Unlocking the Pharmaceutical Potential of Cannabinoids
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Overview

Biopharmaceutical company developing differentiated, synthetic, proprietary cannabinoid derivatives to treat diseases with significant unmet medical needs

OTCQB: SKYE

NOVEL TECHNOLOGY
Bioengineered, synthetic cannabinoid derivatives designed to significantly enhance therapeutic benefits

COMMERCIAL OPPORTUNITY
$6.6B+ market opportunity for lead indication, glaucoma

INTELLECTUAL PROPERTY
Broad "composition of matter" patent protection

EXPERIENCED TEAM
Track record of rapidly advancing preclinical candidates through to human trials and securing strategic pharma partnerships

MILESTONES
Key preclinical data expected in Q2-21 & first-in-human data in Q1-21
Glaucoma is the leading cause of irreversible blindness

Glaucoma is a disease that leads to the progressive damage of retinal ganglion cells, which make up the optic nerve, and without intervention will gradually lead to irreversible blindness.

Healthy Vision  Early Glaucoma  Advanced Glaucoma
Large & growing patient population

78M
Current Glaucoma Patients

100M
2040 Predicted Glaucoma Patients

$6.6B current global market and expected to reach $11B by 2027 with a growing aging population (CAGR 6.6%)
How does glaucoma cause blindness?

A common trait of glaucoma involves increased pressure in the eye - intraocular pressure (IOP)

**HEALTHY**
- Production/drainage of aqueous humor (fluid) balanced

**GLAUCOMA**
- Drainage canal becomes blocked, fluid builds up and leads to increased pressure
- Increased pressure damages optic nerve cells, resulting in vision loss
Current therapies leave notable unmet needs

- Current drugs aim to lower IOP in order to slow disease progression
- Many patients are non-responders, have poor response, or develop tolerance
- >50% of patients require 2 or more drugs, can increase side effects and reduce compliance
- Lack of innovation, presents an opportunity and need for new classes of therapy

<table>
<thead>
<tr>
<th>Class of Medication</th>
<th>Generic Example</th>
<th>IOP Reduction</th>
<th>MOA</th>
<th>Potential Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandins</td>
<td>Latanoprost</td>
<td>30-35%↑</td>
<td>↑ Outflow</td>
<td>irritation, redness, blurred vision, dry eyes, light sensitivity, headaches, eyelash changes, browning of iris</td>
</tr>
<tr>
<td>β-Adrenergic Blockers</td>
<td>Timolol</td>
<td>20-25%↓</td>
<td>↓ Production</td>
<td>irritation, dry eyes, headache, slowed heart rate</td>
</tr>
<tr>
<td>α-Adrenergic Blockers</td>
<td>Brimonidine</td>
<td>20-25%↑ Outflow</td>
<td>↓ Production</td>
<td>irritation, redness, blurred vision, dry eyes, light sensitivity, fatigue, headaches, nausea, insomnia</td>
</tr>
<tr>
<td>Carbonic Anhydrase Inhibitors</td>
<td>Dorzolamide</td>
<td>20-25%↓</td>
<td>↓ Production</td>
<td>irritation, redness, blurred vision, dry eyes, light sensitivity, fatigue, headaches</td>
</tr>
<tr>
<td>Cholinergic Agonists</td>
<td>Pilocarpine</td>
<td>20-25%↑ Outflow</td>
<td>↑ Outflow</td>
<td>irritation, blurred vision, poor vision in dim light, headaches</td>
</tr>
<tr>
<td>Rho-kinase inhibitors</td>
<td>Netarsudil</td>
<td>16-21%↑ Outflow</td>
<td>↓ Production</td>
<td>irritation, redness, corneal deposits, broken blood vessels</td>
</tr>
<tr>
<td>Nitric oxide-donating prostaglandin</td>
<td>Latanoprostene bunod</td>
<td>32-34%↑</td>
<td>↑ Outflow</td>
<td>irritation, redness, discharge, pain, eyelash changes</td>
</tr>
<tr>
<td>Fc rho-kinase inhibitor/latanoprost</td>
<td>Netarsudil/latanoprost</td>
<td>30-36%↑</td>
<td>↓ Production</td>
<td>irritation, redness, corneal deposits, broken blood vessels</td>
</tr>
</tbody>
</table>
Relevance of THC to glaucoma

- Cannabinoid receptors throughout the body play an important role in managing many vital body functions
- Eye is rich with cannabinoid receptors, specifically in tissues involved in managing fluid production and drainage as well as cells responsible for vision
- THC and the CB1 receptor, specifically, have been shown to be involved in IOP lowering activity
- First report that smoking cannabis lowers IOP appeared in early 1970s
- Multiple human studies have validated THC's ability to lower IOP
Multiple independent studies have demonstrated THC’s ability to lower IOP

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

**Table 1**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Administration route</th>
<th>Observations</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 Male, 18–30 years old</td>
<td>smoking marijuana (12 mg $\Delta^2$-THC)</td>
<td>significant IOP decrease after 80 min, more frequent users showed lower or no IOP drop</td>
<td>[74]</td>
</tr>
<tr>
<td>10 healthy volunteers, 20–30 years old</td>
<td>0.022 or 0.044 mg/kg of $\Delta^9$-THC intravenously</td>
<td>IOP decrease in 5 patients with low dose and all subjects with high dose</td>
<td>[75]</td>
</tr>
<tr>
<td>256 glaucomatous patients</td>
<td>smoking marijuana (1–4% $\Delta^9$-THC) or 5–20 mg oral $\Delta^9$-THC</td>
<td>most patients showed IOP reduction, additive effect was seen with conventional glaucoma drugs</td>
<td>[76]</td>
</tr>
<tr>
<td>A 23-year-old male (suffers of HPPD), 4 young subjects (control), 23–28 years old</td>
<td>smoking marijuana</td>
<td>HPPD in patient, no change in the controls</td>
<td>[77]</td>
</tr>
<tr>
<td>9 patients with end-stage open angle glaucoma, 38–77 years old</td>
<td>smoking marijuana or oral $\Delta^9$-THC capsules</td>
<td>lower IOP, development of tolerance and significant systemic toxicity that limit the usefulness</td>
<td>[78]</td>
</tr>
<tr>
<td>6 patients with ocular hypertension or early primary open angle glaucoma</td>
<td>single sublingual preparation (5 mg $\Delta^9$-THC or 20 and 40 mg CBD)</td>
<td>significant IOP decrease by $\Delta^9$-THC, 40 mg CBD produced a transient IOP increase, no significant side effect</td>
<td>[79]</td>
</tr>
<tr>
<td>8 patients with glaucoma resistant to conventional treatments, 51–72 years old</td>
<td>topical application of WIN55212-2</td>
<td>IOP decreased directly through CB1</td>
<td>[80]</td>
</tr>
<tr>
<td>18 patients suffers of glaucoma</td>
<td>single oral dose of nabilone (0.5 mg)</td>
<td>IOP decreased by 27.9%, 2–6 h after administration, no visual side effect</td>
<td>[81]</td>
</tr>
<tr>
<td>32 patients suffers of glaucoma</td>
<td>BW229Y (5 or 10 mg) or BW414Y (4, 8, or 12 mg)</td>
<td>BW229Y: ineffective, BW414Y: IOP drop, lightheaded, dizzy, disorientation, blood pressure drop</td>
<td>[82]</td>
</tr>
</tbody>
</table>

HPPD: Hallucinogen persisting perception disorder; IOP: intraocular pressure; $\Delta^9$-THC: $\Delta^9$-tetrahydrocannabinol; CBD: cannabidiol; WIN55212-2, Nabilone, BW229Y, BW414Y: synthetic cannabinoids.
Challenges to THC as an effective treatment of glaucoma

**Systemic Delivery**
- Requires relatively high dose to achieve therapeutic effect in the eye
- Variable pharmacokinetics and pharmacodynamics
- Poor oral bioavailability when ingested (<10% due to poor absorption)
- Limited duration of effect when inhaled/smoked (<90 min)
- Systemic side effects – psychoactive effect (high from THC); detrimental drops in blood pressure

**Local Delivery**
- THC is lipophilic – challenging to deliver into and penetrate aqueous tissue, like the eye
- Oil and water don’t mix!
SKYE's approach unlocks therapeutic value of THC

- Rational drug design and bioengineering used to develop a synthetic prodrug of THC, called THCVHS
- Valine-hemi-succinate amide ester (VHS) addition to THC enhances aqueous solubility and polarity characteristics, enabling significantly improved local delivery into the eye and avoiding systemic effects
- Inside the eye, THCVHS is converted back into THC by enzymes that cleave VHS arm of the molecule
- THCVHS is a proprietary molecule with composition of matter patents providing intellectual property protection that is instrumental to value creation

![Diagram of THC and THCVHS molecules]
THCVHS lowers IOP better than both market leaders

- In a rabbit model, THCVHS achieves superior decline in IOP versus latanoprost and timolol
- Superior duration of response
- Potential for once-daily dosing
- No detectable THC or metabolites outside the eye
- Additional head-to-head studies against and in combination with Rhopressa (netardusil) and latanoprost planned for 2Q-21 to further assess/validate IOP-lowering properties
Multi-factorial mechanism of action

• In an *ex vivo* model of human trabecular meshwork, the tissues responsible for fluid drainage

• THC significantly lowered pressure and increased drainage in both healthy and diseased tissue

• THC treatment also significantly reduced markers of fibrosis and inflammation, which are associated with glaucoma

• IOP-lowering capability of THC may be multi-factorial, including anti-inflammatory and anti-fibrotic responses

• Potentially a new class of treatment with therapeutic attributes distinct from existing IOP-lowering drugs
Not all glaucoma patients have elevated IOP

- Large proportion of glaucoma patients present with normal IOP, but still suffer progressive damage to optic nerve cells and vision loss
- Not clear what causes neurodegeneration of optic nerve in these patients
- A disproportionate number of patients have normal IOP levels in Asian countries
- Estimated that $\geq \frac{1}{3}$ of all glaucoma patients globally have normal IOP
- Significant unmet need and tremendous market opportunity for a neuroprotective drug
Cannabinoids demonstrate neuroprotection

- Multiple studies in different animal species & models of glaucoma have demonstrated ability of cannabinoids to promote health and survival of optic nerve cells

- Optic nerve injury model in rats planned in Q2-21 to validate neuroprotection properties of THCVHS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Delivery</th>
<th>Study</th>
<th>Model</th>
<th>Neuroprotective effect versus vehicle (treatment versus control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC</td>
<td>IP</td>
<td>Crandall et al., 2007 [68]</td>
<td>Episcleral vein cauterization</td>
<td>~20–40% increase (10–20% loss)</td>
</tr>
<tr>
<td>THC</td>
<td>IV</td>
<td>El-Remessy et al., 2003 [69]</td>
<td>Intravitreal NMDA</td>
<td>~9% of vehicle</td>
</tr>
<tr>
<td>CBD</td>
<td>IV</td>
<td>El-Remessy et al., 2003 [69]</td>
<td>Intravitreal NMDA</td>
<td>~4% of vehicle</td>
</tr>
<tr>
<td>WIN 55,212-2</td>
<td>Topical</td>
<td>Pinar-Sueiro et al., 2013 [70]</td>
<td>Ischemia-reperfusion (high IOP)</td>
<td>9.88% increase (2.45% loss)</td>
</tr>
<tr>
<td>MetAEA</td>
<td>IVit</td>
<td>Nucci et al., 2007 [44]</td>
<td>Ischemia-reperfusion (high IOP)</td>
<td>18.6% increase (9.4% loss)</td>
</tr>
<tr>
<td>URB597</td>
<td>IP</td>
<td>Nucci et al., 2007 [44]</td>
<td>Ischemia-reperfusion (high IOP)</td>
<td>15.1% increase (12.9% loss)</td>
</tr>
<tr>
<td>URB597</td>
<td>IP</td>
<td>Slusar et al., 2013 [71]</td>
<td>Axotomy</td>
<td>1 week, 19.5% increase (27.9% loss)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 weeks, 22.7% increase (58.9% loss)</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>IP</td>
<td>Sakai et al., 2009 [72]</td>
<td>Ischemia-reperfusion (high IOP)</td>
<td>25.8% increase (39.1% loss)</td>
</tr>
<tr>
<td>SC-58236</td>
<td>IP</td>
<td>Ju et al., 2003 [45]</td>
<td>Ischemia-reperfusion (high IOP)</td>
<td>Central, 28.4% increase (27.3% loss)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Peripheral, 28% increase (26.8% loss)</td>
</tr>
</tbody>
</table>

IP, intraperitoneal; IV, intravenous; IVit, intravitreal; * study reported quantification of tunnel positive cells only.

Phase 1 human clinical trial

OBJECTIVES
- Assess safety, tolerability, pharmacokinetics of single and multiple ascending doses in healthy subjects and subjects with elevated IOP
- Assessment of intraocular pressure

STUDY DESIGN
- 64 subjects, double-blinded, 3:1 randomization
- 5 SAD cohorts, n=8, healthy subjects
- 3 MAD cohorts, n=8, healthy & elevated IOP subjects

ELIGIBILITY
- Healthy cohorts: IOP ≥ 12 to ≤ 22 mmHg
- Elevated IOP cohorts: IOP ≥ 18 to ≤ 26 mmHg
Preclinical optic nerve injury study to validate neuroprotection

First human trial will be fast, low cost, and include assessment of intraocular pressure

<table>
<thead>
<tr>
<th>Year</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q1</th>
</tr>
</thead>
<tbody>
<tr>
<td>2021</td>
<td>Preclinical optic nerve injury study to validate neuroprotection</td>
<td>Phase 1 in Australia</td>
<td>IND-enabling GLP repeat-dose toxicity data</td>
<td>Phase 1 data</td>
<td>2022</td>
</tr>
<tr>
<td>2022</td>
<td>Head-to-head preclinical study with Rhopressa &amp; latanoprost</td>
<td>CBDVHS development plan</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Capitalization

- **350.0 M** Common Shares Outstanding
- **117.6 M** Options & Warrants
- **5.1 M** Convertible Debt Shares (As Converted Basis)
- **472.7 M** Fully Diluted
- **$31.5 M** Market Cap
- San Diego, CA

1. Based on 10K filed 21/03/01
2. Based on principal balance and accrued interest outstanding as of 21/03/01 on multi-draw credit facility which is convertible at $.40 per share
3. Based on 21/03/02 OTCQB closing price of $0.09
Management: Focused on delivering near-term data outcomes

**Punit Dhillon**  
Chief Executive Officer  
- Co-founded and led OncoSec Medical, a cancer immunotherapy company, through early development and a partnership with Merck to launch Phase 2/3 multi-center trial; raised over $200M  
- VP Finance and Operations, Inovio Pharmaceuticals; helped raise more than $160M

**Richard Janney**  
Principal Accounting Officer  
- 30 years of business experience and served as a Vice President to CFO on multiple companies in a wide range of industries both public and private, domestic and international  
- Previously operated consulting firm scaling start-ups to mid-size companies, offering financial services across an array of industries including software and medical devices

**Tu Diep, MSc**  
Sr Vice President, Development  
- Senior leaderships positions at Element Biosciences, Emerald Health Science, OncoSec Medical and Protox Therapeutics  
- Over 15 years experience in research, clinical and strategic operations, business process, CMC, regulatory affairs, and business development

**Karam Takhar**  
VP, Corporate Development & Investor Relations  
- Life sciences executive with over 15 years experience in research, project management, operations, finance, business development, sales and investor relations  
- Previously held with various leadership roles at Emerald Health Science, Promega Corporation and Stemcell Technologies

**Tom Kim, Esq**  
General Counsel & Director of IP  
- Previously SVP and Corporate Secretary for Inovio Pharmaceuticals built global patent portfolio, led M&A transactions, closed license and partnering deals with large pharma  
- Practiced law at large firms and Fortune 100 companies, eg. Monsanto and DuPont. 20 years experience counseling biotech companies
Board Directors & Advisors Offer Expert Guidance

Eminent experts in ophthalmology, research, and development applying their knowledge to Emerald’s mission

Board of Directors

Punit Dhillon
Chair
Former co-founder, CEO, and director of OncoSec Medical. Experienced in finance, M&A, licensing, strategy implementation, and collaborations with industry and academic partners

James Heppell, Esq
Director
Former founder, CEO, director of BC Advantage Life Sciences venture fund. Director of multiple life science companies. Extensive experience in corporate finance law

Margaret Delsandro, PhD
Director
25+ years drug development experience in pharmaceutical, biotechnology and diagnostics industries. Currently President of Brecon Pharma Consulting

Clinical Advisors

Robert Ritch, MD
Professor of Ophthalmology, Mt. Sinai
Shelley and Steven Einhorn Distinguished Professor of Ophthalmology; Surgeon Director Emeritus and Chief, Glaucoma Services, The New York Eye & Ear Infirmary; Professor of Ophthalmology, The New York Medical College

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

Louis Pasquale, MD
Professor of Ophthalmology, Mt. Sinai
Professor Ophthalmology, Icahn School of Medicine, Chair, Department of Ophthalmology, Vice Chair of Translational Ophthalmology Research, Mount Sinai Healthcare System

Scientific Advisors

Giovanni Appendino, PhD
Professor of Organic Chemistry, UPiedmont
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

Eduardo Muñoz, MD, PhD
Professor 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
Unique competitive position

- Demonstrated greater IOP lowering than market-leading glaucoma therapeutics
- Potential neuroprotection capabilities would be a game changer
- Key preclinical data (IOP/neuroprotection) in Q2-2021
- First clinical trial: fast; low-cost; will include assessment of intraocular pressure
- Many glaucoma licensing deals have been completed in phase 2 or earlier
To learn more please contact:

Punit Dhillon  
Chief Executive Officer  
ir@skyebioscience.com  
1 (949) 336-3437

Karam Takhar  
VP, Corporate Development & Investor Relations  
ir@skyebioscience.com  
1 (949) 336-3437