Developing Innovative Medicines to Treat Obesity and Other Metabolic Diseases

skye

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Nasdaq: SKYE

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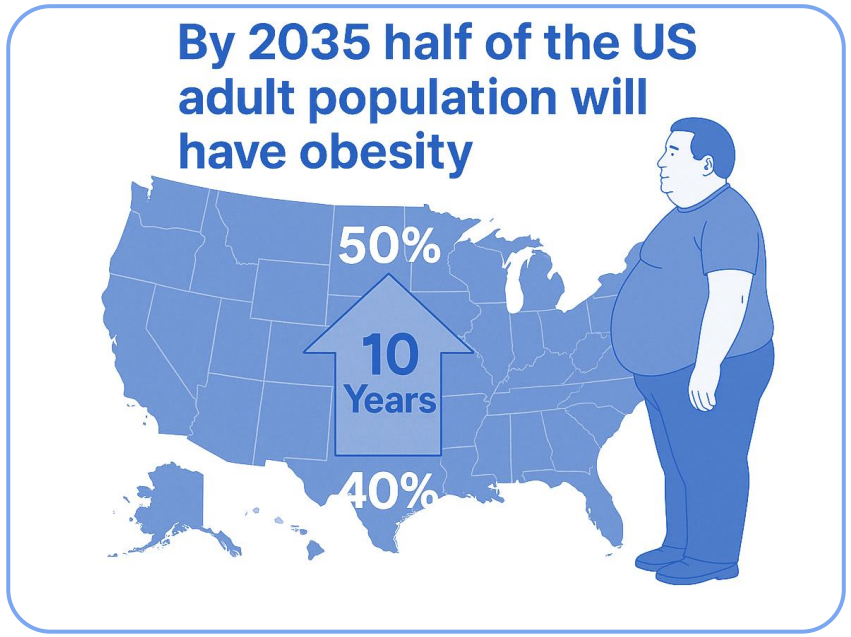
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Mission

Pioneer and commercialize the first CB1 antibody to tackle current and future unmet needs of obesity



GLP-1s



GLP-1 Drugs in Development

Phase 3	Phase 2	Phase 1	Preclinical
MariTide	AZD5004	AZD9550	NLy12
Orforglipron	AZD6235	GS-4571	DD03
Sema (oral)	Mazdutide	KAI-9531	DD15
Survodutide	GSBR-1290	KAI-4729	DD14
Retatrutide	LY359424	PB-110	PB-2301
Pemvidutide	ARD-101	PB-718	PB-2309
KAI-9531	KAI-7535	CT-388	
	MET-097i	CT-996	
	CT-868	TERN-601	
	VK2735		
	VRB-101		
	Dapiglutide		

OPPORTUNITY

Nimacimab has the potential to become the first-to-market CB1 antibody that can address a large patient segment that does not respond to or cannot tolerate GLP-1s, while also providing a combination option for those that need additional weight loss.

The GLP-1 space is incredibly crowded with multiple marketed and soon-to-be-approved drugs - and they all have the same **issues with safety and adherence**.

Semaglutide (Ozempic/Wegovy) is expected to go off-patent in 2031, enabling a wave of generics.

Wave of incretin-mimetics competition from China.

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Significant Opportunity Remains in Anti-Obesity Drug Market

GLP-1RA have issues with tolerability and lean mass loss

		Opportunity
Gastrointestinal Issues	Wegovy® and Zepbound® cause significant rates of **nausea** (31-53%), **diarrhea** (23-35%) and **vomiting** (12-30%)	 **Improved tolerability**
Discontinuation Rates and Rebound Weight Gain	**Blue Health Intelligence**[2] survey reported **30% of patients dropped out of treatment after 4 weeks. 58% of patients did not reach the prescribed treatment of a minimum of 12 weeks** and were **unlikely to achieve clinically meaningful weight loss.**	 **Greater adherence/ compliance over time**
Response Rates	Wegovy® STEP Trials showed **10.2-16.7% non-responder rate.** Real-world data suggests that patient % achieving >10% weight loss is lower than that reported in Phase 3 trials.[1]	 **Optimal weight loss via mono or combo therapy**
Lean Mass Loss	Lean mass loss is common with any significant weight reduction: ~25% is typical. Lean mass loss accounted for **~40% of total weight loss with Wegovy®.**	 **Healthier and more sustained weight loss**

Source:
1 Dandelion Research: Measuring GLP-1 Efficacy in the Real World https://dandelionhealth.ai/glp1-real-world-efficacy
2 Real-World Trends in GLP-1 Treatment Persistence and Prescribing for Weight Management. Issue Brief: May 2024 https://www.bcbs.com/media/pdf/BHI_Issue_Brief_GLP1_Trends.pdf

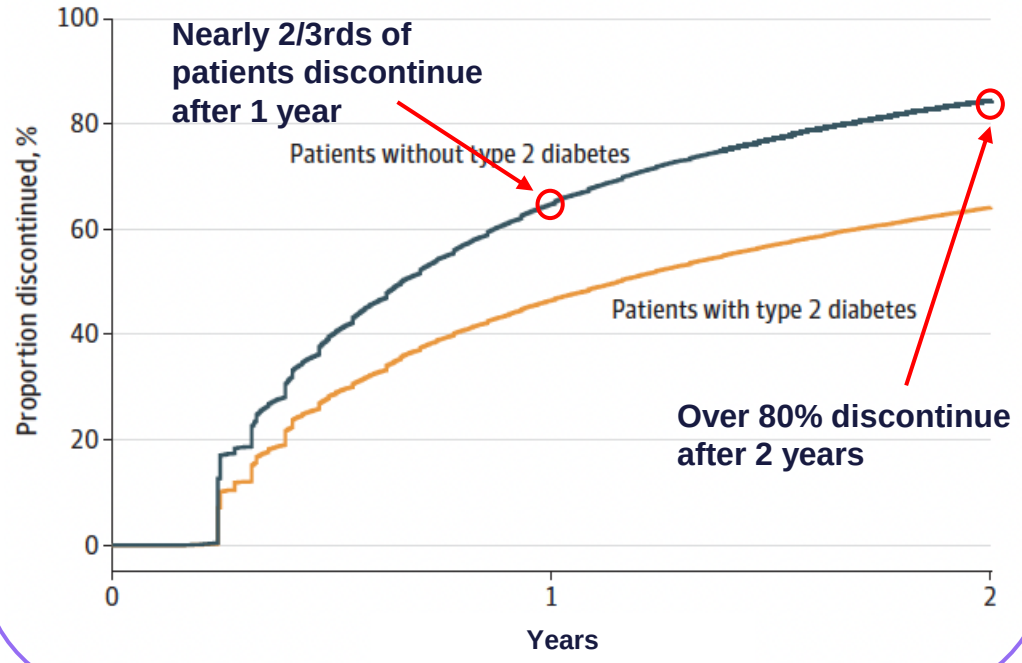
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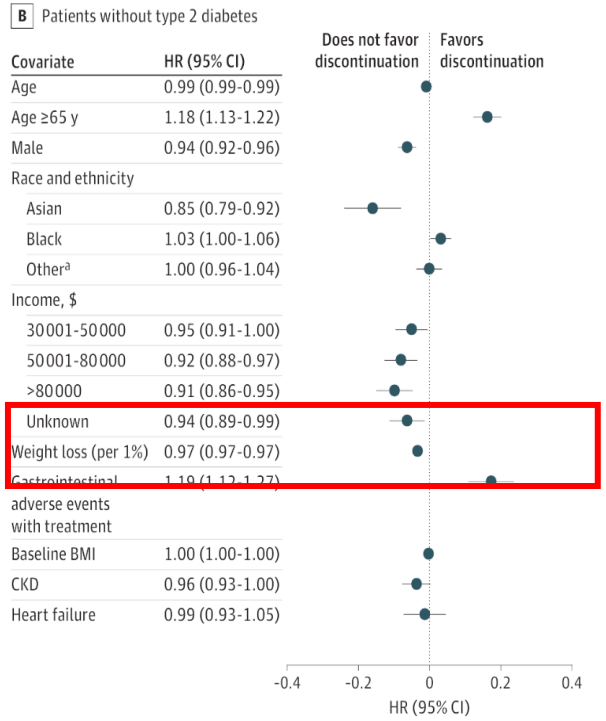
Pattern of GLP-1 Discontinuation

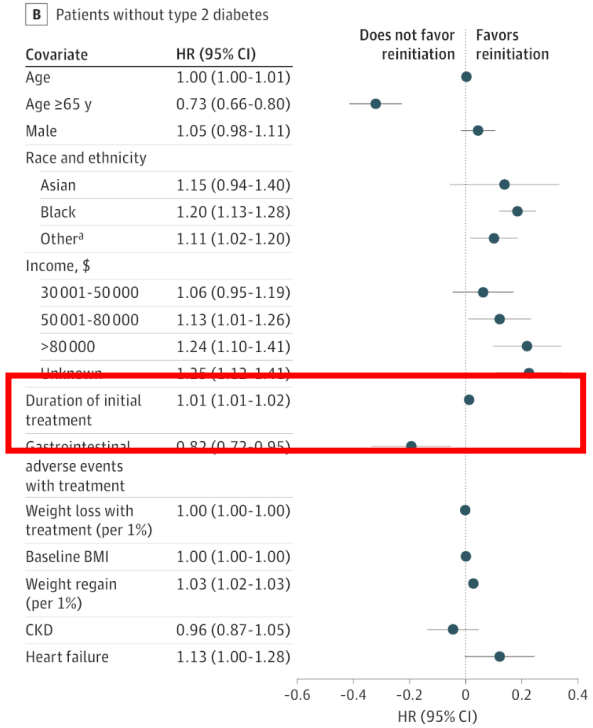
Most adults with overweight or obesity discontinue GLP-1 RA therapy within one year

Time to Primary Discontinuation of GLP-1 RA Therapy



Discontinuation and Reinitiation Rates Strongly Correlated with GI Intolerability





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Source:
1 Rodriguez et al., Discontinuation and Reinitiation of GLP-1 Receptor Agonists Among US Adults with Overweight and Obesity. JAMA Network Open. 2025;8(1)e2457349 doi:10.1001/jamanetworkopen.2024.57349

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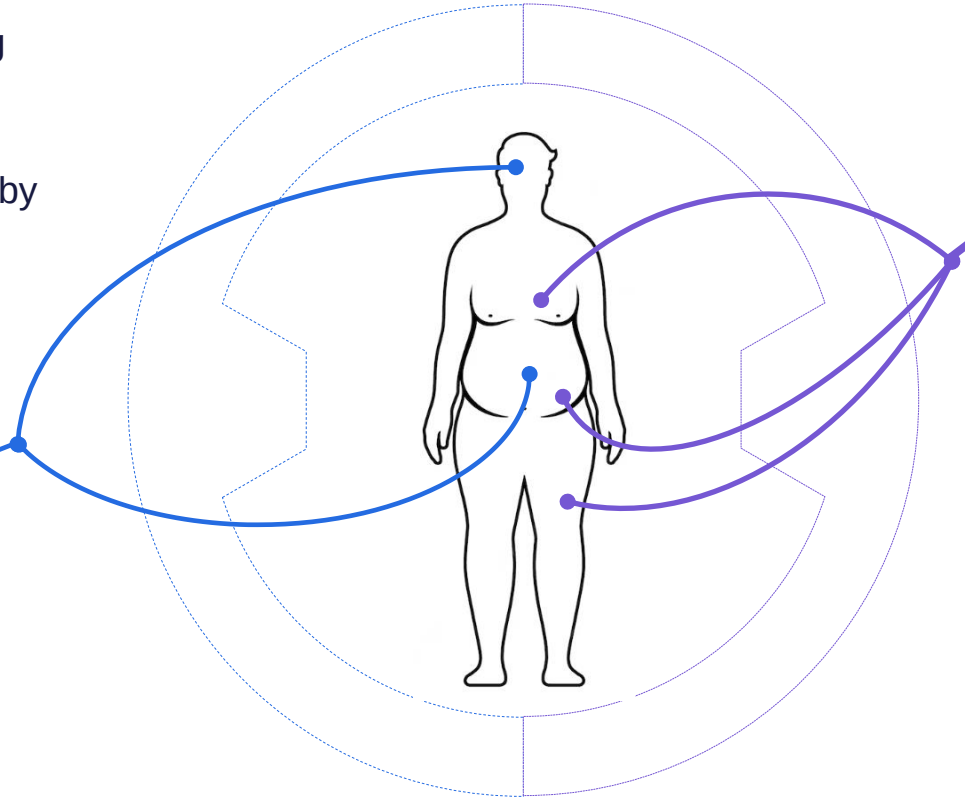
CB1: Overlooked Non-incretin Strategy to Tackle Weight Loss

Non-incretins target peripheral receptors and generally do not have central activity

Incretin-based Approaches, Using Food-intake and Blood-sugar Regulating Hormones:
Weight loss is predominantly driven by caloric restriction without additional metabolic gains

Current targets:
- GLP-1
- GIP
- Glucagon
- Amylin

Adverse events associated with incretins include nausea, vomiting and diarrhea



Non-incretin-based Approach:
Opportunity for healthier, sustainable weight loss

Current targets:
- **CB1**
- Activin
- Myostatin
- Apelin

Address fundamental driver of disease:
- **Increase energy expenditure**
- **Target adipose tissue to reduce fat mass + control hyperleptinemia**
- **Re-establish key metabolic path-ways, incl. insulin/leptin sensitivity**
- **Productive shift in appetite-regulating hormones to curb calorie input safely**

CB1: only non-incretin target clinically validated by multiple agents

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CB1 Inhibition Can Result in Meaningful Weight Loss, as Demonstrated by Rimonabant and Monlunabant

	16-Week Placebo-Adjusted Weight Loss	GI Tolerability
Monlunabant[1,2]	~6%	~30%
Rimonabant[3]	~3%	~30%
Oral Semaglutide[4] (50 mg)	~5%	~80%

Monlunabant looks competitive on efficacy, but with better GI tolerability (vs. oral semaglutide)

However, monlunabant's neuropsychiatric adverse events reignited the debate on safety of CB1 inhibition

Source:
1 Novo Nordisk Press Release Sep 2024. https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=170501
2 Crater et al., Effects of CB1R inverse agonist, INV-202, in patients with features of metabolic syndrome. A randomized, placebo-controlled, double-blind phase 1 study. *Dia. Ob. Metab.* 08 Nov 2023.
3 Van Gaal et al., SUPPLEMENT 2, FEB 2008
4 Knop et al., Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS1): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. Vol 402.26Aug2023

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Nimacimab Target Product Profile

Opportunity across multiple treatment settings

	Monotherapy	Maintenance	Combination
Addressable Population	Patients who are contraindicated, intolerant, and/or unresponsive to GLP-1 therapy		Patients with high BMI or who require additional weight loss after reaching a plateau on GLP-1 therapy
Opportunities	Novel anti-obesity drug required beyond GLP-1s and other incretin-based approaches	Physicians recognize the need for chronic treatment and would value a more tolerable option than current GLP-1s	Body weight reduction is most important clinical endpoint; a more potent and tolerable regimen will support utilization and product perception

THIS REPRESENTS A MULTI-BILLION DOLLAR OPPORTUNITY

AOM: Anti-obesity Medication
Source: Primary Market Research (N=10 Endocrinologists, N=14 PCPs)

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Nimacimab

Targeting CB1 – Broad Metabolic Potential with Clinically Validated Mechanism of Action

Nimacimab: First-in-Class, Peripherally-restricted CB1-inhibiting Antibody

Engineered IgG4

- Stable antibody with half-life of 18-21 days (potential 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
- NOAEL > 75 mg/kg. MTD not reached.

Specific for CB1

- Selective for only CB1 and not other GPCRs
- Binds to CB1 allosterically; inhibits CB1 signaling independent of binding by CB1 agonists

Potent Inhibitor

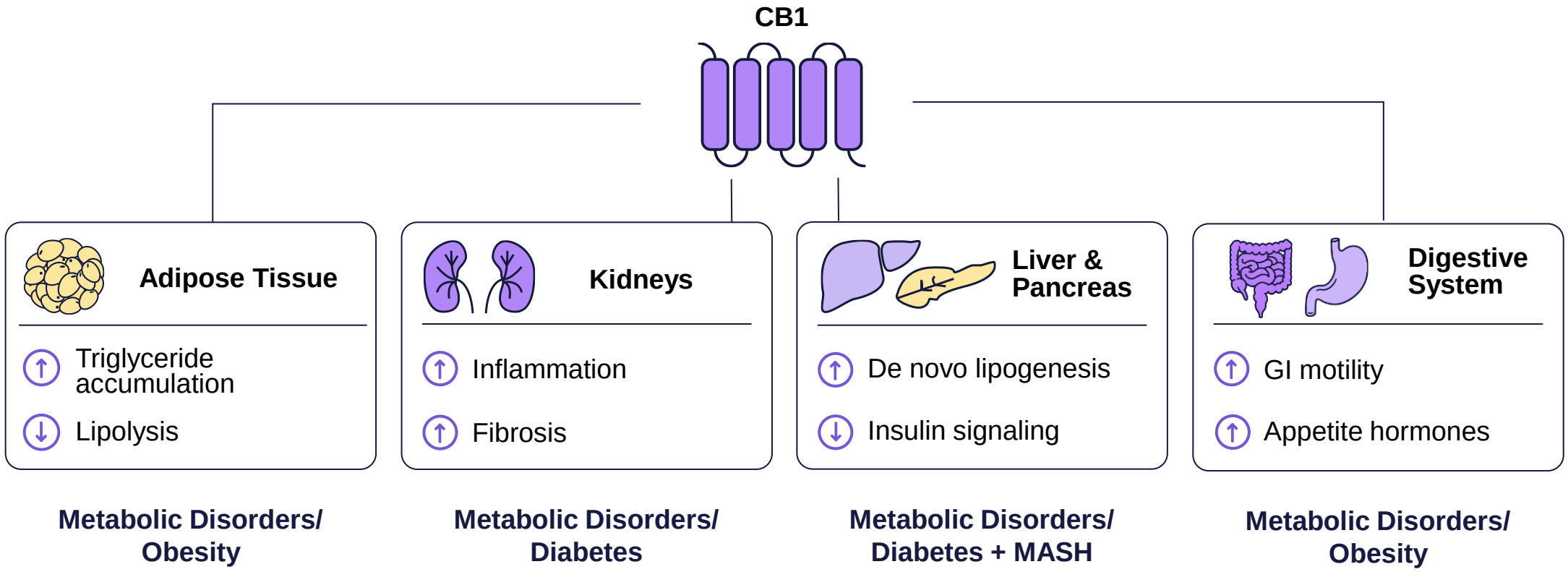
- Functions as an **antagonist** (in the presence of CB1 agonist, with B-arrestin endpoint)
- Functions as an **inverse agonist** (twice as potent as rimonabant with cAMP endpoint)

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Peripheral CB1 Signaling: Metabolic-focused Targets

In organs with significant prevalence of CB1 ligands (activators), active CB1 engagement promotes inflammation, fibrosis, and metabolic dysfunction; ***blocking*** peripheral CB1 can reverse negatively-trending pathologies



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

NHP and Ph1 data highlight 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%

Phase 1 data showed absence of negative neuropsychiatric effects in humans

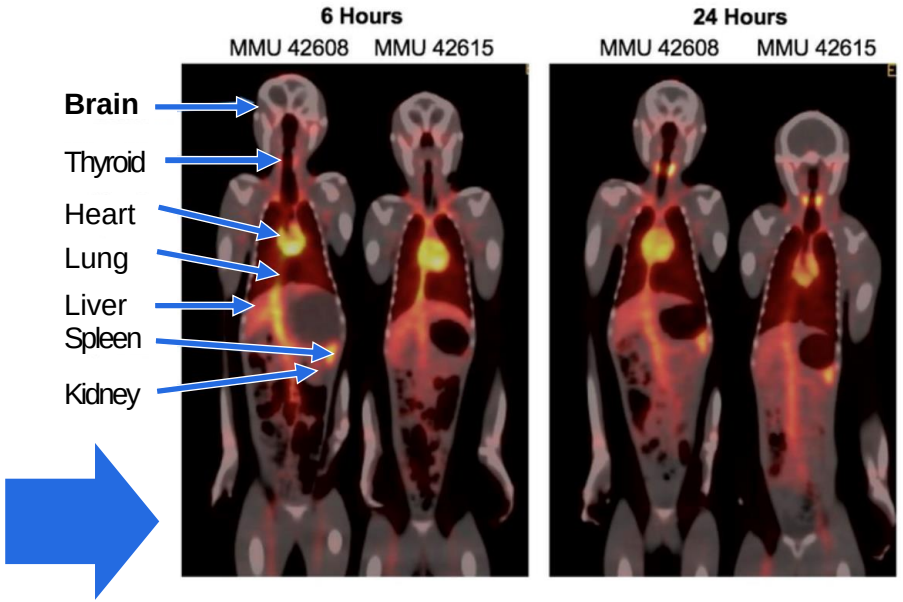
Cyno	9 hours
CSF/Serum 40 mg/kg IV	0.01%

— Level in CSF determined using quantitative ELISA

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

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



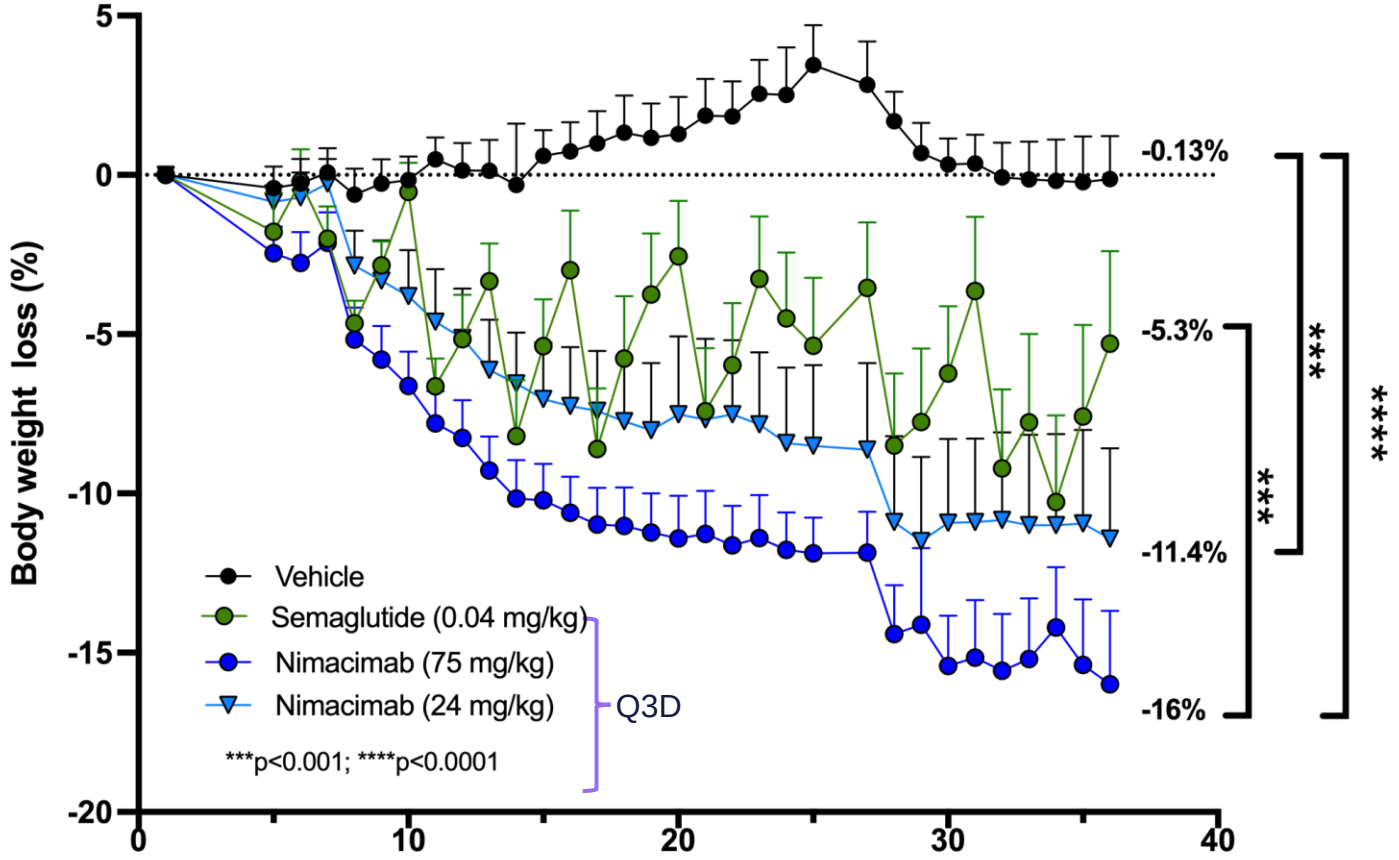
- *Tissues harvested without perfusion*
- *Tissue to plasma assuming 1 mL = 1 g*

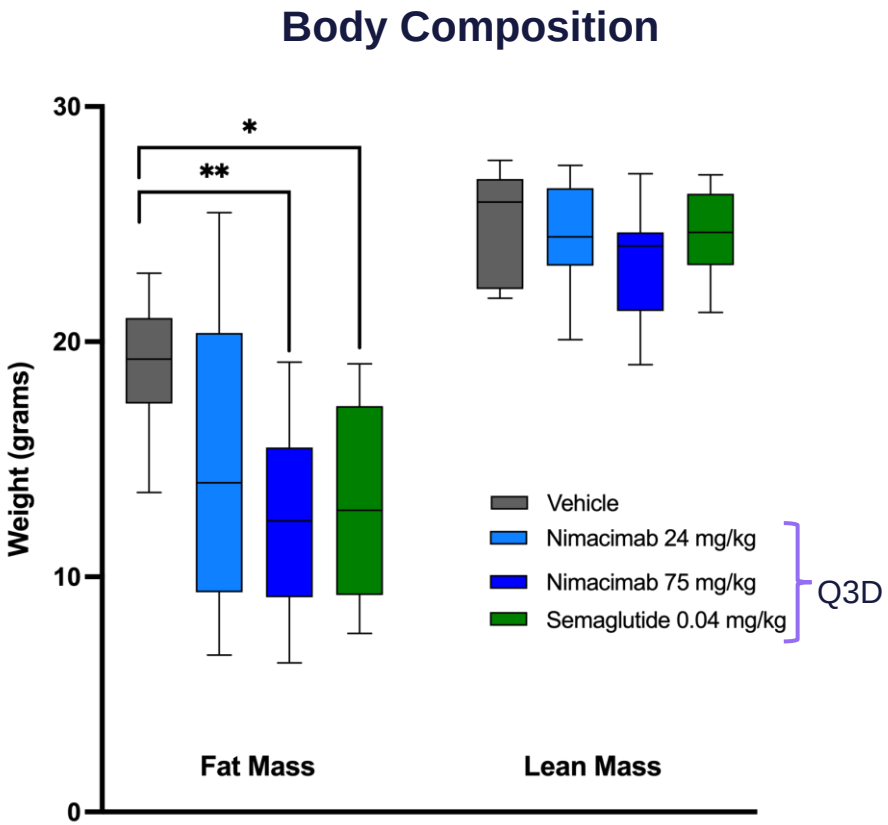
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Dose-dependent Weight Loss with Nimacimab in Diet-Induced Obesity Model

Weight loss complemented with reduced fat mass and lean mass preservation



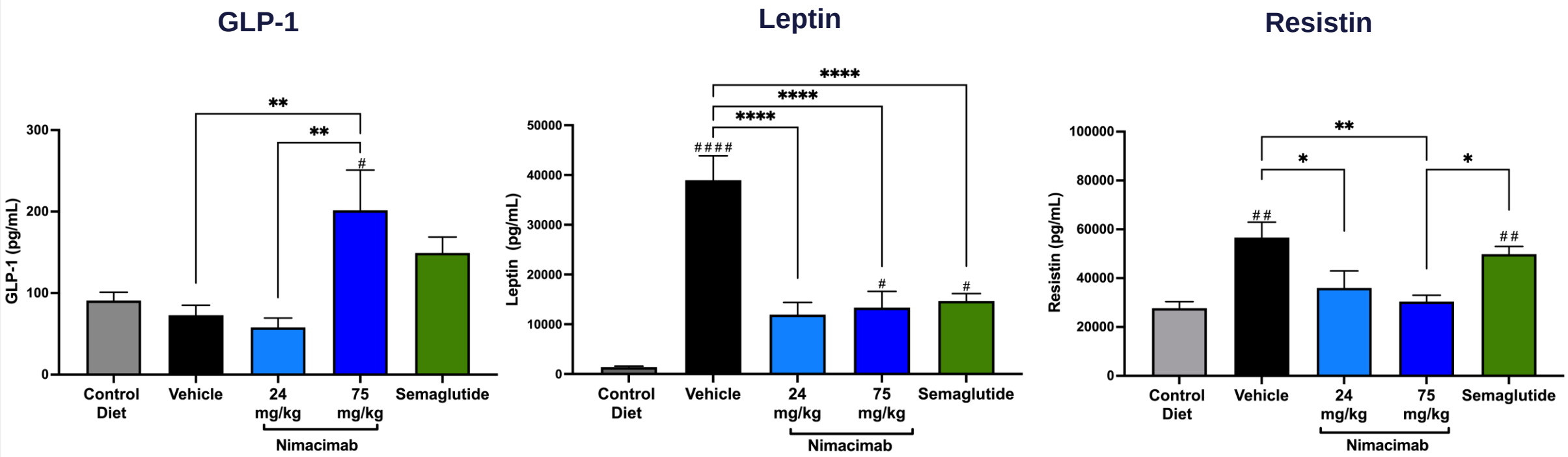


Body weight analysis was performed with two-way ANOVA repeated measurements. Body composition analysis was performed by One-way ANOVA. Tukey's Multiple comparison tests were then performed for all pairwise comparisons. Body weight reporting at day 36 of treatment. Body composition measured with echo MRI on day 35

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Productive Modulation of Key Hormones with Nimacimab Treatment



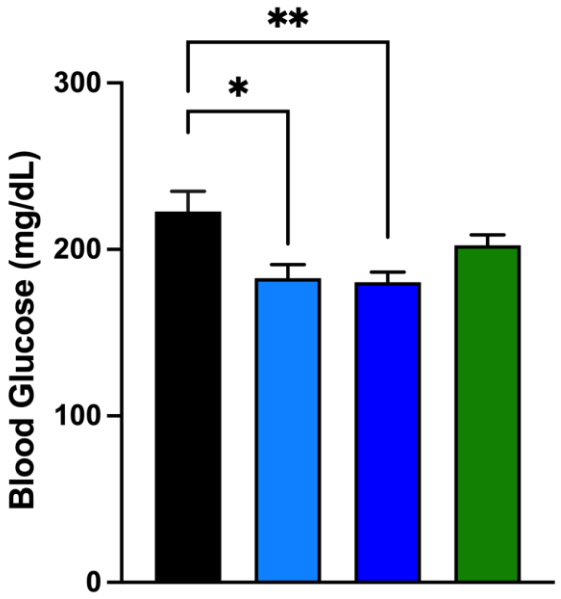
Serum was collected on day 36 and hormone levels were determined with a Bio Plex Multiplex immunoassay. For all analyses: one-way ANOVA repeated measurements (Tukey multiple comparison test). # denotes significance to the control diet group.

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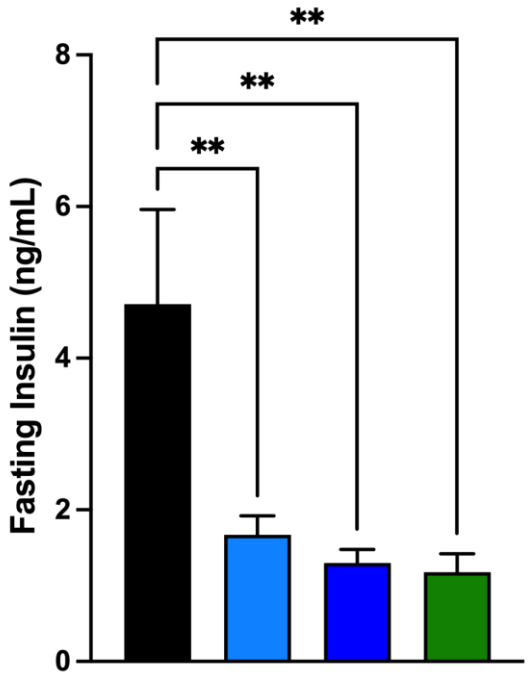
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Nimacimab Improve Glycemic Control

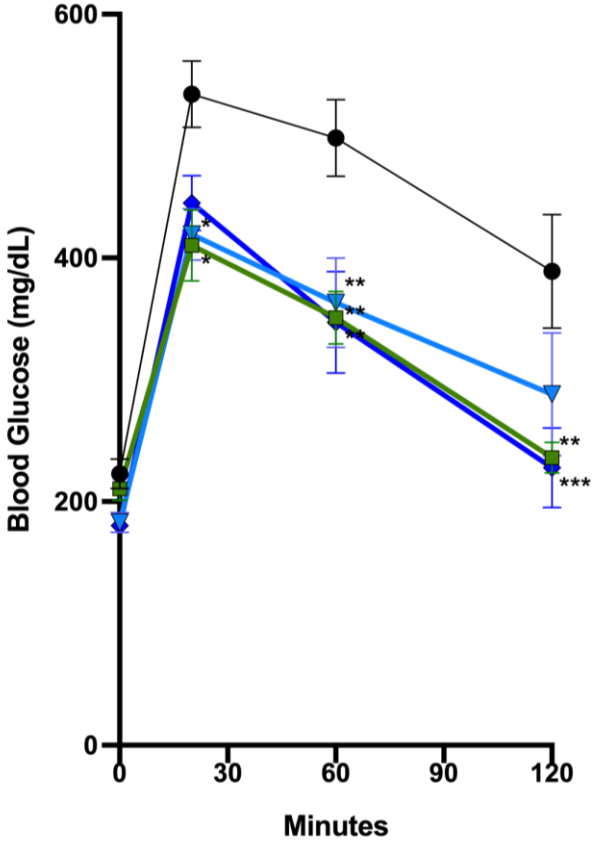
Fasting Glucose



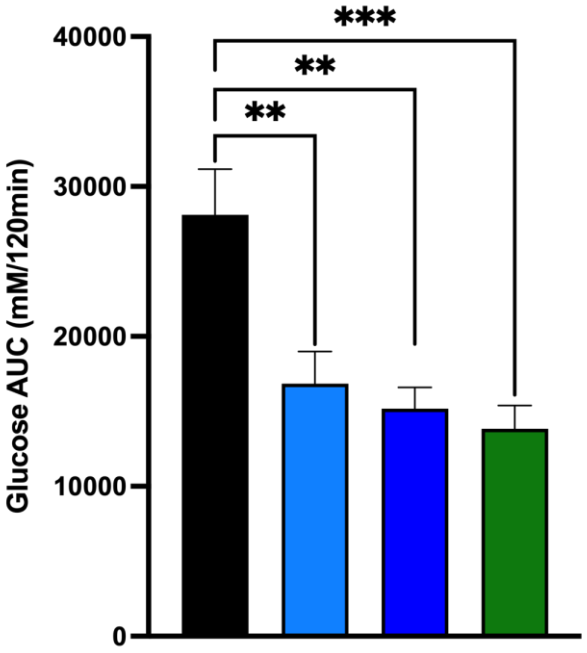
Fasting Insulin



Glucose Tolerance Test



GTT AUC Analysis



Legend

- HFD Vehicle
- Nimacimab 24 mg/kg
- Nimacimab 75 mg/kg
- Semaglutide 0.04 mg/kg

Day 27 mice were fasted for 4h before collecting serum to measure glucose and insulin levels

Day 27 mice were fasted for 4h before ip injection of 2g/kg glucose

GTT analyses: 2-way ANOVA repeated measurements (Tukey multiple comparison test); baseline subtracted AUC analysis was performed with a one-way ANOVA with Tukey multiple comparison test.

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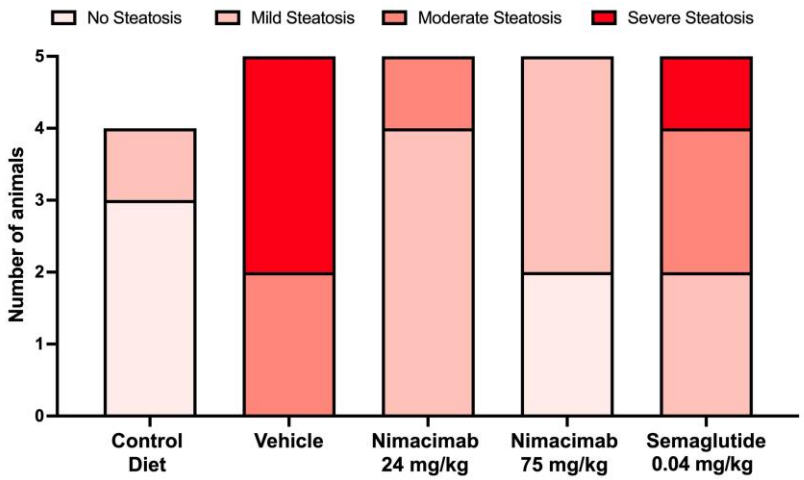
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Nimacimab Treatment Promotes Lipid Metabolism

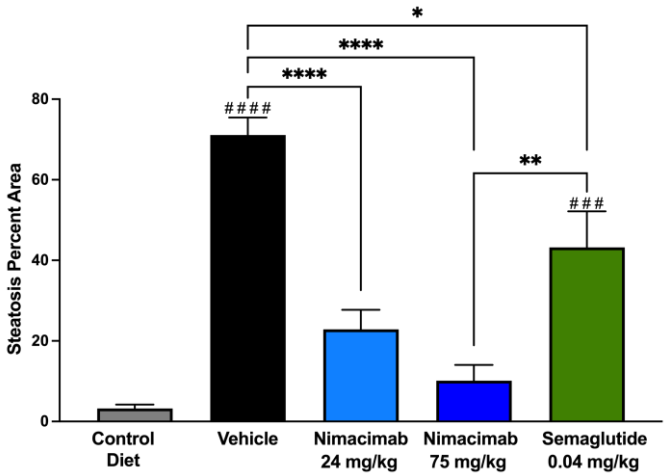
Dose-dependent reduction in steatosis and serum cholesterol

Steatosis Analysis (Liver)

Steatosis Score

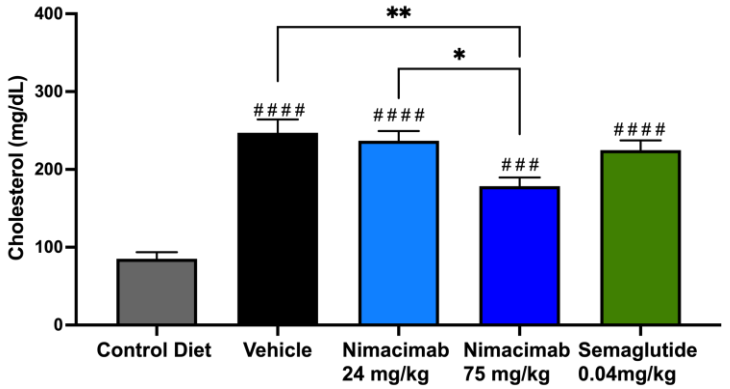


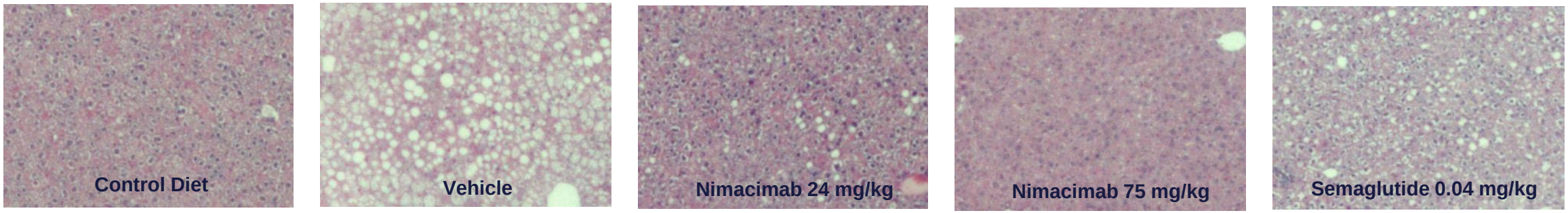
Steatosis Percent Area



Serum

Cholesterol





*Liver sections scored by a pathologist using computer-aided analysis. A score of 0-3 was assigned based on % of hepatocytes with fat. 0 = no steatosis (<5%), 1=mild (5-33%), 2=moderate (>33-66%), 3=severe steatosis (>66%). (B) steatosis percent area was analyzed using computer-aided analysis with Cellprofiler. (C) Cholesterol levels were measured in serum using a commercial kit. n=4-5 One-way ANOVA followed by Tukey's multiple comparisons test. **p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. # p vs control diet.*

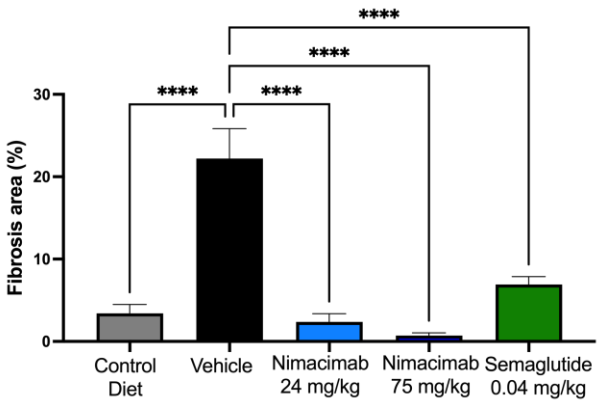
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Nimacimab Improves Obesity-related Inflammation

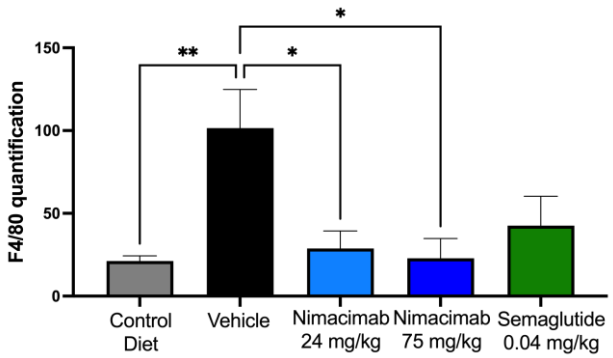
Reduced Inflammation and Fibrosis

Fibrosis Area (Liver)

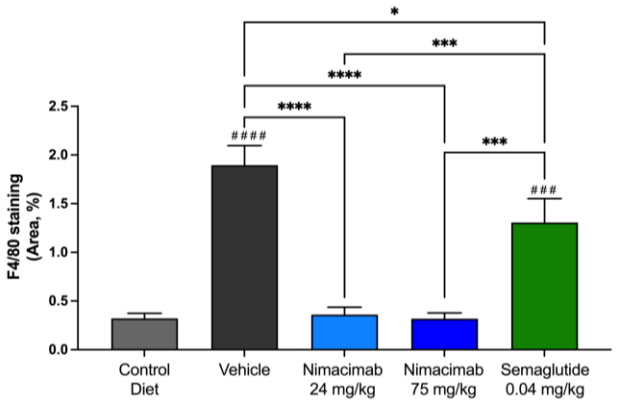


Macrophage (F4/80) Density

(Liver)



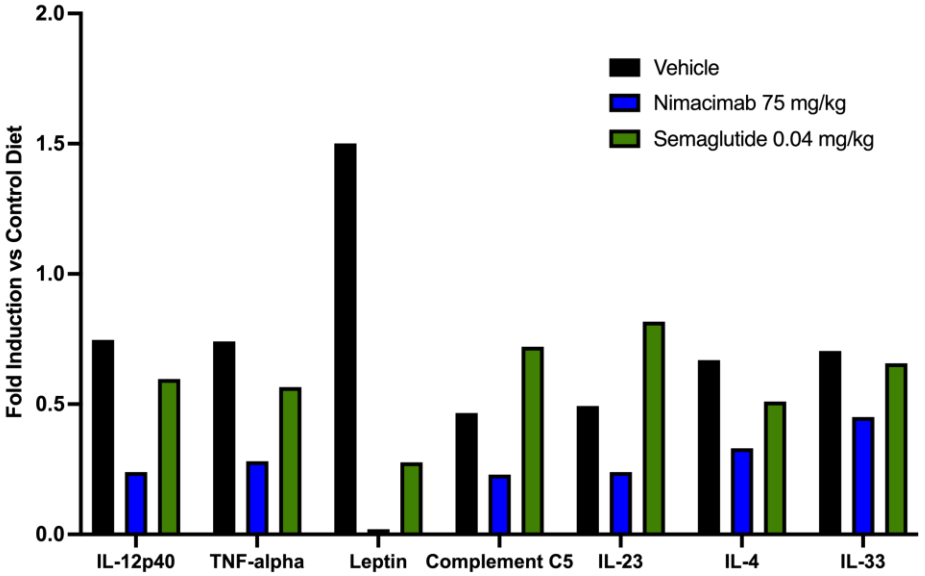
(iWAT)



Four fields per slide were quantified for liver F4/80 staining and five for iWAT F4/80 staining. Two to three fields per slide were quantified for Picrosirius Red staining. Analysis was performed using a one-way ANOVA with a Tukey multiple comparison test. # denotes significance to the control diet group.

Serum Inflammation Markers

Cytokine Array



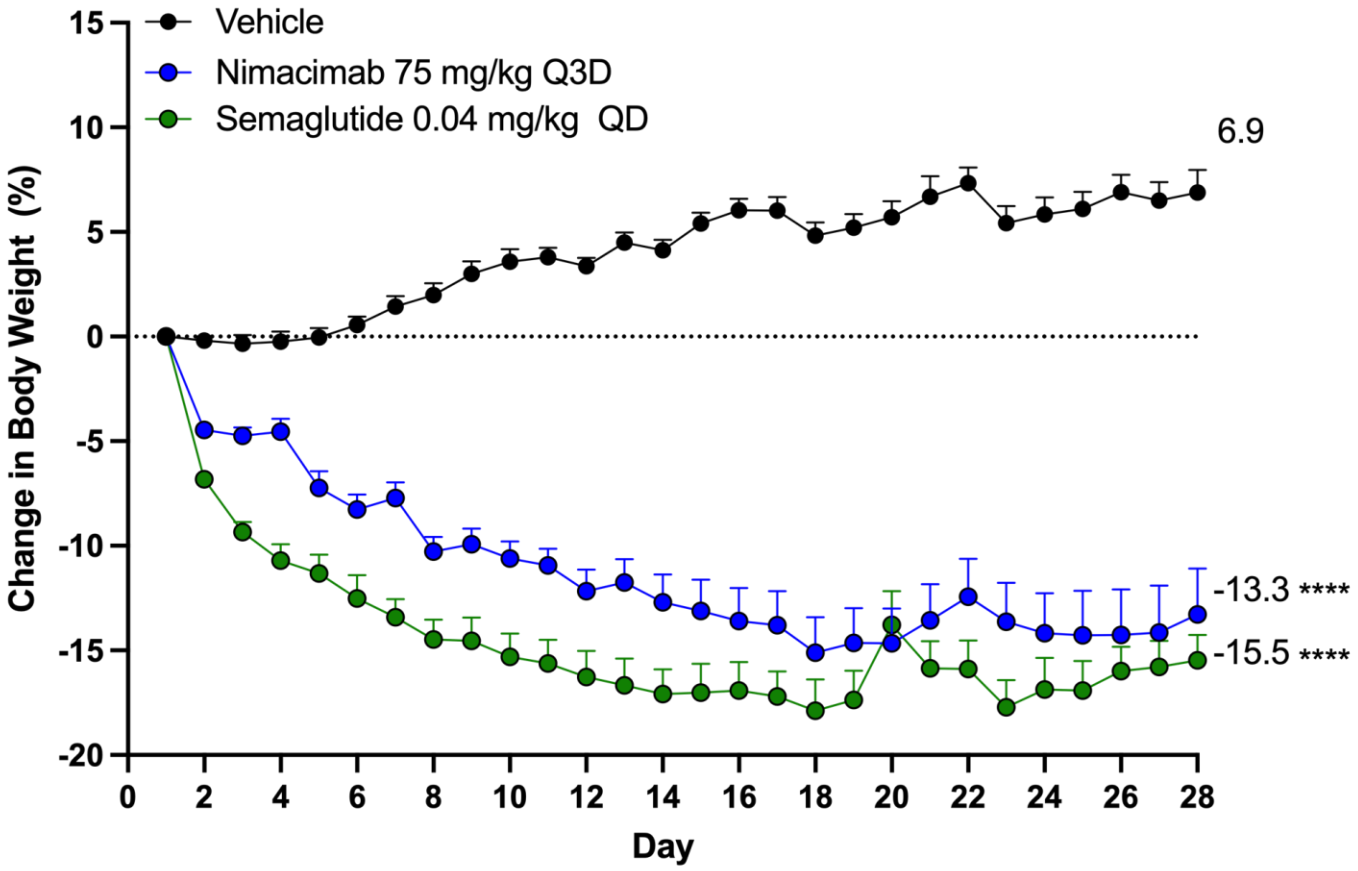
Serum samples were pooled for each group (n=7-8 per group) and assayed for cytokine expression using the Proteome Profiler Mouse XL Cytokine Array.

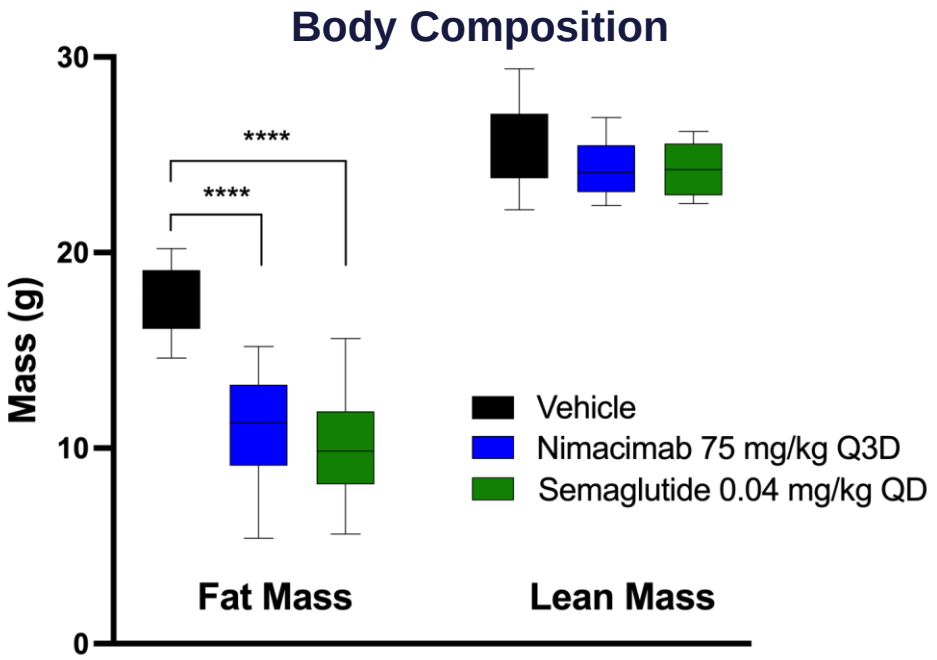
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Comparable Results: Repeat DIO Study in 2nd Independent Lab

Independent repeat of weight loss with lean mass preservation + reduced fat mass





*Body weight analysis was performed with a mixed-effect multiple comparisons test. Body composition analysis was performed by One-way ANOVA. Tukey's Multiple comparison tests were then performed for all pairwise comparisons. Body weight reporting at day 28 of treatment. Body composition measured with EchoMRI on day 25. ** p<0.01, *** p<0.001, ****p<0.0001*

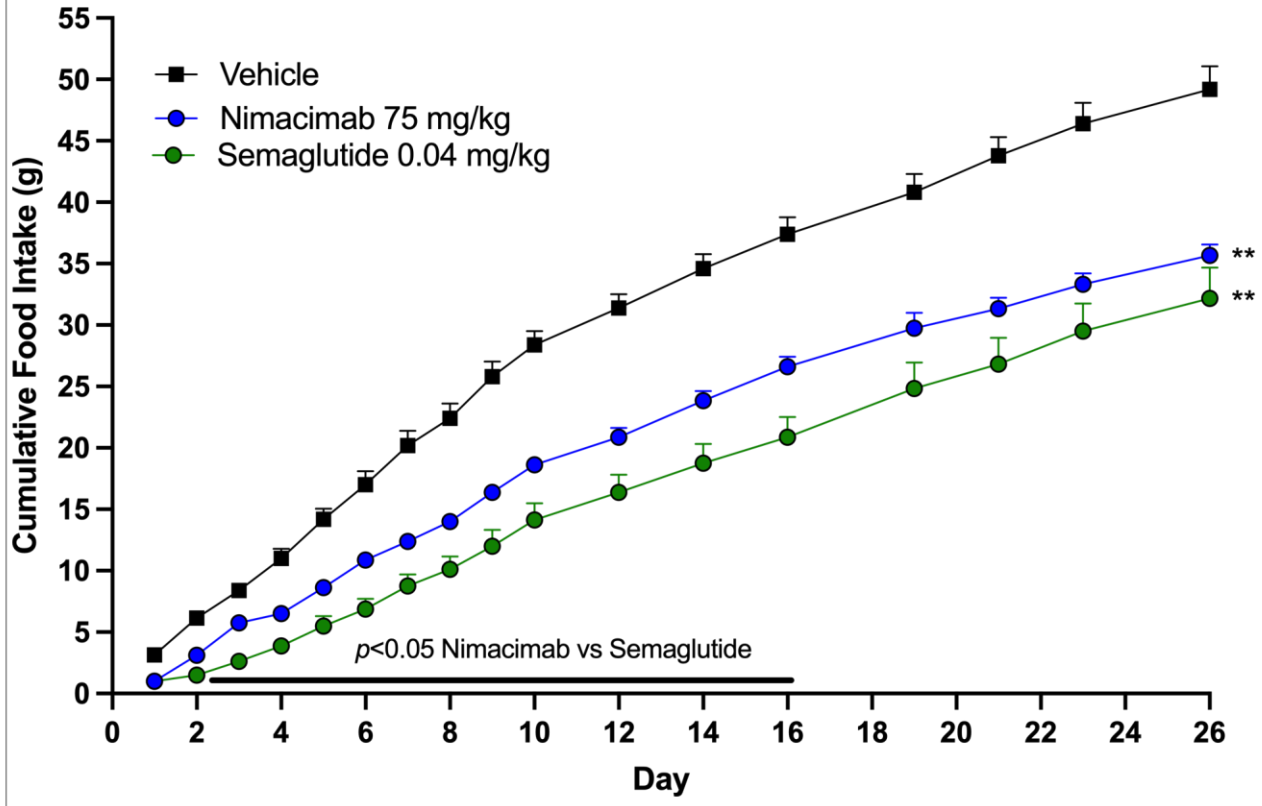
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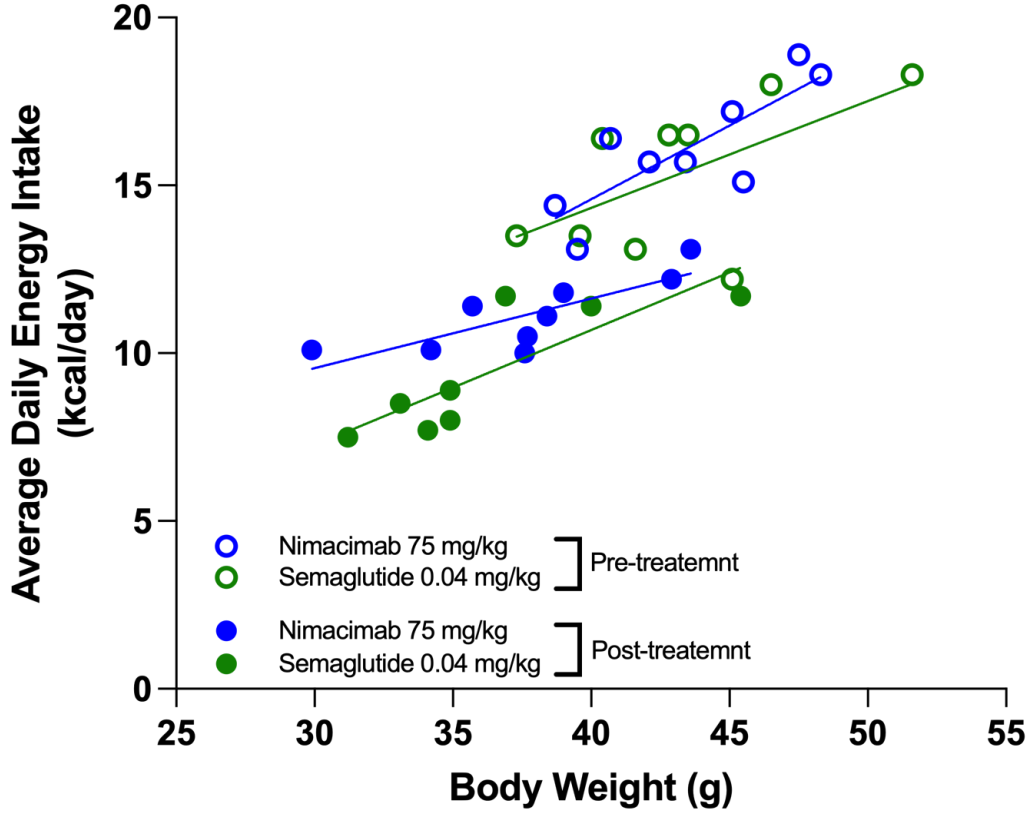
Nimacimab Led to Reduced Food Intake

Reduced caloric intake with nimacimab comparable to semaglutide

Cumulative Food Intake



Caloric Intake vs Body Weight



*Mixed-effect analysis of cumulative food intake, followed by Tukey's multiple comparisons test. Cumulative food intake reporting at day 28 of treatment. The pre-treatment average daily energy intake was calculated from day -14 to day 0. The pre-treatment weight was measured on day 1 before dosing. The post-treatment average daily energy intake was calculated from day 1 to day 28 and weight was measured on day 28. * p<0.05, ** p<0.01*

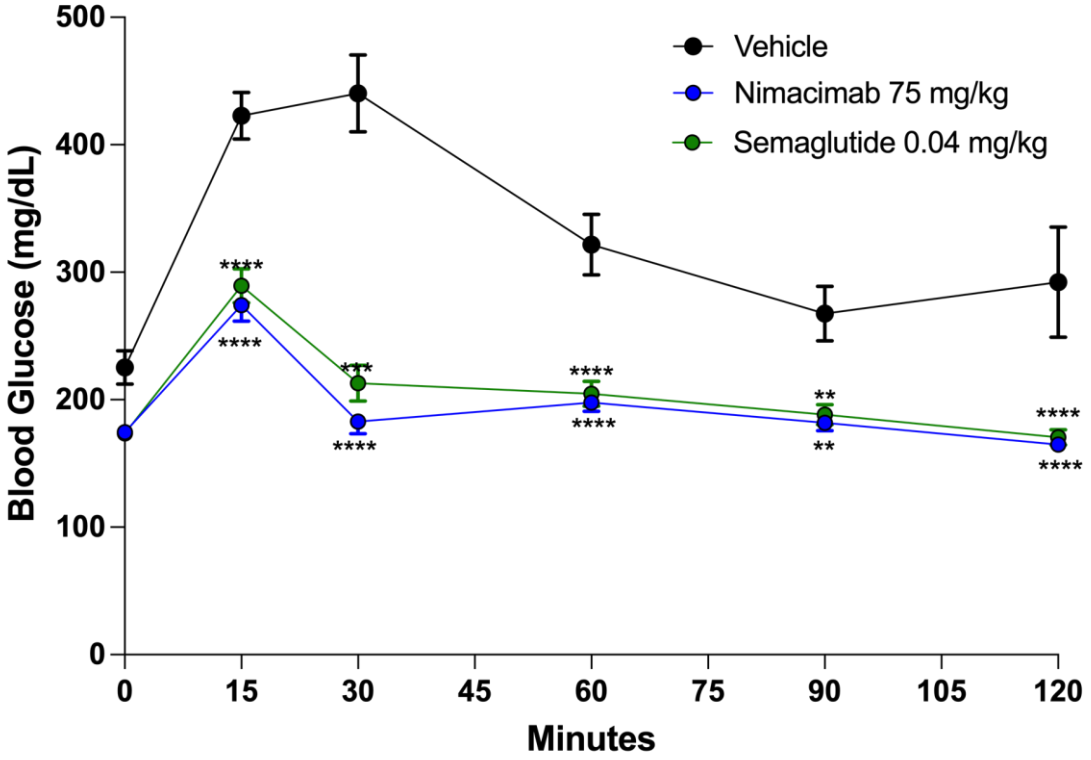
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Glycemic Control with Nimacimab Consistent w/ Previous Study

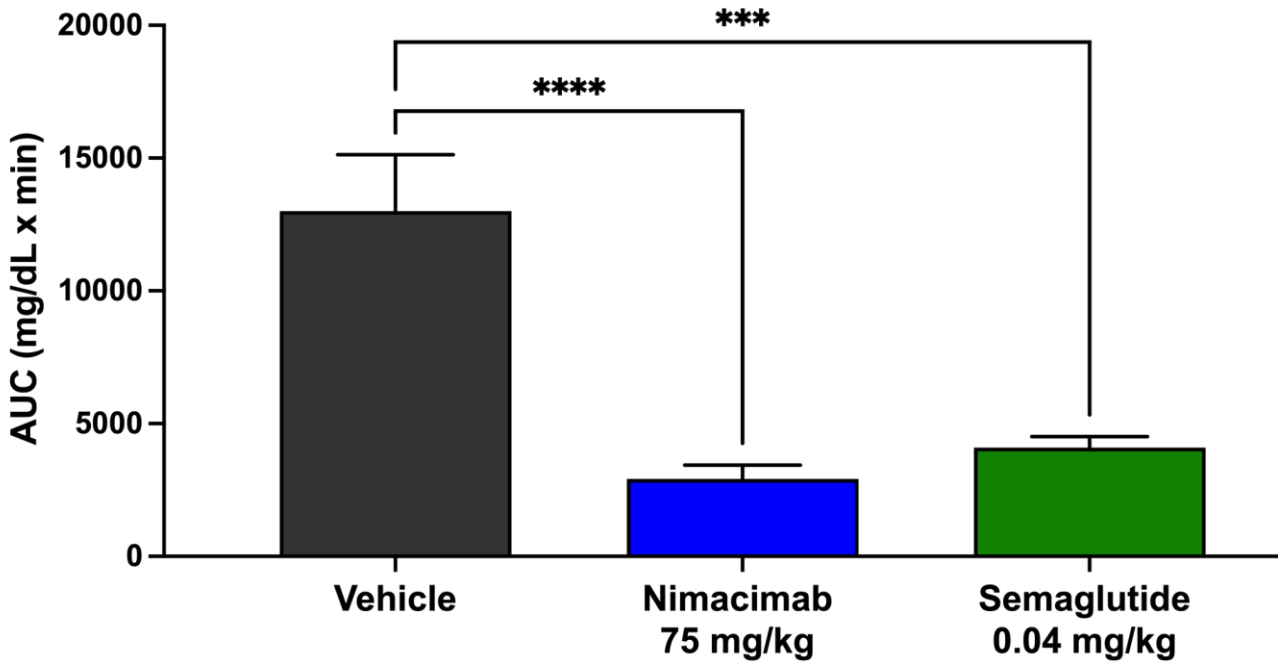
Semaglutide and nimacimab improved glycemic control in obese mice

Glucose Tolerance Test



Day 17 mice were fasted for 6h before 2 g/kg of glucose was administered via oral gavage.

Glucose AUC



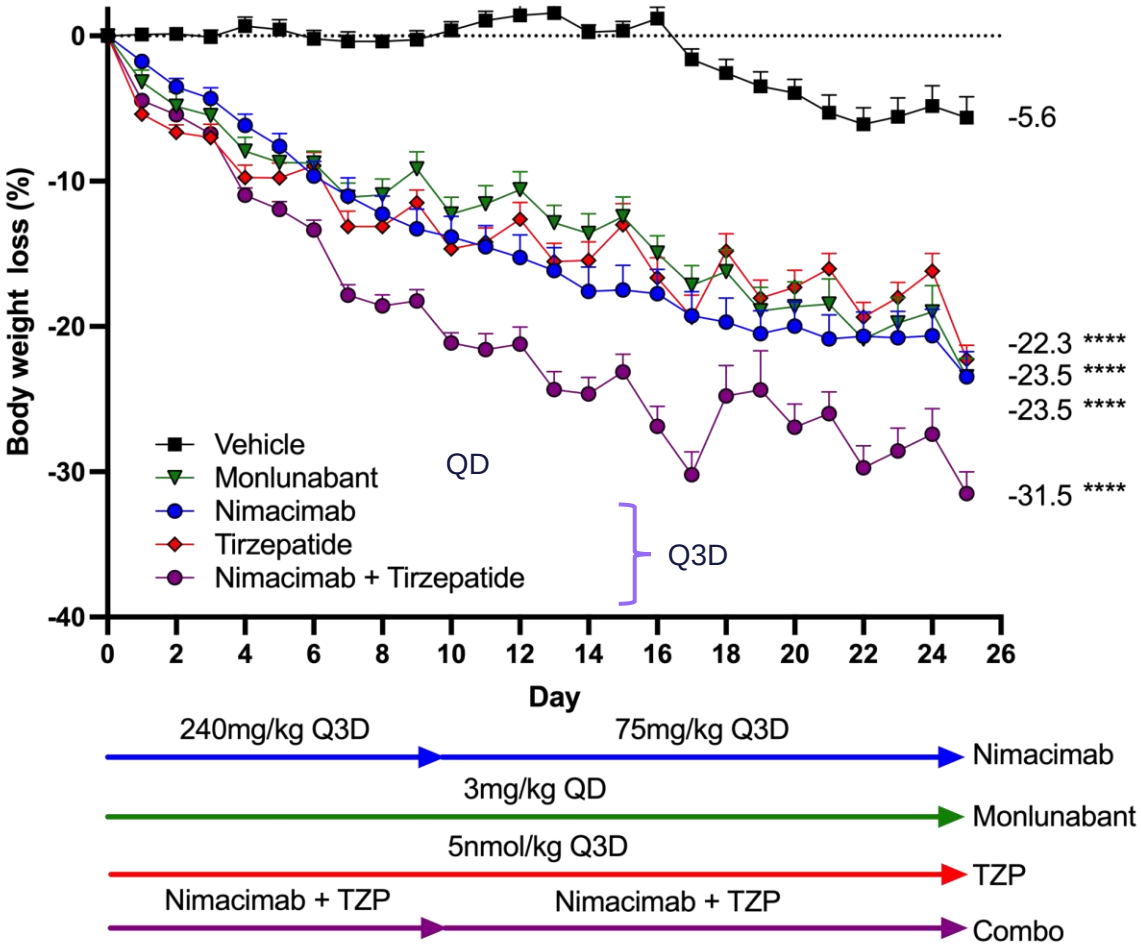
GTT analyses: two-way ANOVA repeated measurements (Tukey multiple comparison test); baseline subtracted AUC analysis was performed with one-way ANOVA with Tukey multiple comparison test.

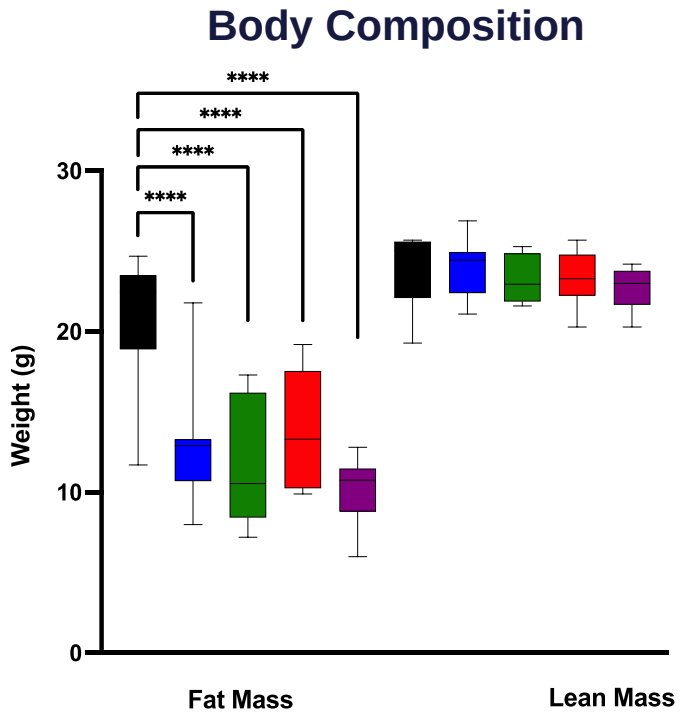
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Potential for Combination with Tirzepatide

Improved weight loss and body composition in diet-induced obesity model using clinically translatable dosing of nimacimab





Nimacimab was dosed at 240 mg/kg on days 0, 3, 6, and 9. The nimacimab dose was lowered to 75 mg/kg on days 12, 15, 18, 21, and 24. This dosing provides a similar exposure to translate this DIO model to our Ph2 clinical dose based on PK studies.
*Body weight and composition analyses were performed with two-way ANOVA repeated measurements. Tukey multiple comparison test was then performed for all pairwise comparisons. Body weight reporting at day 25 of treatment. Body composition was measured with EchoMRI on day 25. Only comparisons against vehicle are plotted. ** p<0.01, *** p<0.001, ****p<0.0001*

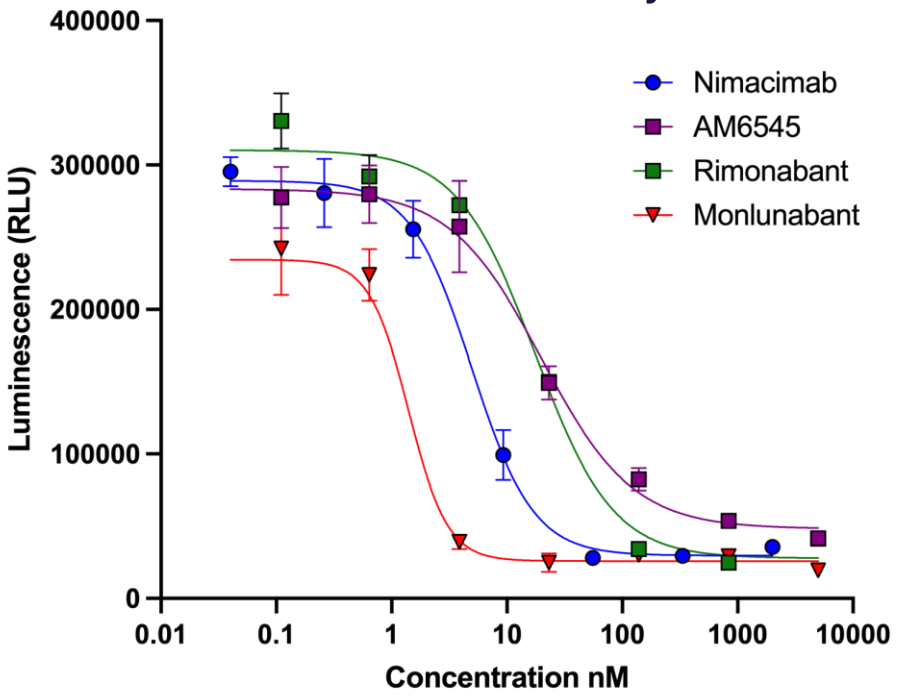
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Nimacimab Potency Similar to Small Molecule Inhibitors

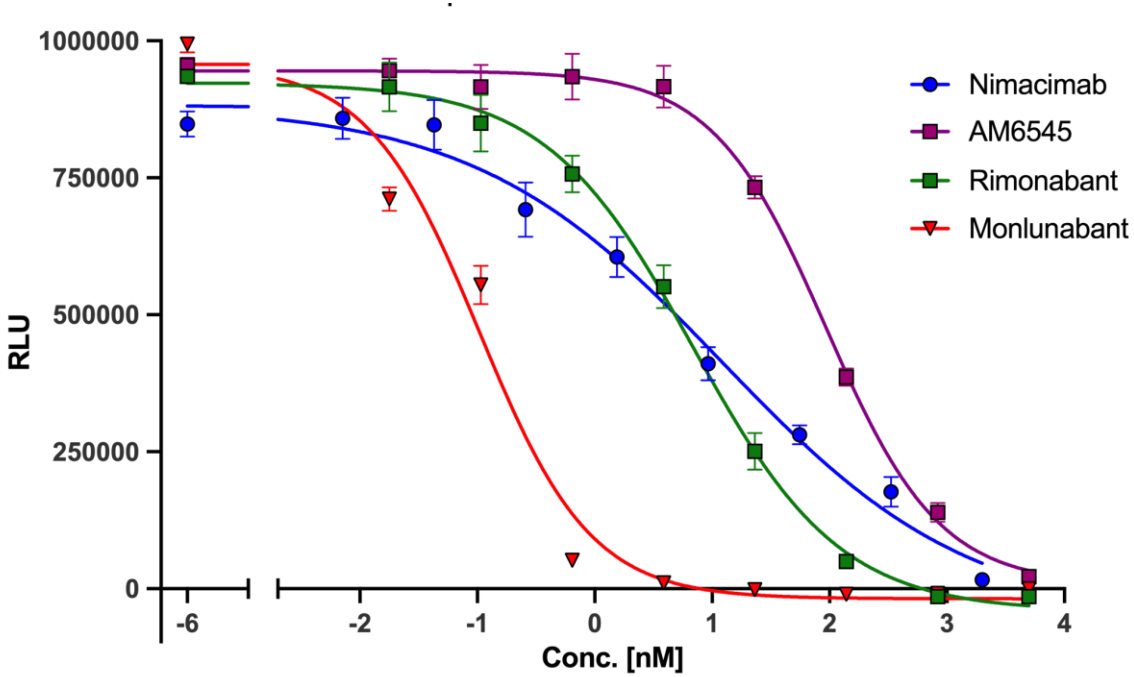
Based on both cAMP and β-arrestin assays

cAMP-based Assay



CB1 Inhibitor	IC_{50} (nM)
Nimacimab	4.96
AM6545 (neutral antagonist)	19.95
Rimonabant	17.6
Monlunabant	1.4

β-arrestin-based Assay



CB1 Inhibitor	IC_{50} (nM)
Nimacimab	10.83
AM6545 (neutral antagonist)	47.62
Rimonabant	5.36
Monlunabant	0.07

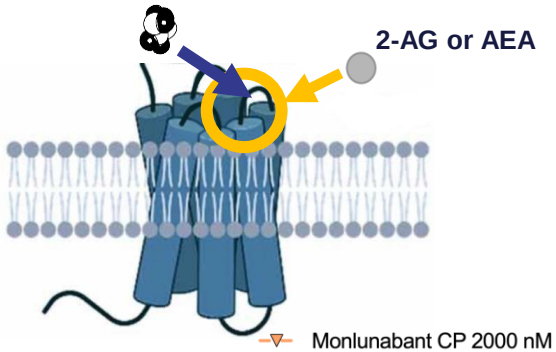
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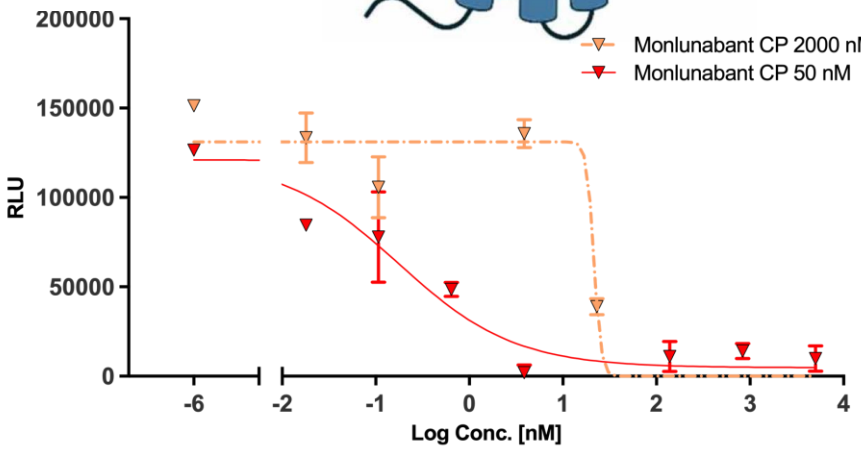
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Non-competitive CB1 Inhibition: Differentiation of Nimacimab's Allosteric Modulation

Monlunabant

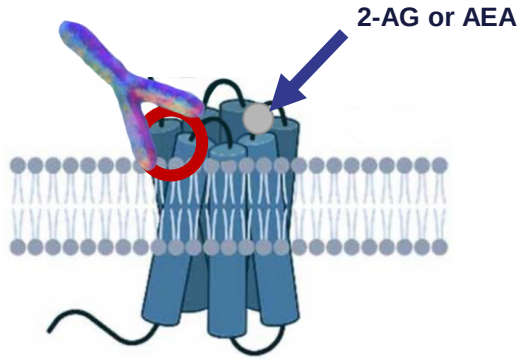
Monlunabant **competes** with AEA/2-AG for binding to the orthosteric site

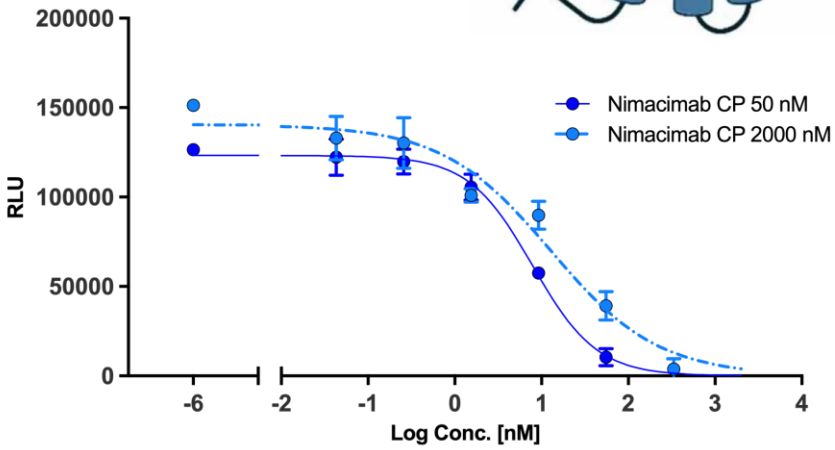




Nimacimab

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





CB1 Inhibitor	Agonist: CP55940		Reduction in Fold Potency
	EC_{80} (50 nM)	40x EC_{80} (2000 nM)	
Nimacimab IC_{50} (nM)	7.9	12.7	**1.6**
Monlunabant IC_{50} (nM)	0.2	21.44	**107**

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Complementary, Not Competitive

CB1 impacts key metabolic pathways that complement existing products & strategies

	KEY TARGETS / MECHANISMS					
Key Targets Characteristics	**GLP-1[1]**	**GIP[1]**	**Glucagon[1]**	**Amylin[2-4]**	**Myostatin[5-7]**	**CB1[8-9]**
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[10]
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
- ✓ Maintenance dose/setting beyond GLP-1 RA
- ✓ Combinability with other mechanisms/agents

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

Source: 1. Guggenheim Obesity Report; 2. Boyle. J Clin Med. 2022; 3. Dehestani. J Obes Metab Syndr. 2021; 4. Suh. J Bone Metab. 2020; 5. Roth. PNAS. 2008; 6. Choi. Am J Physiol Endocrinol Metab. 2011; 7. Schurgers. Cells. 2021; 8. RBC Capital Markets (February 2024); 9. Skye Internal Data 10. small molecule CB1 inhibitors

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Nimacimab's Differentiation

Differentiated Receptor Engagement

Allosteric modulation leads to non-competitive inhibition and superior potency in disease states.



Superior Exclusion from the Brain

As an antibody, nimacimab has little to no penetration into the brain, resulting in improved safety compared to current small molecule CB1 inhibitors.



Clinical and Preclinical Validation

CB1 inhibition for weight loss has been validated in multiple preclinical studies, as well as large Phase 2 and 3 studies.



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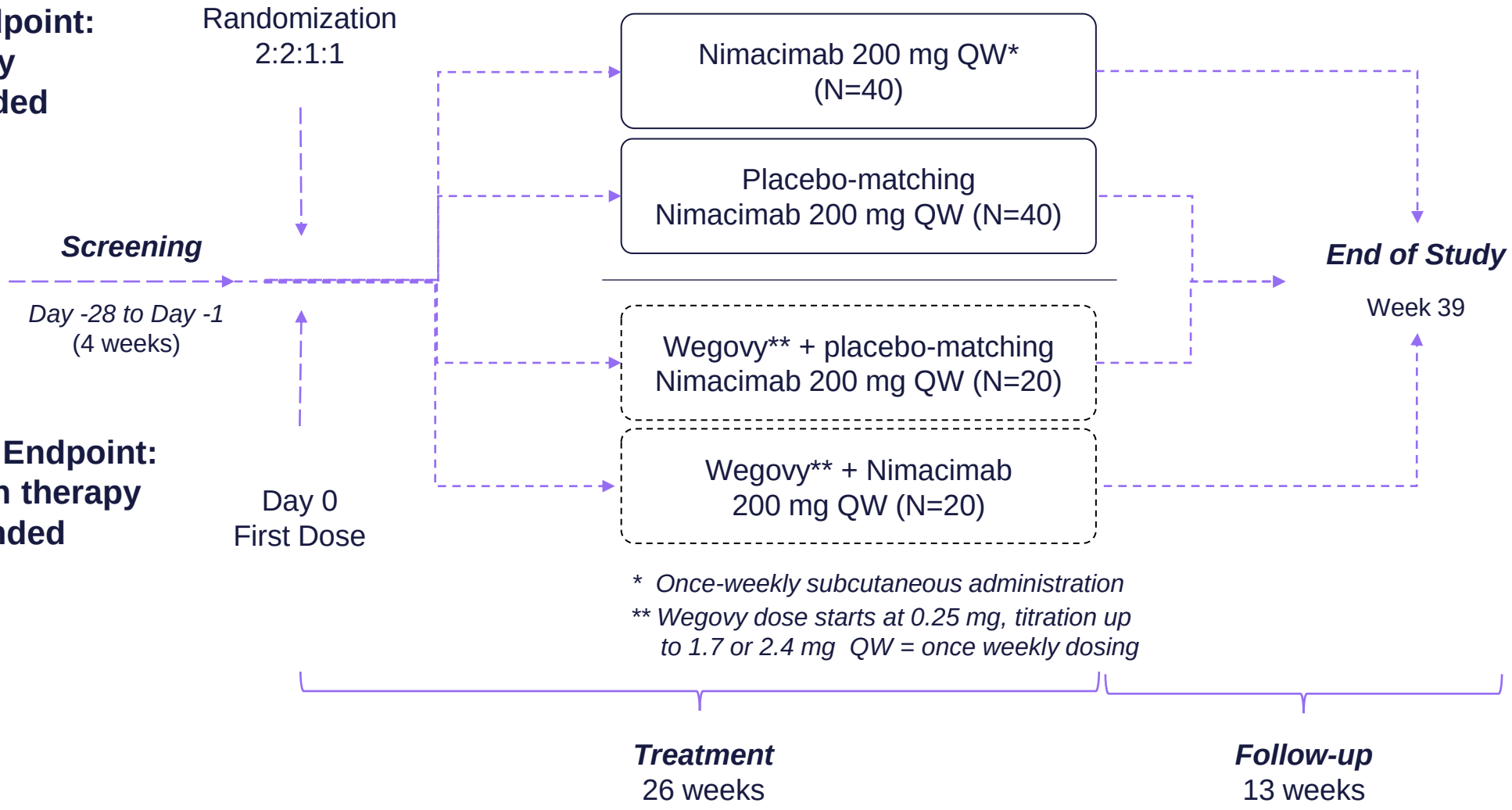
Clinical & Regulatory



Phase 2a CBeyond™ Trial: Patients with Overweight or Obesity

Enrollment completed for initial 26-week treatment period

Primary Endpoint:
Monotherapy
Double-blinded



Exploratory Endpoint:
Combination therapy
Partially blinded

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Nimacimab and Adverse Events of Interest

- AESIs associated with CB1 inhibitors are concerned with neuropsychiatric and neurological effects
- Skye has included multiple questionnaires and tests to evaluate the frequency of AESIs, which are provided to and reviewed by the DSMC

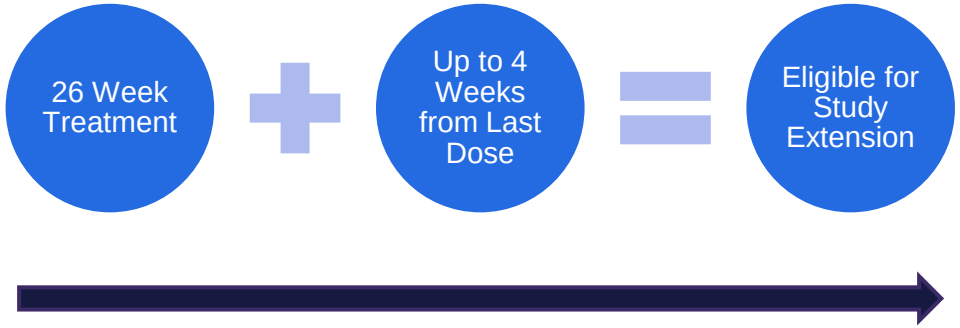
Questionnaire/Test	Purpose
Columbia-Suicide Severity Rating Scale (C-SSRS)	Validated questionnaire: identifies if someone is at risk for suicide, assesses severity and immediacy of risk, and gauges level of support the person needs.
Patient Health Questionnaire-9 (PHQ-9)	Validated to measure frequency and severity of depressive symptoms.
SF-36v2® Acute Form	Designed as brief yet comprehensive measure of general health status. Consists of eight scales yielding two summary measures: physical and mental health.
IWQOL-Lite CT	A 20-item measure with two primary domains (physical [7 items] and psychosocial [13 items]). Validated based on FDA guidance on patient-reported outcomes.
Patient Global Impressions of Severity (PGI-S) for Physical Activity	Global index used to rate the severity of a specific condition. This index evaluates limitations in a participant's physical activity.
Cognitive Testing with Digit Symbol Substitution Test (DSST)	Measures 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.

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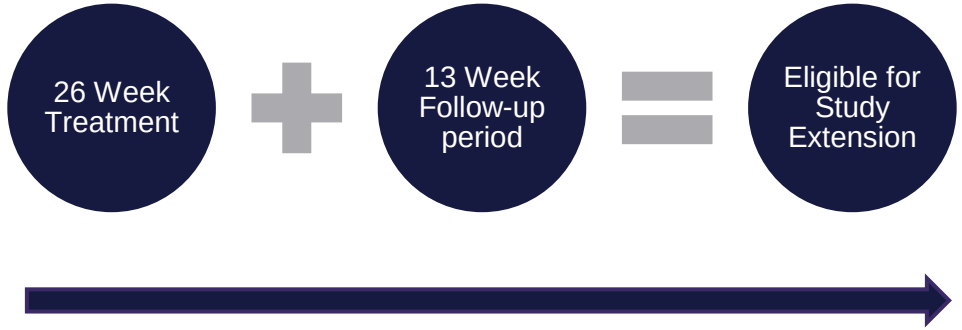
CBeyond™ Phase 2 Study Extension

Continuing Combination Arms (52 Weeks)



- ✓ Participants who have completed 26 weeks of treatment, are still enrolled in the study, and are still in the 4-week period post last dose of study drug are eligible to enroll into the study extension (maintaining current assigned therapy and blinding).

Monotherapy Arms (~July 2025)



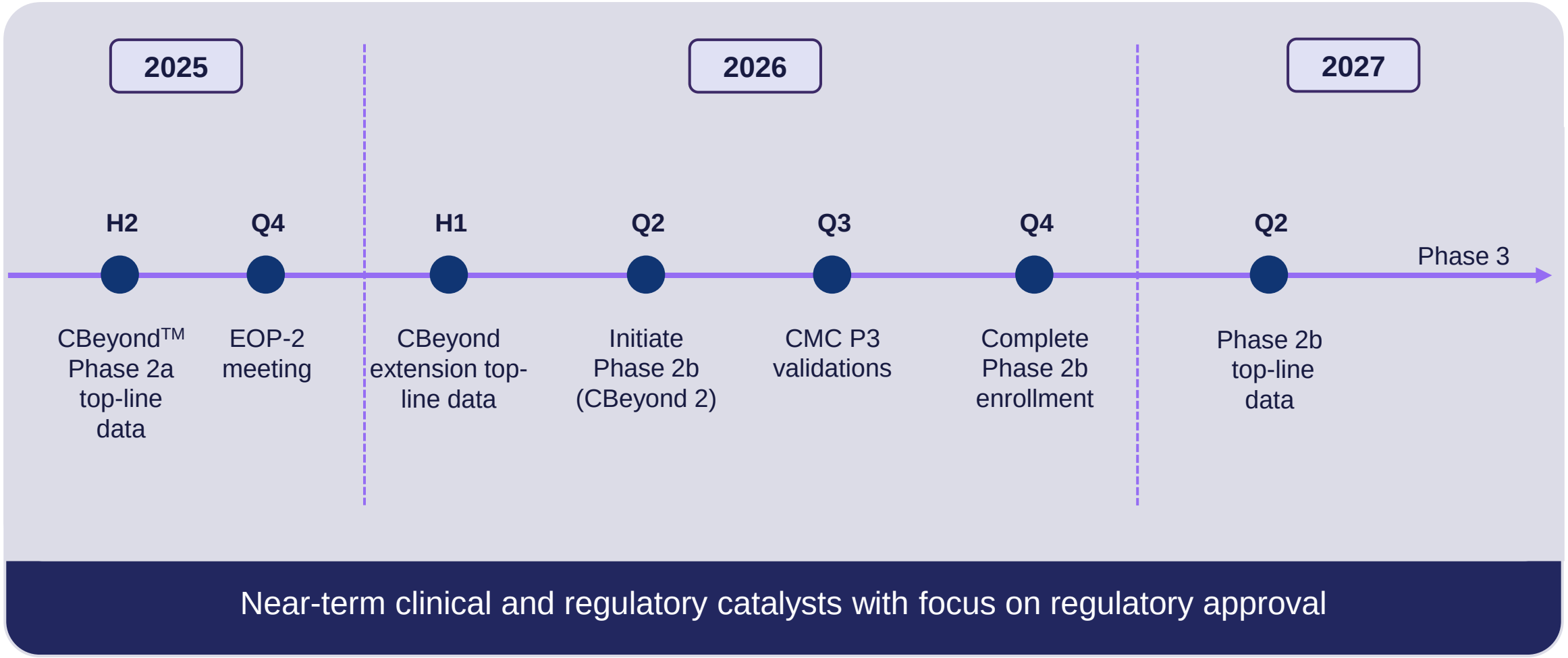
- ✓ Participants who have completed 26 weeks of treatment and are still enrolled in the study (even if in the follow up period and not currently on drug) are eligible to enroll into the open-label study extension at the beginning of August 2025
- ✓ Will provide 52-week data, new 26-week cohort, and also aid retention in current Phase 2 CBeyond study.

****Participants who 1) discontinued treatment for any reason during the 26-week treatment period, and 2) continued to attend study visits off drug are not eligible for the study extension.*

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Clinical and Regulatory Milestones



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Well-positioned to Become Fully Integrated Metabolic Company

Experienced in therapeutic drug regulatory process through approval and commercialization

1	**Robust IP, Life-Cycle and Development Strategy**	Planned nimacimab EOP2 by 2027 and IP/composition of matter protection through 2035*
2	**Novel Biologics Pipeline**	Team and collaborators focused on GPCR antibody targets, biomarker and other metabolic pathway R&D
3	**World-Leading Obesity Experts**	Clinical advisory board composed of Key Opinion Leaders from leading academic institutions
4	**Meaningful Near-Term Data Inflection Points**	Strong funding track record with specialist healthcare investor base
5	**Experienced Leadership**	Board and management has been involved in or directly brought 40+ drugs to market
6	**Full CMC Capabilities**	GMP manufacturing supporting future clinical trials underway

** May be eligible for up to five years (2040) of extension (Hatch-Waxman)*

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Select Financial Figures & Metrics

- $107M in equity capital raised since August 2023
- Supported by top-tier specialist life science investors
- Funded at least through Q1 2027
- Ongoing strategic investments in scaling manufacturing, operations, R&D, and advancing the clinical pipeline

Stock Information

Listed: Nasdaq	**SKYE**
Stock Price[1]	**$1.98**
Shares Outstanding[2]	**31.0M**
Shares Fully Diluted[2]	**47.5M**
Cash & Equivalents[3]	**$59.2M**
Market Cap[1]	**$61.4M**
Avg. 3-Mo. Daily Trading Volume[1]	**698.2K**

[1] May 30/25 [2] May 6/25 [3] Mar 31/25

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Leadership

Contributed to commercialization of 40+ drugs/diagnostics, led high-value strategic transactions, and co-founded multiple companies

Executive Management



Punit Dhillon
President & CEO



Kaitlyn Arsenault, CPA
Chief Financial Officer



Tu Diep, MSc
Chief Operating Officer



Chris Twitty, PhD
Chief Scientific Officer



Puneet Arora, MD
Chief Medical Officer



Brennen Brodersen, JD
General Counsel

Board of Directors



Paul Grayson
Chairman of Skye BOD; Pres./CEO, Radionetics



Annalisa Jenkins, MBBS, FRCP
Managing Director, Annalisa Jenkins LLC



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



Andy Schwab
Managing Partner, 5AM Ventures



Karen Smith, MD, PhD, MBA, LLM
Global pharma/biotech exec and C-suite advisor

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THANK YOU!

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San Diego, CA 92130

Please learn more or contact us at:

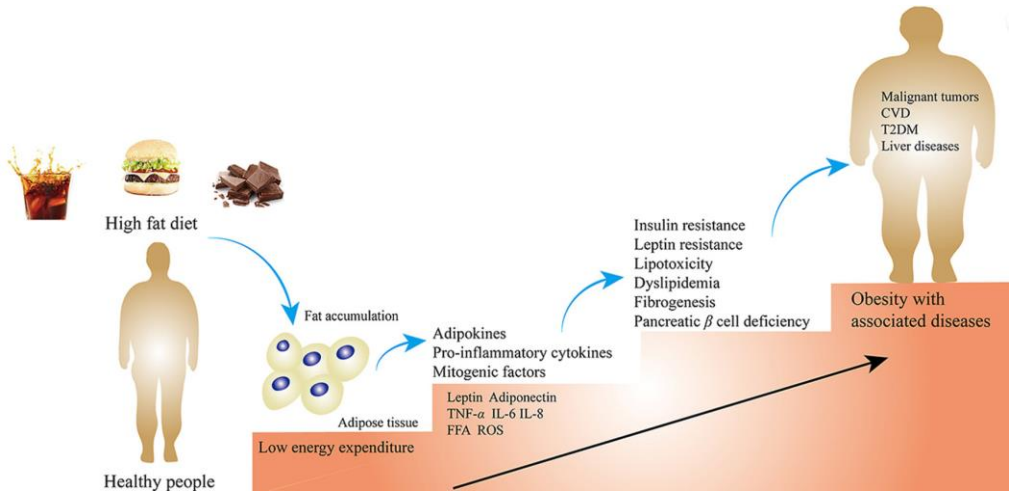
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Obesity Disease Overview

Obesity is a chronic disease characterized by excessive body fat and adipose tissue inflammation, driven by a complex and multifactorial etiology



- Obesity: a medical condition characterized by **excessive body fat**, often linked to mild, chronic **inflammation of adipose tissue**
- Morbidity and mortality associated with obesity are **rising global health concerns** in both adults and children
  - Excess adiposity leads to increased risk of hypertension, T2D, cardiovascular disease, and certain cancers[1,2]

Pathophysiology

- **Energy Imbalance:** Obesity results from chronic positive energy balance due to energy intake greater than energy expenditure
- **Metabolic inflammation of Adipose Tissue:** Secretion of pro-inflammatory cytokines/hormones alters metabolic pathways[3]

Genetic Underpinning

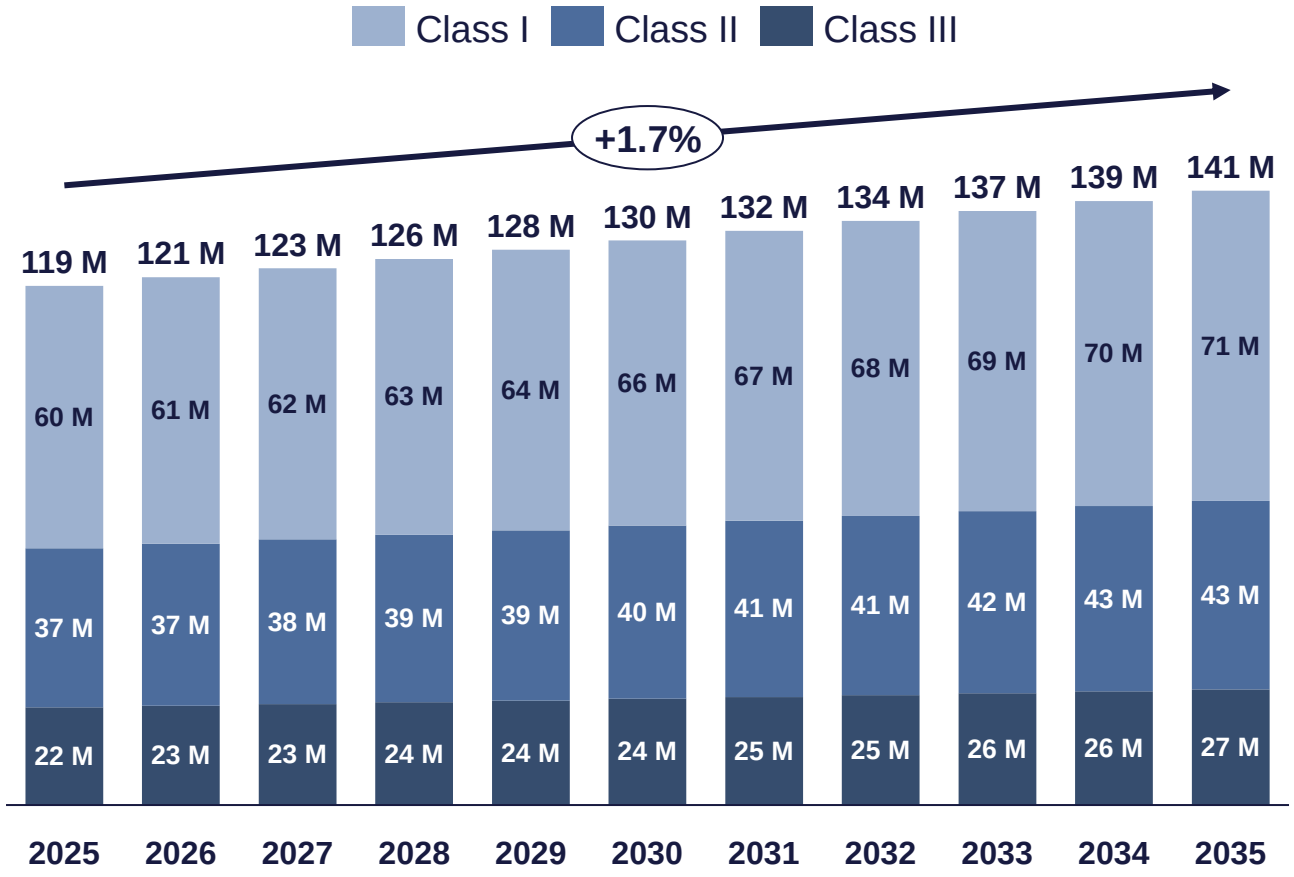
- **Genetic Contributions:** Body weight variations among individuals are influenced by genetic and environmental factors; obesity can be categorized as monogenic or polygenic (also known as common obesity) based on genetic characteristics[4]
- **Monogenic Mutations:** Most mutations are caused by genes encoding leptin, melanocortin 4, and leptin receptor[4]
- **Association with Gene Variants**: Polygenic obesity is common and linked to *ADRB3, BDNF36, CNR1, MC4R38, PCSK1,* and *PPARG*[4]

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Obesity U.S. Patient Population

Prevalence of obesity among U.S. adults is expected to reach ~141 M by 2035, outpacing general U.S. population growth

U.S. Adult Prevalence of Obese Individuals



Obesity Population Dynamics

- **Prevalence:** Obesity prevalent in ~119 M patients in the U.S. (~40% of U.S. population) in 2025
- **Segmentation:** Patients are typically categorized into Class I-III based on BMI[2-5]
  - Class I (35 > BMI ≥ 30): ~50%
  - Class II (40 > BMI ≥ 35): ~31%
  - Class III (BMI ≥ 40): ~19%
- **CAGR:** Projected to be ~1.7% based on NHANES data between 1999 and 2018[8], which exceeds the growth rate of the overall U.S. population (~0.9%)
  - Continued growth is expected, driven by poor nutritional education, activity levels, and access to healthy food alternatives

NHANES: National Health and Nutrition Examination Survey. Sources: 1. UpToDate; 2. U.S. Census Bureau; 3. childstats.gov (link); 4. Ward et al., 2019 (link); 5. CDC National Health Statistics Report 2017 – 2020 (link); 6. Stokes et al., 2018 (link); 7. CDC National Health Statistics Report 1960–1962 Through 2015–2016 (link); 8. CDC National Health Statistics Report 2017 – 2018 (link).

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Obesity Comorbidities

Obesity associated with significant comorbidities, ie. diabetes, hypertension, and kidney disease

- Obesity is a whole-body condition that **affects numerous organ systems** including the cardiovascular, respiratory, endocrine, neurologic, and musculoskeletal systems, among others
- Its broad systemic impact means obesity is associated with a **significant degree of comorbidity that drives increased morbidity and mortality** for overweight and obese patients
    - Studies show that **increasing BMI is positively correlated with increased prevalence** of numerous other diseases; common examples include:

Type 2 diabetes: 16%

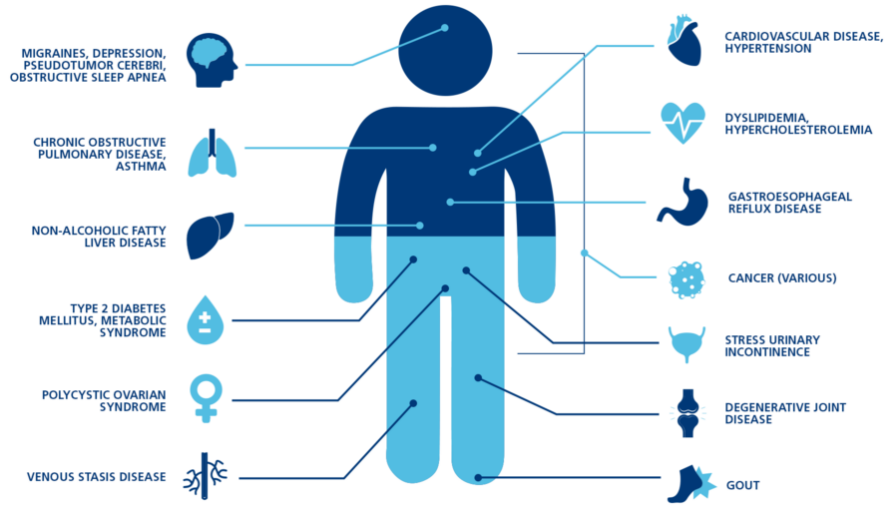
Osteoarthritis: 22%

Chronic kidney disease: 33%

Obstructive sleep apnea: 40%

Hypertension: 45%

Dyslipidemia: 48%



People with obesity have a **54% *(Class I)* – 124% *(Class III)* higher likelihood** of having one disease vs.

Concurrent comorbidities are also strongly associated with obesity, demonstrating a **33% *(Class I)* – 44% *(Class III)* prevalence** in obese individuals vs. 23% in normal-weight comparators

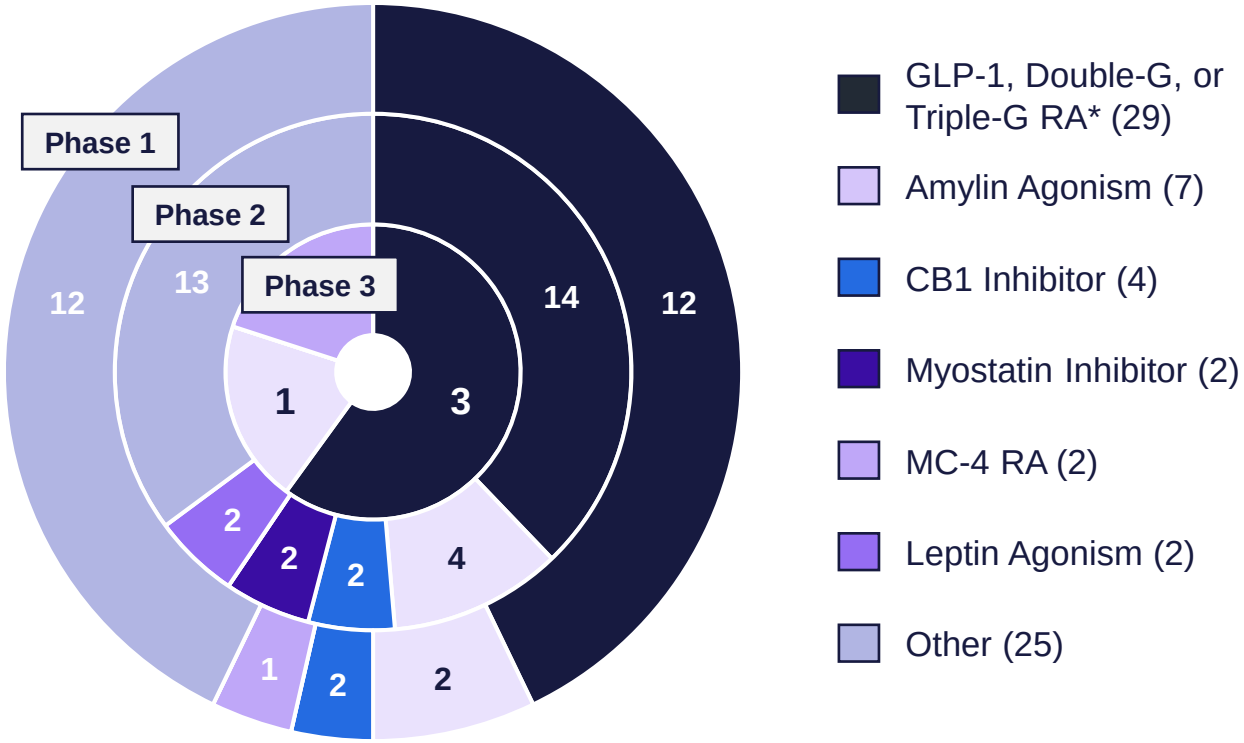
- Source: Lim & Boster, 2023. Apovian et al., 2022. CDC – Adult Obesity (2022). NHSR (2022). Stokes et al., 2018. Tchang et al., 2021. Li et al., 2015.

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U.S. Obesity Clinical-stage Competitive Pipeline

U.S. obesity market faces intense/increasing competition: 5 Phase 3, 36 Phase 2, and 29 Phase 1 programs are primarily focused on GLP-1s; only 3 CB1 assets in clinical development

Unique Competitors in the U.S. Obesity Clinical Pipeline



*Double-G is inclusive of GIP / GCG and GLP-1 receptor agonists; triple-G is inclusive of GCG, GIP, and GLP-1 receptor agonists. ^Inclusive of amylin monotherapy and combination therapy with other MOAs. Note: Other is inclusive of but not limited to activin receptor 2a antibody, activin receptor A antibody, myostatin (GDF-8) inhibitor, monoacylglycerol acyltransferase 2 inhibitor, microbiome regulator, apelin receptor agonist, alpha-glucosidase inhibitor & lipase inhibitor, atrial natriuretic peptide agonist, and unclassified products in development. Sources: 1. EvaluatePharma; 2. PharmaProjects; 3. Clinicaltrials.gov; 4. Company websites. mAb: monoclonal antibody

Key Pipeline Insights

- **Prioritization of GLP-1 Receptor Agonists**: GLP-1-targeting assets are spread across stages of development, representing ~42% of all products
  - Key late-stage assets include orforglipron (P3 oral GLP-1 RA), danuglipron (P2 oral GLP-1 RA), cagrisema (P3 amylin/GLP-1 RA) and retatrutide (P3 GLP-1/GIP/GCG RA); all four may launch by 2026 – 2027
- **CB1 Clinical Presence:** There is limited CB1 inhibitor competition in the clinical pipeline (N=3)
  - Monlunabant (Novo Nordisk): P2 oral small molecule; currently initiating a P2b trial
  - Nimacimab (Skye Bioscience): P2 mAb
  - INV-347 (Novo Nordisk): P1 oral small molecule; limited data released
  - CRB-913 (Corbus): P1 oral small molecule

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