Nasdaq: SKYE

Unlocking the Pharmaceutical Potential of the Endocannabinoid System

April 2024

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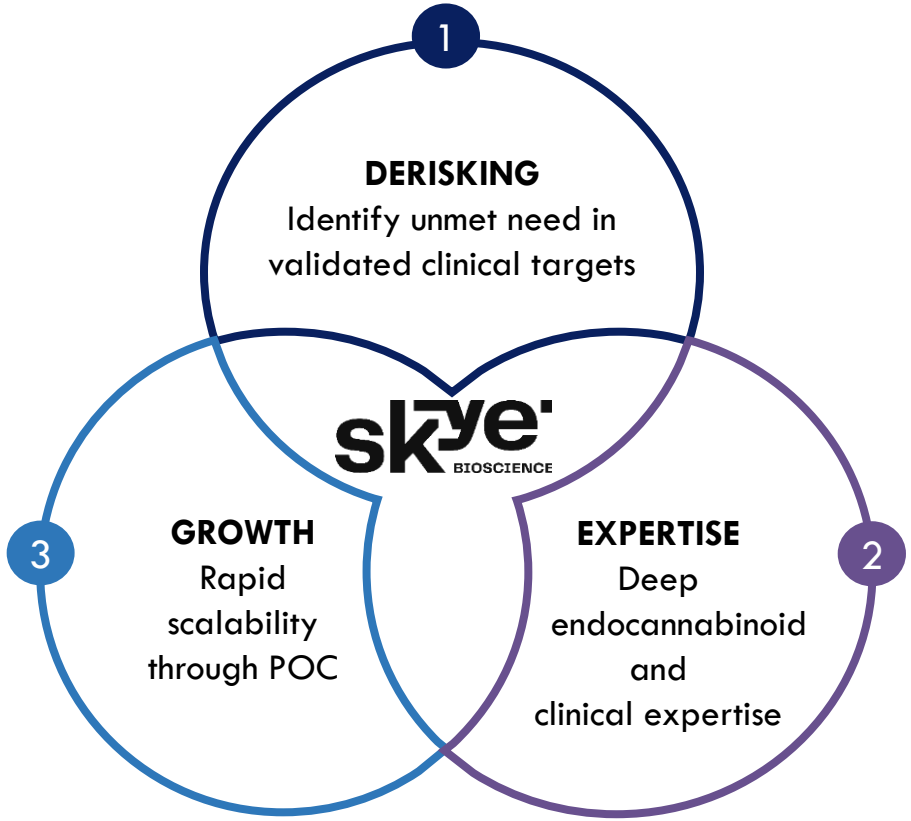
Skye is Building an Endocannabinoid System-targeting Pharmaceutical Company

Our Mission

To pioneer and lead the development of new medicines that unlock the pharmaceutical potential of the endocannabinoid system, initially through modulation of the CB1 receptor, to advance the standard of care and treatment alternatives for patients worldwide to treat diseases with neuropathic, inflammatory, and metabolic processes.

Highly productive clinical development strategy optimized for speed, probability of success

Pipeline focused on CB1 axis and potential best-in-class molecules



Convergence of Right Space, Technology and Team

ENDOCANNABINOIDS	**Endocannabinoid system** is a renewed area of interest. **Two Phase 2** differentiated, endocannabinoid-system-targeting drugs in development.
TOP TIER INVESTORS	Supported by **5AM Ventures, Versant, Perceptive, GSK, Ally Bridge, Sphera, Altium, Driehaus, and other respected investors.**
ASSETS IN CLINIC	**Nimacimab:** differentiated ***peripheral CB1 inhibitor*** targeting obesity. **SBI-100 Ophthalmic Emulsion ("OE"):** ***CB1 agonist/activator*** targeting glaucoma/ocular hypertension.
CLINICAL MILESTONES	**Multiple clinical and development milestones** across pipeline through 2024 and 2025.
LARGE COMMERCIAL OPPORTUNITIES	**Significant disease prevalence** in **targeted therapeutic areas,** addressing multi-billion commercial opportunity.
INTELLECTUAL PROPERTY	Robust **intellectual property strategy:** composition of matter protection through 2037 (nimacimab) and 2029 (SBI-100 OE).
EXPERIENCED TEAM	Highly experienced group of experts, leaders, scientists and advisors **guiding clinical development strategy.**

Leadership

Contributed to commercialization of 47+ drugs/diagnostics, led high-value strategic transactions and co-founded multiple companies

Executive Management

Punit Dhillon
CEO & Chair of BOD

Tu Diep, MSc
Chief Development Officer

Chris Twitty, PhD
Chief Scientific Officer

Kaitlyn Arsenault, CPA
Chief Financial Officer

Board of Directors

Andy Schwab
Managing Partner,
5AM Ventures

Annalisa Jenkins, MBBS FRCP
Managing Director,
Annalisa Jenkins LLC

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Praveen Tyle, PhD
Founder, Potens Pharma

Deborah Charych, PhD
Co-founder and ex-CTO,
RayzeBio

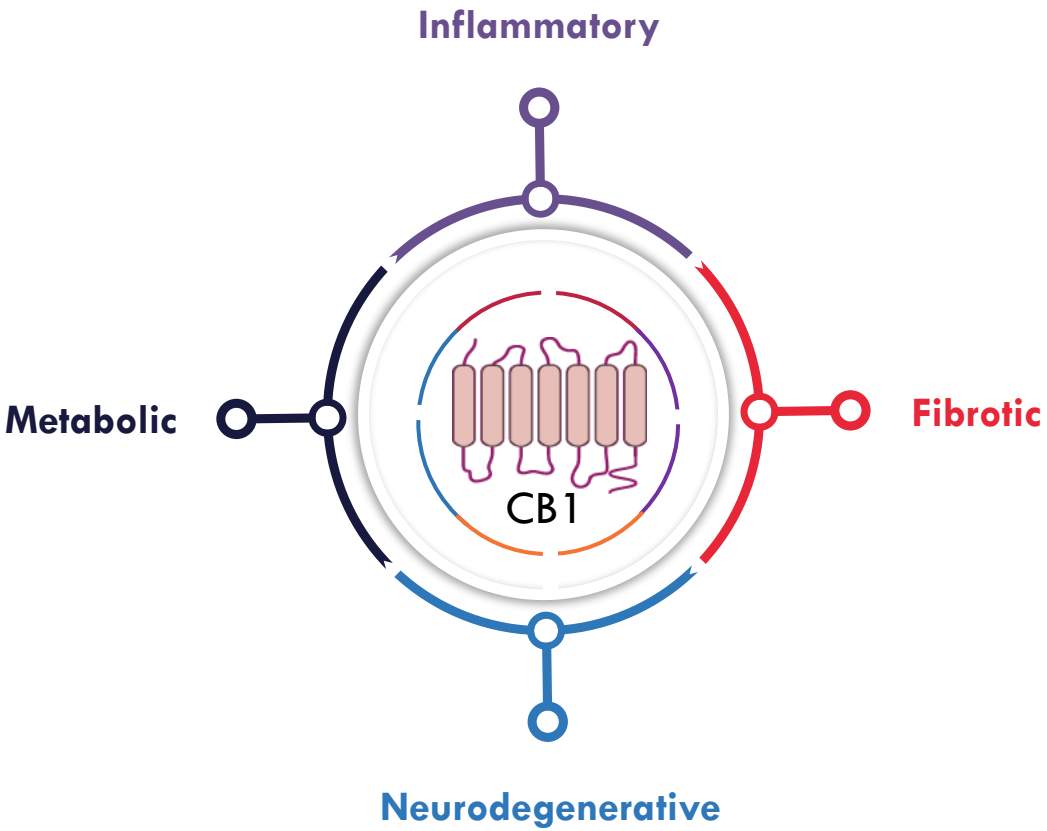
Keith Ward, PhD
Founder, Pres./CEO, & Chair,
Kuria Therapeutics

Margaret Dalesandro, PhD
Pharma. Dev. Consultant,
Brecon Pharma Consulting

CB1: High-potential Target for Physiological Regulation

CB1 is involved in many disease processes

- Cannabinoid receptor 1 (CB1) is a renewed target of interest for drug discovery.
- Modulation of CB1 signaling can impact key biological processes including:
  - Inflammatory, metabolic, fibrotic, and neurodegenerative pathways.
- CB1 plays an important role in promoting/blunting disease progression in peripheral tissues and their associated disease pathologies including:
  - Obesity
  - Various cardiometabolic diseases
  - Glaucoma



Sources: Barutta F, Bruno G, Mastrocola R, Bellini S, Gruden G. The role of cannabinoid signaling in acute and chronic kidney diseases. Kidney Int. 2018 Aug;94(2):252-258. doi: 10.1016/j.kint.2018.01.024. Epub 2018 Apr 27. PMID: 29706358.
Dao Myriam, François Helene Cannabinoid Receptor 1 Inhibition in Chronic Kidney Disease: A New Therapeutic Toolbox. Front. Endocrinol. 2021 July; 12 DOI=10.3389/fendo.2021.720734

Key Milestones Position Skye for Near Term Value Generation

Multiple data catalysts across two key programs through early 2025

References are to calendar years. All drugs are investigational and subject to regulatory approval. For investor audiences only.
1: In reference throughout presentation to primary open angle glaucoma (POAG) & ocular hypertension (OHT)

Nimacimab

Novel CB1-targeting mAb therapeutic for cardiometabolic conditions: peripheral CB1 inhibitor

Best–in-class Monoclonal Antibody	Phase 2-ready molecule with open IND for obesity/weight loss. Only CB1 negative allosteric modulating humanized monoclonal antibody (mAb) in clinic. A highly selective inhibitor of CB1, with no detectable binding to CB2 or other GPCRs. Mechanism of action has therapeutic potential in fibrotic, inflammatory and metabolic diseases.
Past Comp Clinical Development History	Rimonabant validated CB1 receptor as effective target for obesity. Past safety challenge: anxiety, depression, and suicidal ideations due to CNS exposure.
Favorable Safety Profiles	Evolved drug design. Very limited brain penetration. Encouraging safety and tolerability identified through preclinical and Phase 1 data, with no CNS issues identified.

SBI-100 Ophthalmic Emulsion

Improving CB1-targeting drug design for glaucoma

SBI-100 OE

MOA	Disease	R&D	Phase 1	Phase 2a
CB1 Receptor Agonist Topical	**Glaucoma**			

Best–in-class Molecule	First/only prodrug of THC developed and currently in the clinic for glaucoma.
Clear Clinical Endpoint	Lowering intraocular pressure (IOP) prevents subsequent progression of functional damage in the retina and is accepted as an approvable clinical endpoint.
Clinical Development History of Class	THC known to reduce intraocular pressure since 1970s.[1,2,3,4] Also known to protect against neurodegeneration.[5,6] Past safety challenge: psychotropic effects due to CNS exposure.
New Drug Design/ Improvements	New drug design, local delivery with eye drop in a novel formulation. Prodrug design for improved bioavailability in the eye. Designed for minimal or no psychotropic effect.

All drugs are investigational and subject to regulatory approval. For investor audiences only.

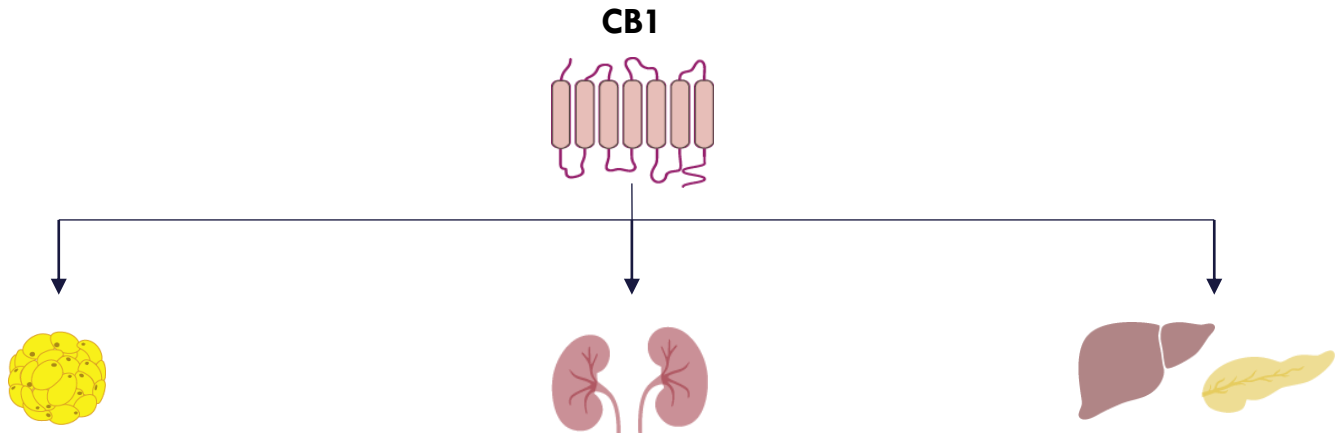
1: Hepler RS, Frank IR. Marihuana smoking and intraocular pressure. JAMA. 1971 Sep 6;217(10):1392. PMID: 5109652.
2: Hepler R.S., Petrus R.J. Experiences with administration of marihuana to glaucoma patients. In: Cohen M., editor. *The Therapeutic Potential of Marihuana*. Springer; New York, NY, USA: 1976. pp. 63–75
3: Hepler R.S., Frank I.M., Petrus R. Ocular effects of marihuana smoking. In: Braude M.C., Szara S., editors. *The Pharmacology of Marihuana*. Raven Press; New York, NY, USA: 1976.
4: Tiedeman J.S., Shields M.B., Weber P.A., Crow J.W., Cocchetto D.M., Harris W.A., Howes J.F. Effect of synthetic cannabinoids on elevated intraocular pressure. *Ophthalmology*. 1981;88:270–277. doi: 10.1016/S0161-6420(81)35052-0.
5: Crandall J., Matragoon S., Khalifa Y.M., Borlongan C., Tsai N.T., Caldwell R.B., Liou G.I. Neuroprotective and intraocular pressure-lowering effects of (-)Delta9-tetrahydrocannabinol in a rat model of glaucoma. *Ophthalmic Res.* 2007;39:69–75. doi: 10.1159/000099240.
6: Pinar-Sueiro S., Zorrilla Hurtado J.A., Veiga-Crespo P., Sharma S.C., Vecino E. Neuroprotective effects of topical CB1 agonist WIN 55212-2 on retinal ganglion cells after acute rise in intraocular pressure induced ischemia in rat. *Exp. Eye Res.* 2013;110:55–58. doi: 10.1016/j.exer.2013.02.009.

Nimacimab

Broad Metabolic Potential With Clinically Validated Mechanism of Action

Nimacimab: Differentiated Therapeutic in Obesity

Upregulation of CB1 signaling is involved in multiple inflammatory, fibrotic and metabolic diseases in various organs with significant prevalence and unmet needs



Adipose Tissue	Kidneys	Liver & Pancreas
↑ De novo fatty acid synthesis	↑ Inflammation	↑ De novo lipogenesis
↑ Triglyceride accumulation	↑ Fibrosis	↓ Insulin signaling
↓ Lipolysis		↑ Fibrosis
Metabolic Disorders/ Obesity	**Chronic Kidney Disease**	**Metabolic Disorders/ Diabetes**

Nimacimab Key Differentiators

1. Target clinically validated
2. Peripherally restricted MOA
3. 21-day ½ life supports monthly dosing
4. Preserve lean muscle mass
5. Strong rationale for incretin combination

Nimacimab in Obesity

Source: Company data.
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The Promise of CB1 Inhibition

Clinically validated MOA

sanofi

Rimonabant (Accomplia) developed by Sanofi and approved for weight loss in 2006 in EU

Demonstrated up to 10% weight loss over 1 year

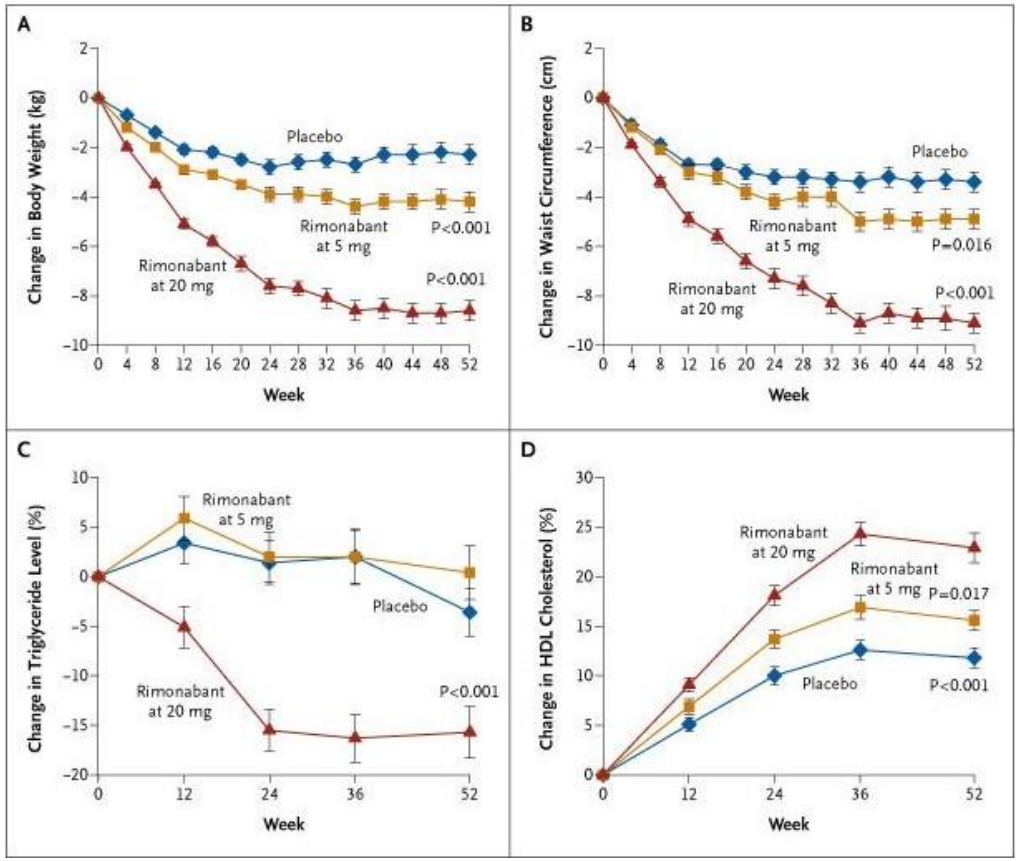
Improvements in metabolic outcomes as well

Removed from market due to CNS liabilities - depression and suicidal ideation

Resulted in multiple pharmas to drop their CB1 inverse agonist programs.

Rimonabant

RIO-lipids Phase 3 study placebo (n=342); 5 mg rimonabant (n=345); \20 mg rimonabant (n=346)



Source: Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia, Després et al, NEJM, Nov 2005.
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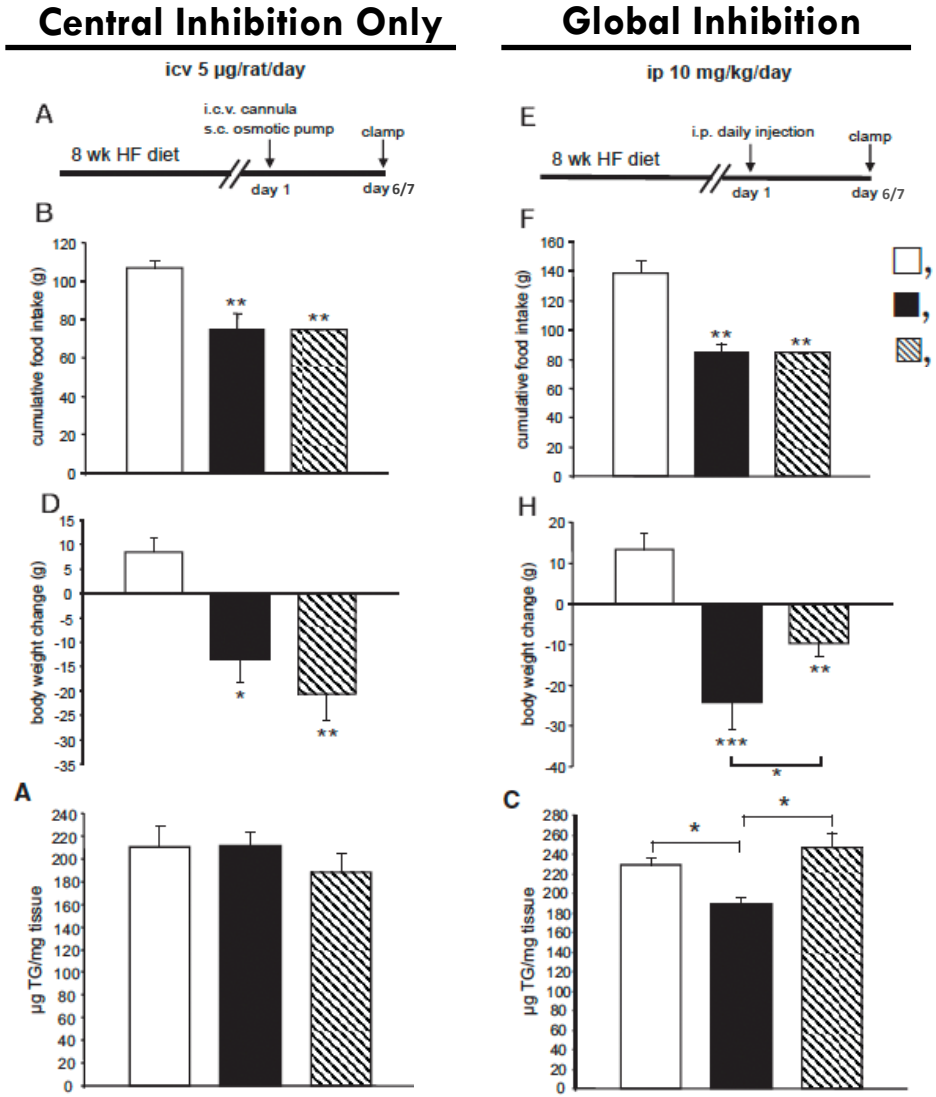
Rimonabant in the Periphery: Metabolic Benefits Beyond Caloric Restriction

Study highlights impact of peripheral CB1 inhibition

Using a DIO model with a specific vehicle arm to control for the anorexigenic effect (hashed bars = vehicle-pf) by matching the caloric intake of CB1 blockade

Blockade of peripheral, but not central, CB1 is a key driver of metabolic changes

- Body weight loss beyond caloric restriction highlights mechanisms beyond central anorexigenic effects
- Data is consistent with peripheral CB1 blockade decreasing body fat relative to mean mass



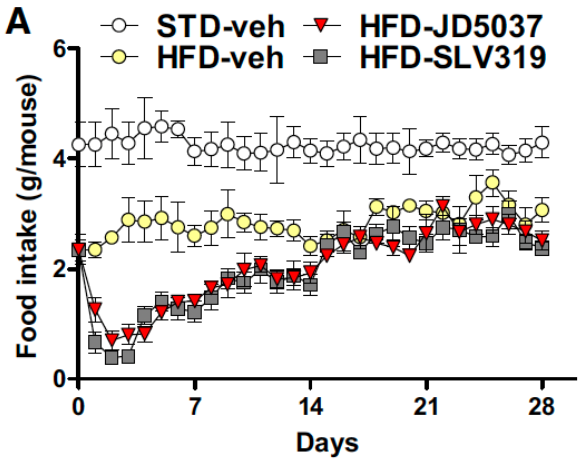
Abbreviations: DIO: a diet-induced obesity
Source: Nogueiras et al., Diabetes, 2008
For investor audiences only.

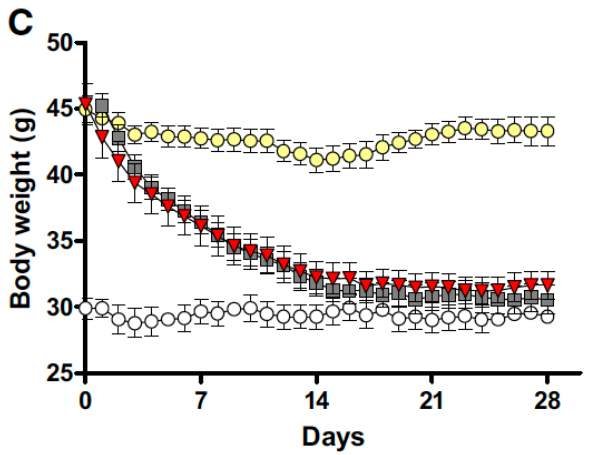
2nd Generation Peripherally Restricted CB1 Inhibitors Remain Efficacious

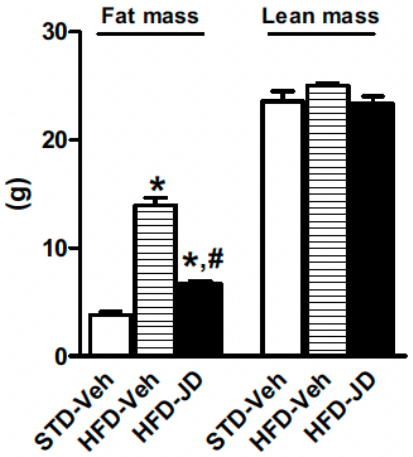
Peripherally restricted CB1 inhibitors reduce food intake and body weight (DIO model) comparable to non-restricted CB1 inhibitors

Peripheral CB1 inhibitors mediate reduction in fat mass but not lean mass

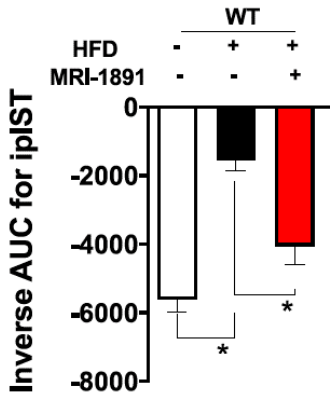
Blockade of peripheral CB1 can drive anorexigenic effects with additional metabolic gains (lean mass: body fat ratios, increased insulin/leptin sensitivity)



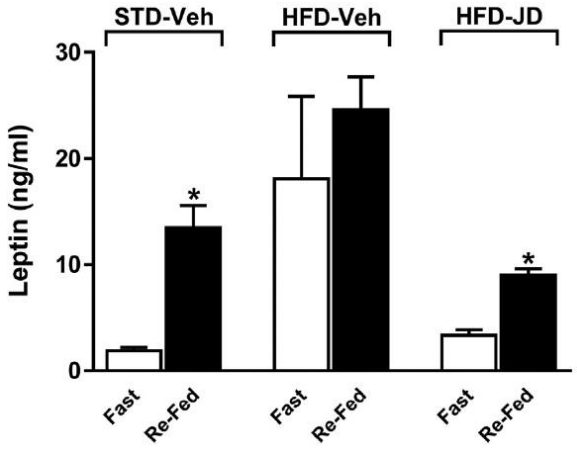


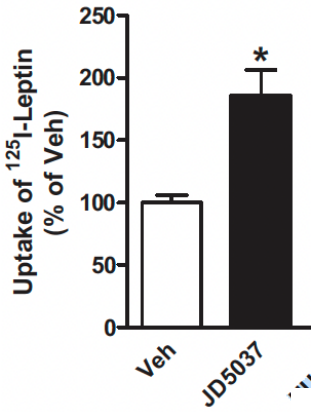


Insulin Sensitivity



Leptin Sensitivity





Source: Modified from Tam et al., Cell Metabolism 2012;Tam et al., Molecular Metabolism 2017; Liu et al., ACS Pharmacol Transl Sci. 2021
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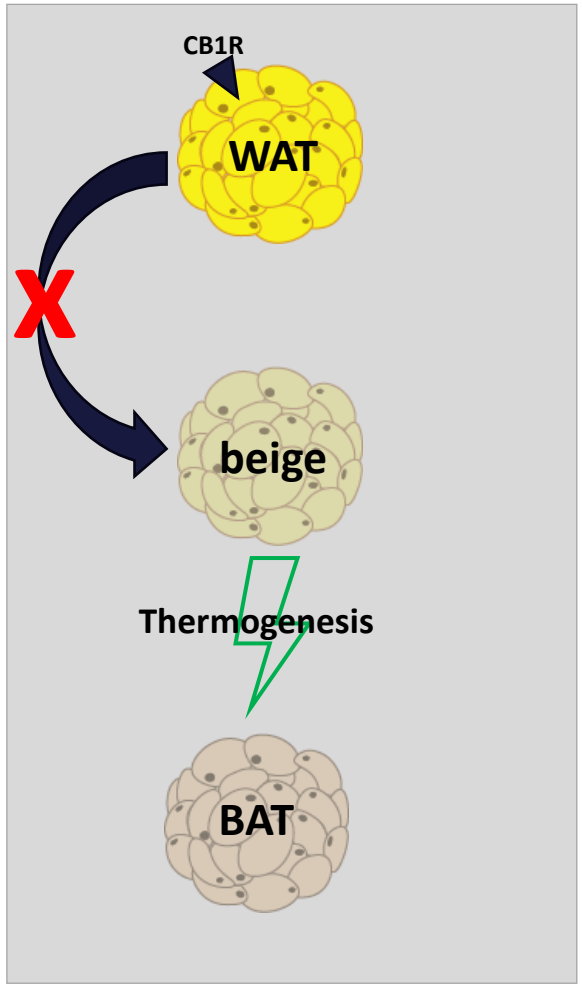
Peripheral CB1 Receptors and Fat Metabolism

Blocking CB1 potentially triggers metabolic reprogramming in adipose tissues, mediating conversion of white adipose tissue to beige adipose tissue



- The ECS is deeply involved in controlling energy metabolism.
- CB1 is highly expressed in adipose tissue and increases with obesity.
- Data suggests that blockade of CB1 could induce the trans-differentiation of white adipose tissue (WAT) towards thermogenic brown adipose tissue (BAT).
- Increase in UCP-1 expression correlated with upregulation in endocannabinoid expression.

Source: Rossi et al., Int J Mol Sci. 2018 Sep; 19(9): 2690.; Krott et al., J. Lipid Res. 2016, 57, 464–473;
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Targeting Obesity Comes in Different Flavors

CB1 impacts key metabolic pathways that complement existing products & strategies

	KEY TARGETS / MECHANISMS			
Key Targets Characteristics	GLP-1	GIP	Glucagon	CB1
Decreases Appetite / Increases Satiety	✓	? *(limited)*	x	✓
Delays Gastric Emptying	✓	x	✓ *(limited*	x
Stimulates Insulin Secretion	✓	✓	✓	✓ *(limited)*
Insulin/Leptin Sensitivity	x	x	x	✓
Lean Mass Preservation	x	x	x	✓
Tolerability	x	x	x	✓
Key Safety Concerns	Nausea, vomiting, diarrhea	Nausea, vomiting, diarrhea	Increased heart rate, LFT, glucose	Neuro-psychiatric symptoms
Other Notable Considerations	Reduces glucagon secretion	Perceived synergistic in CNS w/ GLP1	Metabolic benefits/mimic exercise	Complements incretin backbone

Opportunities for Nimacimab

- ✓ Magnitude and sustainability of weight loss
- ✓ Safety/tolerability profile (e.g. GI side effects)
- ✓ Frequency of drug administration
- ✓ Need for dose titration (PK/PD)
- ✓ Maintenance dose / setting
- ✓ Combinability with other mechanisms / agents

Prescribers/patients/payors will consider multiple different product attributes based on individual needs

Abbreviations: GLP-1: glucagon-like peptide-1; GIP: glucose-dependent insulinotropic peptide; LFTs: Liver Function Tests
Source: Company Data; Guggenheim Obesity Report
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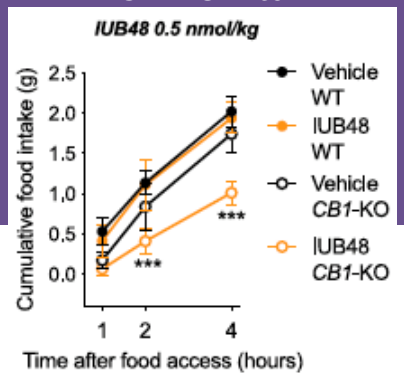
Preclinical Rationale for Combination of CB1 and GLP-1

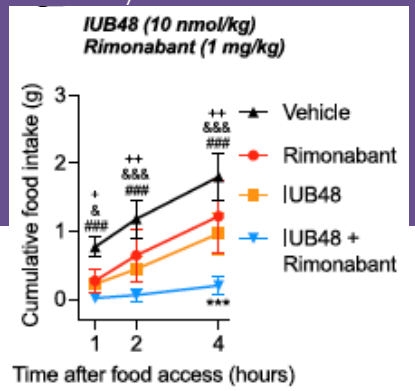
Complementary pathways may provide additive therapeutic effects for GLP-1 agonists

CB1 and GLP-1-dependent caloric restriction

CB1 KO mice

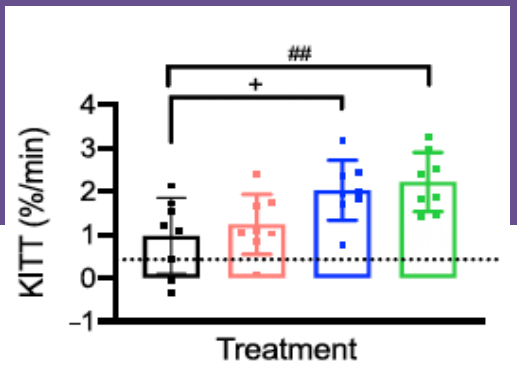


+/- Rimonabant



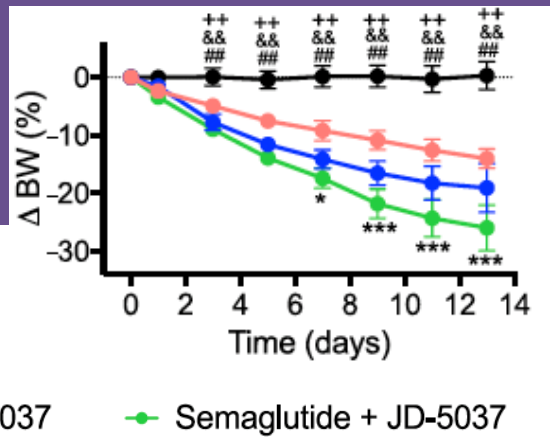
- Knockout mice and small molecule blockade both suggest that CB1 may augment anorexigenic effect of GLP-1
- Consistent with clinical data that associates CB1 signaling with reduced incretin secretion[2]

Increased insulin sensitivity with CB1 inhibition



- CB1 blockade may drive key orthogonal metabolic pathways
- In addition to leptin sensitivity, insulin sensitivity may further augment more durable metabolic gains

Significant weight loss with combination



- Both semaglutide and CB1 inhibitor drive weight loss
- Combination data suggest that effects may be driven by non-overlapping MOA

Nimacimab: Development Plan for Obesity

Phase 1 Clinical Data and Phase 2 Update

Nimacimab Biodistribution

Little to no accumulation in the brain

Cyno	Day 1 (post 1st dose)	Day 8 (post 2nd dose)	Day 15 (post 3rd dose)
CSF/Serum 3 mg/kg IV q1w	BLQ	<0.02%	<0.02%

Cyno	9 hours
CSF/Serum 40 mg/kg IV	0.01%

Level in CSF determined using quantitative ELISA at the time points studied.

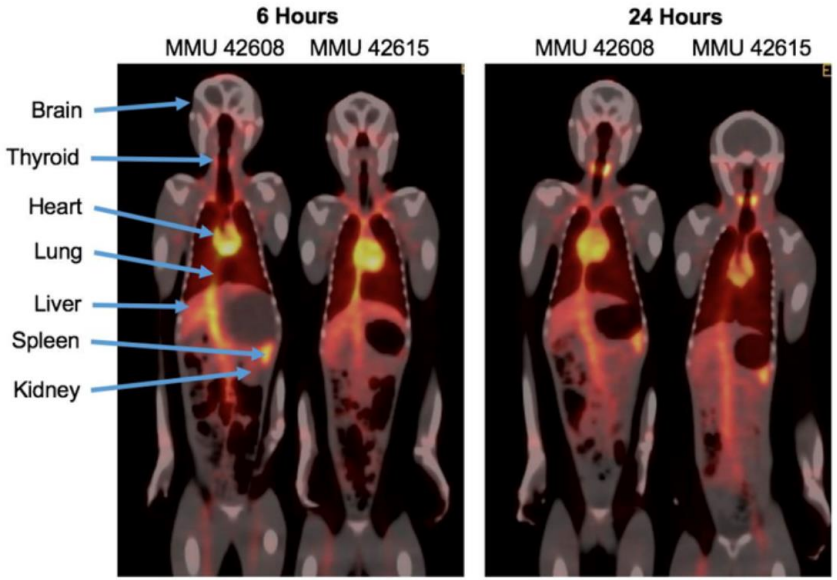
Rhesus	48 hours
CSF/Plasma	0.05%
Prefrontal Cortex/Plasma	0.83%
Cerebellum/Plasma	0.84%
Liver/Plasma	16.44%

Uptake of isotope^{124}-labeled nimacimab antibody in tissues at the timepoints studied. PET imaging also confirmed no accumulation in brain

- Tissues harvested without perfusion
- Tissue to plasma assuming 1 mL = 1 g

Little to no nimacimab found in the brain

High levels of nimacimab found in the plasma at 24 hours



Source: Company data. BLQ: Below limit of quantification; CSF: Cerebrospinal Fluid
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Nimacimab Toxicology – NOAEL > 75 mg/kg

IND-enabling toxicology studies: safe with significant safety window established

- **4-week study in cynomologus monkeys completed with up to 75 mg/kg nimacimab administered weekly IV**
    - No nimacimab-related observations in toxicology assessments performed including neurological observations.
- **Three-week and 26-week toxicology studies cynomologus monkeys completed with up to 75 mg/kg nimacimab administered bi-weekly subQ.**
    - No nimacimab-related clinical signs or changes in ophthalmology, electrocardiography, blood pressure, blood chemistry, hematology and histopathology.
    - NOAEL of > 75 mg/kg.
    - Long half-life of ~21 days and high exposure at the end of the study.

Source: Company data. NOAEL: No Observed Adverse Effect Level
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Nimacimab Phase 1 Data

Demonstrated encouraging tolerability, pharmacokinetics and encouraging evidence of efficacy

- SAD
  - 24 healthy volunteers enrolled (18 subjects used as PK population)
  - 0.6 mg/kg, 1.2 mg/kg and 2.5 mg/kg administered IV over 30 minutes
- MAD
  - 82 **patients** enrolled **with NAFLD (diabetic/pre-diabetic)**
  - 0.6 mg/kg, 1.2 mg/kg and 2.5 mg/kg administered IV over 30 minutes on weeks 0, 1, 2 and 3
- PK: 18-22 days
- ADA < 10% of subjects dosed
- No neuropsychiatric side effects
- Biomarkers
  - Significant dose-dependent reduction in LDL-c observed at day 67; **reduction** of 7.4% (2.5 mg/kg) vs. **increase** of 8.2% in placebo from baseline (p=0.0073)
  - Significant change in hyaluronic acid (HA) along with additional trends in reduction of markers of inflammation and fibrosis

SKYE has received FDA clearance of its IND for a Phase 2 clinical trial for nimacimab in obesity

Rimonabant – A Closer Look at Safety

Beyond psychiatric adverse events, rimonabant safety compares favorably to GLP-1RAs

Rimonabant was generally well-tolerated, especially as it relates to gastrointestinal adverse events compared to GLP-1RAs.

	Rimonabant[1]	Semaglutide[2]
Gastrointestinal disorders	**30.4%**	**74%**
Nausea	4.9%	44.2%
Diarrhea	4.8%	31.5%
Vomiting	2.2%	24.8%
Rate of discontinuation due to GI disorders	0.1%	4.5%

CB-1 inhibition appears to be better tolerated than GLP-1RAs, especially when comparing GI disorders, which are the most frequent adverse events related to GLP-1RAs.

Safety profile of CB-1 inhibitors, like rimonabant, coupled with lack of CNS penetration of nimacimab suggests that nimacimab will have superior safety compared to GLP-1RAs and older generations of small molecule CB-1 inverse agonists.

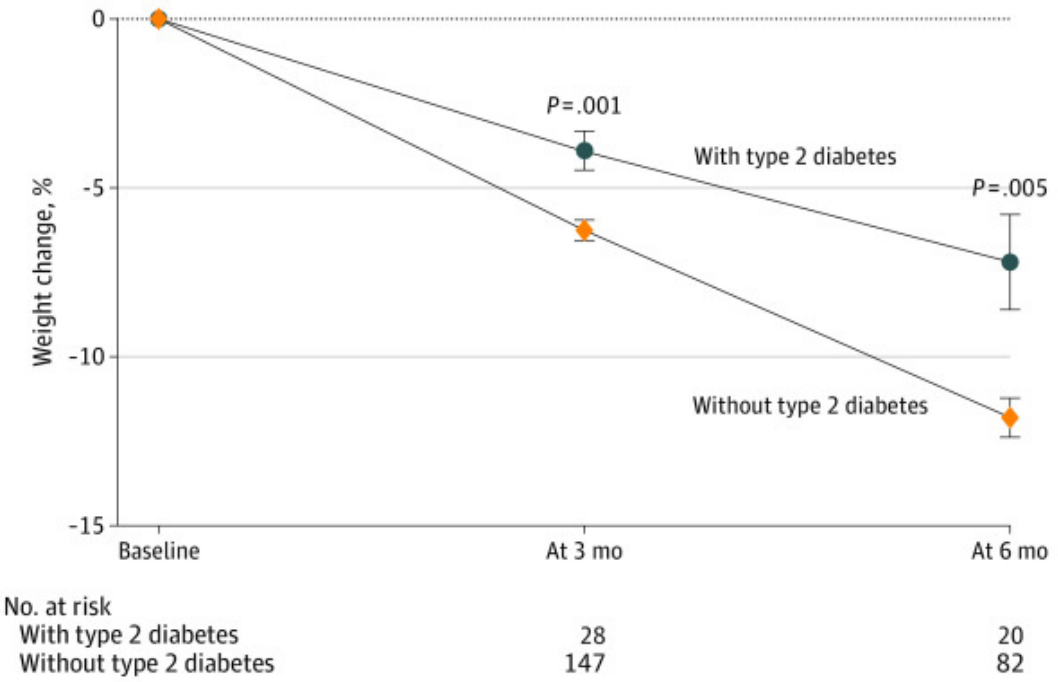
skye BIOSCIENCE

1 Van Gaal et al., Efficacy and Safety of Rimonabant for Improvement of Multiple Cardiometabolic Risk Factors in Overweight/Obese Patients. Diabetes Care, Vol. 31, SUPPLEMENT 2, FEB 2008
2 Wilding et al., Once-Weekly Semaglutide in Adults with Overweight or Obesity. New Eng J Med, 384;11, 2021

Why Did Weight Not Change in Phase 1 NAFLD Study?

Body composition phenotypes are highly heterogeneous based on type of disease

- Phase 1 study enrolled NAFLD patients who were both diabetic and pre-diabetic
    - 83% diabetic; 17% pre-diabetic
- Novo studies using semaglutide in patients with diabetes consistently demonstrate patients lose less weight and at a lower rate than non-diabetic patients
    - STEP 3 and 4
    - SUSTAIN 1, 2, 3, 4 and 5
- Ghusn et al. (2022) evaluated 2.4 mg dose of semaglutide and demonstrated weight loss at 3 and 6 months was only 3.9% and 6.2%
- We believe the encouraging signs in LDL and other biomarker parameters are an indication that nimacimab is effective
- At 1 month (4 weeks), we do not believe weight loss in this heavily diabetic and co-morbid population would be expected



Source: Company data.
Guhsn et al., JAMA 2022 Sep; 5(9)
Ahren et al., Diabetes Obes Metab.2018;20
Rubino et al., JAMA. 2021;325(14):1414-1425
Wadden et al., JAMA. 2021;325(14):1403-1413
For investor audiences only.

Nimacimab Bioavailability Study

Intravenous versus subcutaneous dosing

Study Design:

- Single 100 mg SC dose vs. single 100 mg IV dose of nimacimab
- 10 subjects dosed SC vs. 10 subjects with IV

Conclusions:

- Absolute bioavailability approximately 60% after a single dose
- No new trends in safety parameters
- As expected, slower absorption for SC than IV dosing
- SC dosing in Phase 2 enabled
- Similar ADA effect on PK (10%-20%) of subjects in IV and SC groups

Source: Company data. SC: sub cutaneous; IV: intravenous
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Proposed Phase 2 Clinical Trial Design: CB1/GLP1 Combo in Obesity

Key Inclusion Criteria

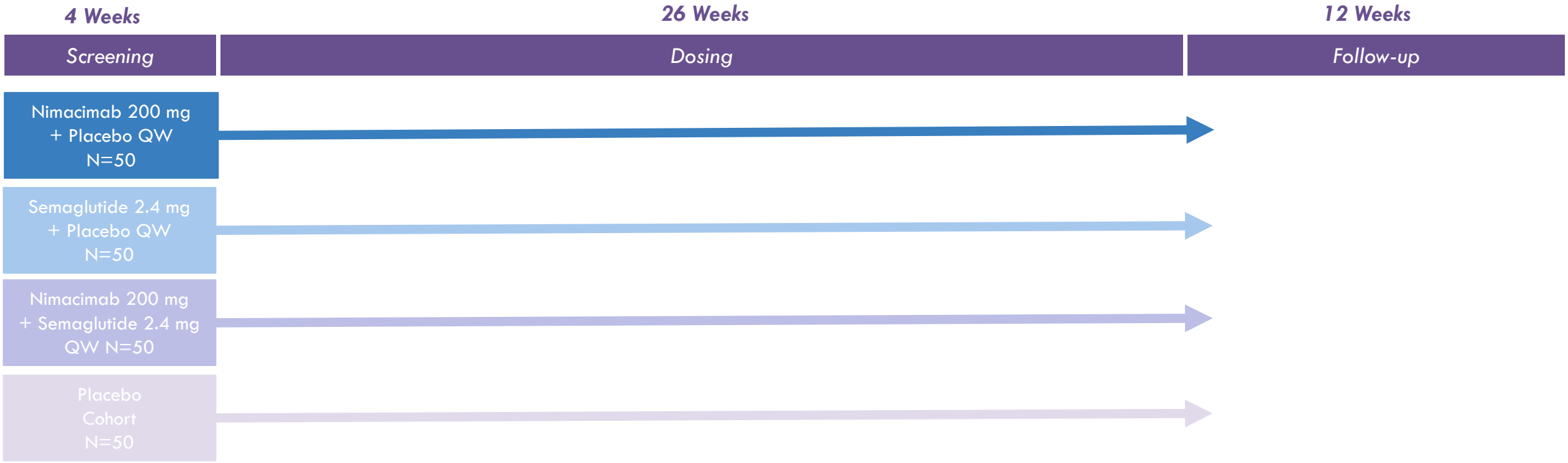
- Obese: BMI ≥ 30 kg/m^2
- Overweight: BMI ≥ 27 with at least one weight-related co-morbidity
- Stable body weight for at least 3 months prior to study
- HbA1c <6.5%

Primary Endpoint

- Percent change in weight from baseline at week 26

Secondary Endpoint

- Safety and tolerability
- Change in waist circumference
- Change in body composition
- Change in fasting triglycerides and cholesterol
- Change in A1c



Source: Company data. BMI: Body Mass Index; HbA1c or A1c: Hemoglobin A1c
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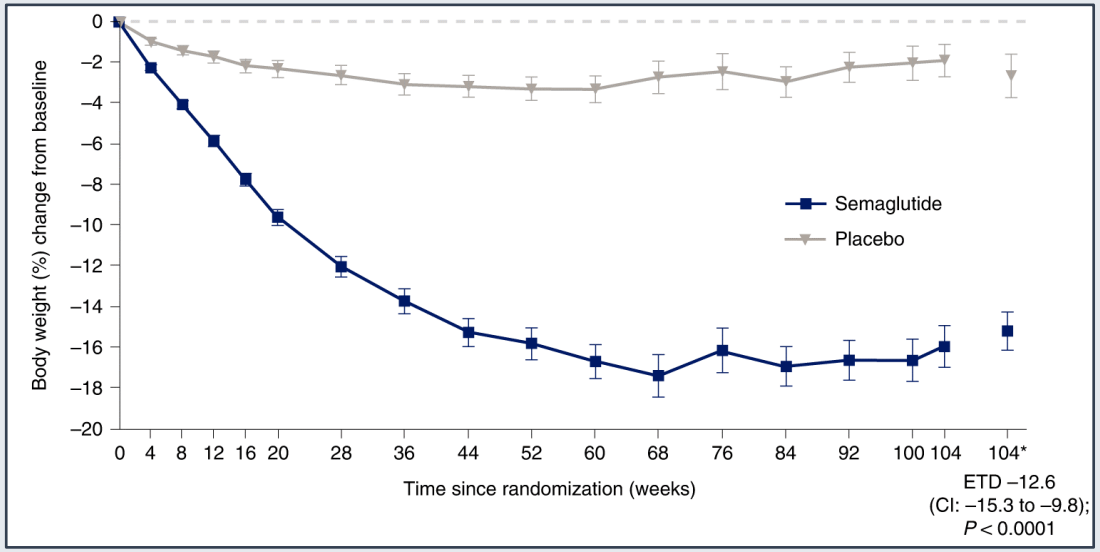
Challenges Associated with Long-Term Use of GLP-1 RA Treatment

Plateau and rebound effect

Considerations of Long-term Treatment with GLP-1 Receptor Agonists

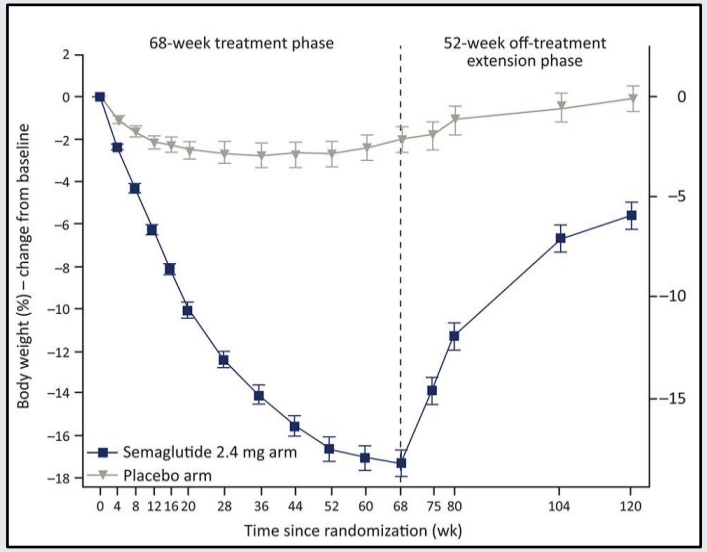
STEP 5: Durability of Weight-loss Over 2 Years



Garvey et al., Nat Med. 2022

- The STEP-5 trial demonstrated patients treated with semaglutide were able to achieve significant weight loss over the first 68 weeks
- After 68 weeks of treatment, additional treatment w/ semaglutide did not result in additional weight loss as weight plateaued

STEP 1 Trial Extension: Withdrawal of Semaglutide



Wilding et al., Diabetes Obes Metab. 2022

- Results from the STEP 1 trial extension showed that withdrawal of semaglutide was associated with weight gain
- Approximately 1-year after treatment withdrawal, most patients had regained ~66% of the weight initially lost on treatment

Abbreviations: RA: Receptor Agonist
Sources: Garvey et al., 2022. Wilding et al., 2022.
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GLP-1 RA Effects on Muscle Wasting

Opportunities for improvement

Clinical Data

- As the FDA has not required body composition as a primary endpoint in weight loss studies, **data surrounding GLP-1's effect on lean body mass and skeletal muscle is lacking**
- **Lean loss is inevitable with significant weight reduction;** ~25% lean body weight loss is typical
- From sub-studies of 178 and 140 semaglutide-treated patients in SUSTAIN and STEP trials, **lean mass accounted for ~40% of total weight loss**
- As the FDA suggests only a minority of trial participants should receive body composition measurements, the **muscle atrophy effect is unlikely to prevent products from reaching market**
- **Despite the incomplete data, muscle atrophy is highly publicized and frequently cited as a danger of GLP-1 treatment**

General sentiment from health commentators

Ongoing Collaborations

- **Lilly and Bioage Labs announced a collaboration** (Oct 2023) to conduct a Phase II trial to assess weight loss for patients treated with Mounjaro (tirzepatide) in combination with BGE-105 (azelaprag)
- BioAge previously presented clinical data showing that azelaprag **prevented muscle atrophy in older healthy volunteers** who were placed on 10 days of strict bed rest
- In preclinical mice models, **administration of tirzepatide + azelaprag was linked to healthier weight loss than tirzepatide alone**
- **Lilly** also **recently acquired Versanis** which is **testing** their **product in combination with semaglutide for its ability to preserve muscle mass during weight loss**

Source: Fierce Biotech, 2023; McCrimmon et al., 2020; FDA Guidance, 2007;
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Nimacimab Clinical Development Summary

Broad metabolic potential

- **Nimacimab has significantly improved peripheral restriction than INV-202**
  - Potentially better safety
- **Nimacimab has potential to treat multiple metabolic indications**
  - Rimonabant demonstrated clinical efficacy of CB1 inhibition in obesity
  - Preclinical data demonstrate peripheral CB1 inhibition independent of central control in metabolic benefits
  - Multiple clinical/preclinical data demonstrating CB1 expression and relevance in inflammatory and fibrotic mechanisms of disease
- **Phase 2 clinical trial design places nimacimab (CB1) + GLP1 combo ahead in development for obesity indication**
  - Phase 2 design provides signal detection across multiple metabolic-related biomarkers
- **Obesity market is nascent and constantly changing with better understanding of impacts on long-term use of GLP-1 receptor agonists**
  - Combination opportunities
  - Post-GLP-1 RA failure opportunities

SBI-100 OE

Significant Unmet Needs in Glaucoma with Opportunity for New Class of Medicine

SBI-100 OE Phase 1 Safety Profile/Data Summary

Good Safety Profile: Generally safe and well-tolerated. No participants dropped out due to SBI-100 OE.

Transient Discomfort: Main side effect is discomfort/pain upon drop instillation, but average duration of discomfort was less than 15 minutes.

Lack of Systemic Side Effects: Little to no presence of THC in plasma following multi-day dosing supports lack of systemic side effects observed in Phase 1 study.

Minimal Hyperaemia: Little to no hyperaemia compared to other leading classes of drugs.

Efficacy: IOP data suggests encouraging activity in participants with high baseline IOP (>17 mmHg)

SBI-100 OE Phase 2 Glaucoma Proof-of-Concept Study

Primary open-angle glaucoma and ocular hypertension; dosed 56 patients, of 54 planned topline data Q2

Key Inclusion Criteria

21mmHg ≥ IOP < 34mmHg

No prior surgical interventions for POAG or OHT

Primary Endpoint

Change in diurnal IOP vs placebo

Secondary Endpoint

Safety and tolerability

Evaluation of psychotropic effects

Change in diurnal IOP from baseline

Exploratory biomarkers

Source: Company data. BID: bis in die or twice a day; IOP: Intraocular pressure; mmHg: millimeters of mercury, a unit of measurement of pressure
For investor audiences only.

Summary

Capitalization

Cap Table: December 31, 2023[1]		
Common shares o/s[2]		12.3 M
Options and RSUs		1.3 M
Warrants		3.3 M
Convertible note (as-converted basis)		1.0 M
Common shares f/d		17.9 M
Float[3]		3.2 M
Financings: Jan 31, 2024 [a] and Mar 13, 2024 [b]		
Common shares (unregistered) [a]	@ $2.305	11.8 M
Pre-funded warrants (unregistered) [a]	@ $2.3049	10.0 M
Common shares (unregistered) [b]	@ $10.00	4.0 M
Pro Forma Aggregates		
Pro forma o/s (Dec 31 + Jan/Mar financing common)		28.1 M
Pro forma f/d (Dec 31 + Jan/Mar financings)		44.7 M

Capital	
Cash & cash equivalents: Dec 31, 2023[1]	$1.3 M
Gross proceeds from 2024 PIPE financings	$90.0 M
Restricted cash posted as appellate bond[1]	$9.1 M
Convertible note repayable August 2024[1]	$5.0 M
Ticker: SKYE (Nasdaq)	
Avg. daily volume (3-month average)[4]	28.9 K
Market cap (pro forma o/s)[4]	$359.4 M
~ 21 inst investors, $102M invested via 3 PIPEs	~ 86 %

1 Per 2023 10K filing
2 Bulk of 8.4 M August 2023 acquisition/financing shares restricted to Aug 2024
3 Excludes restricted/unregistered shares.
4 Based on share price 24/04/10

Skye Next Steps

- Advance nimacimab into clinical trials
- Demonstrate IOP-reducing proof-of-concept for SBI-100 OE
- Maintain focused operational and clinical development strategy

Expected Clinical Development Milestones

2024

- ☑ SBI-100 OE Phase 2a completed enrollment – Q1
- ☑ Nimacimab obesity IND clearance – Q1
- SBI-100 OE Phase 2a topline data – Q2
- Nimacimab Phase 2 obesity clinical trial initiation – mid-'24
- Planned SBI-100 OE Phase 2b glaucoma study initiation – Q4
- ☑ Continued in vivo studies, biomarker development, next-gen efforts

2025

- Nimacimab interim data with partial enrollment – Q1
- Nimacimab topline data – Q4

Thank you

Learn more, please contact:

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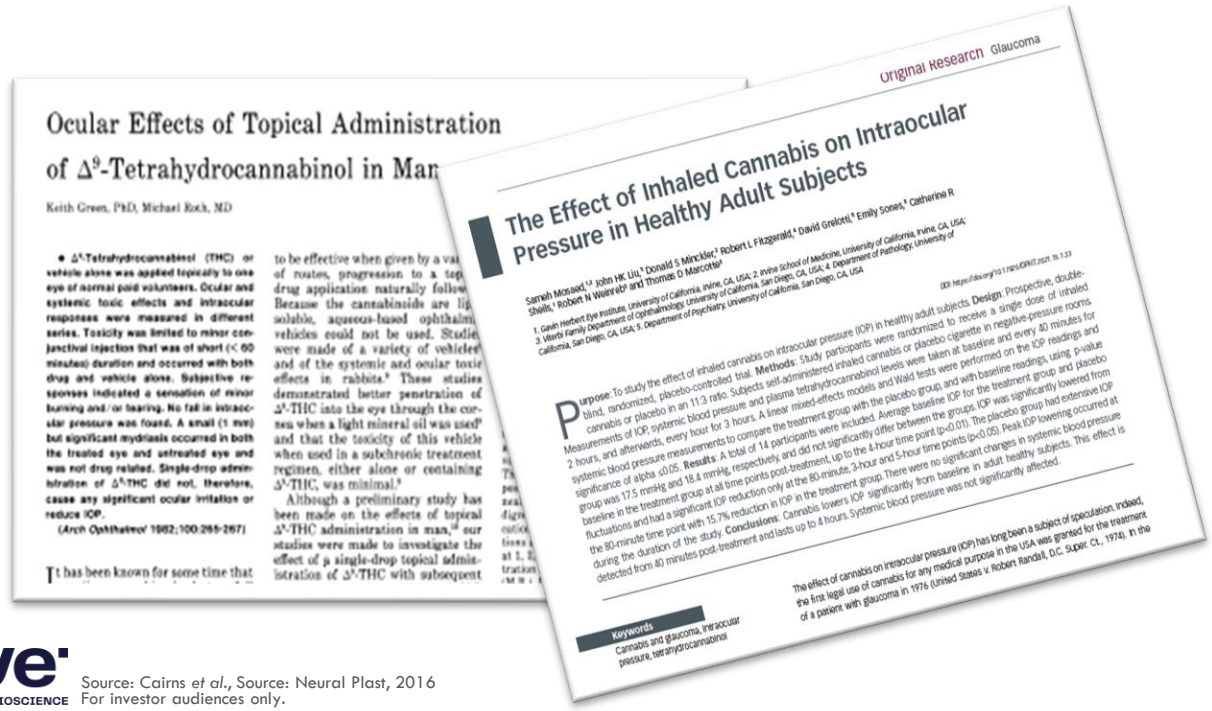
CB1 Agonism as New Therapeutic Class to Treat Glaucoma

Reduced IOP and associated mechanisms suggest potential for a novel therapeutic

- Research with THC and other CB1 agonists have highlighted relevant mechanisms to support the use of cannabis as a treatment option
- Multiple clinical trials demonstrate the use of cannabis to reduce IOP
- ***Significant hurdles*** have prevented meaningful development
  - Side effects with inhalation/systemic delivery
  - Solubility, stability and bioavailability

CB1 is expressed in key ocular tissues and its engagement[1]:

- Reduces aqueous humor ("AH") production
- Promotes AH outflow
- Supports neuroprotection



Ocular Effects of Topical Administration of Δ^9-Tetrahydrocannabinol in Man

Keith Green, PhD, Michael Rock, MD

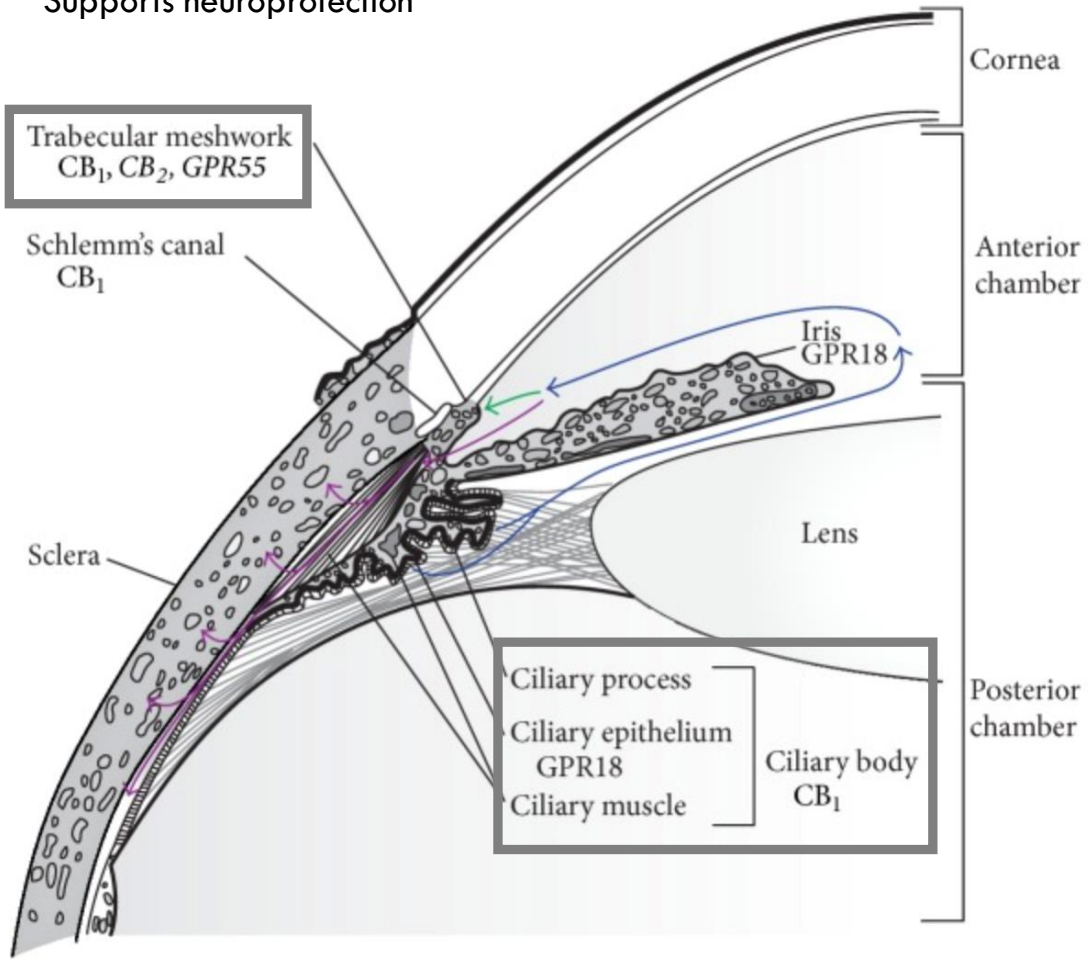
Arch Ophthalmol 1982;100:265-267

Original Research Glaucoma

The Effect of Inhaled Cannabis on Intraocular Pressure in Healthy Adult Subjects

Sameh Mosaed,[1,2] John HK Liu,[1] Donald S Minckler,[2] Robert L Fitzgerald,[4] David Grelotti,[4] Emily Sones,[3] Catherine R Sheils,[1] Robert N Weinreb[1] and Thomas D Marcotte[4]

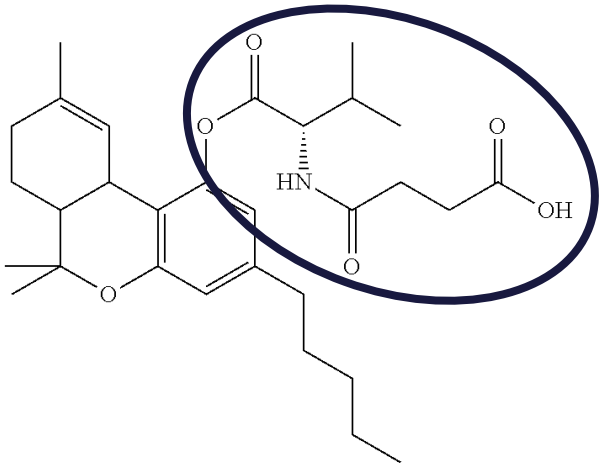
Keywords: Cannabis and glaucoma, intraocular pressure, tetrahydrocannabinol



Source: Cairns *et al.*, Source: Neural Plast, 2016

SBI-100 Ophthalmic Emulsion: Synthetic THC-based Prodrug

Prodrug technology and novel formulation addresses hurdles with THC therapeutics

DESIGN FACTOR	RATIONALE	SBI-100 STRUCTURE
Tetrahydrocannabinol (THC)	Therapeutic backbone is not water soluble and has poor bioavailability.	
Prodrug design	Improves solubility, stability and bioavailability. Prodrug moiety is rapidly released once inside the eye.	
Prodrug moiety (valine-hemisuccinate)	Valine-hemisuccinate is added to THC in a scalable and proprietary synthetic method under GMP control.	
Nanoemulsion formulation (ophthalmic emulsion)	Improved delivery of SBI-100 into multiple structures of the eye.	

Chemical Formula: $C_{30}H_{43}NO_6$
Molecular Weight: 513.6655
THC-valinate-hemisuccinate (15)

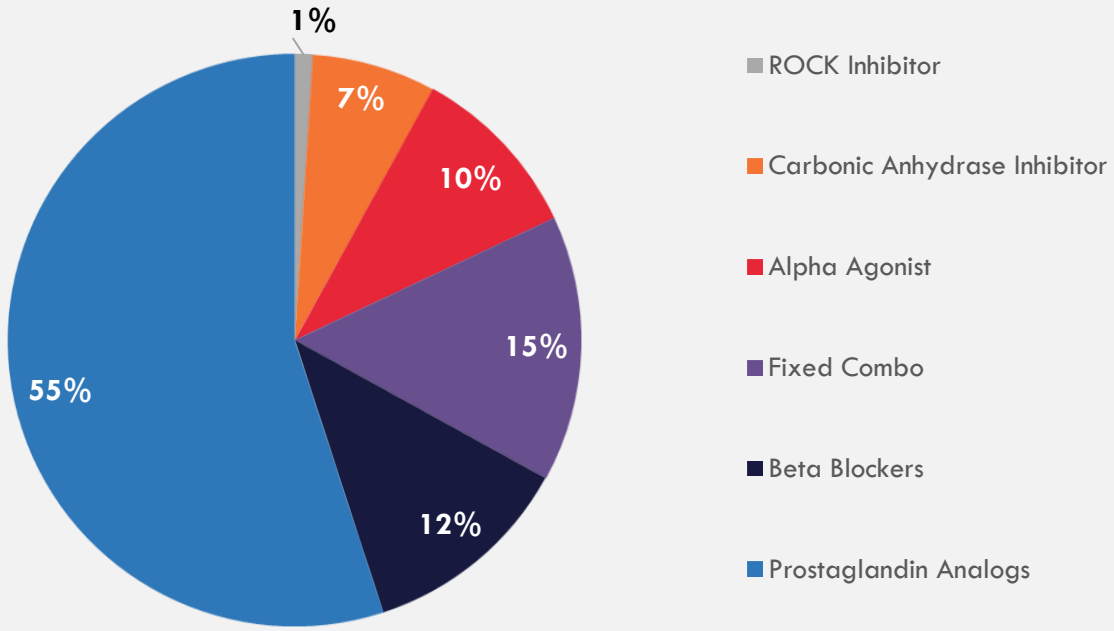
Targeting Glaucoma (POAG & OH): Large Market, Unmet Needs

A leading cause of irreversible blindness worldwide

$7B	Overall glaucoma drug market worldwide (2020)
~69M	Patients POAG patients worldwide (2020)
~112M	Estimated patients (all glaucoma) worldwide (2040)
40%	Fail 1st line therapy
50%	Require 2 therapies
~7.1M	US prevalence of OH patients[3]

MARKET LACKS INNOVATION

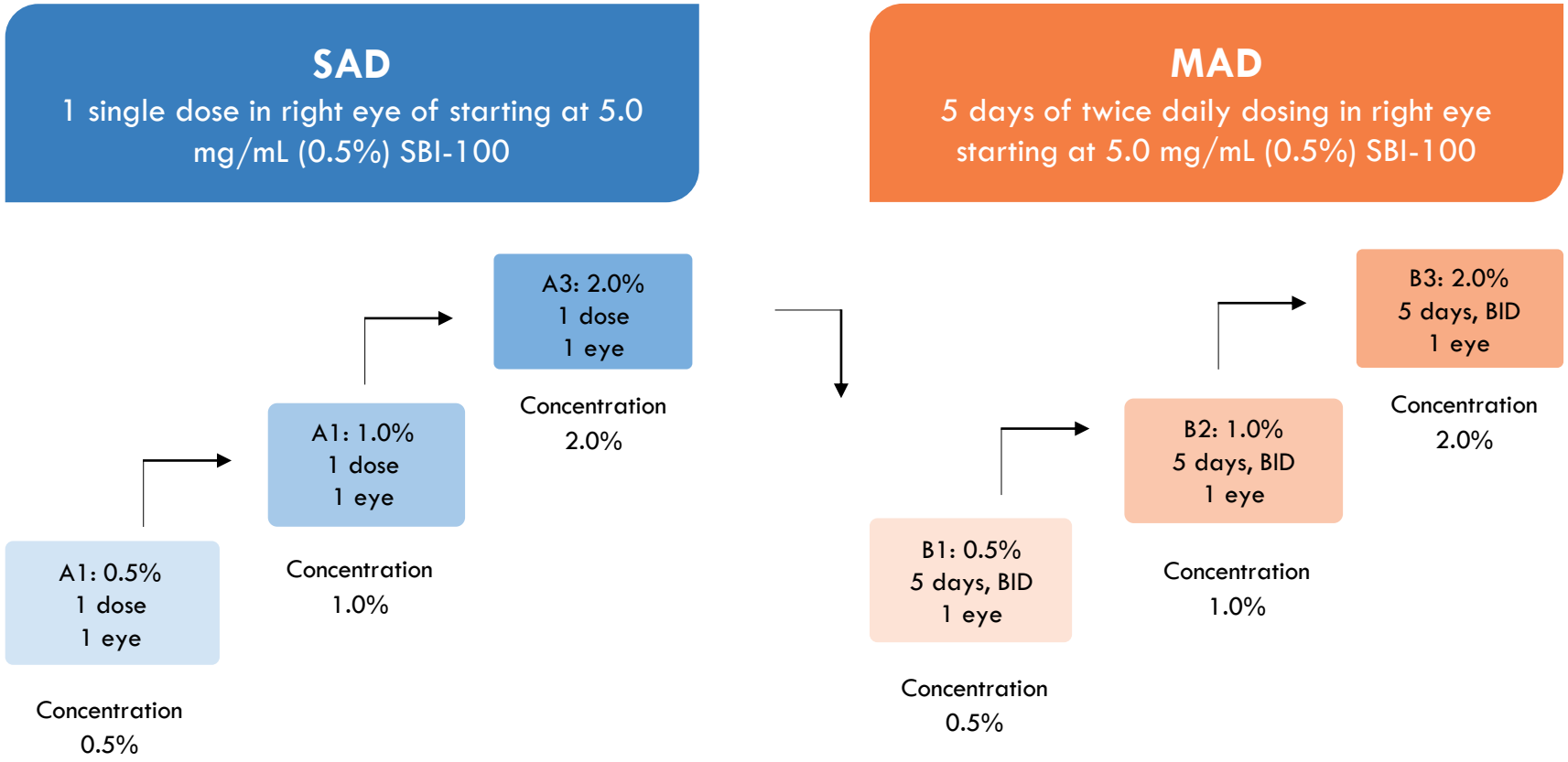
Predominantly using legacy classes of drugs and generic compounds.



Sources: Kass et al 2010; Vantage Market Research: Glaucoma Medications Market Global Industry Assessment & Foreast (2021); Zhang et al, 2021; Tham et al 2014. LifeSci Primary Market Research (N=10 U.S. KOL Ophthalmologists, N=5 U.S. payors, N=3 Strategics); For investor audiences only

Phase 1 Clinical Trial – SAD/MAD Randomized Placebo-Controlled: Completed

- Randomized, placebo-controlled study in up to 48 healthy volunteers across 6 treatment cohorts.
- Primary objective: establish safety and tolerability of single ascending and multiple ascending doses of SBI-100 Ophthalmic Emulsion relative to placebo



Pharmacokinetics – Little to no Exposure of THC in Plasma

MAD PK population

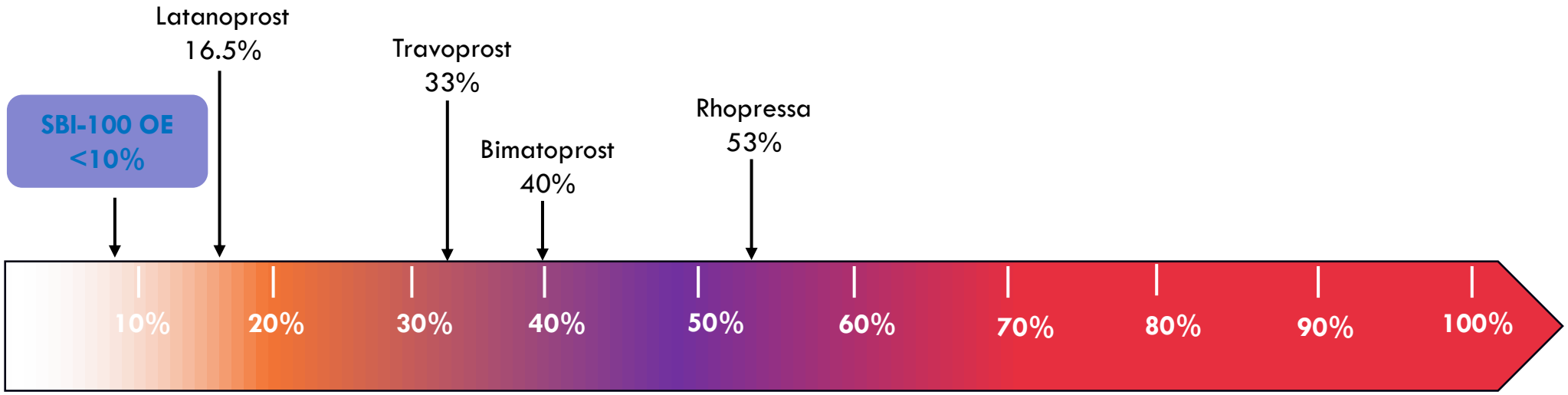
	0.5% SBI-100 N=6	1.0% SBI-100 N=6	2.0% SBI-100 N=6
Day 1 PK Parameters, Mean (SD)			
AUC (h*ng/mL) SBI-100	0.9184 (0.4252)	0.8252 (0.2533)	2.131 (1.139)
Cmax (ng/mL) SBI-100	0.2742 (0.07336)	0.2973 (0.1103)	0.7202 (0.3403)
Day 5 PK Parameters, Mean (SD)			
AUC (h*ng/mL) SBI-100	3.003 (1.014)	1.948 (0.6637)	4.459 (3.025)
Cmax (ng/mL) SBI-100	0.5066 (0.1285)	0.4875 (0.1587)	0.8672 (0.6459)
Tmax (h) SBI-100	0.500 (0.000)	0.417 (0.129)	0.550 (0.274)

- SBI-100 OE was detected in plasma of all cohorts.
- However, THC and its more psychoactive metabolite 11-OH-THC were not detected across all cohorts (except one patient in the 1.0% SBI-100 OE cohort [M2-04]).
- Lack of THC and 11-OH-THC detected in plasma support the minimal systemic side effects observed.

SBI-100 OE Demonstrates Significantly Less Hyperaemia Compared to Other Therapies

Hyperaemia (red eyes) has notable impact on patient adherence to drug regimen

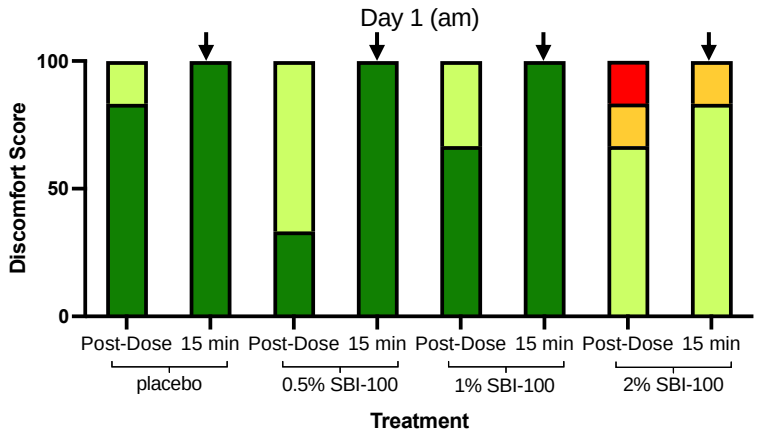
Incidence of hyperaemia in SBI-100 OE vs. currently approved drugs

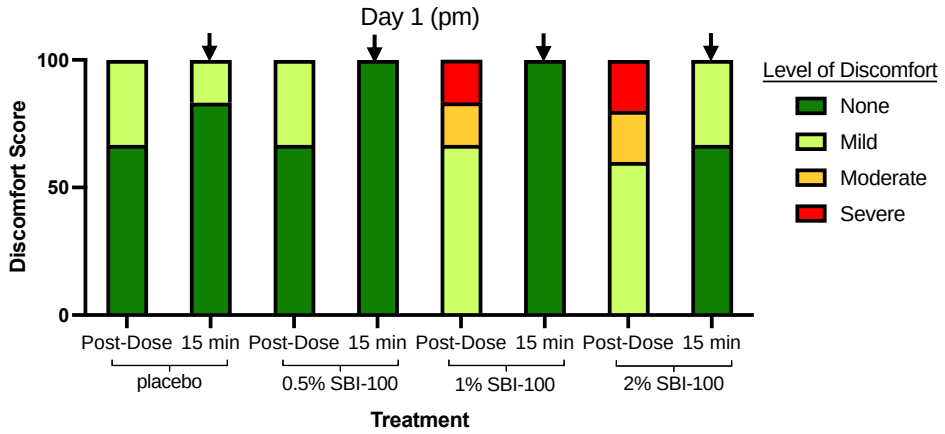


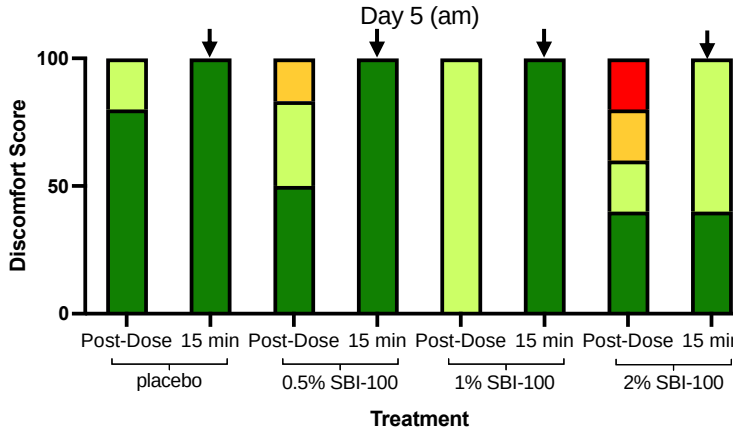
Sources: Honrubia et al., Br J Ophthalmol. 2009 Mar; 93(3): 316–321; Rhopressa® (netarsudil ophthalmic solution) 0.02% Prescribing Information, Aerie Pharmaceuticals, Inc., Irvine, Calif. 2019

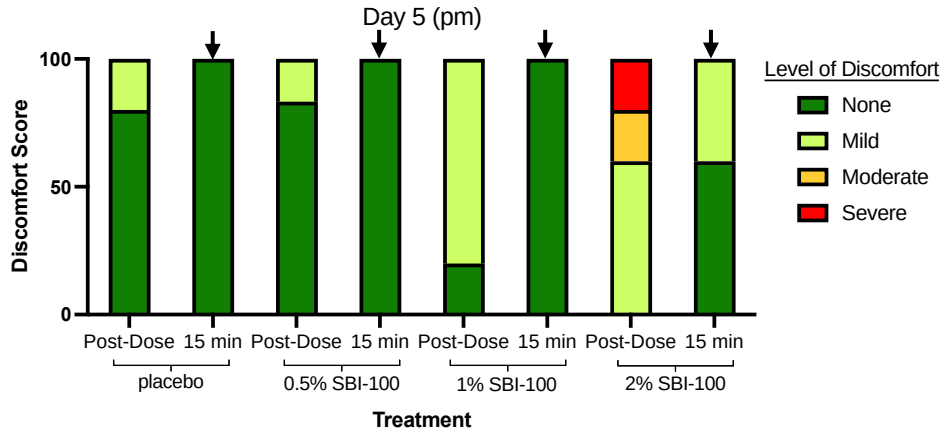
For investor audiences only.

MAD Day 1 & 5 – Discomfort is Transient and Quickly Resolves









Discomfort/pain upon instillation was usually mild and any discomfort was transient and resolved on average in less than 15 minutes.

Intraocular Pressure Analysis – Full Population

Low baseline IOP across all subjects

- Historically, glaucoma drugs do not significantly reduce IOP in healthy volunteers
- Participants receiving placebo and active had similar reductions in IOP.
- This is potentially due to the lower baseline IOP measured across all participants.

Treatment (N)	Mean Baseline IOP (mmHg)	Mean reduction of all IOP Measurements Post-Dose 1 (mmHg)*
Placebo (6)	14.6	-2.02
Active (18)	15.3	-1.99

Baseline IOP measured on Day 1 prior to first dose (approximately 8am)
****IOP measured at pre-dose, 1hr, 2hr, 4hr and 8hr post-dose each day***

Subgroup Analysis[1] – "High IOP"

- Because of the relatively low mean baseline IOP in this healthy volunteer population, we did not see any significant reductions in IOP when evaluating active against placebo.
- A subgroup analysis of participants with "high" baseline IOP was evaluated.
- We evaluated participants with baseline IOP of 17mmHg or greater.
  - 1 placebo participant; 5 active participants

Patient#	Treatment	Baseline IOP (mmHg)	Mean reduction of all IOP Measurements Post-Dose 1 (mmHg)*	% IOP Reduction
M1-01	Placebo	19.2	-2.8	14%
M1-03	0.5% SBI-100	17.7	**-4.5**	**25%**
M1-04	0.5% SBI-100	19.3	**-4.5**	**23%**
M1-07	0.5% SBI-100	18.9	**-5.9**	**31%**
M2-02	1.0% SBI-100	17.4	**-4.2**	**24%**
M2-03	1.0% SBI-100	18.9	**-2.6**	**14%**

***IOP measured at pre-dose, 1hr, 2hr, 4hr and 8hr post-dose each day**

For investor audiences only.

1: A subgroup analysis of participants, not pre-specified in the trial design, with "high" baseline IOP was evaluated.