Metabolic Rewiring with CB1 Inhibition
Virtual KOL Event

Nasdaq: SKYE

Disclaimer and Important Information for Investors

This presentation ("Presentation") has been prepared solely for general information purposes by or on behalf of Skye Bioscience, Inc. (together with its subsidiaries and affiliates, "Skye"). This Presentation is for informational purposes only and is not intended to form any basis of any investment decision. You should consult your own legal, regulatory, tax, business, financial and accounting advisors concerning the information described herein. Any discussion of the potential use or expected success of our product candidates is subject to our product candidates being approved by regulatory authorities. In addition, any discussion of clinical trial results for Nimacimab relate to the results of the Phase 1 clinical trial for Nimacimab.

Cautionary Language Regarding Forward Looking Statements

This Presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Forward-looking statements may be identified by the use of words such as "estimate," "plan," "goal," "project," "forecast," "intend," "will," "expect," "anticipate," "believe," "seek," "target" or other similar expressions that predict or indicate future events or trends or that are not statements of historical matters. These forward-looking statements include, but are not limited to: statements concerning Skye's future plans and prospects, the potential for Nimacimab to become an ideal therapeutic and/or combination therapeutic for the treatment of obesity and related diseases, any expectations regarding the safety, efficacy, tolerability or dosing of Nimacimab, including based on the clinical information from the Nimacimab Phase 1 study in NAFLD, the ability of Nimacimab to treat obesity or related indications, the initiation of Skye's Phase 2 obesity study and Phase 2 development plan for Nimacimab in obesity and the timing thereof, and the planned timing of the continued development of Nimacimab. Forward looking statements are neither historical facts nor assurances of future performance. Although Skye believes the expectations reflected in such forward-looking statements are reasonable, Skye can give no assurance that such expectations will prove to be correct. Readers are cautioned that actual results, levels of activity, safety, efficacy, performance or events and circumstances could differ materially from those expressed or implied in Skye's forward-looking statements due to a variety of risks and uncertainties, which include, without limitation, risks and uncertainties related to enrollment and completion of Skye's phase 2 study for Nimacimab, Skye's ability to advance Nimacimab, obtain regulatory approval of and ultimately commercialize Nimacimab, competitive products or approaches limiting the commercial value of Nimacimab, Skye's ability to fund development activities and achieve development goals, the impact of any global pandemics, inflation, supply chain issues, rising interest rates and future bank failures on Skye's business, Skye's ability to protect its intellectual property and other risks and uncertainties described in Skye's most recent Annual Report on Form 10-K and Quarterly Report on Form 10-Q and future reports Skye may file with the Securities and Exchange Commission from time to time. All forward-looking statements contained in this Presentation speak only as of the date on which they were made and are based on management's assumptions and estimates as of such date. Skye undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made, except as required by law.

Industry and Market Data, and Third-Party Reports

The views and statements provided in this Presentation are based on information derived from Skye's internal estimates and research, studies, publications, surveys and other information provided by third parties and also from publicly available sources. In this Presentation, Skye relies on, and refers to, publicly available information and statistics regarding market participants in the sector in which Skye competes and other industry data. Any comparison of Skye to any other entity assumes the reliability of the information available to Skye. Skye has not independently verified the accuracy or completeness of these sources. Certain information contained in this Presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources. Skye has not independently verified, and makes no representation as to, the adequacy, fairness, accuracy or completeness of any information obtained from third-party sources. All of the market data included in this Presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions.

No Representations and Warranties

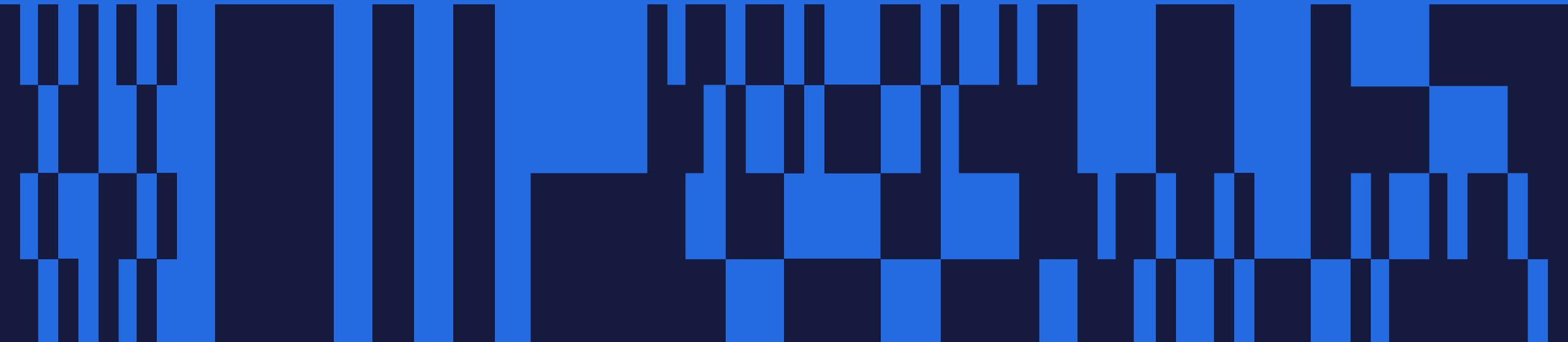
No representation, warranty or undertaking, express or implied, is made or will be given by Skye and its affiliates and representatives as to the fairness, accuracy, completeness or reliability of this Presentation and the information and or statements contained therein.

Trademarks and Copyrights

This Presentation may contain trademarks, service marks, trade names and copyrights of other companies, which are the property of their respective owners, and Skye's use thereof does not imply an affiliation with, or endorsement by, the owners of such trademarks, service marks, trade names and copyrights. Solely for convenience, some of the trademarks, service marks, trade names and copyrights referred to in this Presentation may be listed without the TM, © or ® symbols, but Skye will assert, to the fullest extent under applicable law, the rights of the applicable owners, if any, to these trademarks, service marks, trade names and copyrights. All images are copyright to their respective owners and are protected under international copyright laws.

skye Bioscience

- Chapter 01 | Punit Dhillon
- Welcome & Introduction



Event Agenda and Objectives

1. **Welcome and Introduction** (5 min)
   Speaker: Punit Dhillon
2. **Why Treat Obesity in the Healthcare System?** (10 min)
   Speaker: Lee M. Kaplan, M.D. Ph.D.
3. **Intro to Nimacimab & Scientific Rationale for Peripheral CB1 Inhibition** (20 min)
   Speaker: Christopher Twitty, Ph.D.; Marcus Goncalves, M.D., Ph.D.
4. **Clinical Experience and Endpoints** (15 min)
   Speaker: Louis Aronne, M.D.
5. **Ensuring Safety and Tolerability in Peripheral CB1 Inhibition** (10 min)
   Speaker: Beverly Tchang, M.D.
6. **CBeyond™: Phase 2 Study Design** (10 min)
   Speaker: Tu Diep, M.Sc.
7. **Panel Session and Q&A** (10 min)
   Speaker: Panel and Punit Dhillon
8. **Closing Remarks and Next Steps** (5 min)
   Speaker: Punit Dhillon

Mission, Who We Are

Mission

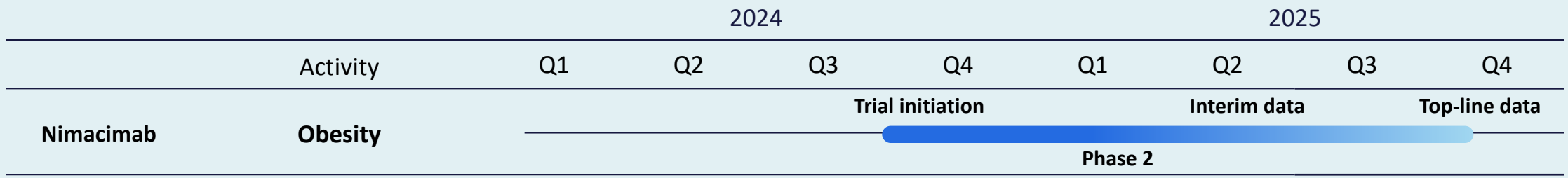
To develop innovative medicines to treat obesity and metabolic diseases for patients to achieve better health and quality of life.

Approach

Harness the power of groundbreaking research and technology to develop medicines that are both clinically and commercially differentiated, transforming patients' lives across the globe.

Program

Nimacimab, a new and distinct class of CB1 inhibitor, has the potential to become a leader in treating patients with obesity.



Note: Future periods represent Skye's expectations

Skye Leadership and Key Opinion Leader Panel

Skye Executive Management

Punit Dhillon
CEO & Chair of BOD

Tu Diep, M.Sc.
Chief Development Officer

Chris Twitty, Ph.D.
Chief Scientific Officer

Kaitlyn Arsenault, CPA
Chief Financial Officer

Key Opinion Leader Panel

Louis Aronne, M.D.
Former President, Obesity Society

Marcus Goncalves, M.D., Ph.D.
Associate Professor, NYU Langone Health

Lee M. Kaplan, M.D., Ph.D.
Weight + Wellness, Dartmouth Health

Beverly Tchang, M.D.
Endocrinologist, Obesity Expert

All drugs are investigational and subject to regulatory approval.

We are Well-Positioned to Successfully Become a Fully Integrated Metabolic Company

Our team has the building blocks to bring Nimacimab through clinical development

Robust IP and Development Strategy
Planned Nimacimab EOP2 by 2027 and IP/composition of matter protection through 2037

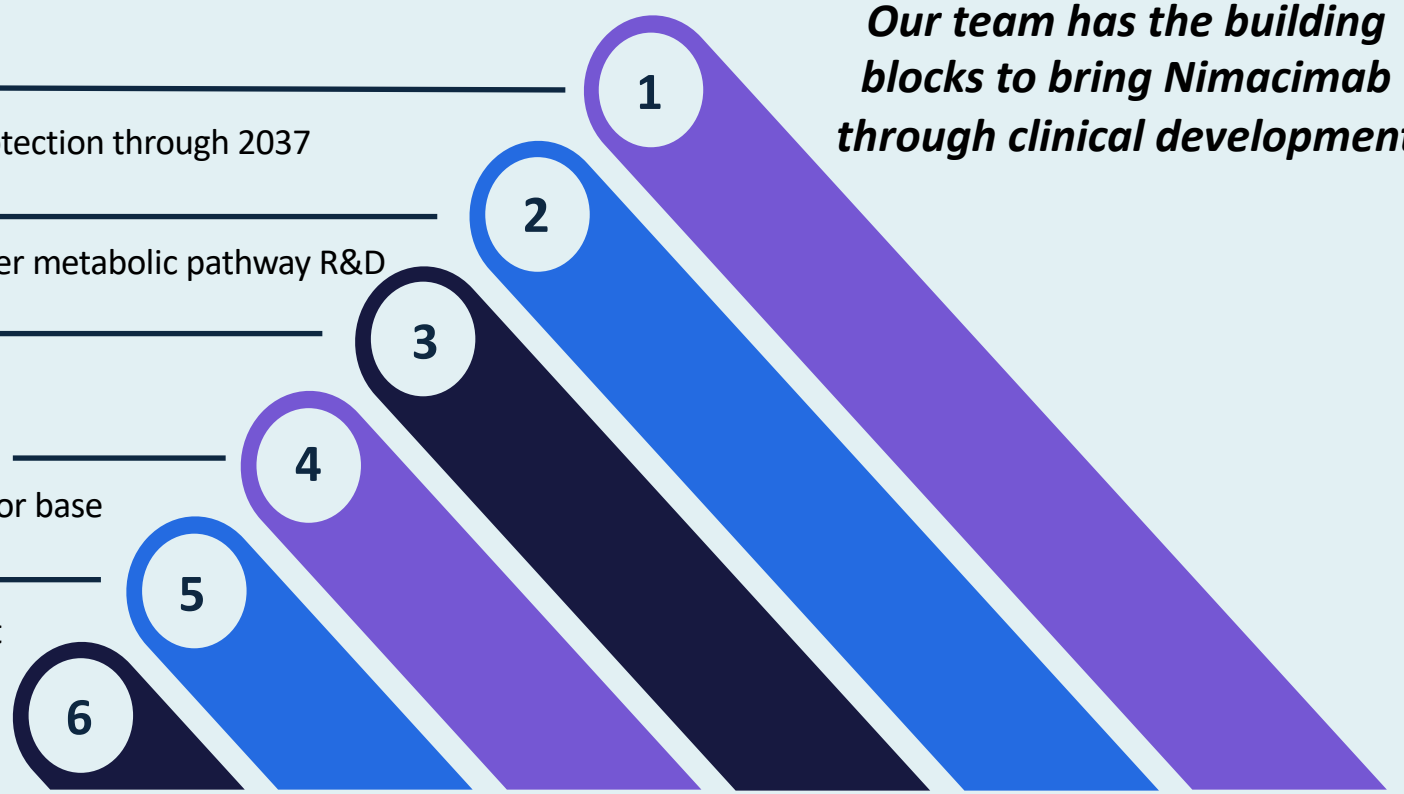
Novel Biologics Pipeline
Team and collaborators focused on GPCR antibody, biomarker & other metabolic pathway R&D

World-Leading Obesity Experts
Experienced in approval of all current obesity agents on the market

Meaningful Near-Term Data Inflection Points
Strong funding track record with existing specialist healthcare investor base

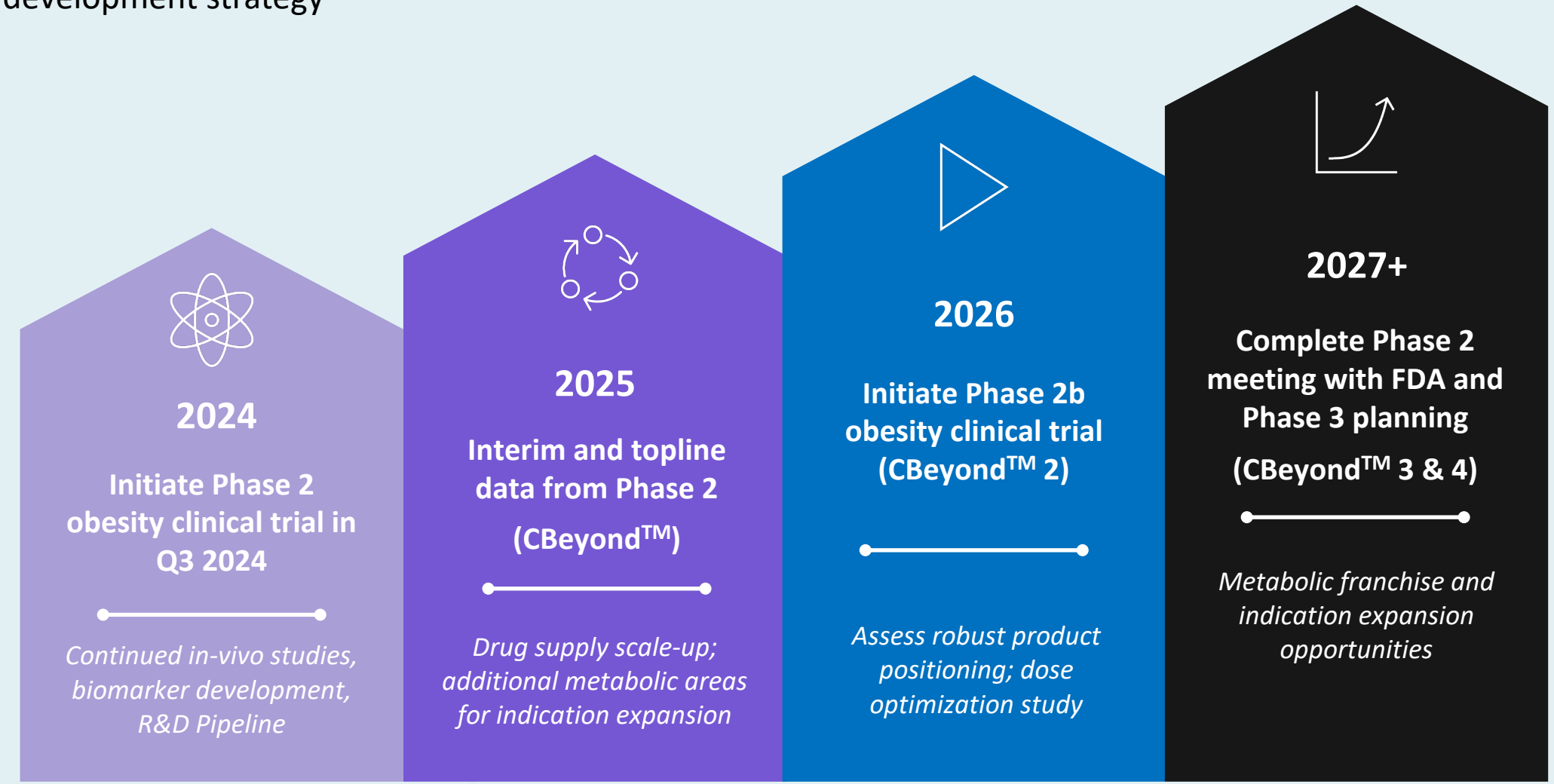
Experienced Leadership
Board has been involved or directly brought 40+ drugs to the market

Full CMC Capabilities
GMP manufacturing to support future clinical trials underway



Strategic Roadmap I Vision through 2027 and Beyond

Clinical development strategy



All drugs are investigational and subject to regulatory approval.

Nimacimab: The Future of Metabolic Therapeutics

Innovative scientific strategy to shape the optimal metabolic product profile

Improved Safety

No neuropsychiatric adverse events in Nimacimab NAFLD trial, with benchmark pre-clinical bio-distribution data

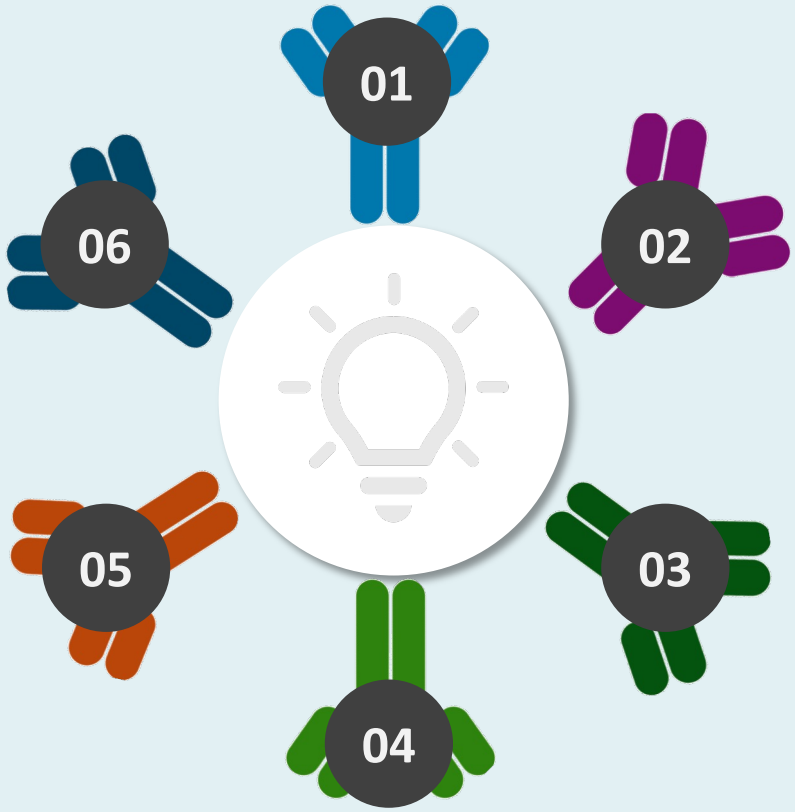
GI Tolerability

Low incidence of GI adverse events and product discontinuations

Long-term Dosing

Favorable PK/PD profile; potential to go higher in dose and reduce frequency

New Product Benchmark



Meaningful Weight Loss

CB1 inhibition has demonstrated clinically meaningful weight loss data

Lean Mass Preservation

Preserves muscle mass better than alternative mechanistic approaches

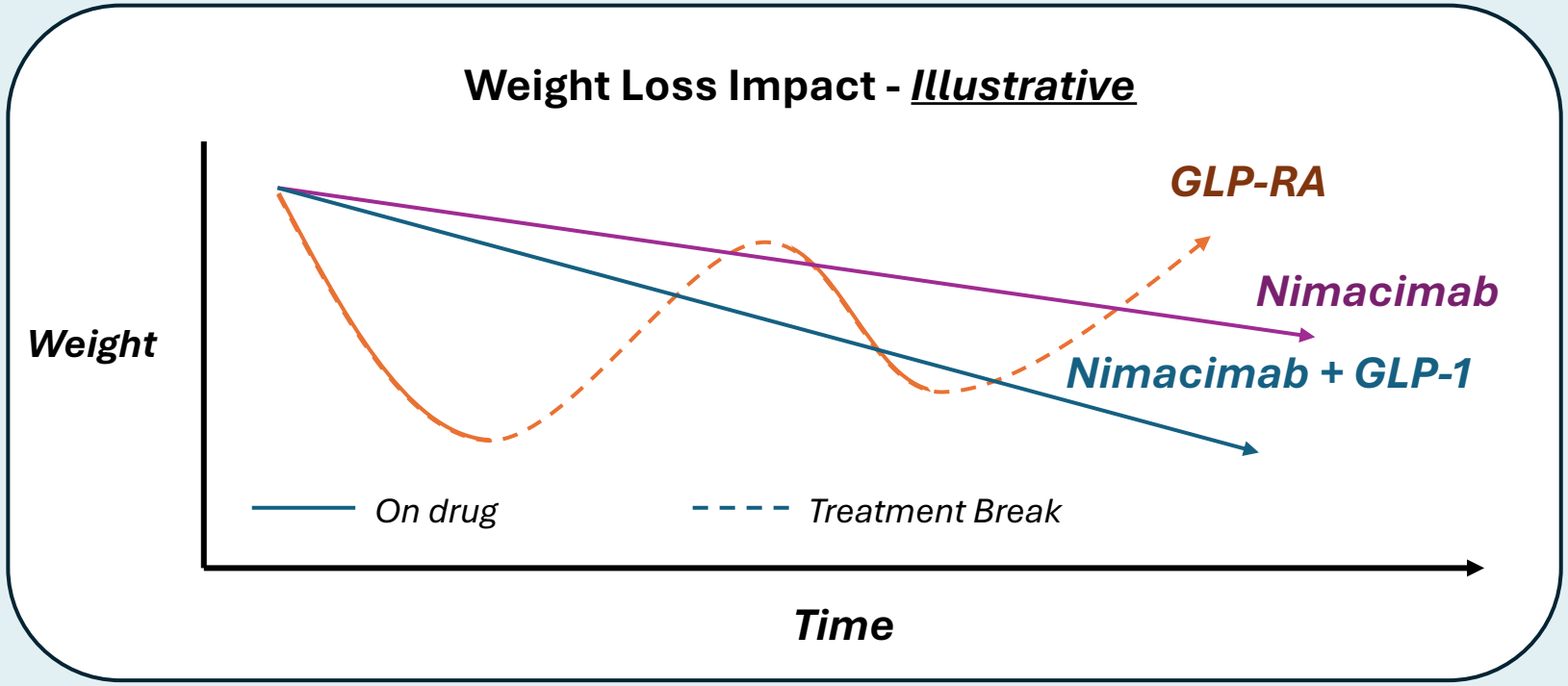
Combinability

Distinct mechanisms provide a strong rationale for combination with standard of care to address maintenance, enhanced weight loss or additional metabolic comorbidities

All drugs are investigational and subject to regulatory approval.

Nimacimab May Promote Sustainable and Healthy Weight-Loss

Opportunities in the current AOM landscape to address heterogeneity in patients with obesity



Nimacimab's improved tolerability may enable extended dosing, preserve muscle mass, and avoid "rebounding" to facilitate sustainable weight loss

Potential Monotherapy Benefits

- **Effective weight loss**
- **Sustainable results**
- **Improved tolerability**

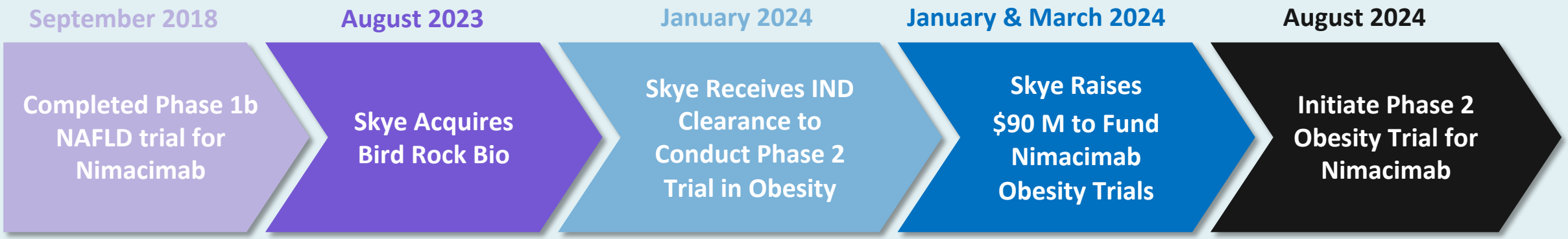
Potential Combination Benefits

- **Enhanced efficacy**
- **Synergistic tolerability effects**
- **Facilitates tailored tx approach**

All drugs are investigational and subject to regulatory approval.

Nimacimab's History

We intend to advance Nimacimab into the clinic within 12 months of product acquisition



All drugs are investigational and subject to regulatory approval.

Phase 2 Success Catalyzes Growth of Metabolic Franchise

CB1 inhibitor with comprehensive therapeutic benefits for therapeutic pipeline

Nimacimab

MoA	Disease	R&D	Phase 1	Phase 2
CB1 Receptor Inhibitor *Sub-cutaneous*	**Obesity**			
	Additional Metabolic Disorders			Future

First-in-class mAb

- **Only CB1 Negative Allosteric Modulating mAb in Clinic**
- **High Selectivity to CB1**
- **Extended Half-life**

Multimodal MoA

- **Anti-fibrotic activities**
- **Multifaceted metabolic benefits**
- **Anti-inflammatory effects**

Favorable Safety Profile

- **No neuropsychiatric concerns**
- **Excellent GI tolerability**

All drugs are investigational and subject to regulatory approval.

skye Obesity

- Chapter 02 | Lee M. Kaplan, M.D., Ph.D.

- Why Treat Obesity in the Healthcare System?

What is Obesity?

World Health Organization[1]:

A **disease** characterized by abnormally placed or excessive fat that presents a risk to health

Widely accepted description:

A complex, chronic, possibly progressive **disease**

Why is it a disease?

It results from **abnormal metabolic regulation of body fat mass**

Alone, it directly causes **pathology** and **diminishes health**

It is **also** a **risk factor** for many other diseases

But it is a **disease** in its own right

Whatever the external causes or contributors,

The **final common pathway** to obesity is **internal** to the body and reflects disrupted physiology

World Health Organization, 2022. Obesity; available at https://www.who.int/health-topics/obesity#tab=tab; Kaplan LM, 2023

The Fundamental Question

Is obesity a disorder that is best treated within the healthcare system…

… or in a commercial environment?

Kaplan LM, 2024

The Purpose of Health Care

To relieve suffering arising from disturbances in the human body …

… from symptoms

… from disability

… from fear

… of complications

… of dying

… of developing a disability

… of not being able to participate in the world

Obesity causes suffering in all these ways

Relief of suffering from obesity-induced symptoms and fear falls squarely within the responsibilities of normal medical care

Kaplan LM, 2024

Body Fat Mass is Physiologically Regulated

Body fat mass and distribution vary predictably across the lifecycle

Loss of baby fat

Fat changes with puberty

Fat changes with aging and menopause

Fat changes during and after pregnancy and lactation

At any given time, fat mass is defended by metabolic adaptation

Fat regain after resolution of acute illness or injury

Fat loss in response to acute overeating

Fat regain in response to calorie restriction

Obesity occurs when this regulatory system seeks and defends an inappropriately high fat mass

Kaplan LM, 2012

The Body Vigorously Defends its Desired Fat Mass through a Protective Physiological Response that Limits the Effectiveness of Voluntary Calorie Restriction

This response is called 'metabolic adaptation'[5-6]

It includes increased appetite and decreased energy expenditure

Increased food focus or preoccupation

Increased hunger

Decreased satiation and satiety

Decreased energy expenditure (thermogenesis)

It is mediated by changes in multiple gastrointestinal and CNS peptides

↑ Ghrelin

↓ Peptide YY

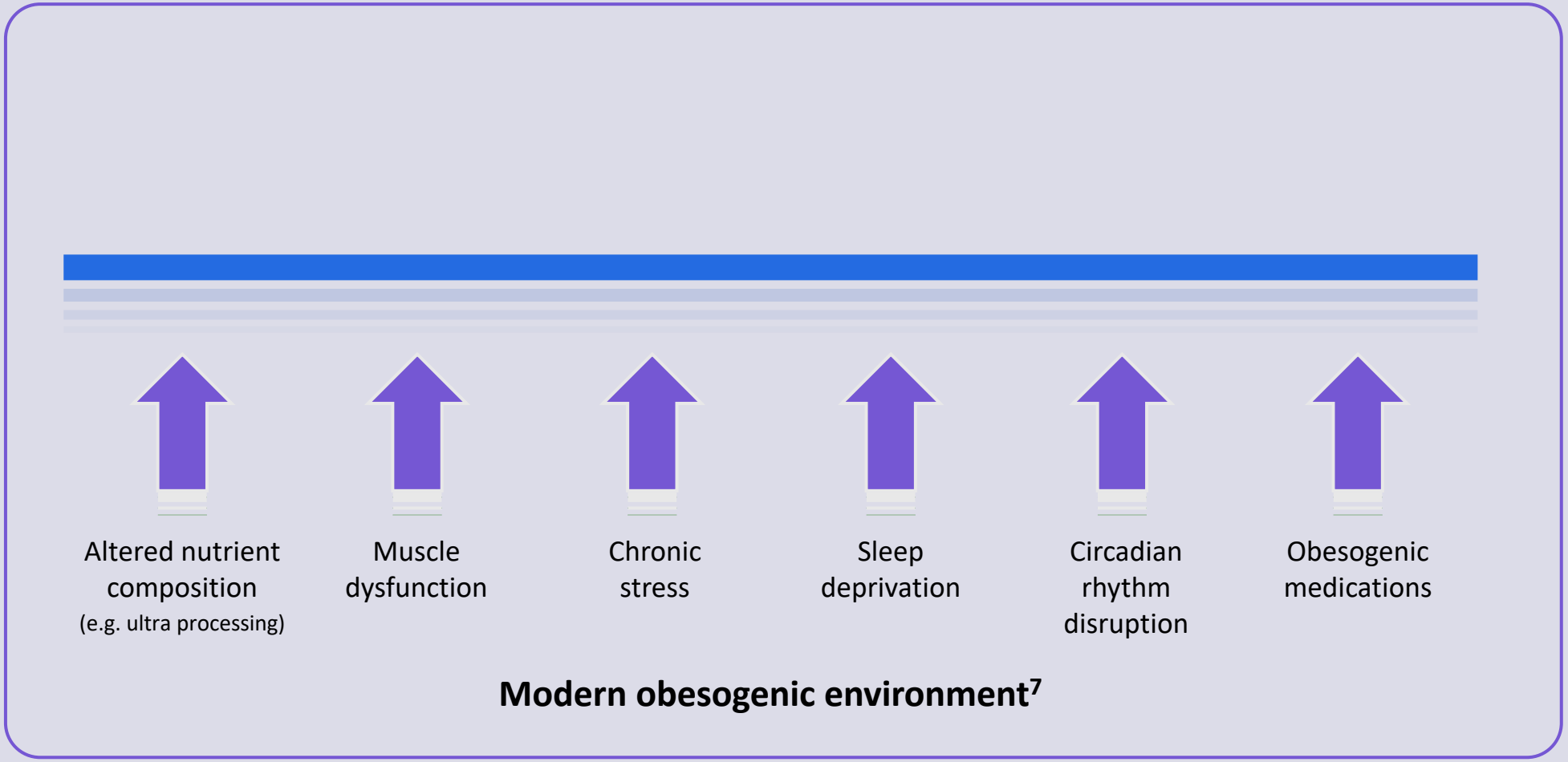
↓ Cholecystokinin (CCK)

↓ Amylin

It leads to regain of the lost weight

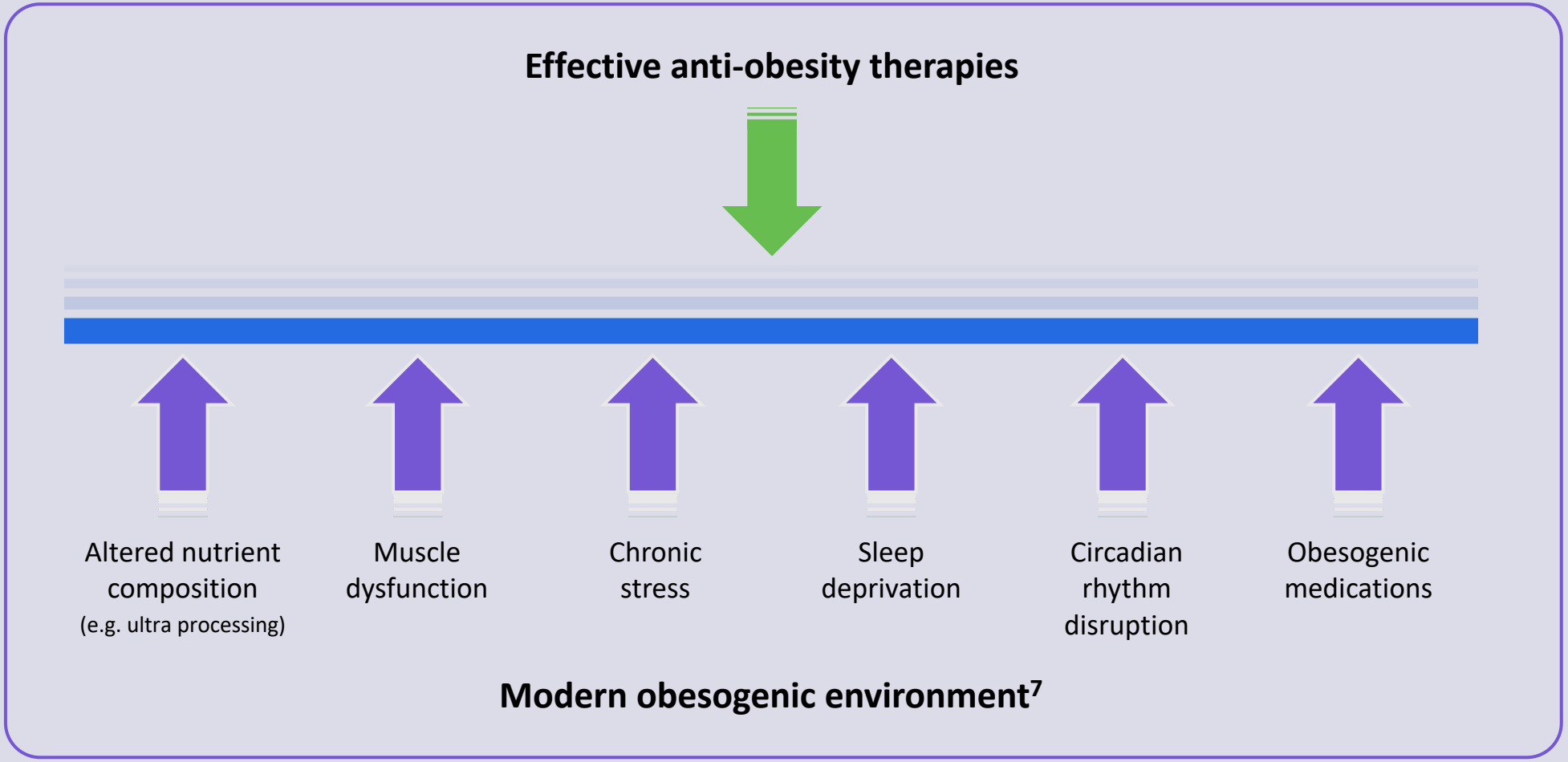
Adapted from Sumithran P et al. N Engl J Med 2011; Leibel R et al. N Engl J Med 1995; Kaplan LM, 2023

In Obesity, the Target Fat Mass is Dysregulated (Elevated) from Environmental Influences on Biologically Susceptible Individuals



Kaplan LM, 2006

Effective Obesity Treatments Normalize Fat Mass Regulation Leading to Decreased Weight Without Activating Metabolic Adaptation



Kaplan LM, 2006

Goals of Obesity Treatment

Weight loss

Improvement in obesity symptoms

- Ingestion-related
- Physical
- Dysphoric

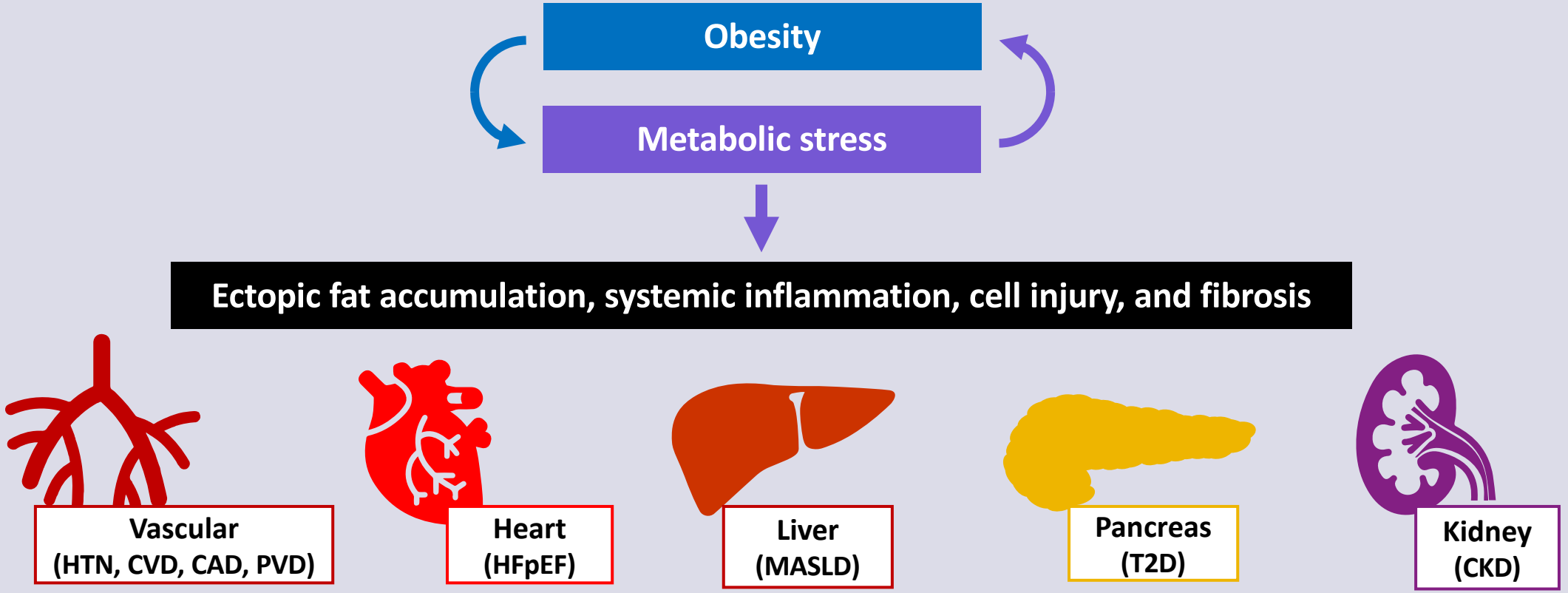
Improvement in existing obesity complications

- Metabolic
- Inflammatory and autoimmune
- Neoplastic
- Structural
- Cognitive and psychosocial

Prevention of future obesity complications

Kaplan LM, 2024

Obesity also Stimulates a Multi-System Metabolic and Inflammatory Syndrome



The ideal therapy would be **safe** and **tolerable**, **improve cardio-metabolic, liver, kidney, and pancreatic outcomes**, and **reduce** the risk of **cancer**[8]

Adapted from Sanyal AJ, 2024

There is a Growing List of Diseases that Have Now Been Demonstrated to Benefit from Effective Treatment of the Underlying Obesity

- Type 2 diabetes (T2D) – **2014**
- Atherosclerotic cardiovascular disease (ASCVD) – **2023**
- Heart failure with preserved ejection fraction (HFpEF) – **2023**
- Chronic kidney disease (CKD) – **2024**
- Metabolic dysfunction-associated steatotic liver disease (MASLD/MASH) – **2021**
- Obstructive sleep apnea (OSA) – **2024**
- Obesity-associated cancers – **2022**
- Osteoarthritis – **2021**
- Polycystic ovary syndrome (PCOS) – a major cause of infertility in women – **2024**

... and with the new, highly effective medications, **this list is growing very rapidly**

Kaplan LM, 2024

Given the Size of the Problem, IF We are Successful in Overcoming These Barriers…

We should see an impact on obesity at a population level

First, a reduction in the severity of the existing obesity

Later, a reduction in the rate of obesity, as **effective treatments predict effective prevention strategies**

We should see an improvement or reduction in the major complications of obesity, especially diabetes, heart disease, kidney disease, liver disease, and obesity-associated cancers[3]

We should see significant advances in mental health and quality of life

Which may lead to beneficial effect on **social capital**

We may see a reversal of the recent trend toward reduced life expectancy

We may see a decrease in health care costs

We may see an improvement in economic productivity

We may see food industry incentives moving from quantity to quality

All of these changes would be predicted to generate the greatest benefit in populations with the highest current rates of obesity

Providing that **access to obesity care** is both **sufficient** and **equitably distributed**

Kaplan LM, 2024

skye Obesity

- Chapter 03 | Christopher Twitty, Ph.D.; Marcus Goncalves, M.D., Ph.D.

- Introduction to Nimacimab Peripheral CB1 Inhibition

Obesity and CB1 Introduction

Upregulation of CB1 signaling is involved in metabolic diseases, including obesity; inhibition of CB1 addresses fundamental drivers of obesity

Obesity

- Obesity can be defined as excessive fat deposition that impairs health, simplistically driven by a biased relationship of food intake relative to energy expenditure.
- More specifically, it is a complex disease characterized metabolic dysregulation that promotes inappropriate hormone expression, increased adipogenesis and chronic inflammation which act in concert to drive this pathological state

CB1 in Obesity

- CB1 axis globally favors intake and conservation of energy across diverse tissues – resource scarcity vs food abundance
- The CB1 axis (both endocannabinoids and receptor) is highly active in obese or fasting states and promotes adiposity
- Blockade of CB1 promotes reduced caloric intake and additional metabolic gains in peripheral tissues

Central versus Peripheral CB1 Inhibition

- Central (brain/CNS) inhibition may drive psychiatric adverse events and ultimately halted development of the 1st generation inhibitors
- CB1 is readily expressed throughout periphery and controls key metabolic pathways that are addressable with Nimacimab
- **Sufficiency peripherally restricted inhibitors:** 2nd generation molecules have demonstrated metabolic gains beyond anorexigenic effects

Nimacimab is a First-in-Class, Peripherally Restricted Cannabinoid Receptor 1 (CB1)-Inhibiting Antibody

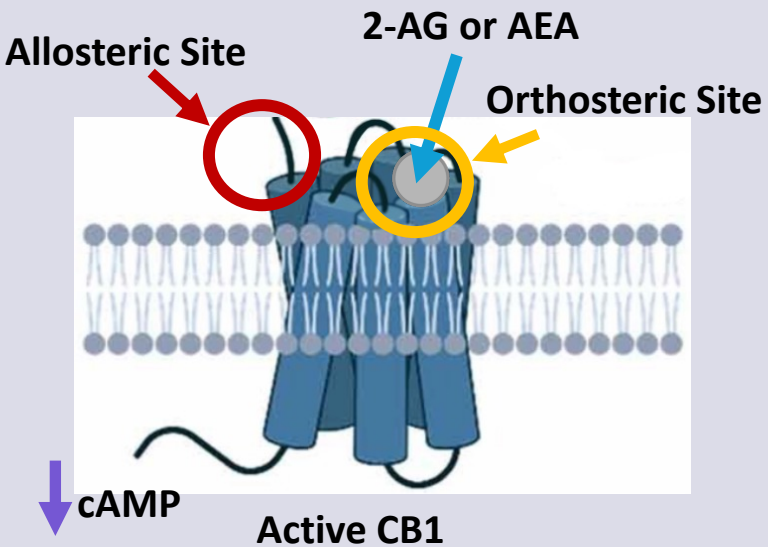
Engineered IgG4	Stable antibody with a half-life of 18-21 days (potential for bi-weekly or monthly dosing) Single mutation in the hinge region that prevents antibody Fab exchange
Peripheral Restriction	Multiple NHP studies: background levels of antibody in CNS/brain (even at high doses) No accumulation of antibody in CNS/brain despite multiple weekly doses
Specific for CB1	Nimacimab is selective for only CB1 and not other GPCRs Binds to CB1 allosterically and inhibits CB1 signaling independent of the binding by CB1 agonists
Potent Inhibitor	Nimacimab also functions as an **antagonist** (in presence of CB1 agonist with B-arrestin endpoint) Nimacimab functions as an **inverse agonist** (twice as potent as rimonabant with cAMP endpoint)

Nimacimab's Unique Inhibition of CB1: Negative Allosteric Modulation

Small molecule inverse agonists competes with endocannabinoid for CB1 binding; NAM antibody blocks CB1 signaling independent of endocannabinoid binding

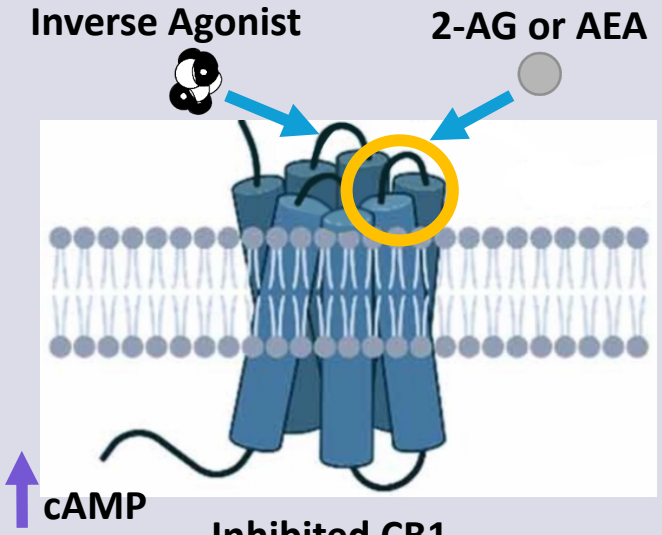
Productive CB1 Signaling

Endocannabinoid (2-AG/AEA) binds orthosteric site

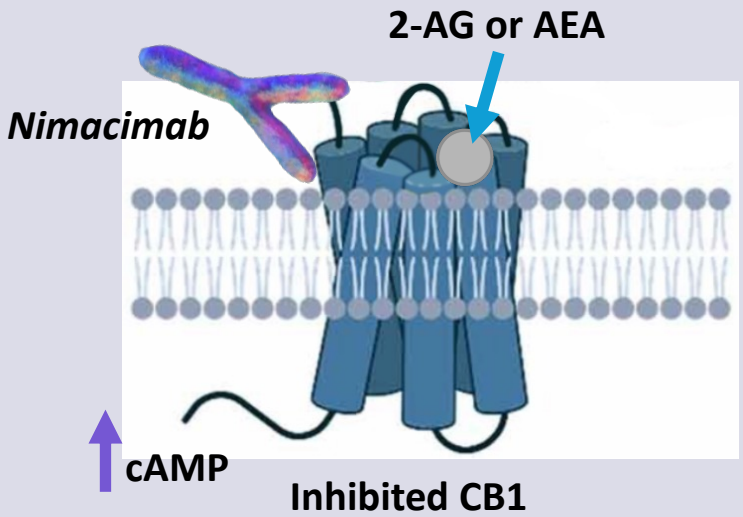


Inhibition of CB1 Signaling

Inverse agonist competitively binds orthosteric site with 2-AG/AEA



Nimacimab non-competitively binds allosteric site; 2-AG/AEA binds orthosteric site



skye

All drugs are investigational and subject to regulatory approval

Key MoA for Peripheral CB1 Inhibition in Obesity

Summary of key MoAs that make CB1 inhibition a promising approach in treating obesity

Appetite Hormones	Peripheral modulation of appetite regulating hormones (CCK/ghrelin/leptin/GLP1) can safely promote hypophagia. Fundamental mechanism to support limited caloric intake/fasting states
White Adipose Tissue	Promotes lipolysis and increased energy expenditure (mitochondrial biogenesis/mUCP) while re-establishing productive levels of adipokines (adiponectin and inflammatory cytokines)
Leptin Axis	Control of hyperleptinemia and restoration of this critical axis is a key to long-term weight loss
Insulin Sensitivity	Reversing insulin resistance is not only key for comorbid (pre-diabetic) patients but helps limit lipogenesis and fat storage in the liver

skye Obesity

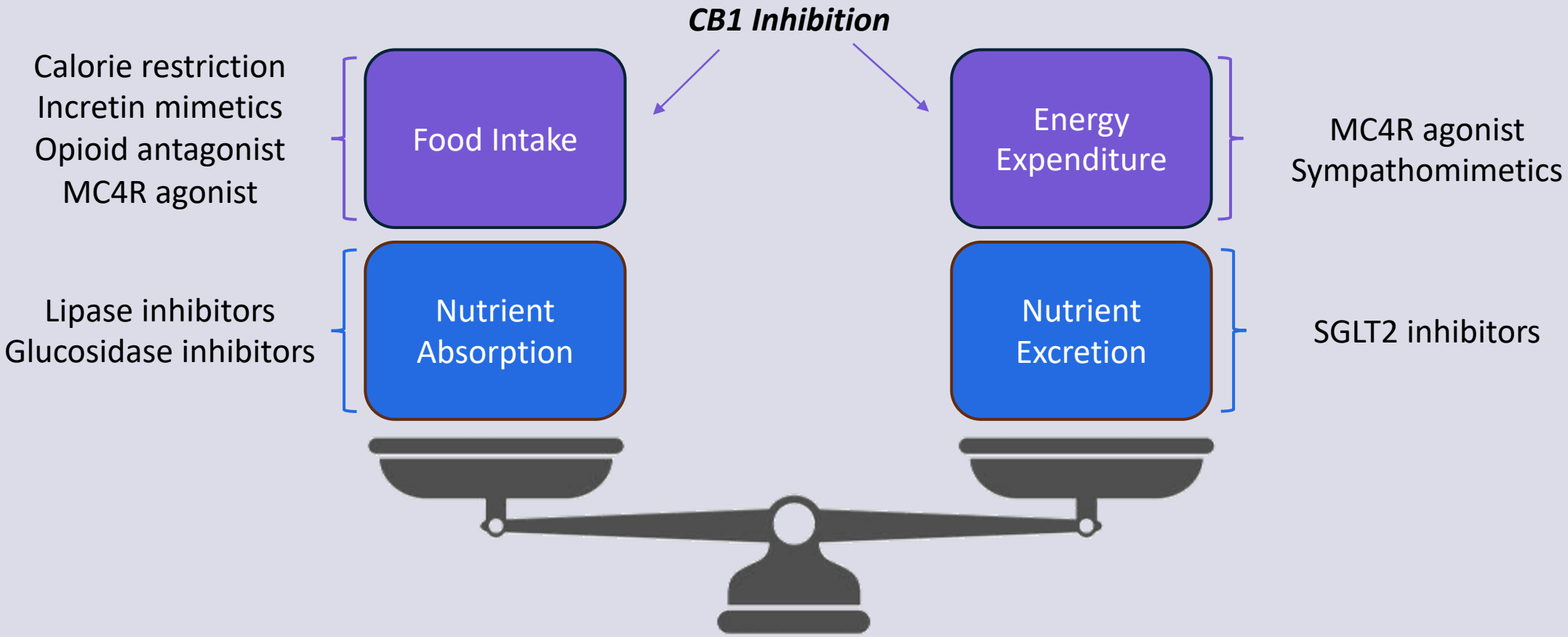
- Chapter 03.1 | Marcus Goncalves, M.D., Ph.D.
- Scientific Rationale for Peripheral CB1 Inhibition

Scientific Rationale for Peripheral CB1 Inhibition

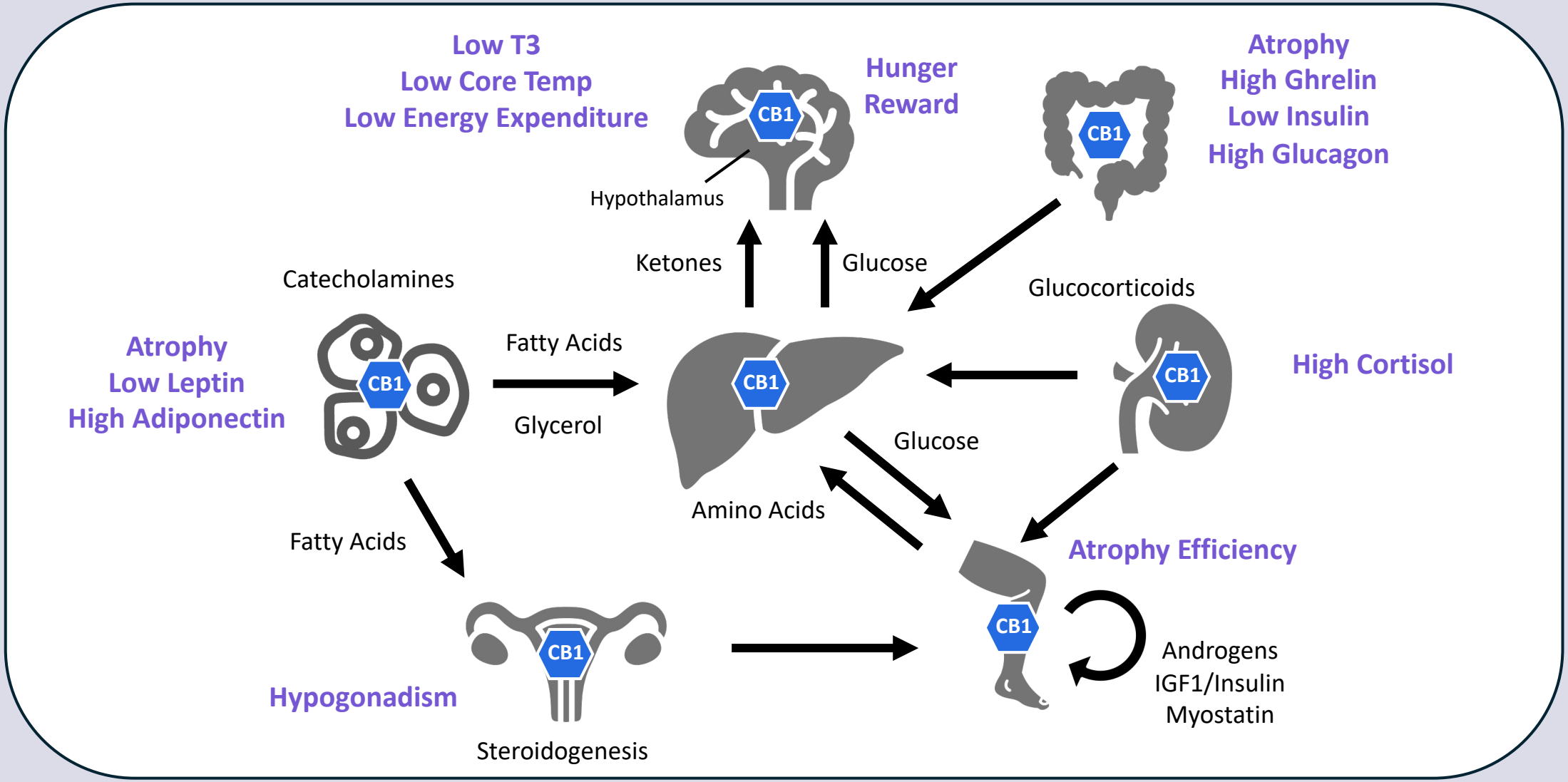
Overview of key mechanisms behind CB1 inhibition in obesity treatment

Fundamentals of Body Weight Regulation	Body weight regulation and obesity treatments; physiological features of weight loss
Role of ECS in Obesity	Human endocannabinoid system; CB1 inverse agonist reduces food intake and increases energy expenditure; CB1 increases food intake via peripheral sensory neurons
Central vs. Peripheral MoA of CB1	Understanding and separating central versus peripheral effects
Therapeutic Impact of Peripheral CB1 Inhibition	Peripheral CB1 inverse agonist reduces food intake and increases energy expenditure; peripheral CB1 inverse agonist reverses leptin resistance; CB1 loss in adipose protects against obesity; CB1 loss in adipose reduces food intake and increases energy expenditure
Peripheral Effects and Therapeutic Potential	Summary of known peripheral effects

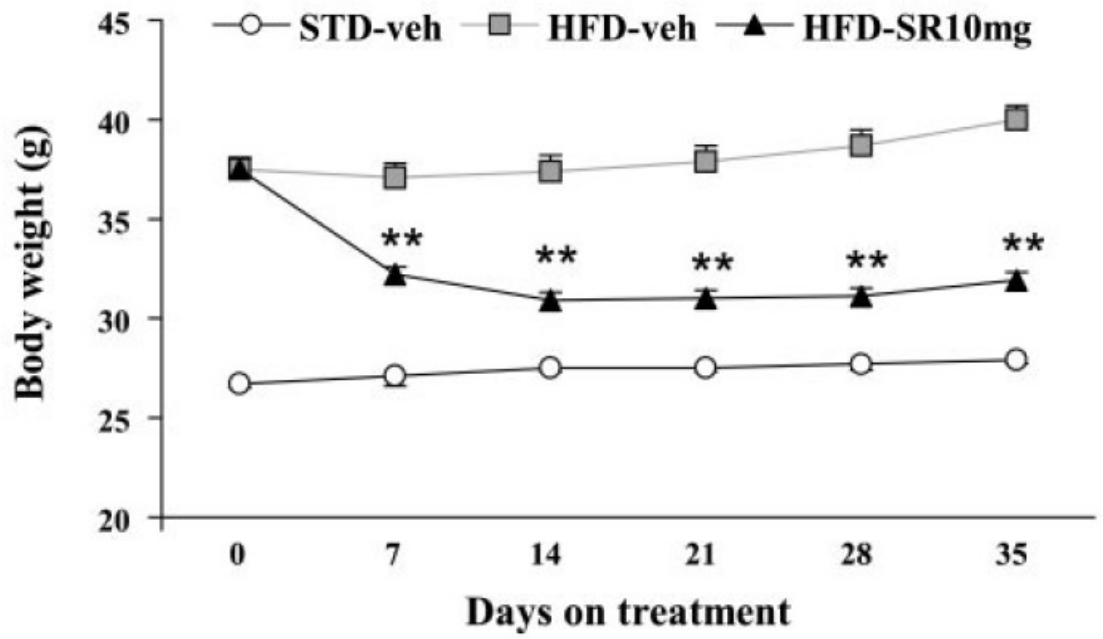
Body Weight Regulation and Treatments

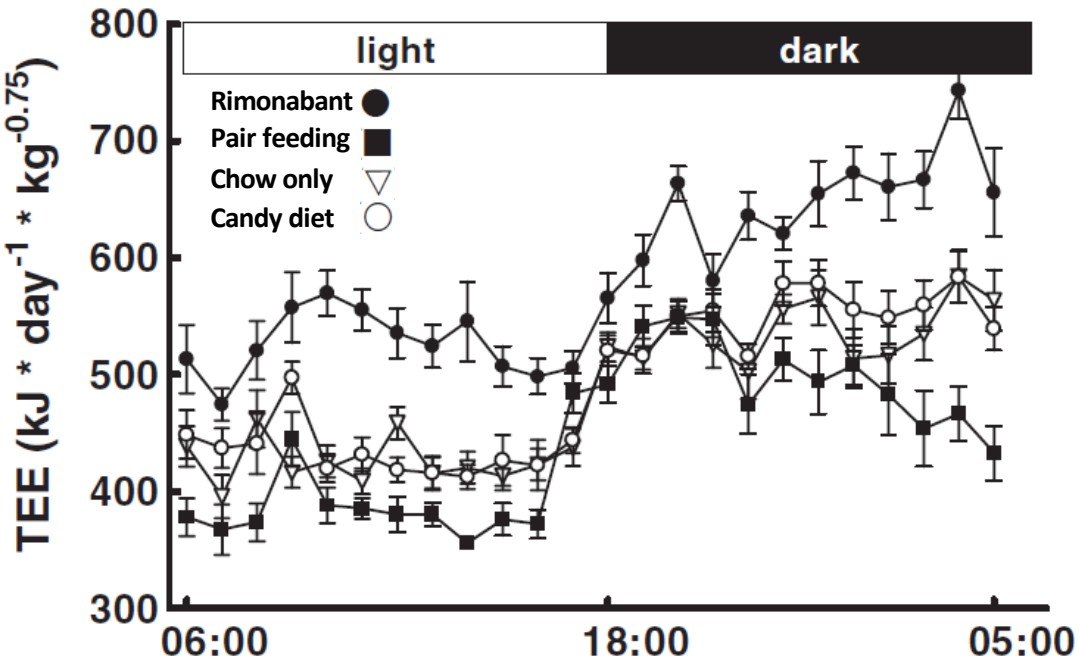


Physiologic Features of Weight Loss



CB1 Inverse Agonist Reduces Food Intake and Increases Energy Expenditure





CNS adverse events limit utility[9,10]

CB1 Increases Food Intake via Peripheral Sensory Neurons

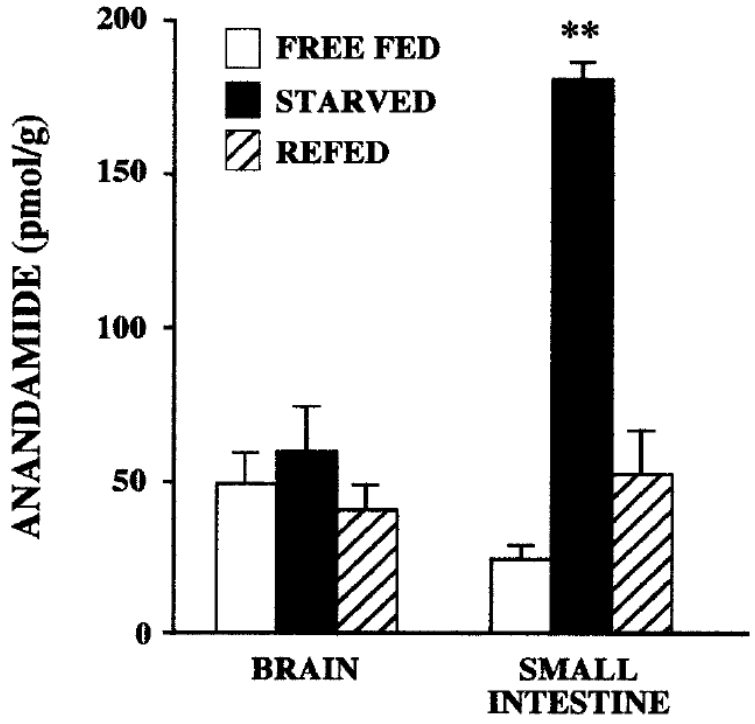


Figure 1[11]

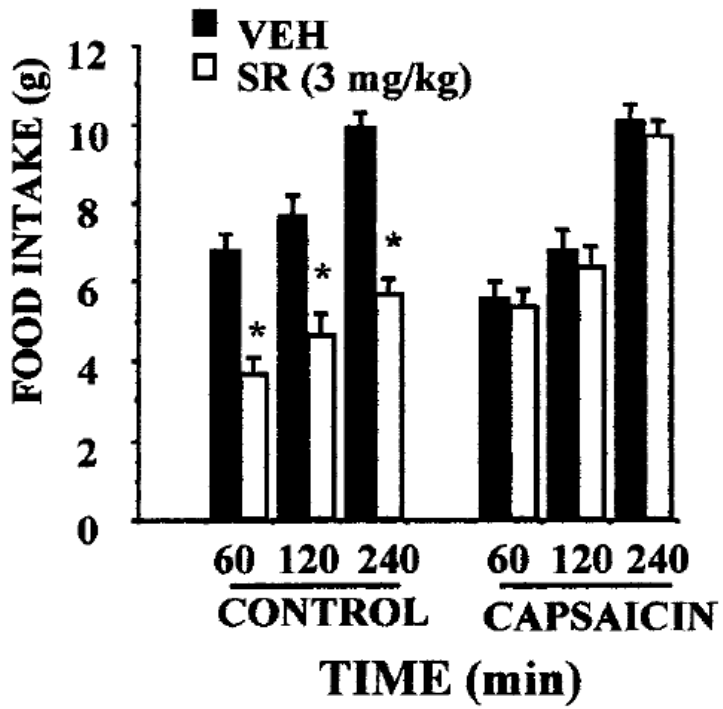
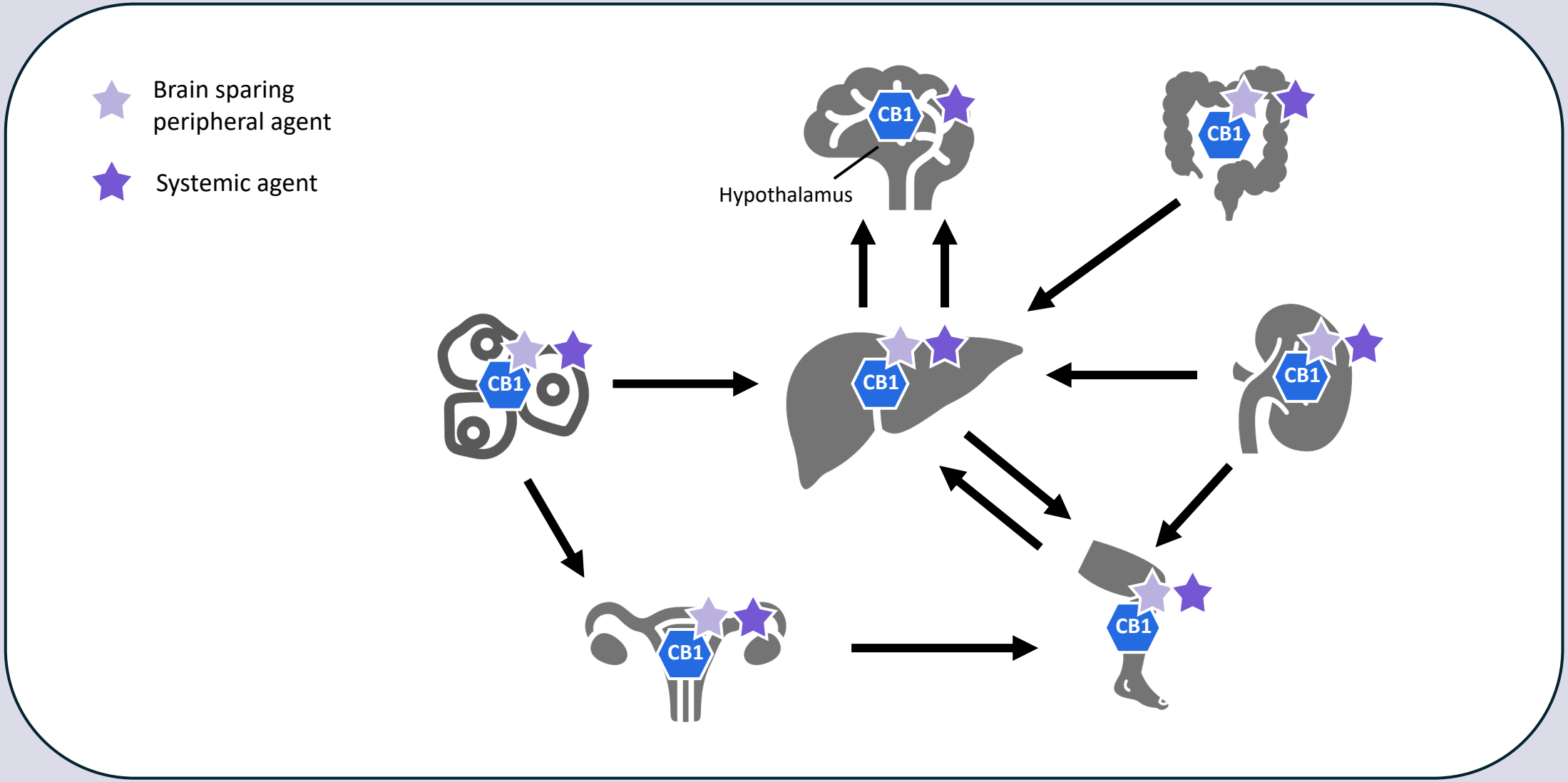


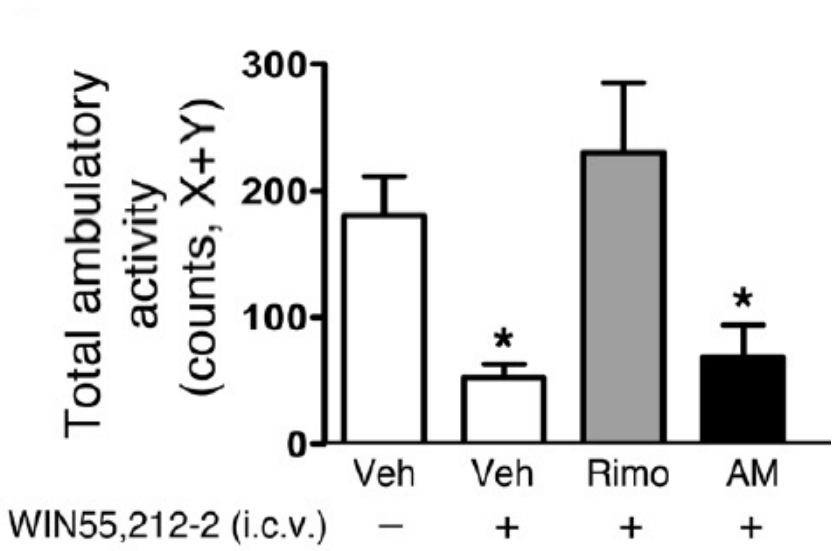
Figure 2[11]

Central vs Peripheral Effects



Separating Central vs Peripheral Effects

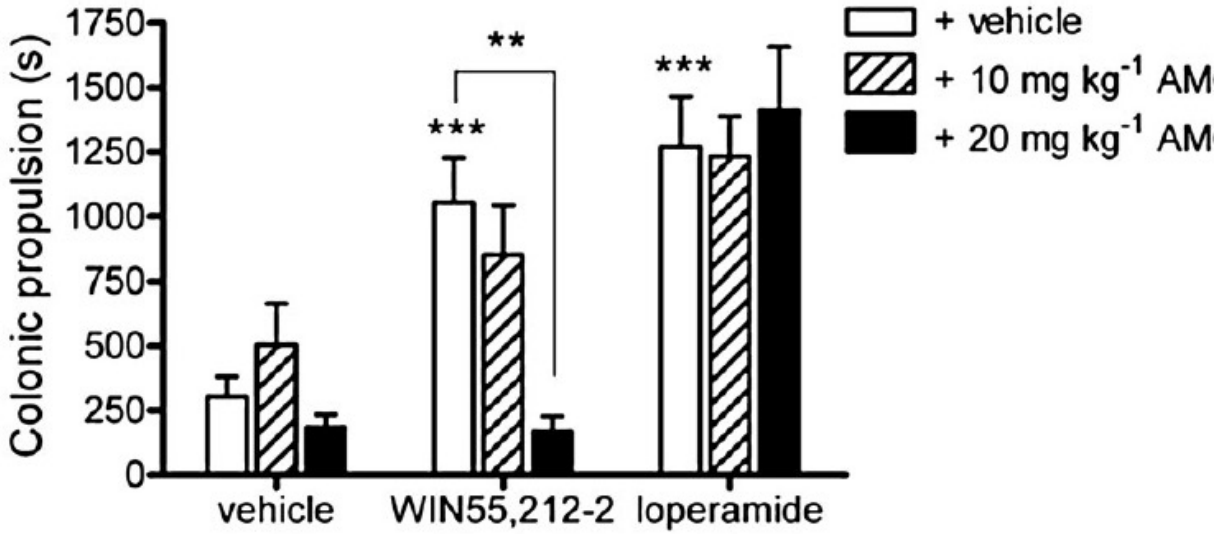
Central: Hypomotility[12]



Systemic

Peripheral

Peripheral: GI Transit[13]



Peripheral

Peripheral CB1 Inv Agonist Reduces Food Intake and Increases Energy Expenditure

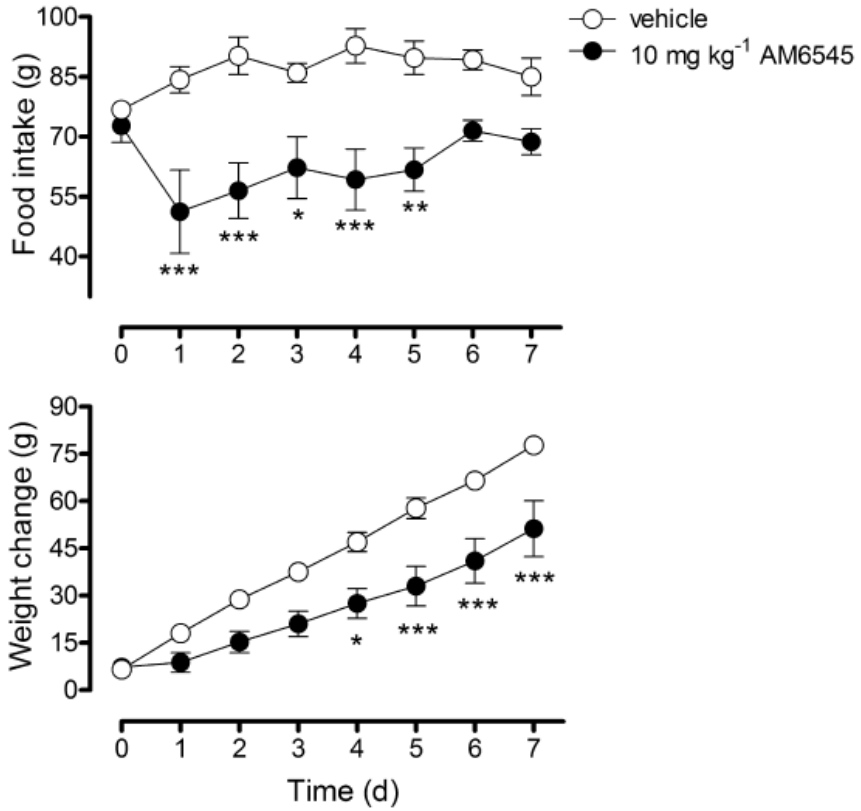


Figure 1[12]

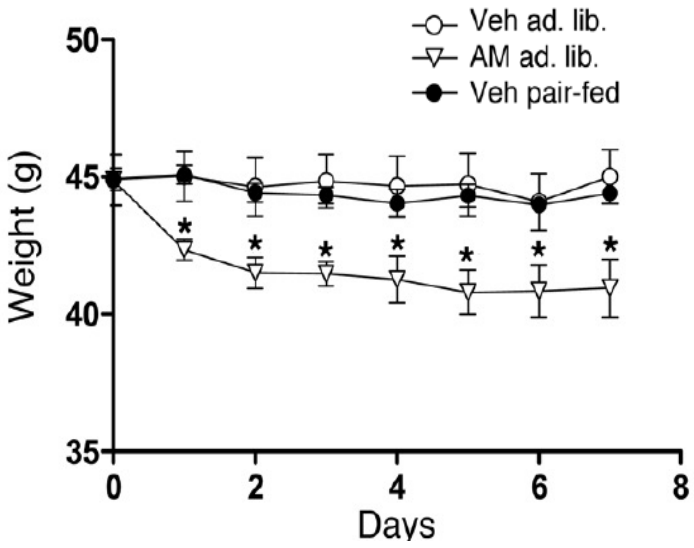


Figure 2[13]

Peripheral CB1 Inhibitor Reverse Leptin Resistance

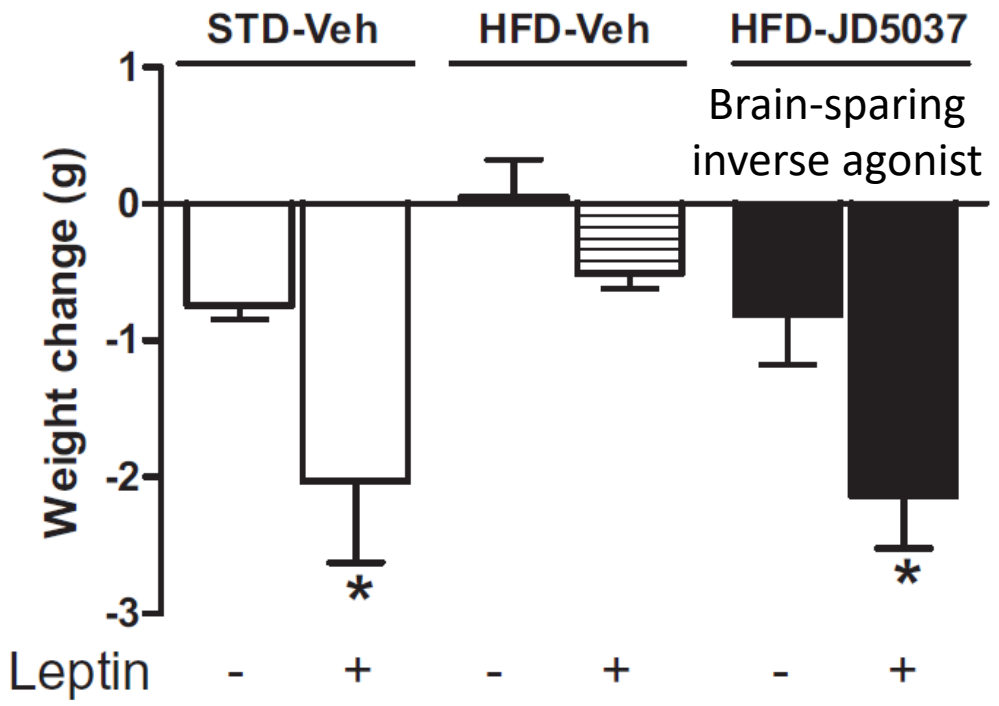


Figure 1[14]

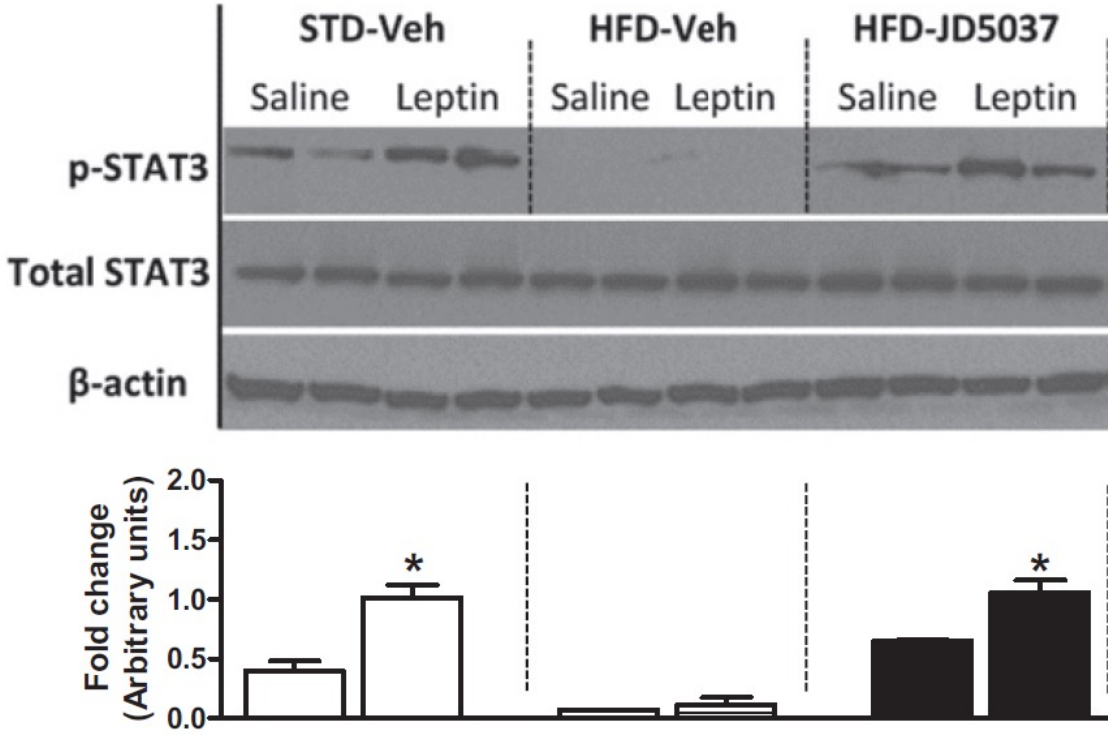
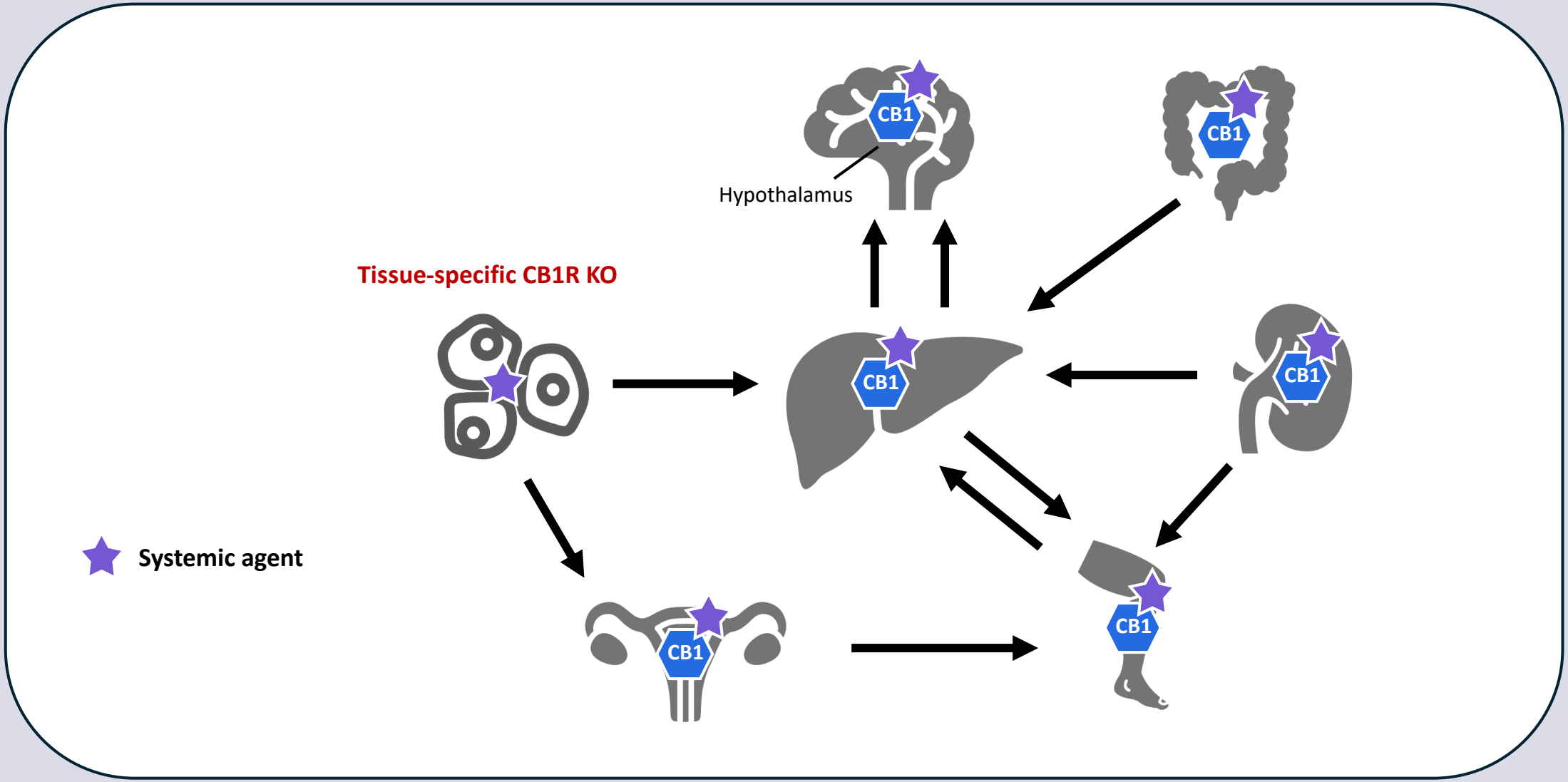


Figure 2[14]

Central vs Peripheral Effects



CB1 Loss in Adipose Protects Against Obesity

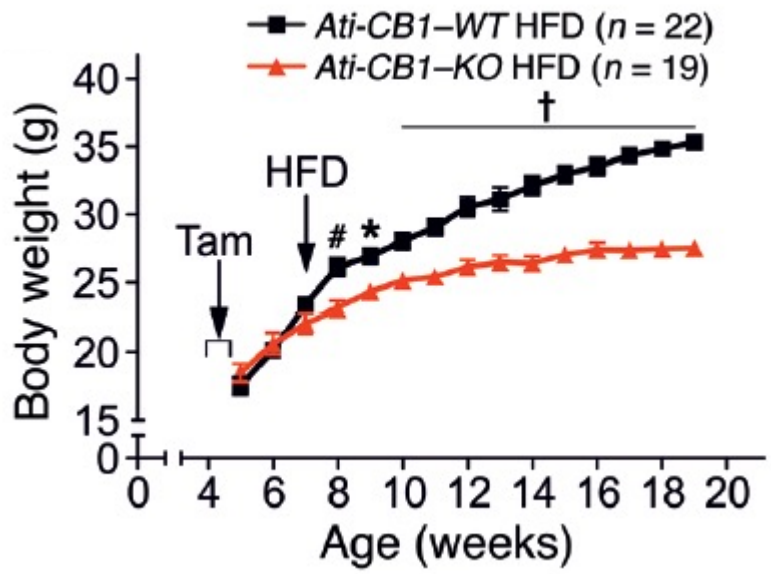


Figure 1[15]

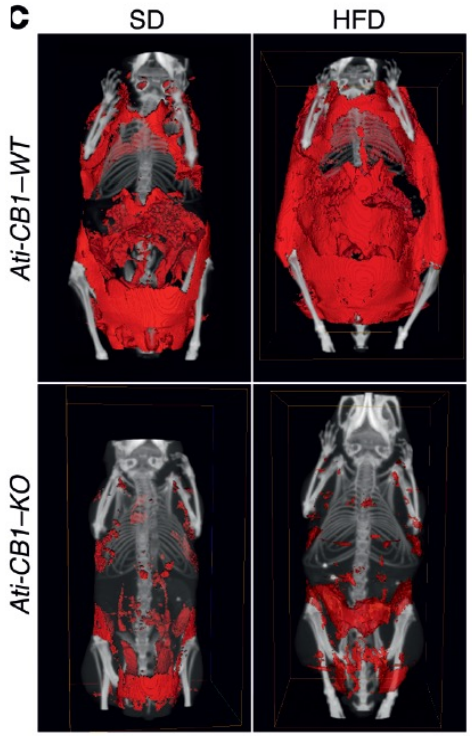
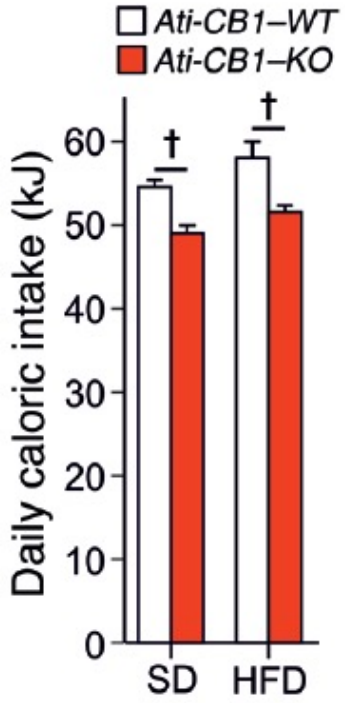
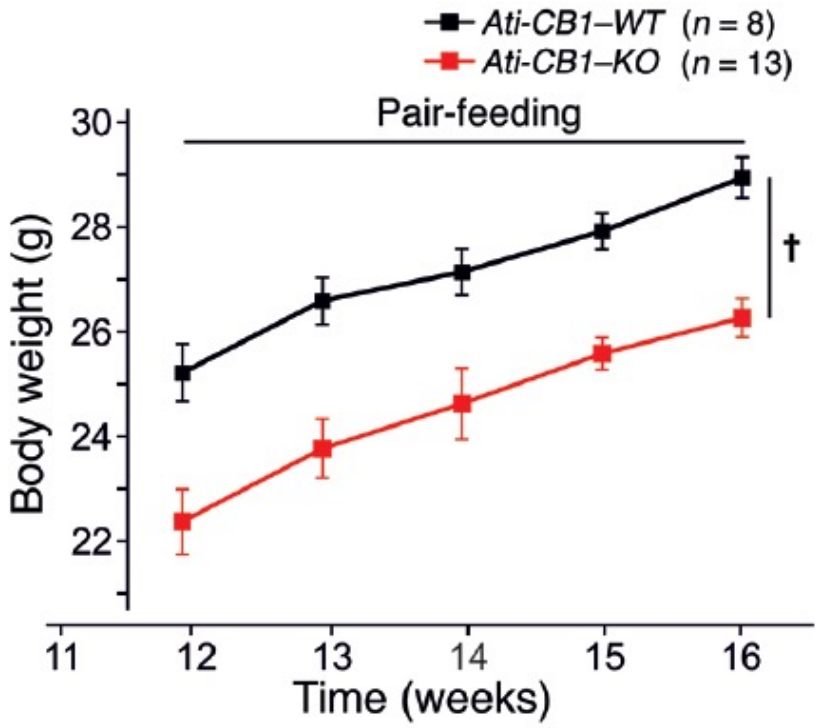
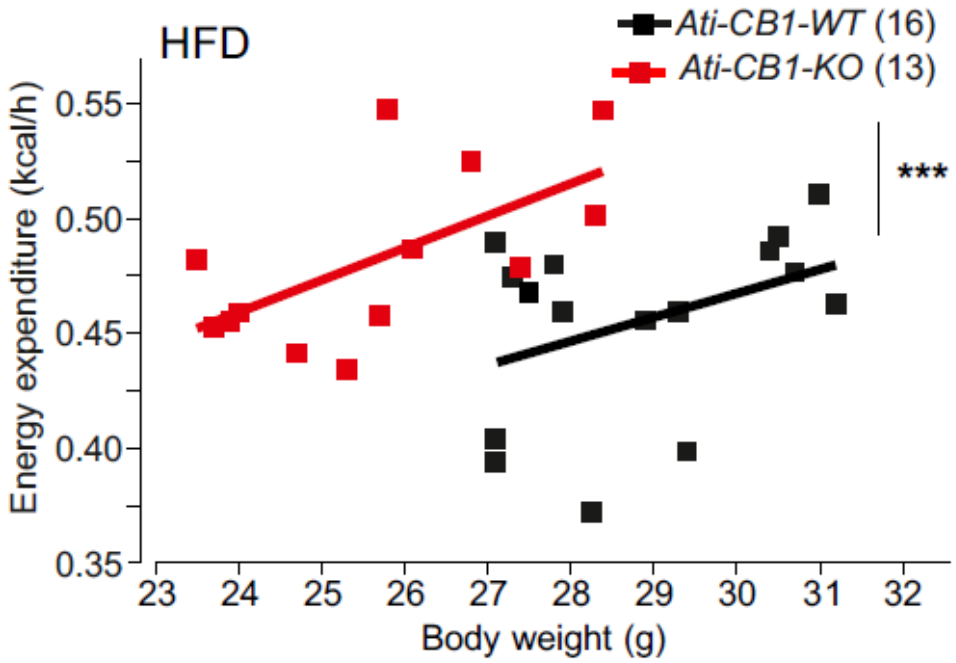


Figure 2[15]

CB1 Loss in Adipose Reduces Food Intake and Increases Energy Expenditure







Enhanced sympathetic innervation[15]

Coordinated Effects of Peripheral CB1 Inhibition

Adipose Tissue

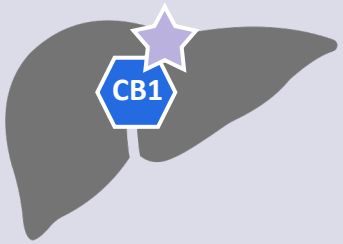
Low food intake[15]

High energy expenditure

Fat mass loss

Reduced leptin[12]

Liver



High insulin sensitivity[16]

Less steatosis despite obesity

Less leptin resistance

GI Tract

Less preference for fatty food

Slow gut transit[17]

Muscle Tissue

High food intake yet same weight[18]

Improved insulin sensitivity

Longer running distance

Peripheral CB1 Inhibition is an Important Therapeutic Modality

Mechanisms address key metabolic drivers of obesity

- **Blockade of CB1 in peripheral tissues**, including adipose tissue, GI tract, muscle, and liver promotes insulin and leptin sensitivity, **reduces adiposity and caloric intake** while **increasing energy expenditure**
- The preclinical data provide a strong rationale for **additive therapeutic effects** when used in combination **with GLP-1 receptor agonists**
- Peripheral modulation of the CB1 pathway represents a **fundamental therapeutic approach to address obesity** and other metabolic disorders
- Currently developing a research plan to collaborate with Skye to **further understand the role of the peripheral CB1 inhibition in obesity**

skye Obesity

- Chapter 03.2 | Chris Twitty, Ph.D.
- Biodistribution and Preclinical Toxicology

Superior Exclusion of CB1 Inhibitor from Brain & No Neuropsychiatric Side Effects

High preclinical dosing concentration highlights Nimacimab's lack of CNS accumulation

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%

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

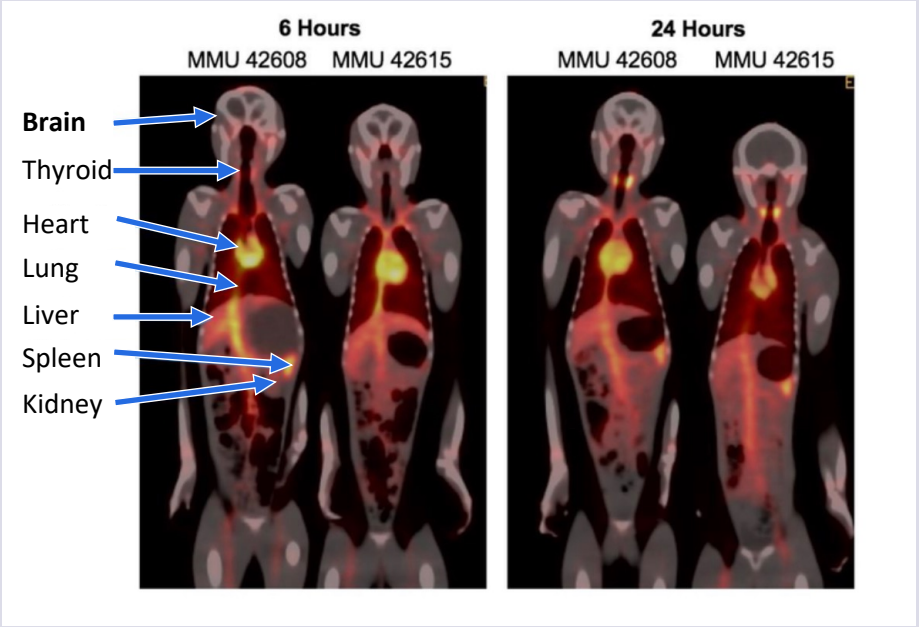
- Tissues harvested without perfusion
- Tissue to plasma assuming 1 mL = 1 g

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

— Uptake of isotope^{124}-labeled Nimacimab antibody in tissues at the timepoints studied

PET imaging also confirmed broad antibody distribution in tissues having upregulated CB1 expression, with no accumulation in the brain

Phase 1 data showed absence of negative neuropsychiatric effects in humans



Nimacimab Toxicology – NOAEL > 75 mg/kg

Safe with significant safety window established

- **IND-enabling toxicology study completed with up to 75 mg/kg Nimacimab administered weekly IV for 4 weeks**
  - No Nimacimab-related observations in toxicology assessments performed including neurological observations
- **Three-week and 26-week toxicology studies 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

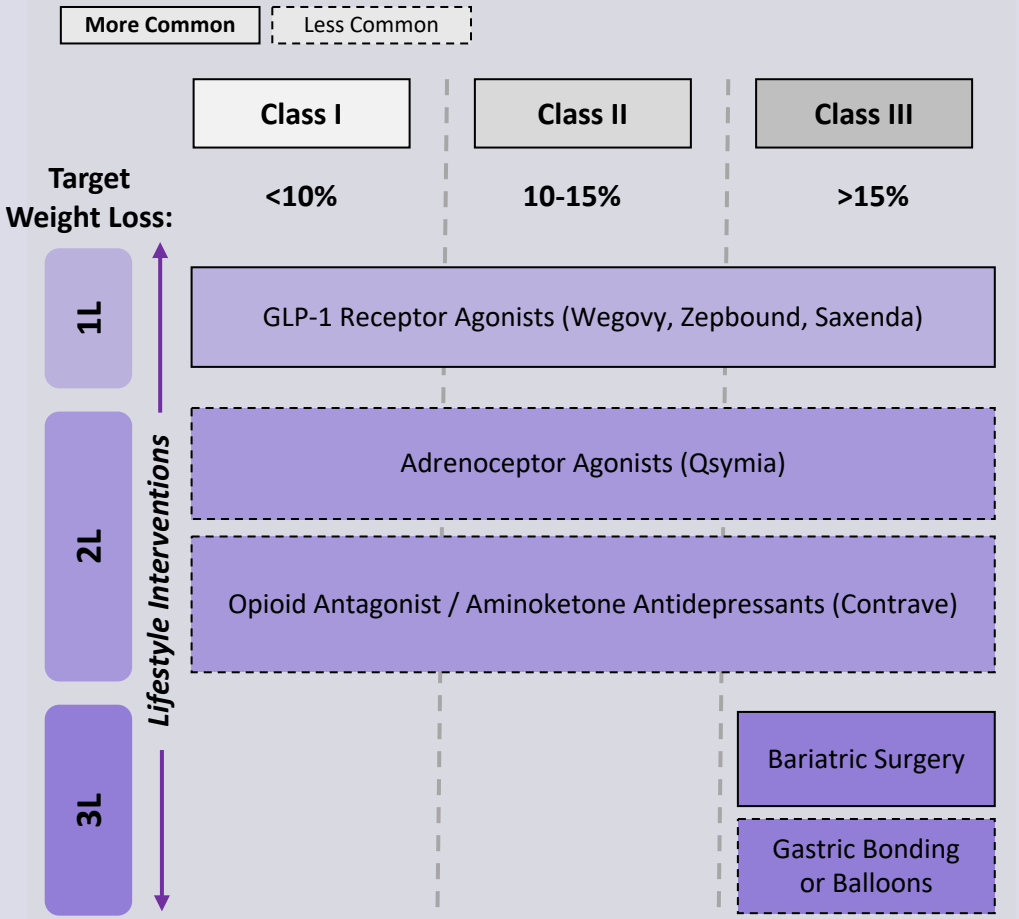
skye Obesity

- Chapter 04 | Louis Aronne, M.D.
- Clinical Experience and Endpoints

Overview of Current AOM Landscape

GLP-1 receptor agonists are the preferred treatment option for patients with obesity

Obesity Pharmacologic Treatment Paradigm[19-30]



Product	Class	ROA	US Approval	Efficacy		Safety	
				% Losing ≥5% / ≥10% of Baseline	Mean % Weight Loss vs. Placebo	Most Common AEs	Discontinued
Zepbound (Tirzepatide)	GIP / GLP-1 Dual Agonist	Injectable	2023	91% / 84% *(15 mg)*	18% *(15 mg)*	Nausea, diarrhea, constipation	7%
Wegovy (Semaglutide)	GLP-1 RA	Injectable	2021	84% / 66% *(2.4 mg)*	12% *(2.4 mg)*	Nausea, diarrhea, vomiting, constipation, abdominal pain, headache	7%
Imcivree (Setmelanotide)	MC4R Agonist	Injectable	2020	-- / 46-80% *(depending on genetic subtype)*	-- *(single arm)*	Skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression	16%
Saxenda (Liraglutide)	GLP-1 RA	Injectable	2014	62% / 34%	5%	Nausea, diarrhea, constipation, vomiting, dyspepsia	10%
Contrave (Naltrexone / Bupropion)	Opioid Antagonist / Aminoketone Antidepressant	Extended -Release Tablets	2014	57% / 35%	3%	Nausea, constipation, headache, vomiting, dizziness, insomnia	24%
Qsymia (Phentermine / Topiramate)	Sympathomimetic Amine Anorectic / Anti-Epileptic	Extended -Release Capsules	2012	67% / 47%	9%	Constipation, paresthesia, dry mouth, dysgeusia, insomnia	16%
Alli (Orlistat)	Lipase Inhibitor	Capsule	1999	21% / 12%	3%	Steatorrhea, bloating, oily spotting, fecal urgency, fecal incontinence	33%

Complementary, Not Competitive

CB1 impacts key metabolic pathways that complement existing products & strategies

	KEY TARGETS / MECHANISMS					
Key Targets Characteristics	GLP-1[31]	GIP[31]	Glucagon[31]	Amylin[32-34]	Myostatin[35-37]	CB1[38-39]
Decreases Appetite / Increases Satiety	✓	? *(limited)*	x	✓	x	✓
Delays Gastric Emptying	✓	x	✓ *(limited)*	✓	x	✓ *(limited)*
Stimulates Insulin Secretion	✓	✓	✓	x	x	✓ *(limited)*
Insulin Sensitivity	x	x	x	✓	✓	✓
Leptin Sensitivity	x	x	x	✓	✓ *(limited)*	✓
Lean Mass Preservation	x	x	x	x	✓	✓
GI Tolerability	x	x	x	x	?	✓
Key Safety Concerns	Nausea, vomiting, diarrhea	Nausea, vomiting, diarrhea	Increased heart rate, LFT, glucose	Nausea, vomiting, headache	Vascular side effects, erythema	Neuro-psychiatric symptoms
Other Notable Considerations	Reduces glucagon secretion	Perceived synergistic in CNS w/ GLP1	Metabolic benefits/ mimic exercise	Reduces glucagon secretion	GLP-1 combination regimen	Complements incretin backbone

Opportunities for Nimacimab

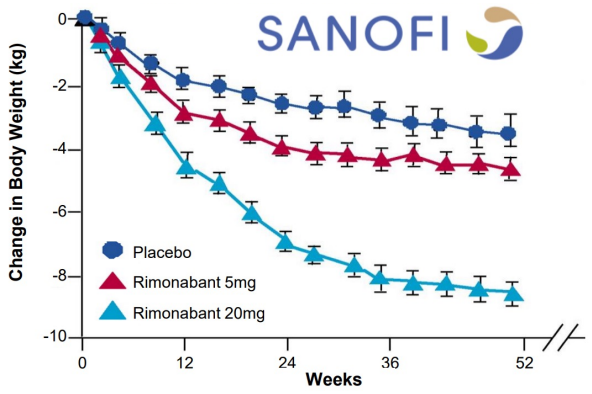
- ✓ Magnitude and sustainability of weight loss
- ✓ Improved safety/tolerability profile (e.g. limited GI side effects)
- ✓ No neuropsychiatric symptoms observed in clinical trials
- ✓ Potential for reduced frequency of drug administration
- ✓ Need for dose titration (PK/PD)
- ✓ Maintenance dose/setting beyond GLP-1 RA
- ✓ Combinability with other mechanisms/agents

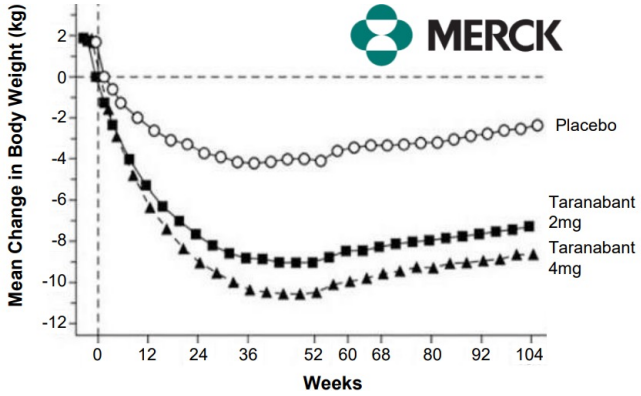
Prescribers/patients/payors will consider differentiated product attributes based on individual needs

Overview of Clinical Experience with CB1 Inhibition as an AOM

CB1 inhibition is a clinically validated MoA; peripherally-directed CB1 inhibitors such as Nimacimab avoid neuropsychiatric adverse events

Clinical Validation – 1st Generation CB1 Inhibitors

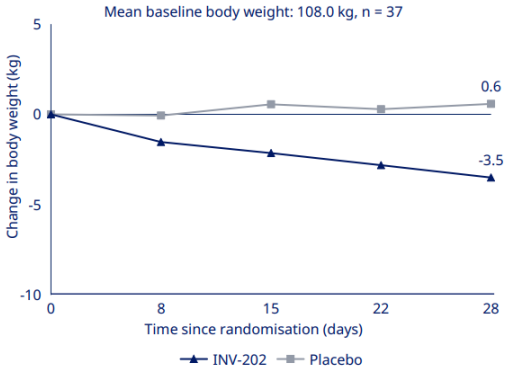




- In Phase 3 trials, **~50% of patients with obesity** treated with Sanofi's rimonabant **achieved ≥5% weight loss** after one year of treatment[38,40]
- In Phase 2 trials, **~65% of patients with obesity** treated with Merck's taranabant **achieved ≥5% weight loss** after one year of treatment[38,41]

Both products were discontinued due to increased risk of suicidality; at the time, **rimonabant was approved as an AOM by the EMA** and had filed in the US

Competitive Benchmark



novo nordisk®

inversago PHARMA

- In a Phase 1b trial, patients treated with Novo Nordisk's CB1 inverse agonist, monlunabant (INV-202), **achieved 3.5 kg weight loss at day 28**[42-43]
- Phase 1b showed that the product was likely **safe + well-tolerated** with low incidence of neuropsychiatric side effects (4 of 20 patients)[42-43]
- Phase 1b results **supported initiation of Phase 2 obesity trial (N=273); Novo is planning to expand Phase 2** to alleviate safety concerns

Nimacimab Phase 1 Data

Demonstrated positive tolerability, pharmacokinetics, and encouraging evidence of efficacy

Single Ascending Dose

- **24 healthy volunteers (18 subjects used as PK population)**
- **0.6 mg/kg, 1.2 mg/kg and 2.5 mg/kg administered IV over 30 minutes**

Multiple Ascending Dose

- **82 patients enrolled with NAFLD (diabetic/pre-diabetic)**
- **0.6 mg/kg, 1.2 mg/kg + 2.5 mg/kg administered IV over 30 minutes on weeks 0, 1, 2 and 3**

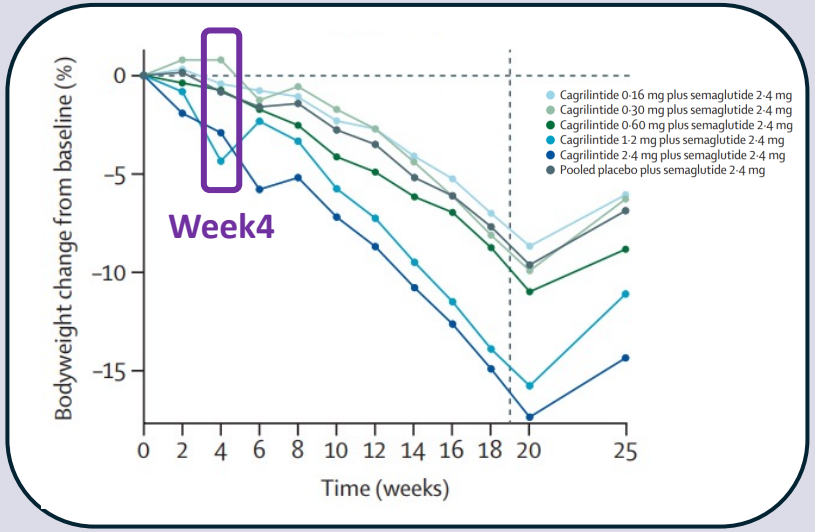
Data and Results

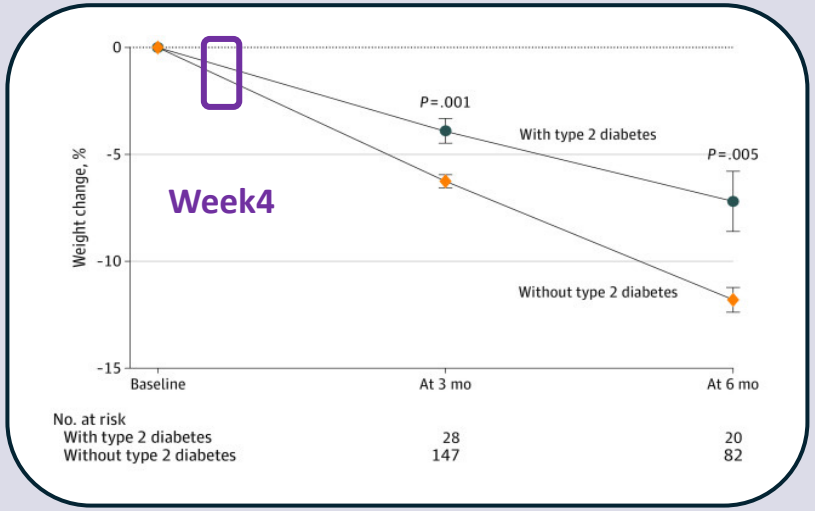
- PK: 18-22 days
- Safety: ADA < 10% of subjects dosed; no neuropsychiatric side effects; positive tolerability
- On average weight was slightly lower or was maintained in all treatment groups across through the end of dosing (Day 28) and at Day 67 (45-day follow-up)
- Placebo group showed a slight increase in weight over most visits, with an increase in weight of 2.57 kg (2.7% increase) in weight at Day 67
- 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 along with additional trends in reduction of inflammation and fibrosis markers

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[39]
- Novo studies using semaglutide in patients with diabetes consistently demonstrate patients lose less weight and at a lower rate than non-diabetic patients[45-47]
  - 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%[44]
- The mean estimated changes in bodyweight from baseline to weeks 2 and 4 in the Phase 1b cagrilinitide studies in the 0.16-0.60 mg plus semaglutide 2.4 mg arm showed a weight increase or very little weight decrease[48]
- 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**





Future AOM Outlook

CB1 inhibitor has the potential to be the key player in the next wave of AOMs

Unmet Needs	Future AOM Outlook	Key Winning Factors
• Accessibility • Sustained weight loss • Safety and tolerability • Broad metabolic benefits	• Oral GLP-1 • GLP-1/GIP/Glucagon combo • CB1 & CB1/GLP-1 combo	• More convenient dosing • Improved tolerability & safety profile • Lean muscle preservation

Key: **CB1 Related**

- CB1 inhibitors represent promising candidates poised to revolutionize the next generation of medicines by directly targeting multiple unmet needs in obesity treatment
- A new entrant may only need to demonstrate a 5-8% reduction in weight, coupled with enhanced safety and improved body composition, to establish sufficiency in the market
- In early studies, Nimacimab has demonstrated positive tolerability, pharmacokinetics, and encouraging efficacy signals

skye Obesity

- Chapter 05 | Beverly Tchang, M.D.

- Ensuring Safety and Tolerability in Peripheral CB1 Inhibition

Overview of CB1 AOM Safety Concerns

CB1 AOM's neuropsychiatric issues and challenges with getting new CB1 AOM approved

Neuropsychiatric Concerns

- Prior brain-penetrated CB1 agents can act directly on CB1 receptors in CNS, potentially disrupting the regulation of mood, cognition, and emotions

Challenges for CB1 Inhibition

- Despite demonstrating clinical benefits, Sanofi's rimonabant was removed from market due to CNS liabilities, including depression and suicidal ideation[49]
- Sanofi's failure resulted in multiple pharmas to drop their CB1 inverse agonist programs[41]

Why Nimacimab?

- Next-generation CB1 inhibitor, Nimacimab, demonstrates excellent brain exclusion in preclinical studies, potentially avoiding neuropsychiatric side effects

Phase 1 MAD – Study Demographics and Baseline Characteristics

Treatment	Placebo n=20	0.6 mg/kg n=21	1.2 mg/kg n=21	2.5 mg/kg n=21	Overall N=83
Sex, n (%)					
Female	11 (55.0)	10 (47.6)	11 (52.4)	9 (42.9)	41 (49.4)
Male	9 (45.0)	11 (52.4)	10 (47.6)	12 (57.1)	42 (50.6)
Age (years)					
Mean (SD)	51.4 (11.08)	52.8 (7.63)	54 (8.21)	52.5 (9.06)	52.7 (8.95)
Race, n (%)					
Asian	3 (15.0)	2 (9.5)	1 (4.8)	0 (0.0)	6 (7.2)
Black or African American	1 (5.0)	3 (14.3)	0 (0.0)	3 (14.3)	7 (8.4)
White	16 (80.0)	16 (76.2)	19 (90.5)	17 (81.0)	68 (81.9)
Other	0 (0.0)	0 (0.0)	1 (4.8)	1 (4.8)	2 (2.4)
Ethnicity, n (%)					
Hispanic or Latino	12 (60.0)	12 (57.1)	14 (66.7)	11 (52.4)	49 (59.0)
Not Hispanic or Latino	8 (40.0)	9 (42.9)	7 (33.3)	10 (47.6)	34 (41.0)

Table 1 - Study Demographics and Baseline Characteristics[39]

Phase 1 MAD – Demographics and Baseline Characteristics *Cont'd*

Treatment	Placebo n=20	0.6 mg/kg n=21	1.2 mg/kg n=21	2.5 mg/kg n=21	Overall N=84
Diabetes History, n (%)					
Diabetes	16 (80.0)	16 (76.2)	19 (90.5)	18 (85.7)	69 (83.1)
Pre-diabetes	4 (20.0)	5 (23.8)	2 (9.5)	3 (14.3)	14 (16.9)
Weight (kg)					
Mean (SD)	94.25 (15.091)	93.77 (17.140)	90.17 (12.364)	92.66 (10.586)	92.69 (13.840)
BMI (kg/m2)					
Mean (SD)	33.815 (4.4220)	33.698 (3.7664)	33.121 (3.6326)	32.526 (2.8976)	33.284 (3.6774)

Table 1 - Study Demographics and Baseline Characteristics[39] – Continued

Phase 1 MAD – Treatment Emergent AEs by Preferred Term

Treatment	Placebo n=20	0.6 mg/kg n=22	1.2 mg/kg n=21	2.5 mg/kg n=21	Active Overall N=63
AE Preferred Term in Descending Order of Frequency (Occurring in 2 or More Patients), n (%)					
Diarrhea*	8 (40.0)	7 (33.3)	13 (61.9)	6 (28.6)	26 (41.3)
Headache	3 (15.0)	5 (23.8)	3 (14.3)	0 (0.0)	8 (21.7)
Upper Respiratory Tract Infection	2 (10.0)	1 (4.8)	2 (9.5)	3 (14.3)	6 (9.5)
Dizziness	1 (5.0)	2 (9.5)	3 (14.3)	1 (4.8)	6 (9.5)
Nausea	2 (10.0)	2 (9.5)	0 (0.0)	2 (9.5)	4 (6.3)
Vomiting	2 (10.0)	1 (4.8)	2 (9.5)	1 (4.8)	4 (6.3)
Abdominal Pain	0 (0.0)	0 (0.0)	3 (14.3)	0 (0.0)	3 (4.8)
ECG QT Prolongation	0 (0.0)	2 (9.5)	0 (0.0)	0 (0.0)	2 (3.2)
Neck Pain	0 (0.0)	2 (9.5)	0 (0.0)	0 (0.0)	2 (3.2)
Dry Mouth	0 (0.0)	0 (0.0)	1 (4.8)	1 (4.8)	2 (3.2)

*** Associated with the de novo lipogenesis protocol**

Table 2 - Treatment Emergent AEs by Preferred Term[39]

Columbia-Suicide Severity Rating Scale (C-SSRS)

Treatment	Placebo n=20	0.6 mg/kg n=22	1.2 mg/kg n=21	2.5 mg/kg n=21	Active Overall N=63
Baseline, n (%)					
Suicidal ideation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Suicidal Behavior	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Follow-up (Day 29), n (%)					
Suicidal ideation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Suicidal Behavior	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 3 - Columbia-Suicide Severity Rating Scale (C-SSRS)[39]

Phase 1 MAD – Safety Summary

Overall Safety	Nimacimab appears to be safe and well-tolerated, with low rate of treatment emergent adverse events and no drug-related treatment discontinuation
GI Tolerability	Little to no gastrointestinal disorder associated adverse events (4.8%)
Neuropsychiatric Events	No significant changes in neuropsychiatric findings as measured by the CSSR-S, and no signs of psychiatric adverse events

Overview of Nimacimab Safety History and Potential

Nimacimab shows promise in establishing a differentiated safety profile for treating obesity

No Neuropsychiatric Event

Superior exclusion of CB1 inhibitor from brain in preclinical studies, and no neuropsychiatric side effects reported in both preclinical studies and Phase 1 trial on 82 healthy volunteers and NAFLD patients[39]

Excellent GI Tolerability

Nimacimab has the potential to provide enhanced gastrointestinal tolerability compared to existing first-line therapies and other CB1 blockades[39]

Differentiated Overall Safety Profile

Safety profile of CB1 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 CB1 inverse agonists[39,41,43,49]

skye Obesity

- Chapter 06 | Tu Diep, M.Sc.

- CBeyond™: Phase 2 Study Design

Nimacimab – Target Product Profile

Target	Minimal Requirement	Ideal
Therapeutic Area	Adults with BMI >30kg/m^2 or >27 kg/m^2 with co-morbidities	
Indications for Use	For use as an adjunct to calorie diet and increased physical activity in chronic weight management.	
Dosage Forms and Strength	200 mg Nimacimab	TBD (200mg – 400mg)
Dosage and Administration	Once weekly subcutaneous injection	Once monthly subcutaneous injection
Clinical Pharmacology/Efficacy	Mean weight loss 5-10%	Mean weight loss >10% Improvement in fat:lean mass ratio Improvement in triglycerides Improvement in leptin/insulin sensitivity
Safety Pharmacology	No psychiatric side-effects Minimal GI side-effects similar to or better than rimonabant	
Proposed Clinical Program	Phase 2 – Proof-of-concept (26 weeks) Phase 2b – Dose ranging/optimization: weekly vs. monthly dosing (52 weeks) Phase 3 – Optimal dose vs. placebo (52 weeks)	

Key Purposes of Nimacimab Phase 2 Clinical Trial Design

Efficacy

Proof of Concept

- Demonstrate that “true” peripheral CB1R inhibition results in meaningful weight loss

Combination Potential

- Demonstrate that CB1R inhibitors, plus GLP-1R agonists, have additive/synergistic effects on weight loss

Lean Mass Preservation

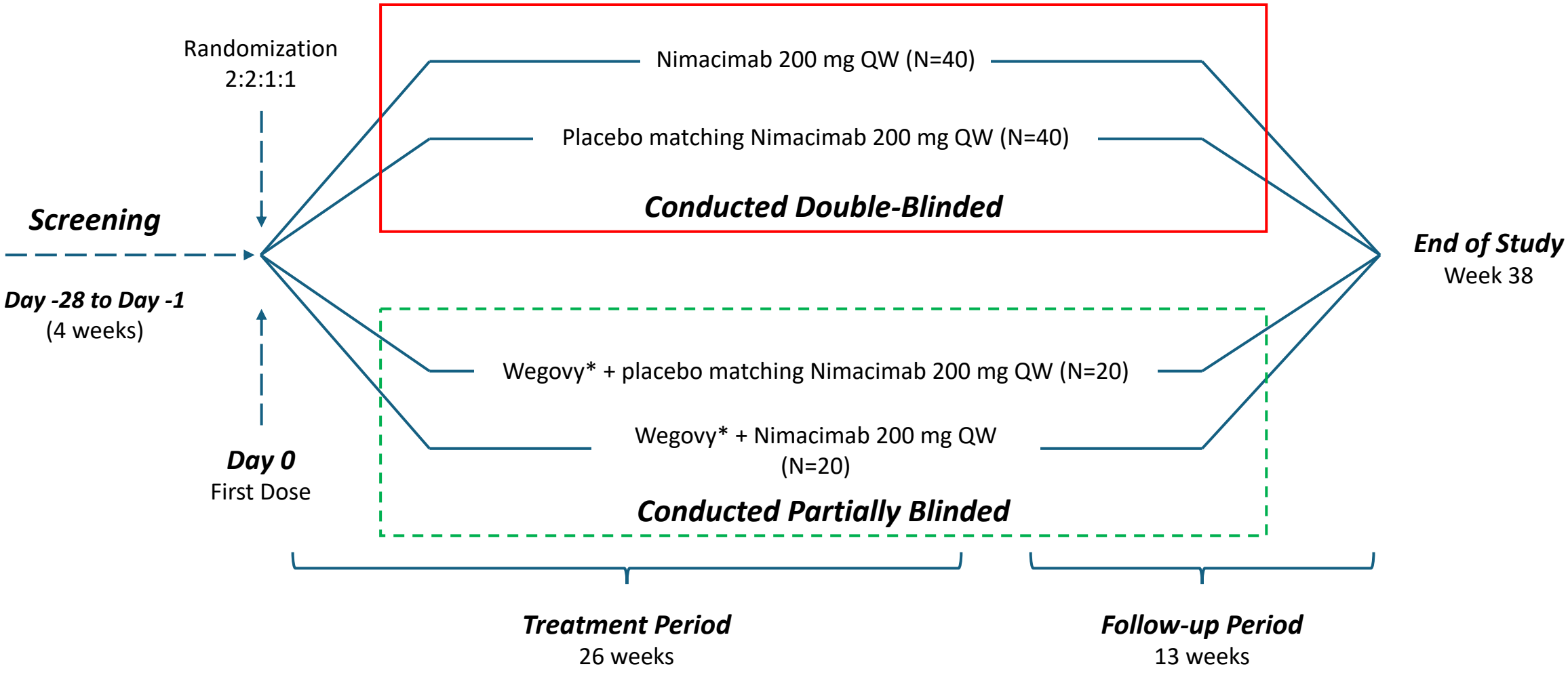
- Demonstrate that weight-loss associated with Nimacimab treatment does not result in significant lean mass loss

Safety & Tolerability

Demonstrate that CB1R inhibition does not result in significant neuropsychiatric side effects

Demonstrate that weight loss with CB1R inhibition is more tolerable than GLP-1R agonist therapies

CBeyond: A Phase 2 Study of Once Weekly Nimacimab Compared with Placebo and Once Weekly Nimacimab Co-administered with Semaglutide in Participants Who are Overweight or Obese



All drugs are investigational and subject to regulatory approval .

*Note: Wegovy dose starts at 0.25 mg, titration up to 1.7 or 2.4 mg
QW = once weekly dosing

CBeyond Clinical Trial Objectives

Overview of Phase 2 clinical trial objectives

Primary Endpoint

- 40 subjects per arm between Nimacimab and placebo is powered to demonstrate 8% difference in mean weight loss at 26 weeks; 80% power

Secondary Endpoints

- Safety and tolerability
- Neuropsychiatric and cognitive evaluation
- Change in body composition by DEXA
- Change in key metabolic parameters
  - Triglycerides
  - Insulin sensitivity
  - Leptin sensitivity

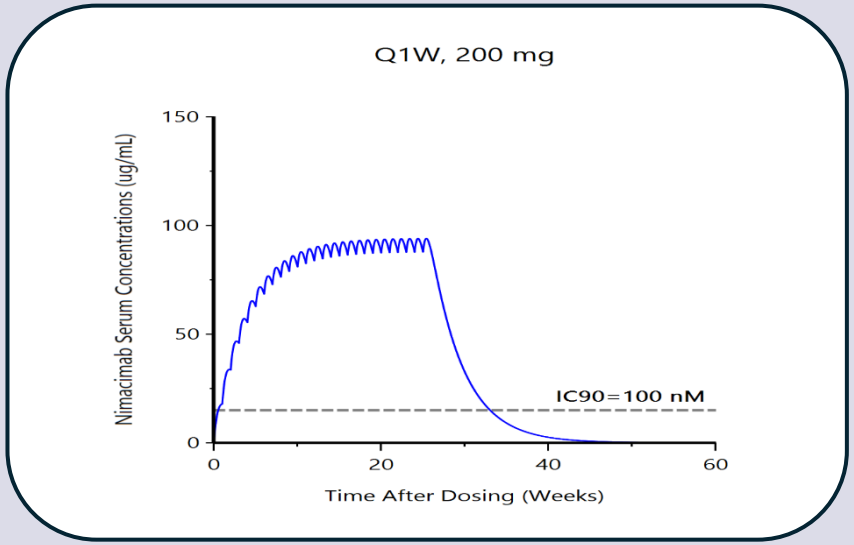
Exploratory Endpoints

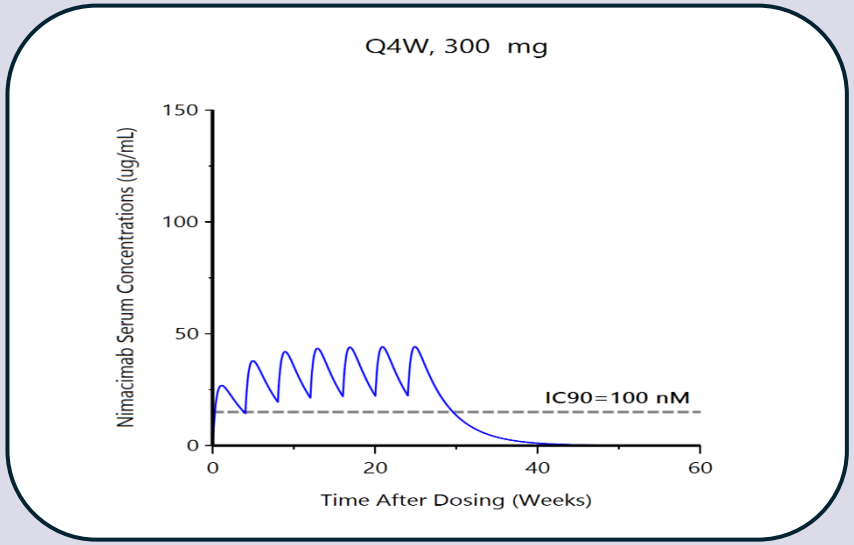
- Evaluation of combination of Nimacimab and semaglutide
- Evaluation of difference in weight loss between Nimacimab and semaglutide
- Evaluation of difference in body composition between Nimacimab and semaglutide
- Improvement in sleep

Modeling Nimacimab Dosing for Phase 2 Study

PK modeling based on Nimacimab's Phase 1 SC bioavailability study

- Mean pharmacokinetic data from the 100 mg SC dose was simulated to predict concentrations that would achieve a target dosing regimen beyond the IC90
- Assumptions:
  - No inter-individual differences modeled
  - No anti-drug antibody effect on PK
- Model suggests that current Phase 2 dose (200mg Q1W) readily exceeds IC90
- Phase 1 safety profile and NOAEL of 75mg/kg provide rationale to safely dose Nimacimab at 300mg monthly and still exceed IC90





Nimacimab Phase 2 Clinical Trial Design – Inclusion Criteria

Key Inclusion Criteria

1. Have Body Mass Index (BMI) of:
   a. ≥ 30 kg/m2 to ≤ 45 kg/m2 ***OR***
   b. ≥ 27 kg/m2 and < 30 kg/m2 with clinically confirmed diagnosis of at least 1 of the following weight-related co-morbidities:
      i. Dyslipidemia
      ii. Cardiovascular disease
      iii. Obstructive sleep apnea syndrome
      iv. Controlled arterial hypertension
2. Have an HbA1c < 48 mmol/mol at screening
3. Have had a stable body weight for the 3 months prior to screening (no more than 5% body weight gain and/or loss)
4. If on cardiovascular, anti-hypertensive, anti-depressant medications or/and hormone replacement therapy, must be controlled on stable dose for 3 months prior to screening

Nimacimab Phase 2 Clinical Trial Design – Exclusion Criteria

Key Exclusion Criteria

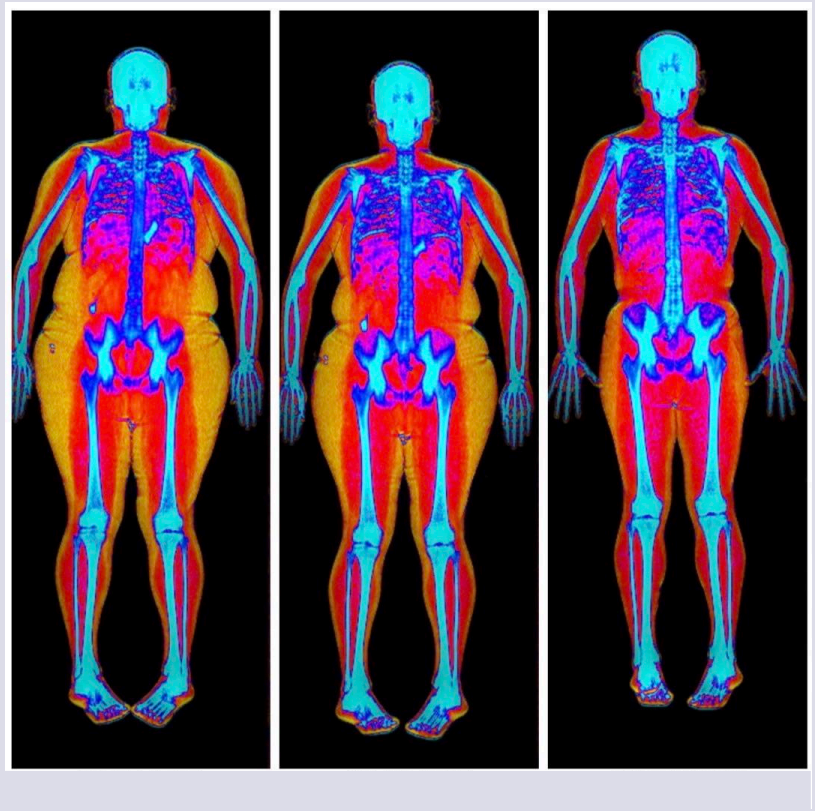
1. Prior diagnosis of T1DM or T2DM, or rare forms of diabetes mellitus or laboratory value suggestive of diabetes during screening
2. Have a prior or planned surgical treatment for obesity
3. Have obesity induced by other disorders, diagnosed monogenetic or syndromic forms of obesity, use of systemic corticosteroids, or uncontrolled hypothyroidism
4. Have or plan to have endoscopic and/or device-based therapy for obesity or have had device removal within the last 6 months prior to screening
5. Renal impairment as eGFR < 30 mL/min/1.73 m2 at screening
6. Have history of any of the following:
    a. Major Depressive Disorder within the last 2 years prior to screening
    b. A lifetime history of suicide attempts
    c. Other severe psychiatric disorder(s)
7. History or presence of alcohol or drug abuse within the 1 year prior to Day 0

Robust Plan to Evaluate Neuropsychiatric, Neurological Changes and Quality of Life

Questionnaire/Test	Purpose
Columbia-Suicide Severity Rating Scale (C-SSRS)	C-SSRS is a validated questionnaire that identifies whether someone is at risk for suicide, assess the severity and immediacy of that risk, and gauges the level of support that the person needs.
Patient Health Questionnaire-9 (PHQ-9)	PHQ-9 is validated to measure the frequency and severity of depressive symptoms.
SF-36v2® Acute Form	SF-36 was designed to be a brief yet comprehensive measure of general health status. It consists of eight scales yielding two summary measures: physical and mental health.
IWQOL-Lite CT	IWQOL-Lite-CT is a 20-item measure with two primary domains (Physical [seven items] and Psychosocial [13 items]) and has been validated based on FDA guidance on patient-reported outcomes.
Patient Global Impressions of Severity (PGI-S) for Physical Activity	PGI-S for Physical Activity is a global index used to rate the severity of a specific condition. This index will specifically evaluate limitations in a participant's physical activity.
Cognitive Testing with Digit Symbol Substitution Test (DSST)	DSST is used to measure attention, processing speed and executive function. These cognitive domains are particularly relevant as they are important for everyday activities such as driving and both occupational and independent living skills.
Scripted Neurological Questionnaire	Battery of questions and evaluations that assess a participant’s cognitive, motor and sensory function.

Secondary and Exploratory Endpoints

DEXA Scan for Body Composition



Evaluation of OSA/Sleep Disturbance

Dreem headband, SpO2 ring, and AI-enabled sleep study

Zepbound (tirzepatide) includes OSA in Labeling Language, with the Potential for OSA to be More Broadly Recognized as an Indication for GLP-1s

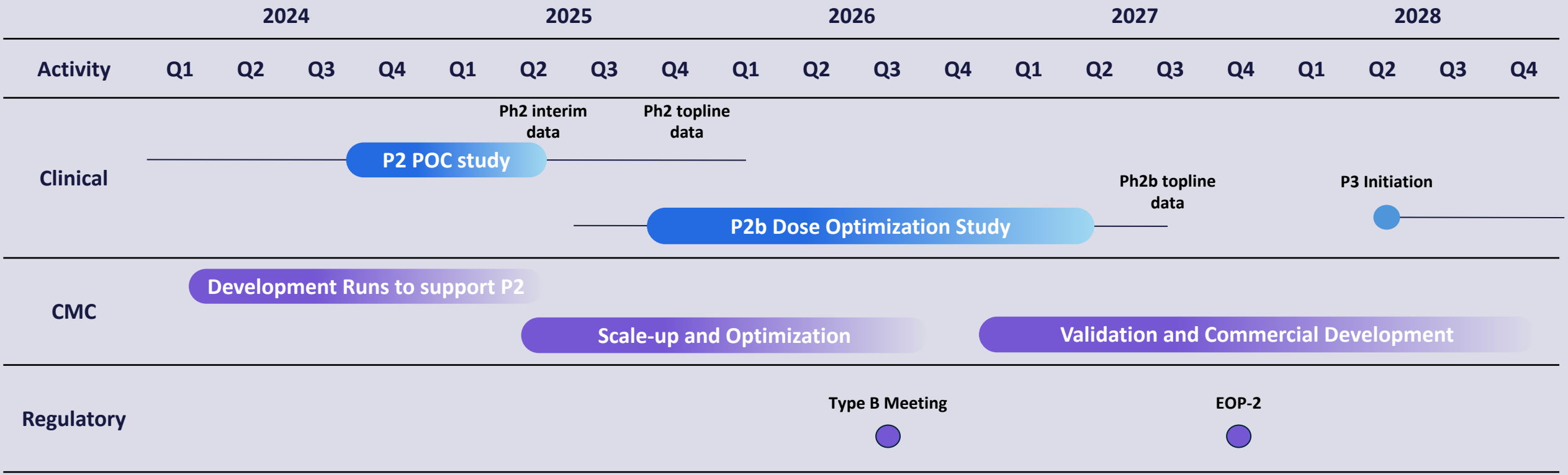
	zepbound™ (tirzepatide) injection Lilly	wegovy® semaglutide injection 2.4 mg novo nordisk®	Saxenda® liraglutide injection 3mg novo nordisk®
Labeled Indication	• Chronic weight management in adults with obesity or overweight plus comorbidities[50]	• Cardiovascular risk management in adults with established cardiovascular disease and either obesity or overweight[51] • Excess body weight reduction and long-term weight reduction maintenance[51]	• Chronic weight management in adults with obesity or overweight plus comorbidities[52]
Specified "Comorbid Conditions"	*"At least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus,* ***obstructive sleep apnea,*** *or cardiovascular disease)."*	*"At least one weight-related comorbid condition, such as treated or untreated dyslipidemia or hypertension."*	*"At least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia)."*

skye

All drugs are investigational and subject to regulatory approval

Clear Development Path for Nimacimab in Obesity

Our key milestones position for value generation



All drugs are investigational and subject to regulatory approval

Nimacimab Subcutaneous Injection – Future Developments

Phase 2 | **Phase 2b** | **Commercial** | **Future**

Pre-filled Syringe with Safe Injection Unit

Pre-filled Syringe with Auto-Injector Unit

Auto-Injector with Smart Technology

Plan for future ease-of-use and implementation of technology to improve compliance

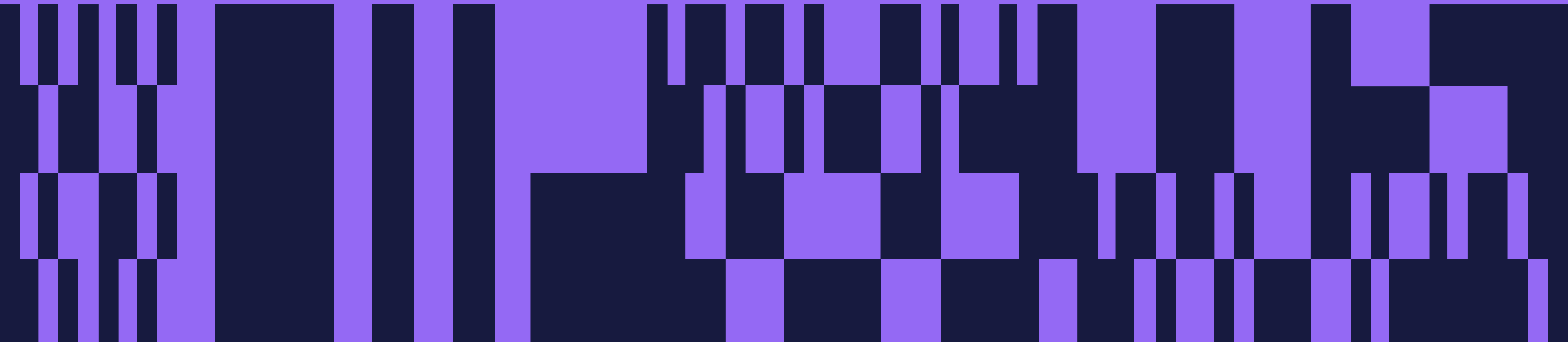
All drugs are investigational and subject to regulatory approval

Key Takeaways

	Description	Goal
Treatment Arms	• Includes **exploratory Nimacimab + semaglutide treatment arm** • Designed to demonstrate the efficacy of multiple Nimacimab treatment approaches and **support the inclusion of combination treatment arm in subsequent trials**	**Improve upon GLP-1 product profile;** **Facilitate treatment flexibility by offering tailored approaches for individual patient needs**
Trial Endpoints	• **Primary**: ≥8% mean change in weight from placebo • **Secondary**: safety, tolerability, PK, change in body composition • **Exploratory**: combination, sleep metrics, biomarkers	**Demonstrate antibody CB1 approach leads to clinically meaningful weight loss;** **Provide differentiated treatment option with superior lean body mass preservation**
Phase 2 Expected Timeline	• **Trial initiation**: August 2024 • **Interim data**: Q2 2025 • **Topline data**: Q4 2025	**Support initiation of Phase 2b trial in 2026**

skye Obesity

- Chapter 07 | Panel and Punit Dhillon
- Panel Session and Q&A



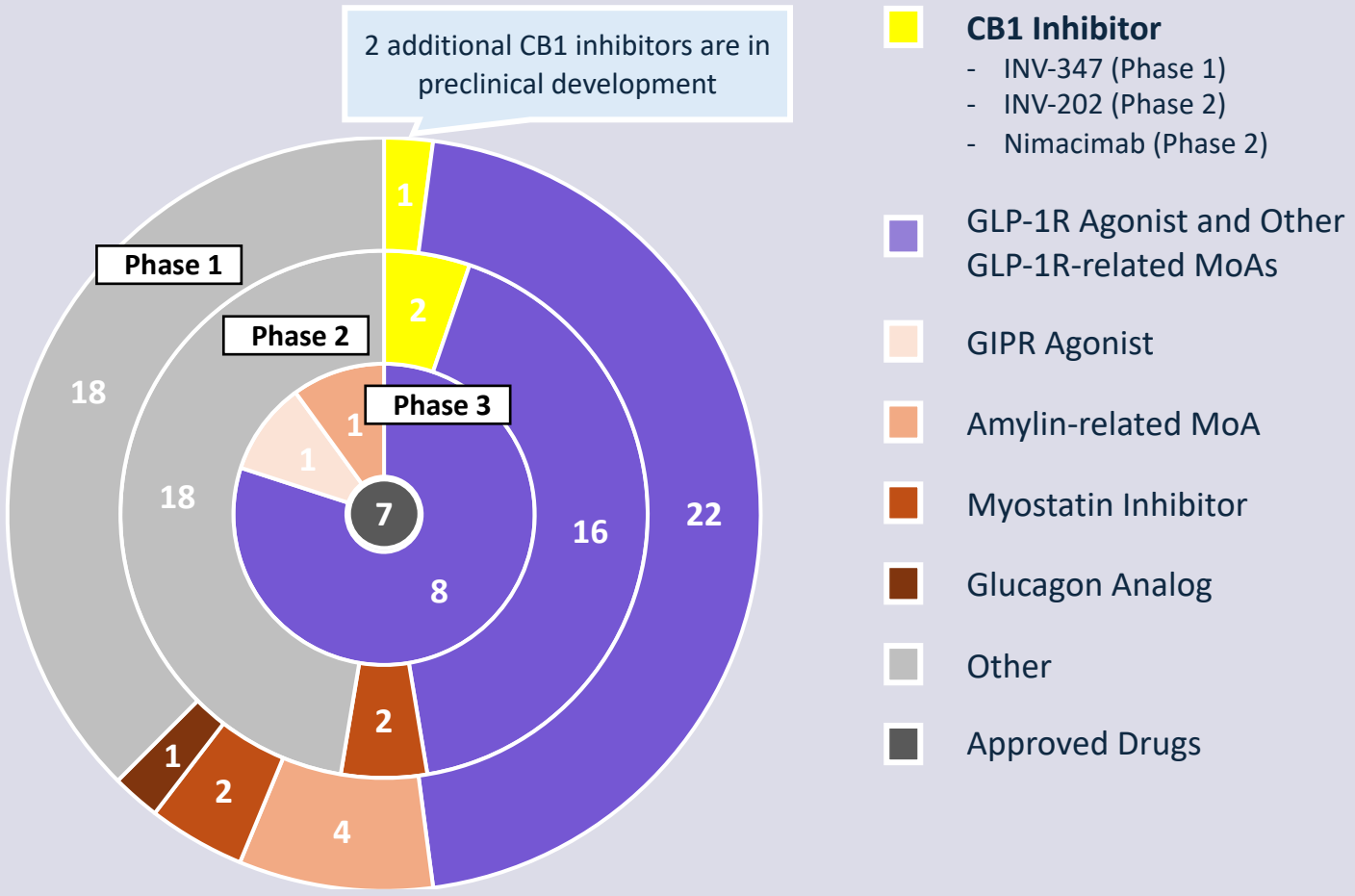
FAQs

Key Question	Response	Section / Speaker
How is Nimacimab different than rimonabant?	Nimacimab is peripherally restricted and does not show neuropsychiatric side effects; first generation CB1 agonists were highly BBB-penetrative	*Ensuring Safety and Tolerability in Peripheral CB1 Inhibition* *(Beverly Tchang, M.D.)*
Will Nimacimab achieve the same level of weight-loss as GLP-1 RAs?	Nimacimab seeks to establish a safer clinical profile and may demonstrate significant weight reduction as a standalone therapy in Phase 2	*Clinical Experience and Endpoints* *(Louis Aronne, M.D.)*
What are the key factors that differentiate your drug in the anti-obesity medication landscape?	1) Composition – preserves lean mass 2) Limited CNS penetration, excellent GI tolerability 3) May maintain long-term weight loss without a rebound	*Welcome and Introduction* *(Punit Dhillon)*
Can you provide more details about the safety and tolerability profile of Nima compared to GLP-1 class drugs?	Nimacimab has potential to provide enhanced GI tolerability; demonstrated no neuropsychiatric events in both preclinical studies and Phase 1 trial	*Ensuring Safety and Tolerability in Peripheral CB1 Inhibition* *(Beverly Tchang, M.D.)*
What is the difference between a negative allosteric modulator and inverse agonist?	Inverse agonists compete for the orthosteric binding site with natural endocannabinoids, while allosteric modulators bind non-competitively to an allosteric site of CB1. However, negative allosteric modulators, like Nimacimab, also function as an inverse agonist by driving a negative signal on the CB1 receptor	*Scientific Rationale for Peripheral CB1 Inhibition* *(Christopher Twitty, Ph.D.; Marcus Goncalves, M.D., Ph.D.)*
What dose are you using for Wegovy (semaglutide)?	Wegovy's recommended dosage: initiate at 0.25 mg once weekly for 4 weeks, increase the dose until a dose of 1.7 mg or 2.4 mg is reached	*Nimacimab Phase 2 Clinical Trial Design* *(Tu Diep, M.Sc.)*
When will the first patient be enrolled in the Phase 2 trial? When will interim data be published?	FPFV: Q3 2024 Interim Data: Expected Q2 2025	*Nimacimab Phase 2 Clinical Trial Design* *(Tu Diep, M.Sc.)*

Obesity Pipeline Overview

Obesity Clinical Pipeline[53]

Number of Assets by Phase



CB1 Inhibitor
- INV-347 (Phase 1)
- INV-202 (Phase 2)
- Nimacimab (Phase 2)

GLP-1R Agonist and Other GLP-1R-related MoAs

GIPR Agonist

Amylin-related MoA

Myostatin Inhibitor

Glucagon Analog

Other

Approved Drugs

Key Pipeline Insights

- Obesity pipeline is primarily focused on GLP-1R-related MoAs, comprising the majority of Phase 3 assets
- Skye's Nimacimab and Novo's INV-202 represent the only CB1 inhibitors in Phase 2 trials
  - Skye's CBeyond Phase 2 trial initiation in August 2024[39]
  - The INV-202 Phase 2 trial initiated in 2023; however, no updates have been provided since Novo's acquisition of the asset
- There are 7 FDA-approved drugs to treat obesity, with GLP-1R agonists including Wegovy and Zepbound preferred

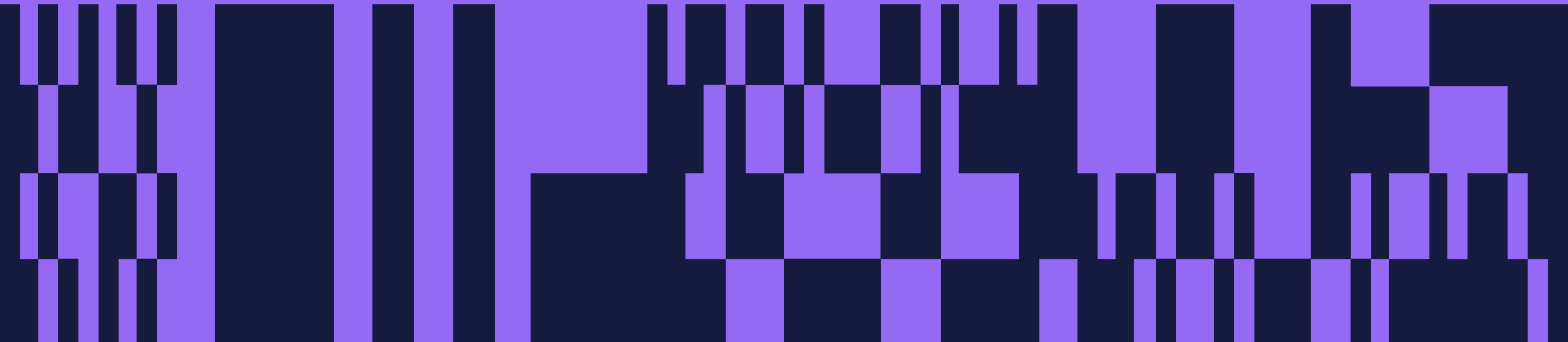
skye

All drugs are investigational and subject to regulatory approval .

Audience Q+A

skye Obesity

- Chapter 08 | Punit Dhillon
- Closing Remarks and Next Steps



Event Summary

Key points of today's KOL discussion

- **NAM antibody blocks CB1 signaling *independent* of endocannabinoid binding**
  - Functions as an **antagonist** (in presence of CB1 agonist with B-arrestin endpoint) and as an **inverse agonist** (twice as potent as rimonabant with cAMP endpoint)
  - Favorable safety profile with mechanism of inhibition may provide a large therapeutic index
- **CB1 blockade in peripheral tissues enhances insulin and leptin sensitivity, reduces adiposity and caloric intake, and increases energy expenditure, complementing incretin mimetics for additive therapeutic effects.**
- **Nimacimab complements other AOMs, offering differentiated and synergistic benefits to other MoAs.**
  - Data validates CB1's role in inflammatory and fibrotic mechanisms of disease mechanisms, addressing obesity co-morbidities
- **Nimacimab demonstrates strong brain exclusion in preclinical + Phase 1 studies; potentially avoids neuropsychiatric side effects; more tolerable GI side effect profile**
- **Phase 2 clinical trial design provides POC in weight loss and signal detection in combo with GLP-1 RA**
  - Demonstrate better tolerability and no neuropsychiatric side effects while preserving lean mass
- **Skye continues rapid development of Nimacimab while continuously identifying opportunities to differentiate the product and create value**
  - ✓ Pre-clinical R&D is ongoing; Additional collaborations with academic centers are expected
  - ✓ Nimacimab is Phase 2-ready in follow-on metabolic indications
  - ✓ Collaboration with Beacon Biosignals will enable the collection of novel sleep disturbance data
  - ✓ 18 clinical trial sites, including academic centers will serve as part of Phase 2 trial

Obesity Program: Planned Next Steps and Upcoming Milestones

Nimacimab's Phase 2 trial is expected to initiate in Q3 2024, with interim data expected by Q2 2025

2024

- ☑ Nimacimab obesity IND clearance – Q1
- ☑ GMP Manufacturing to support future clinical trials – Initiated
- Nimacimab Phase 2 obesity clinical trial initiation – August 2024
- Continued in vivo studies, biomarker development, and R&D pipeline

2025

- Interim data at 50% enrollment 26 weeks dosing – Q2
- Topline data full enrollment – Q4

Obesity Program: Path to Success

Current AOM landscape and aspirational targets for Nimacimab

Future Market Considerations

- GLP-1 market saturation and generic entrants
- Incretin therapies as the "backbone"
- **CB1 blockade being a monotherapy and additive to incretins**

AOM Outlook

- Oral GLP-1
- GLP combo
- Amylin combo
- **CB1 mono and combo**

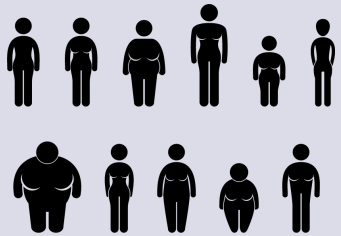
Key Winning Factors

- **Clinically meaningful weight loss**
- **Low Adverse Events**
- **Convenient dosing + Long-term usage**
- **Lean muscle preservation**
- **Address co-morbidities**

Nimacimab Opportunity

- **CB1 blockade being the new backbone**
- **~8% reduction + enhanced safety and improved body composition to achieve market establishment**

Obesity is Highly Heterogeneous with Many Sub-Types



Key: **CB1 Related**

Nimacimab Backbone and Foundation

2024 → **2030+**

All drugs are investigational and subject to regulatory approval

Thank You

Learn more, please contact:

ir@skyebioscience.com

+1 (858) 410-0266

11250 El Camino Real, Suite 100
San Diego, CA 92130

Reference

1. World Health Organization, 2022. Obesity
2. Kaplan LM, 2023
3. Kaplan LM, 2024
4. Kaplan LM, 2012
5. Sumithran P et al. N Engl J Med. 2011
6. Leibel R et al. N Engl J Med. 1995
7. Kaplan LM, 2006
8. Sanyal AJ, 2024
9. Trillou et al., Am J Physiol Regul Integr Comp Physiol. 2002
10. Herling et al. Endocrinology. 2008
11. Gomez et al., J. Neurosci. 2002
12. Tam et al., JCI. 2010
13. Cluny et al., Br J Pharmacol. 2010
14. Tam et al., Cell Metabolism 2012
15. Ruiz de Azua et al., J Clin Invest. 2017
16. Osei-Hyiaman et al., J Clin Invest. 2008;
17. Avalos et al., Nutrients. 2020
18. González-Mariscal et al., FASEB J. 2019
19. AGA Guidelines, 2022.
20. McMahon et al., Arch Intern Med. 2000.
21. Draznin et al., Clin Diabetes. 2022
22. O'Brien et al., National Library of Medicine. 2016
23. Chakhtoura et al., EClinicalMedicine. 2023
24. Drew, Dixon, & Dixon, Vasc Health Risk Manag. 2007
25. Lonneman et al., P T. 2013
26. Sherman et al., P T. 2016
27. Apovian et al., Obesity. 2013
28. Sunyer et al., NEJM. 2015
29. FDA. Wegovy Website
30. Jastreboff et al., NEJM. 2022
31. Guggenheim Obesity Report
32. Boyle. J Clin Med. 2022
33. Dehestani. J Obes Metab Syndr. 2021
34. Suh. J Bone Metab. 2020
35. Roth. PNAS. 2008
36. Choi. Am J Physiol Endocrinol Metab. 2011
37. Schurgers. Cells. 2021
38. RBC Capital Markets (February 2024)
39. Skye Internal Data
40. Després et al., NEJM. 2005;
41. Aronne et al., Int. J. Obes. 2010;
42. Novo Nordisk Company Materials – Obesity Care;
43. Crater et al., Diabetes Obes Metab. 2023
44. Guhsn et al., JAMA 2022
45. Ahren et al., Diabetes Obes Metab. 2018
46. Rubino et al., JAMA. 2021
47. Wadden et al., JAMA. 2021
48. Enebo et al., Lancet, 2021
49. Pi-Sunyer et al., JAMA. 2006
50. Zepbound FDA label
51. Wegovy FDA label
52. Saxenda FDA label
53. LifeSci Obesity Tracker