows favorable characteristics



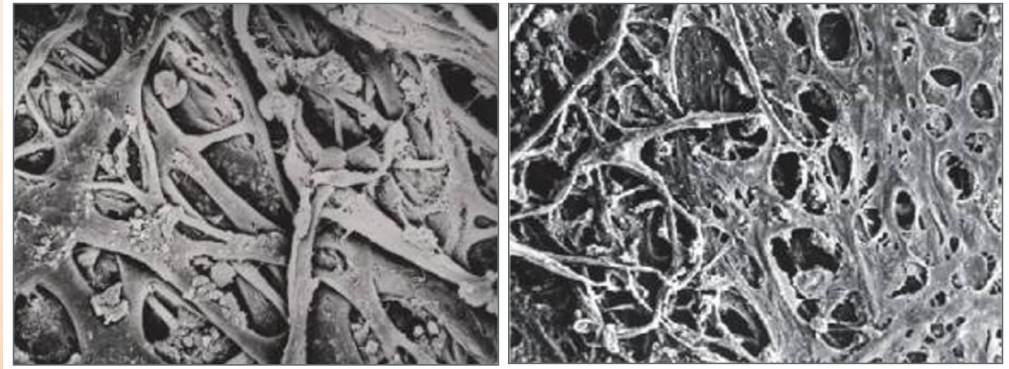


In multiple preclinical studies, SBI-100 demonstrated superior IOP lowering compared to leading therapies as a single agent

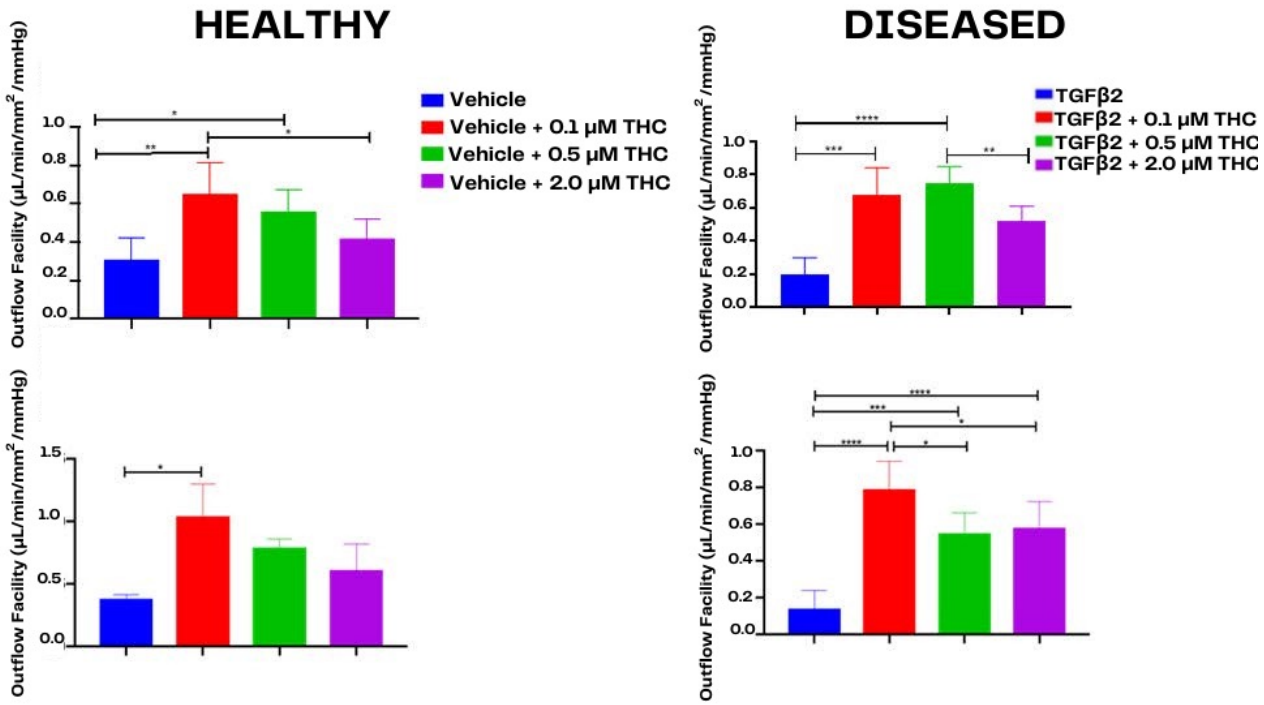
In preclinical studies, SBI-100 demonstrated enhanced efficacy when combined with other approved therapies

INCREASED OUTFLOW VIA TRABECULAR MESHWORK

- The trabecular meshwork (TM) accounts for 90% of aqueous humor outflow (drainage)
- Restricted outflow through TM and fibrosis in tissue may be key to underlying pathophysiology of glaucoma
- The TM is avascular and depends on outflow for nutrients and health; restricted outflow leads to further structural deterioration
- In a 3D model of human TM cells, SBI-100's active pharmaceutical ingredient significantly increased outflow in both healthy and disease-simulated tissue



Normal TM (left), POAG TM (right)



REDUCED MARKERS OF INFLAMMATION & FIBROSIS

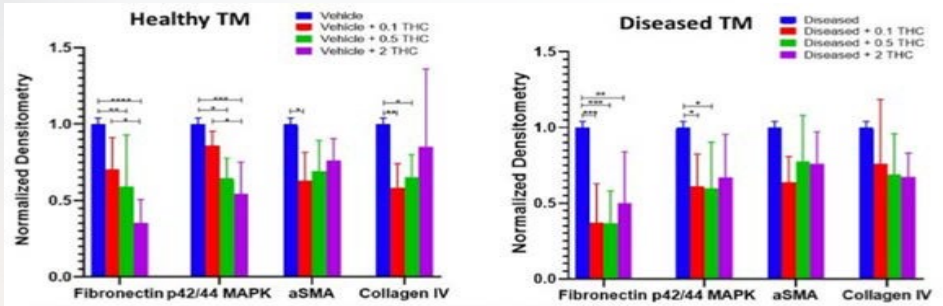


Figure 2. Protein analysis of markers linked to fibrosis at the 3D HTM after 6 days of treatment with THC. All samples of three donors were analyzed using Two-way ANOVA ****P<0.0001, ***P<0.001, **P<0.01, *P<0.05, N ≥ 4 per donor.

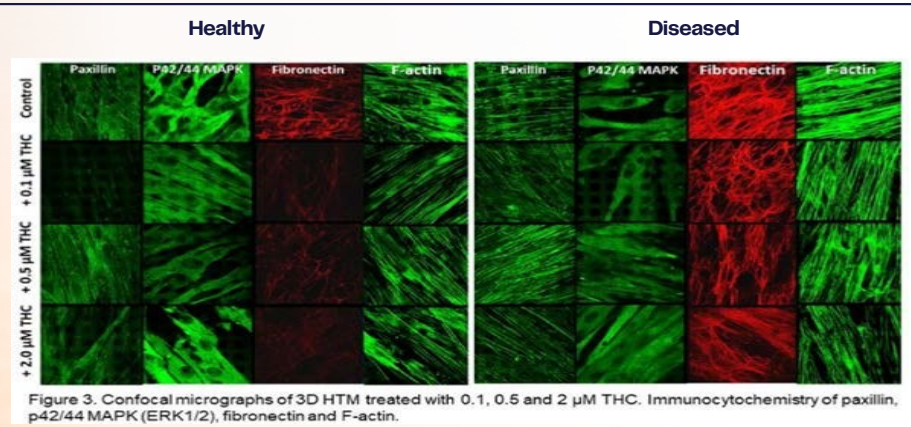
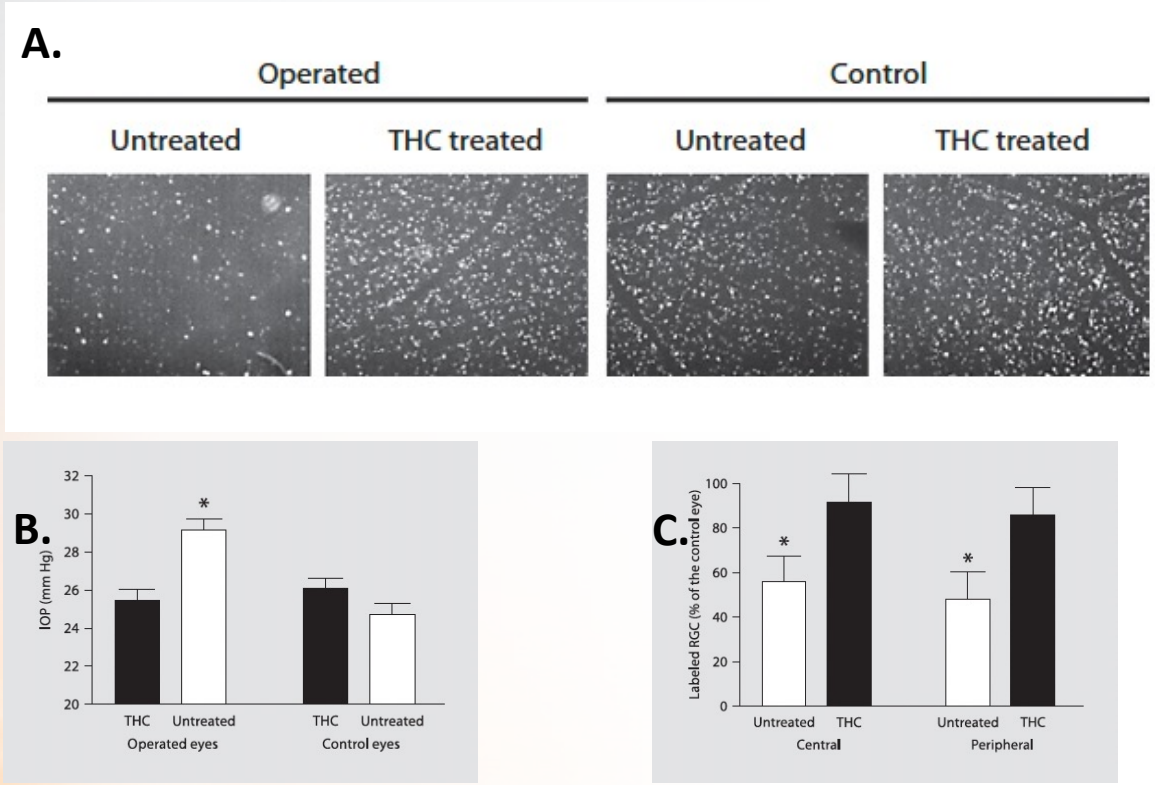


Figure 3. Confocal micrographs of 3D HTM treated with 0.1, 0.5 and 2 µM THC. Immunocytochemistry of paxillin, p42/44 MAPK (ERK1/2), fibronectin and F-actin.

- SBI-100 significantly reduced markers associated with fibrosis and inflammation, which are associated with glaucoma
- Potentially disease-modifying through extracellular matrix remodeling of the trabecular meshwork
- Multi-factorial mechanism of action, including anti-inflammatory and anti-fibrotic responses
- Potential new class of treatment with therapeutic attributes distinct from existing IOP-lowering drugs

SBI-100 HAS POTENTIAL NEUROPROTECTIVE BENEFITS

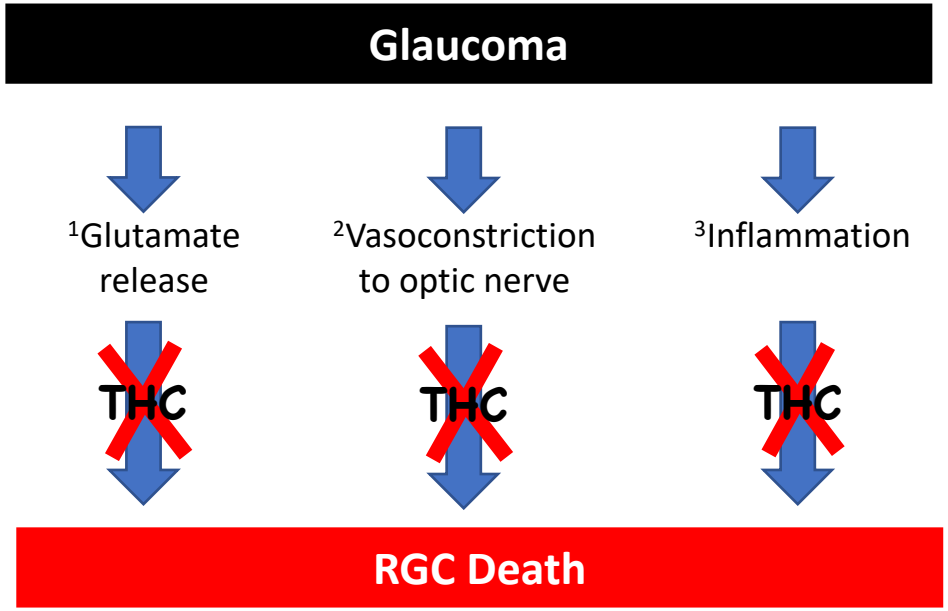
THC preserves retinal ganglion cells in glaucomatous rat model



A) Whole-mount of rats of control and glaucomatous rat eyes. **B**) Reduction of IOP by THC. **C)** Increase in RGC survival in post THC treatment in control and glaucomatous rats.

Crandall et al., Ophthalmic Res 2007;39:69-75

Mechanisms of RGC Death in Glaucoma and THC Neuroprotective Benefits

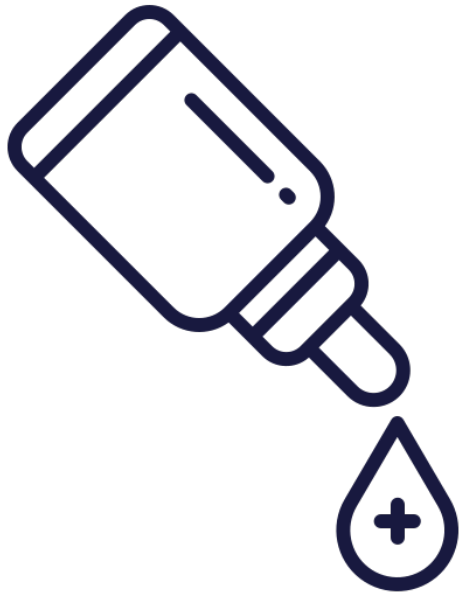


[1] *El-Remessey et al., Am. J. Pathol. 2003 Nov;163(5):1997-2008*
[2] *Green et al., Exp.Eye Res. 1978;26:65-69*
[3] *Krishnan et al., Neuroscience. 2015;284:536-545*

SBI-100 OE: ADDRESSES ISSUES WITH CURRENT TREATMENTS

✓ **Targets area of disease**

- Most drugs do not target the main site of disease-causing increased IOP -- the trabecular meshwork (TM)
- SBI-100 OE directly targets the TM as well as uveoscleral pathways, and may increase flow through the eye
- SBI-100 OE may decrease fibrosis in the TM, the main cause of blockage to flow



✓ **Neuroprotective capabilities**

- Current treatments are not neuroprotective
- This new class of molecule has shown potential benefits to promote health and survival of optic nerve cells – sparing retinal ganglion cells (RGCs) – in glaucoma models

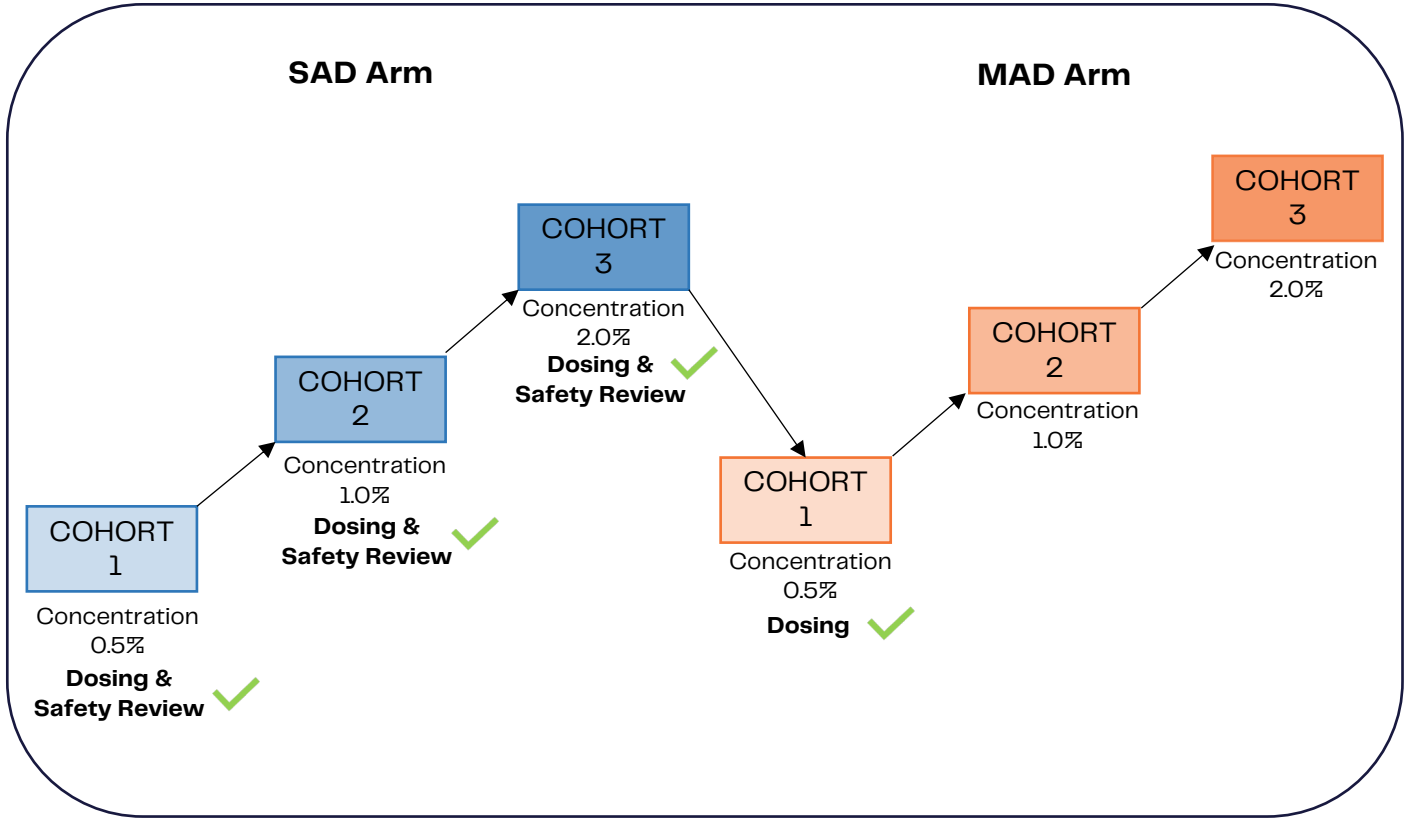
✓ **Potential combination and add-on to current therapies**

- Other drugs cause local and systemic side effects
- Most drugs do not combine well with each other

SBI-100 OE: PHASE 1 SAFETY SAD/MAD DESIGN IN HEALTHY VOLUNTEERS

Dosing of SAD arm complete; final dosing of MAD arm to start before end of Q2

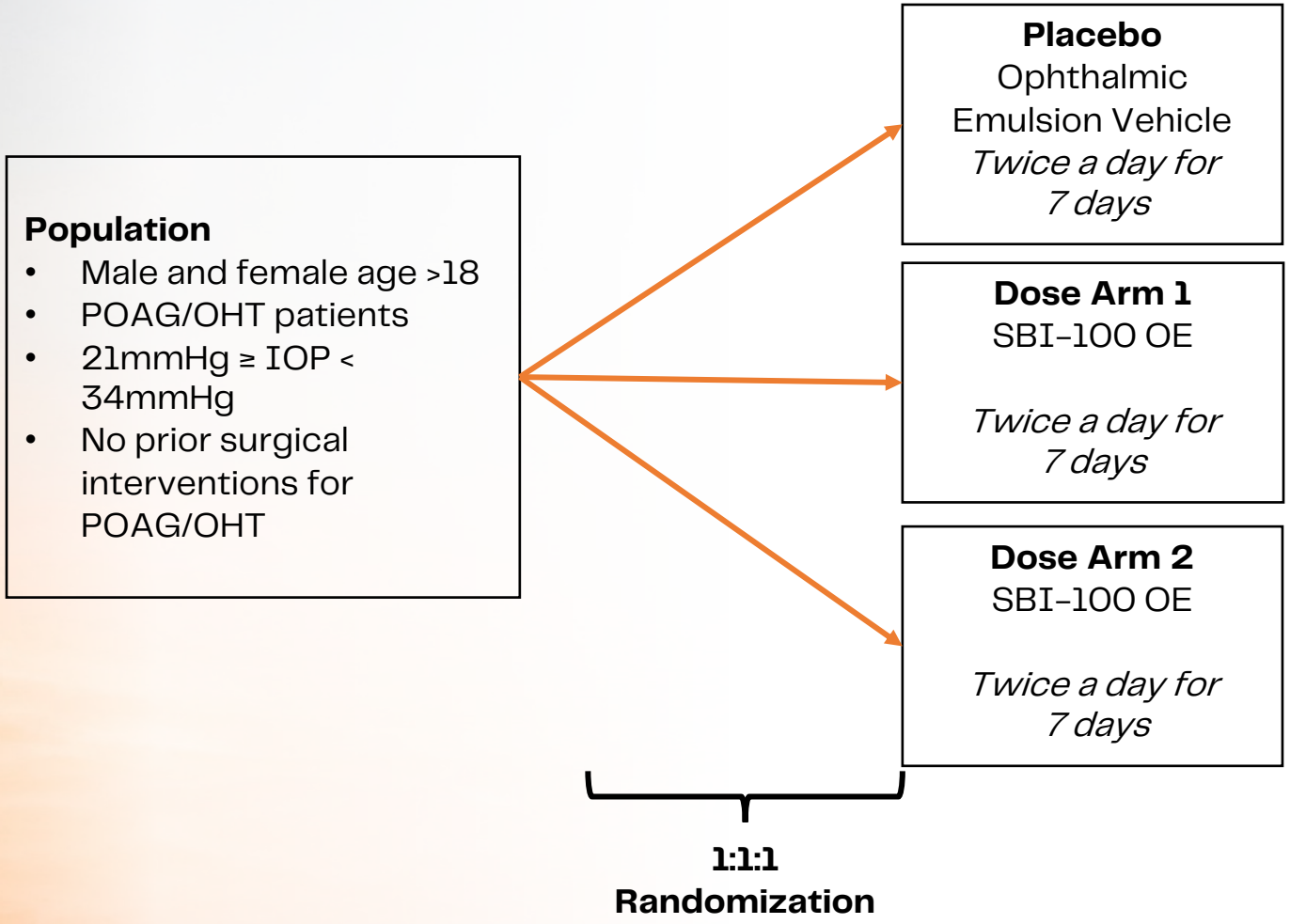
- Randomized, double-masked, placebo-controlled; evaluating safety, tolerability, and effect on intraocular pressure of topically administered SBI-100 OE or placebo on a single eye in ~48 healthy subjects
- Single ascending dose arm: 1 treatment, monitored for 24 hours. Multiple ascending dose arm: 2 treatments/ day for 5 days, monitored for 7 days including treatment days
- Safety review committee reported: SAD arm had no serious adverse events, and mild and moderate drug-related adverse events
- As a new chemical entity and regulated controlled substance, demonstrating safety is important for development of SBI-100 OE



Study comprises 2 arms of 3 cohorts with 8 participants each (6 receiving SBI-100 OE and 2 placebo)

PROPOSED PHASE 2 STUDY DESIGN

First ever cannabinoid eye drop for glaucoma to enter human efficacy study



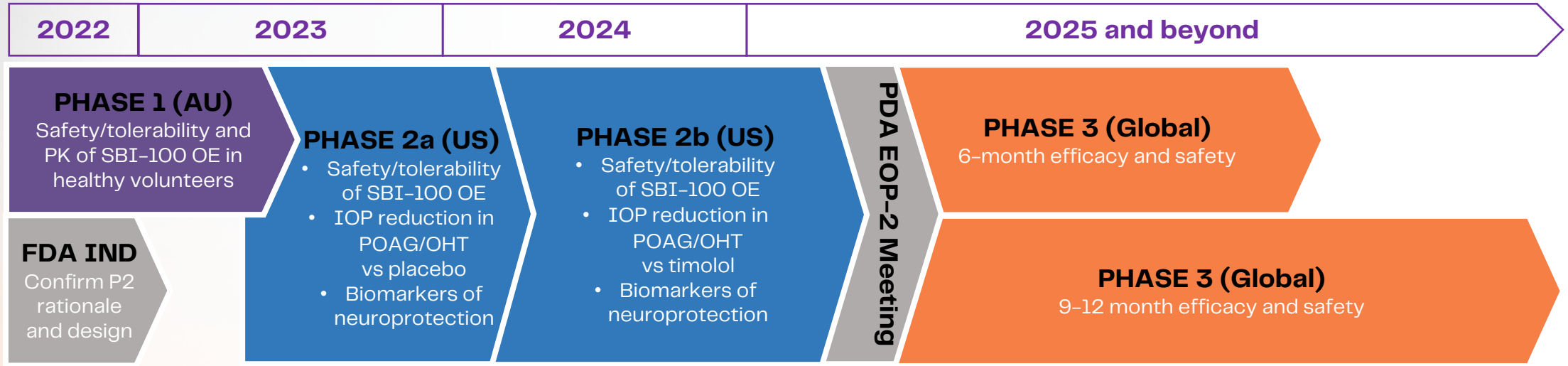
Primary endpoint

- Change in IOP from baseline versus placebo

Secondary endpoints

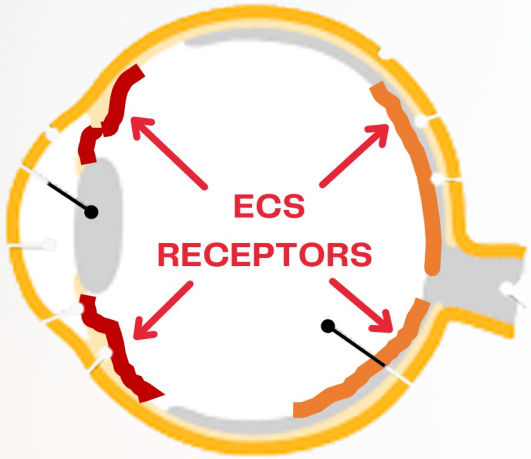
- Measure of psychotropic effects
- Biomarkers of neuroprotection
- Safety and tolerability

SBI-100 OE – REGULATORY AND CLINICAL DEVELOPMENT



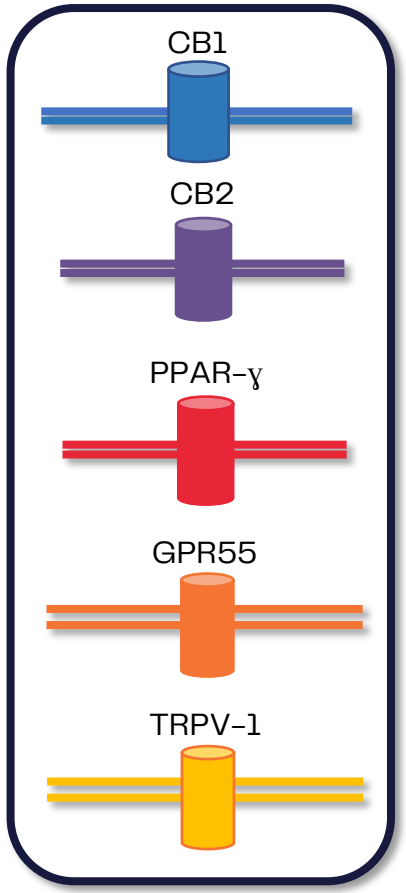
- Phase 1 safety and PK data will guide Phase 2a and Phase 2b study doses.
- Phase 2a study designed as POC to demonstrate IOP reducing capability of SBI-100 OE
- Phase 2b study designed to establish non-inferiority to standard of care (timolol)
- Phase 3 studies expected to start in 2025

NOVEL CLASS OF TARGETS FOR OPHTHALMOLOGY



- ECS plays vital role in controlling an array of functions in the body
- Affecting the ECS may provide therapeutic benefit for multiple diseases, including in the eye
- ECS receptors found throughout the eye shown to be involved in a broad set of ocular functions and pathologies

ECS receptors in the eye



Relate to many ocular pathologies

- Intraocular pressure
- Nociception (pain)
- Inflammation
- Neovascularization
- Wound healing
- Neuroprotection
- Fibrosis
- Pain

Cannabinoid receptor–rich environment of eye creates an opportunity for drugs targeting these receptors to modulate ocular disease

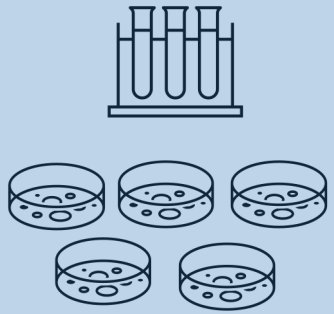
R&D PLATFORM FOR OCULAR DISEASES

Cannabinoid Pharmaceutical Innovation Program (CPIP)

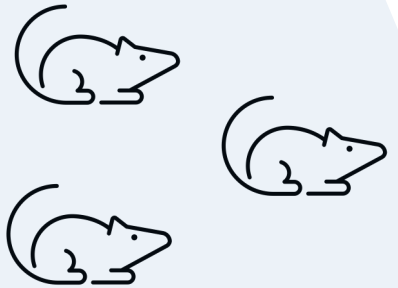
DISCOVERY

80+ novel compounds

IN VITRO SCREENING

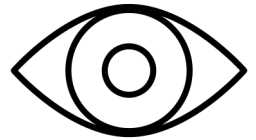


TARGET ENGAGEMENT IN VIVO MODELS



OCULAR INDICATIONS

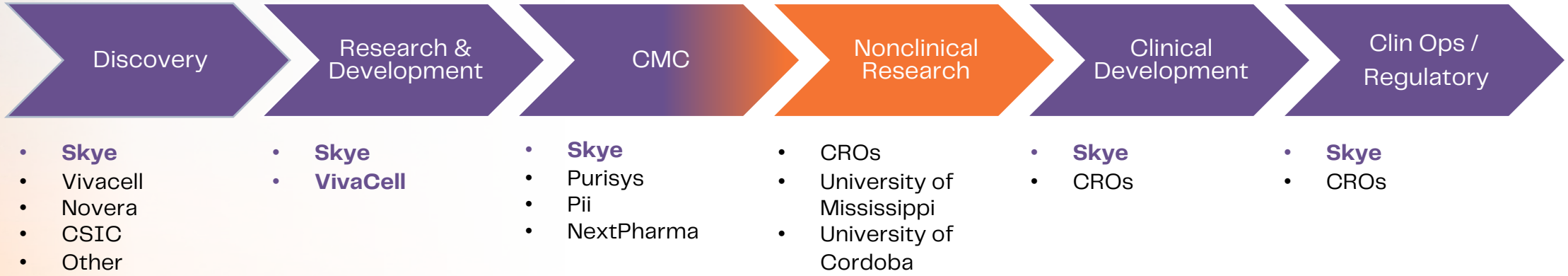
Dry eye
Ocular pain
Uveitis



AMD
Diabetic retinopathy
Uveitis

EXPERT DRUG DEVELOPMENT CAPABILITY

Internal/external resources provide knowledge/flexibility to advance controlled substances through the pharmaceutical drug development path



CATALYSTS TO ADVANCE OUR INNOVATION & GROWTH

Ocular applications to unlock potential of novel class of cannabinoid derivatives

SBI-100 OE: PHASE 1

- ✓ Q1-22: Completion of GLP toxicology studies
- ✓ Q2-22: AUS HREC approval to start Phase 1 study
- ✓ Q4-22: Begin Phase 1 enrollment
- ✓ Q1-23: Enroll single ascending dose arm of P1
- ❑ Q2-23: Dose final cohort of multiple ascending dose arm of Phase 1
- ❑ Q3-23: Phase 1 data

SBI-100 OE: PHASE 2

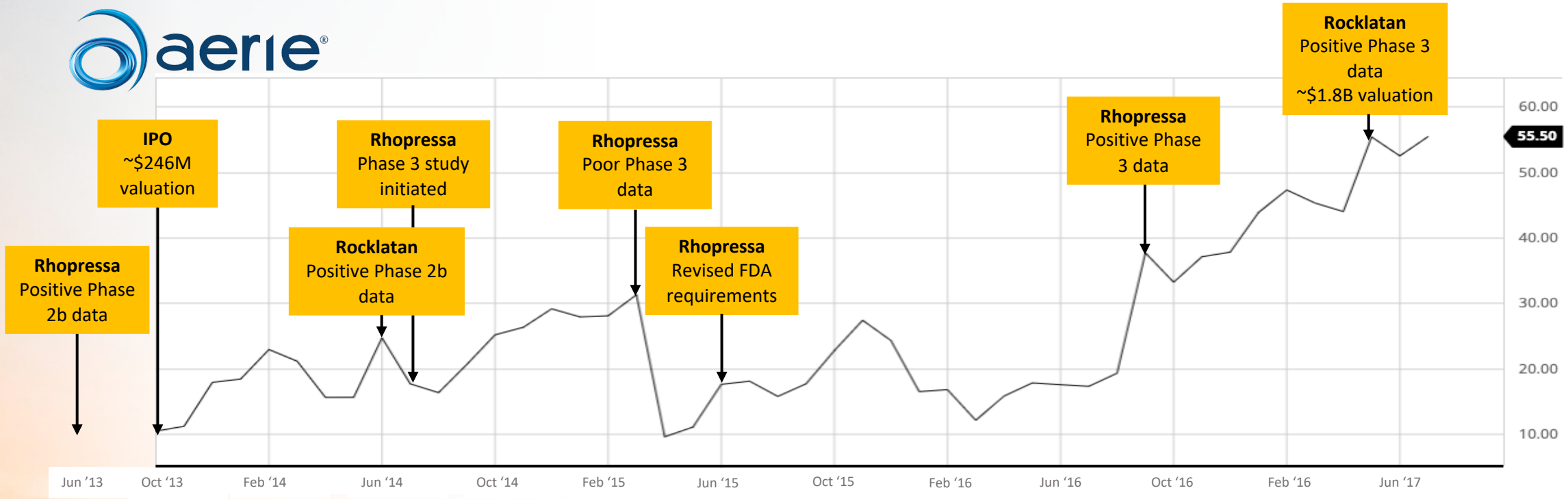
- ✓ Q4-21: Pre-IND meeting with the FDA
- ✓ Q4-22: FDA authorization of Investigational New Drug application
- ✓ Q1-23: Central institutional review board (IRB) approval of Phase 2 study
- ❑ Mid-23: Phase 2 initiation
- ❑ Q1-24: Phase 2 data

STRATEGIC MILESTONES

- ✓ Q4-21: Neuroprotection study to assess SBI-100 potential to spare vision loss
- ✓ H2-22: Close corporate acquisition for capital resources
- ❑ Early-stage research & pipeline expansion
- ❑ H1-23: Phase 2 efficacy study initiation. New product-driven intellectual property

CASE STUDY: VALUE CREATION VIA CLINICAL DEVELOPMENT

Ocular applications to unlock potential of novel class of cannabinoid derivatives



- AERI clinical results lead to important inflection points for the company.
- The glaucoma market is still in need of new classes of compounds, and AERI demonstrated that positive clinical development of compounds with new mechanisms of action are perceived favorably by the market.

MANAGEMENT

Punit Dhillon

Chief Executive Officer & Chair

Co-founded and led OncoSec (NASDAQ: ONCS), a cancer immunotherapy company, through early development and partnership with Merck to launch Phase 2/3 multi-center trial.

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BOARD OF DIRECTORS

Punit Dhillon

Chair

Co-founded and led OncoSec (NASDAQ: ONCS), a cancer immunotherapy company, through early development and partnership with Merck to launch Phase 2/3 multi-center trial.

Keith Ward, PhD

Over 25 years of experience in the biotech and pharmaceutical industry. Led the development of ophthalmic pharmaceuticals.

Praveen Tyle, PhD

Over 37 years of broad pharmaceutical executive leadership. Experienced in ocular disorders with a wealth of academic insight and named on multiple patents including patents related to ophthalmic innovations, drug delivery and glaucoma.

Deborah Charych, PhD

Over 20 years' scientific leadership and pre-clinical and drug development experience. Led preclinical and early clinical development, leading to $1.8B deal with BMS. Also led cannabinoid receptor system research.

Margaret Dalesandro, PhD

Over 25 years of drug development experience in pharmaceutical, biotechnology, and diagnostics industries. Experienced in in/out licensing of molecules for ocular indications.

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REATA PHARMACEUTICALS
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InterveXion Therapeutics

NOVARTIS
BAUSCH + LOMB
PHARMACIA
invectys CANCER IMMUNOTHERAPEUTICS
Osmotica Pharmaceuticals

RayzeBio
NEKTAR
FivePrime
CHIRON

ImClone Systems Incorporated
gsk
centocor inc

ADVISORS

CLINICAL

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Jeffery Goldberg, MD, PhD

Prof. of Ophthalmology, Stanford

Professor and Chair of Ophthalmology and Director of Spencer Center for Vision Research at Byers Eye Institute, Stanford University

SCIENTIFIC

Eduardo Muñoz, MD, PhD

Prof. of Immunology, U. Córdoba

Over 30 years of experience in biomedical research, focused on cannabinoids, pharmacology, and inflammation, providing deep expertise in the mechanism of actions of cannabinoids and the development of novel cannabinoid-derived molecules

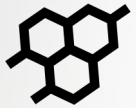
Giovanni Appendino, PhD

Prof. of Organic Chemistry, U. Piedmont

Over 40 years of research in natural products, leading to the discovery and isolation of over 200 novel compounds, including novel cannabinoids and chemistry for cannabinoid-derived molecules

INVESTMENT SUMMARY

Bold innovation in ophthalmology to unlock the potential of proprietary cannabinoid derivatives



Enrolling Phase 1 for CB1R agonist program; Received FDA okay for IND to start studies in US, enabling planned Phase 2

Transformative new class of therapeutics may play a role in multiple ocular indications

Solid clinical and preclinical foundation for glaucoma with upcoming meaningful clinical inflection points

Engaging in academic collaborations to expand pipeline of novel cannabinoid derivatives

Pursuing partnership opportunities for programs

Capitalization

Cash and securities[1]

Common shares o/s	972.5 M[1]
Options, warrants and RSUs	241.5 M[1]
Common shares f/d	1,214 M[1]
Cash	$1.2 M[2]

OTCQB SKYE
Market cap: $14.1 M[3]

Incremental capital: sale of non-core operating facility for $9.48M

Closed sale of Verdélite to C3 Souvenir Holding for aggregate purchase price of $9.48M on 23/02/09

- $0.5 M deposit paid prior to close + $5.6 M paid on 23/02/10
- $0.12 M payable by June 2023 + $0.37 M payable in 5 monthly installments + interest (8%/annum) starting 23/12/31
- Balance of $2.80M payable in 3 installments 18, 30, 42 months after closing + applicable interest

[1]As reported in 2022 Annual Report and recorded on 23/03/29 [2]22/12/31 [3]23/05/10

THANK YOU

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Appendix

CLINICAL RESEARCH SHOWS CANNABINOIDS LOWER IOP

Subjects	Administration route	Observations
15 male, 18-30 years old	Smoking marijuana (12 mg Δ^9 THC)	Significant **IOP decrease** after 80 min, more frequent users showered lower or no IOP drop
10 healthy volunteers, 20-30 years old	0.022 or 0.044 mg/kg of Δ^9 THC intravenously	**IOP decrease** in 9 patients with low dose and all subjects with high dose
256 glaucomatous patients	Smoking marijuana (1-4% Δ^9 THC) or 5-20 mg oral Δ^9 THC	Most patients showed **IOP reduction**, additive effect was seen with conventional glaucoma drugs
A 23-year-old male (suffers HPPD), 4 young subjects (control), 23 -28 years old	Smoking marijuana	HPPD in patient, no change in the controls
9 patients with end-stage open-angle glaucoma, 38-77 years old	Smoking marijuana or oral Δ^9 THC capsules	**Lower IOP**, development of tolerance and significant systemic toxicity that limit the usefulness
6 patients with ocular hypertension or early primary open-angle glaucoma	Single sublingual preparation (5 mg Δ^9 THC or 20 and 40 mg CBD)	Significant **IOP decrease** by Δ^9 – THC, 40 mg CBD produced a transient IOP increase, no significant side effect
8 patients with glaucoma resistant to conventional treatments, 53-72 years old	Topical application of WIN55212-2	**IOP decreased** directly through CB1
18 patients suffering glaucoma	Single oral dose of nabilone (0.5 mg)	**IOP decreased** by 27.9%, 2-6h after administration, no visual side effect
32 patients suffering glaucoma	BW29Y (5 or 10 mg) or BWI46Y (4, 8, or 12 mg)	BW29Y: ineffective, BWI46Y: **IOP drop**, lightheaded, dizzy, disorientation, blood pressure drop

HPPD: Hallucinogen persisting perception disorder; IOP: intraocular pressure; Δ^9 THC: Δ^9 tetrahydrocannabinol; CBD: cannabidiol; WIN55212–2, Nabilone, BW29Y, BWI46Y: synthetic cannabinoids.

Adapted from Y. Panahi et al. / Biomedicine & Pharmacotherapy 86 (2017) 620–627

PRODRUG STRATEGY TO EFFECTIVELY DELIVER THC

Ion-pairing of prodrug allows for enhanced permeability at physiological pH

- Hingorani et al aimed to improve the transcorneal permeability of THC through prodrug derivatization and formulation
- In vitro corneal permeability of THC and its hemisuccinate (THC-HS) and hemiglutarate (THC-HG) ester prodrugs and WIN 55212-2 (WIN), was determined in isolated rabbit cornea
- **Results demonstrate that prodrugs could be an effective strategy for topical delivery of THC**

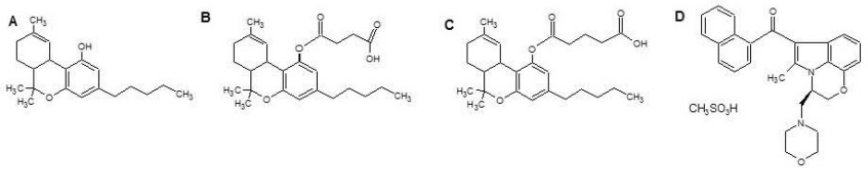


Figure 1.
Chemical structures of A) Δ^9-Tetrahydrocannabinol (THC), B) Δ^9-Tetrahydrocannbinol Hemisuccinate (THC-HS) and C) Δ^9-Tetrahydrocannbinol Hemiglutarate (THC-HG) D) WIN 55-212-2 (WIN).

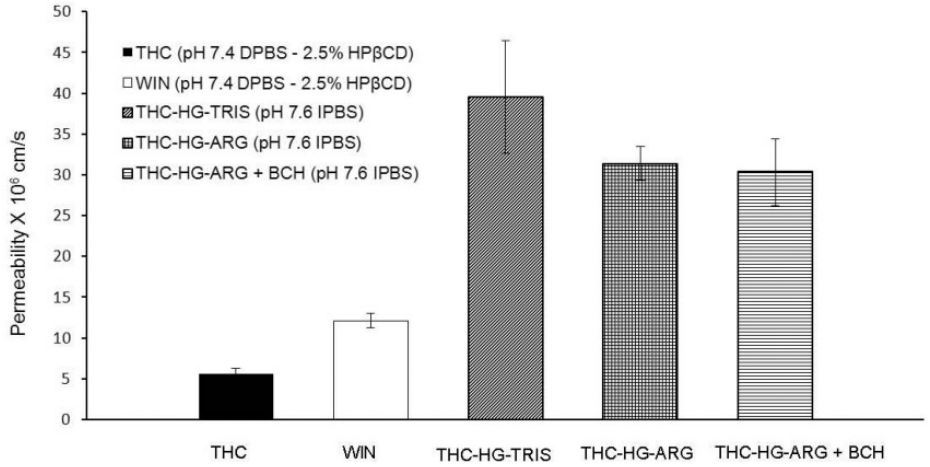
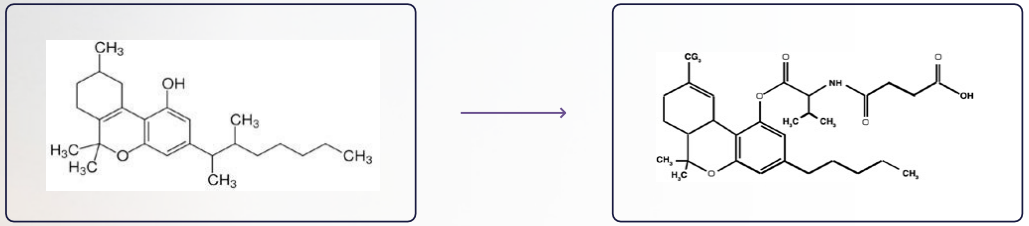


Figure 4.
Comparative permeability (in terms of total THC) of THC, WIN, THC-HG-ARG complex, THC-HG-ARG complex + BCH and THC-HG-TRIS complex at 34 °C across isolated rabbit corneas. The legends indicate the donor solution pH and composition. Receiver medium was 2.5 % HPβCD in DPBS (pH 7.4) for THC and WIN, while for the ion-pair complexes the receiver solution was IPBS containing 2.5% HPβCD (pH 7.4). Results are depicted as a mean ± SD (n=3). *$p < 0.05$.

Hingorani T„ Gul W„ Elsohly M„ Repka MA„ Majumdar S. Effect of ion pairing on in vitro transcorneal permeability of a delta(9) – tetrahydrocannabinol prodrug: potential in glaucoma therapy. *J Pharm Sci.* 2012; 101: 616–626.

WHAT'S DIFFERENT ABOUT TOPICAL ADMINISTRATION

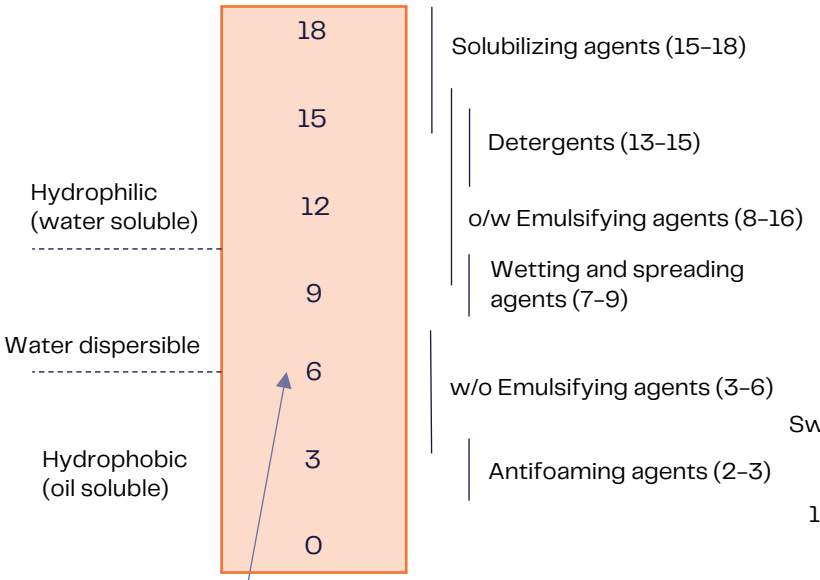
THC is very hydrophobic/lipophilic and insoluble; the ocular surface is aqueous



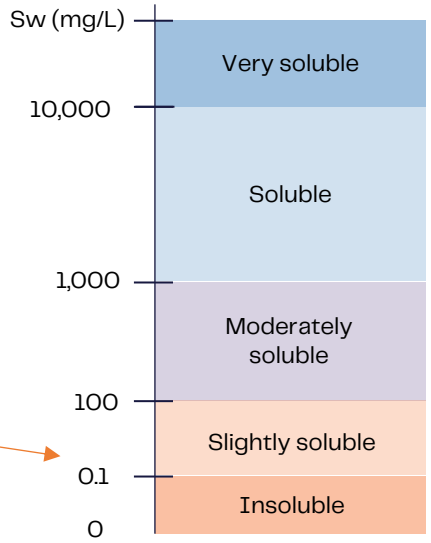
THC

SBI-100

- THC is lipophilic and not easily delivered into the eye topically
- SBI-100 is a prodrug of THC that increases solubility and polarity of THC, allowing it to better penetrate ocular tissue
- Inside the eye, SBI-100 is converted back into THC
- SBI-100 OE proprietary nanoemulsion formulation further enhances delivery of THC to ocular tissue, resulting in greater IOP-lowering effect and duration



- logP=6.42[1]
- Aqueous solubility= 2.8 mg/L



1. Jarho P, Pate DW, Brenneisen R, Jarvinen T. Hydroxypropyl-beta-cyclodextrin and its combination with hydroxypropyl-methylcellulose increases aqueous solubility of delta9-tetrahydrocannabinol. *Life Sci.* 1998; 63: PL381–PL384.