Developing Innovative Medicines to Treat Obesity and Other Metabolic Diseases

skye

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Nasdaq: SKYE

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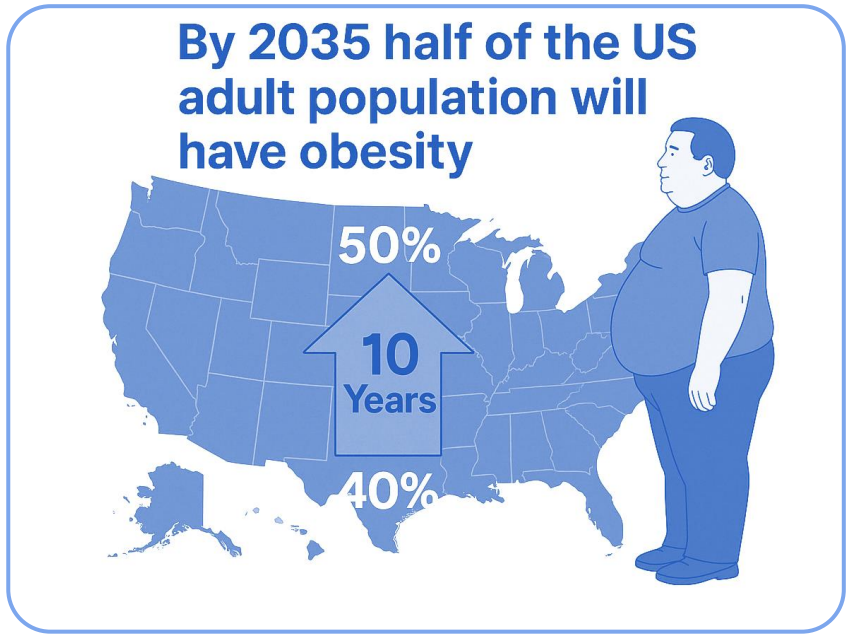
Mission

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



GLP-1s

Byetta (exenatide) injection
VICTOZA liraglutide injection 1.2 mg | 1.8 mg
Saxenda liraglutide injection 3mg
ONCE-DAILY RYBELSUS semaglutide tablets
once weekly trulicity
OZEMPIC semaglutide injection
ONCE-WEEKLY wegovy semaglutide injection 2.4 mg
once weekly mounjaro (tirzepatide) injection
once weekly zepbound (tirzepatide) injection

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.

Significant Opportunity Remains in Anti-Obesity Drug Market

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

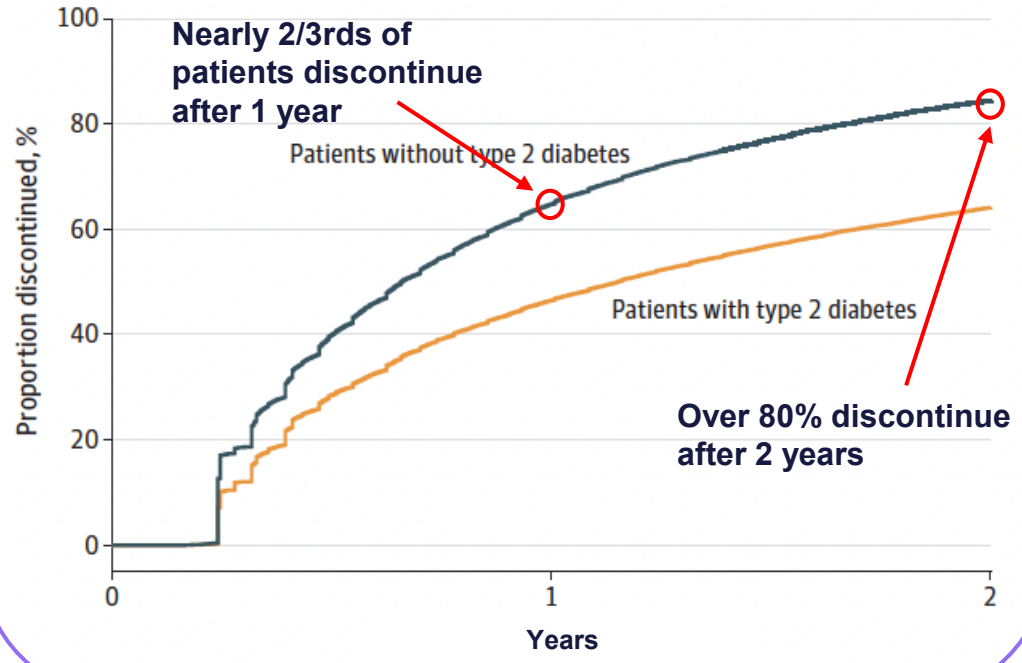
		Opportunity
Gastrointestinal Issues	Wegovy® and Zepbound® cause significant rates of **nausea** (31-53%), **diarrhea** (23-35%) and **vomiting** (12-30%)	 **Improved tolerability**
Discontinuation Rates and Rebound Weight Gain	**Blue Health Intelligence**[2] survey reported **30% of patients dropped 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

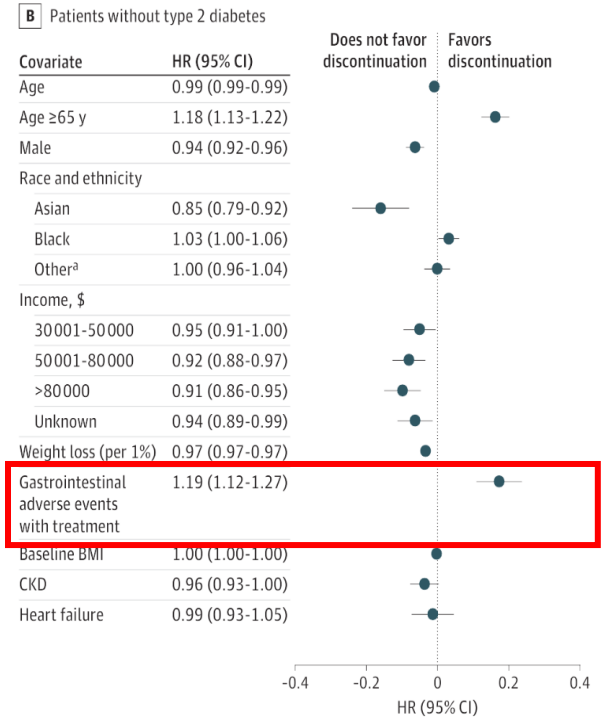
Pattern of GLP-1 Discontinuation

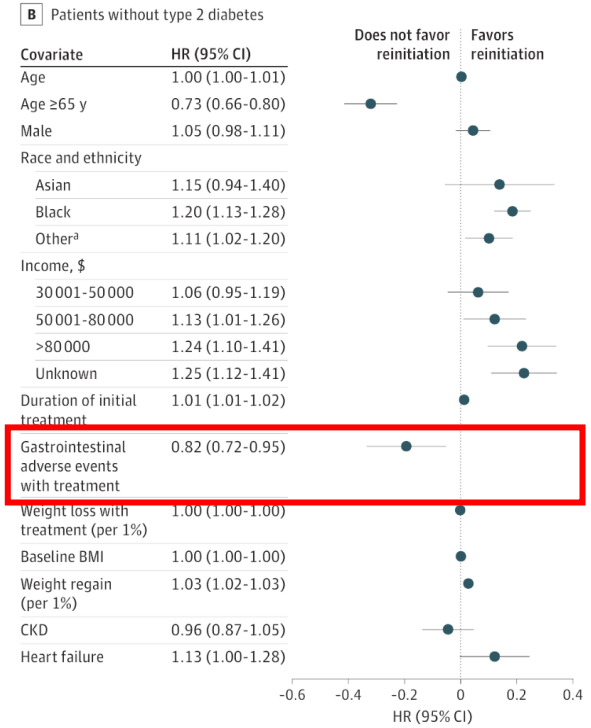
Most adults with overweight or obesity discontinue GLP-1 RA therapy within one year

Time to Primary Discontinuation of GLP-1 RA Therapy



Discontinuation and Reinitiation Rates Strongly Correlated with GI Intolerability





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

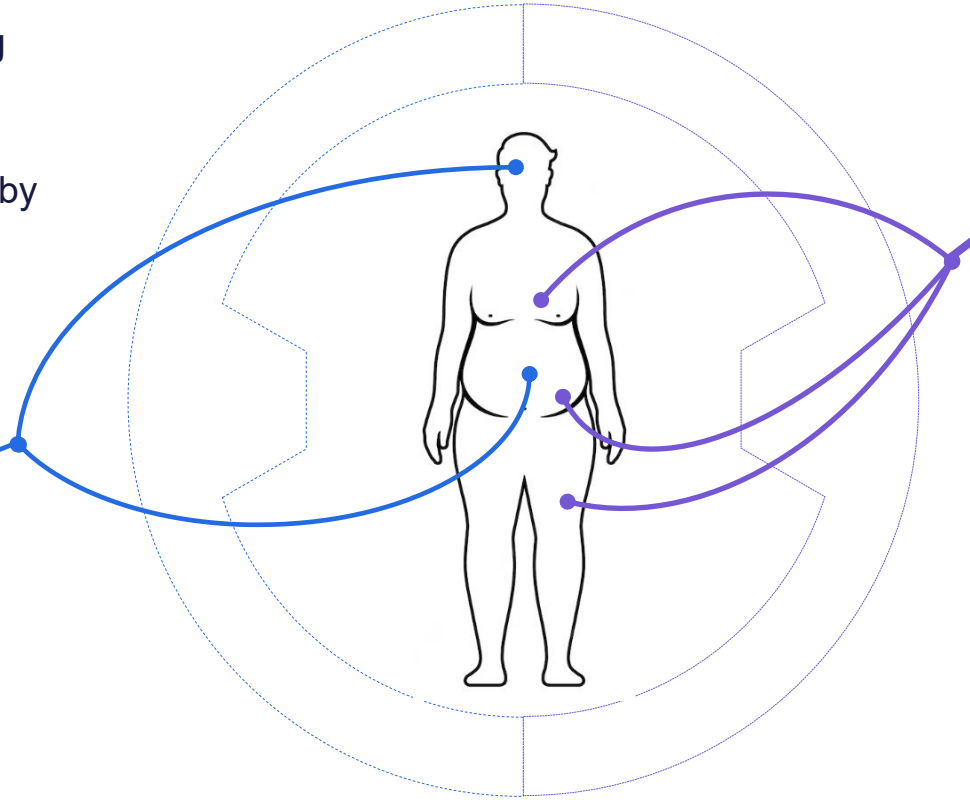
CB1: Overlooked Non-incretin Target to Tackle Weight Loss

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

*non-incretin

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 similar efficacy yet better GI tolerability compared to oral semaglutide

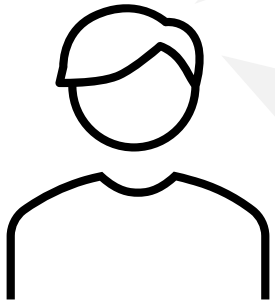
However, monlunabant's neuropsychiatric adverse events reignited the debate on safety of CB1 inhibition

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

Monlunabant – What Novo's Saying and Doing

Confidence in weight-loss potential of CB1, but knowledge that CNS exposure must be minimized to reduce neuropsychiatric concerns

"The phase 2a results indicate the weight-lowering potential of monlunabant and that further work is needed to determine the optimal dosing to balance safety and efficacy"
Novo Nordisk Press Release
September 2024



Martin Holst Lange,
EVP Development at Novo Nordisk

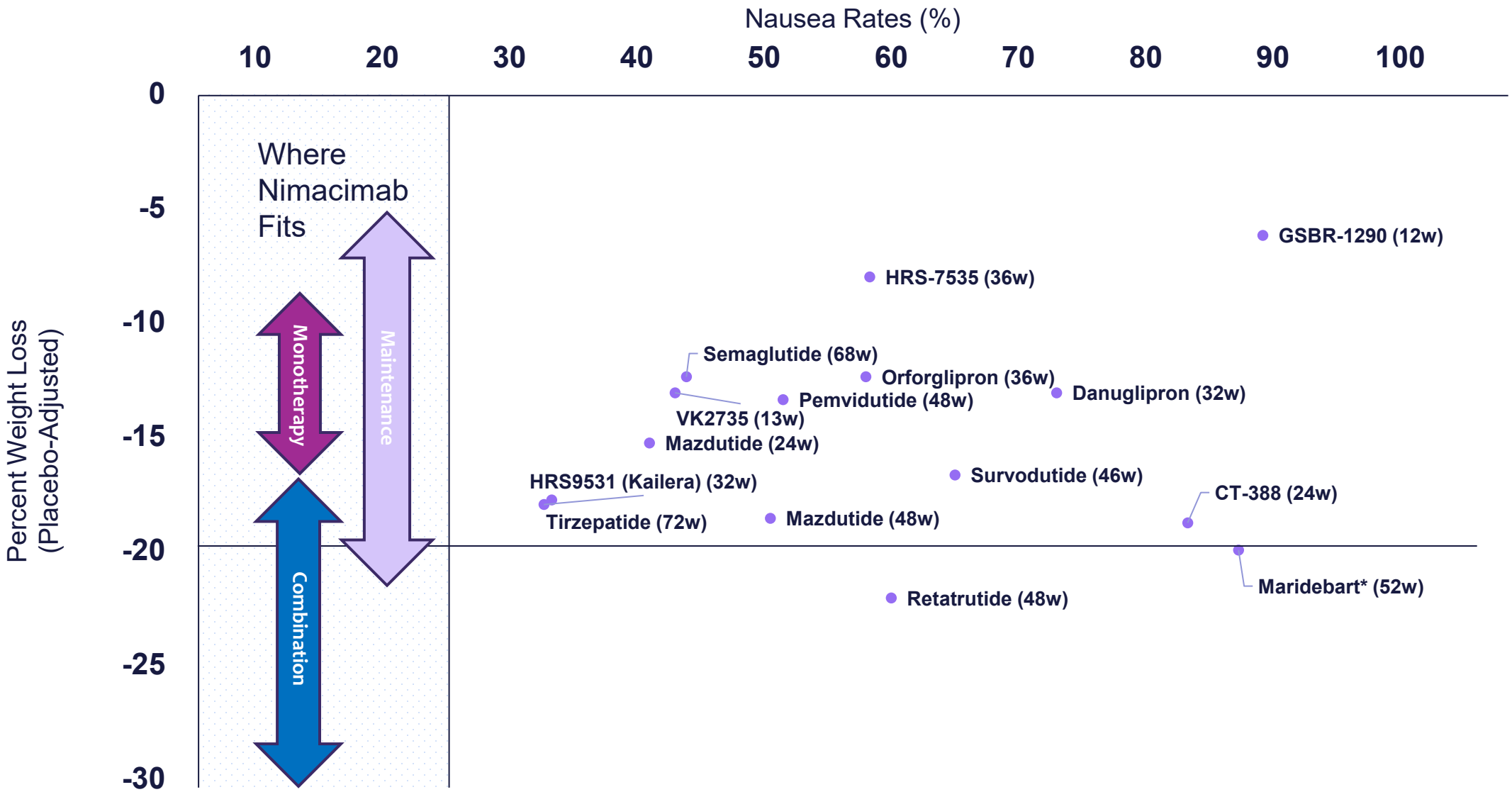
"When we look at the safety and tolerability profile, it was comparable, albeit at a slightly lower rate than in the dedicated obesity study, basically indicating that we can still have an aspiration of exploring this further in phase 2b with lower doses, looking at weight loss potential, but obviously also—and this has been the intent from the get-go—ruling out a potential safety concern."
Novo Nordisk 2024 Earnings Call
Response to an analyst's question about monlunabant DKD data compared to obesity data

Ongoing Clinical Research:
Phase 1 Completed: A Research Study Investigating Safety and Concentration in the Blood After One Dose Tablet of the New Medicine Monlunabant in Healthy Weight Japanese and Caucasian Men (NCT06542536)
Phase 2b Planned in 2025/2026

Termination of INV-347 Program:
INV-347 is a second-generation CB1 small molecule for which Novo has shared multiple updates + planned upcoming obesity conferences. Recently, Novo announced the discontinuation of the program.

Potentially Clinically Meaningful WL with Better Tolerability

Novel MoA can capture significant white space



Nimacimab: Building a Differentiated Profile

Evidence built to date; nimacimab clinical and preclinical differentiation

Established to Date

- **Durable weight loss and restoration of metabolic homeostasis**
- **Improves glycemic control**
- **Modulates lipid metabolism**
- **Reduces obesity-induced inflammation and fibrosis**
- **Additive with incretin therapies**
- **Potency and MOA**
- **No CNS penetration in NHP study**

Recent Preclinical Data

In vivo nimacimab dose titration with monlunabant comparator

- All doses of nimacimab compare favorably to monlunabant both while on treatment as well as highlighting a minimal post-treatment rebound
- Nimacimab and monlunabant display a different weight loss profile
- Nimacimab demonstrates durable weight loss after treatment discontinuation

Repeat DIO studies: productive tirzepatide (TZP) combination + maintenance

- Nimacimab in combination with TZP promotes significant weight loss (up to 46%) with a minimal rebound profile upon treatment discontinuation
- Nimacimab in combination with TZP yielded a notable but similar reduction in caloric intake relative to the TZP alone, yet a significant increase in WL was evident in combination, suggesting additional MOA beyond anorexigenic effects.
- The pair-fed control highlights that Nimacimab-driven efficacy is only partially mediated via caloric restriction
- Nimacimab demonstrates durable weight loss after treatment discontinuation
- Data support using nimacimab as a post-tirzepatide maintenance therapy

Looking Ahead to the Rest of 2025

Clinical proof-of-concept
Initial data from the CBeyond Phase 2a study is expected late Q3/early Q4 2025.

Phase 2b "CBeyond^2" study design
Larger Phase 2 study evaluating multiple doses and dose frequency to determine final Phase 3 dose.

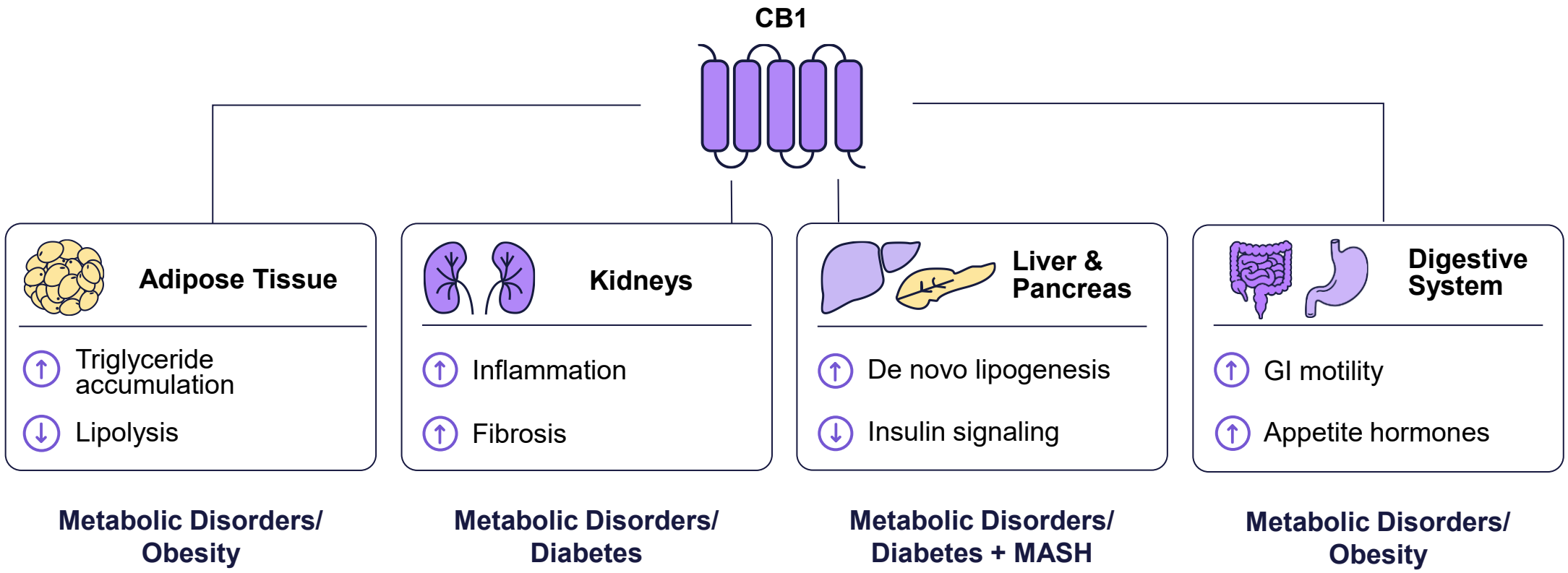
New preclinical data
Established hCB1 mouse colonies will provide opportunities for multiple new preclinical readouts for the rest of 2025 and 2026.

Nimacimab

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

Peripheral CB1 Signaling: Metabolic-focused Targets

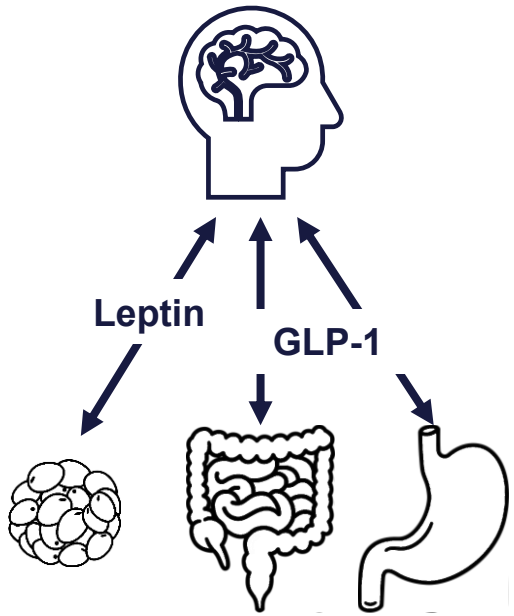
Active CB1 engagement promotes inflammation, fibrosis, and metabolic dysfunction; *blocking* peripheral CB1 can reverse negatively-trending pathologies



Four Mechanistic Pillars of Nimacimab

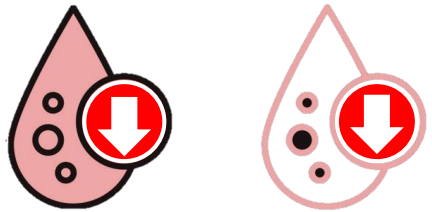
01

Peripheral Modulation of Appetite Regulating Hormones



02

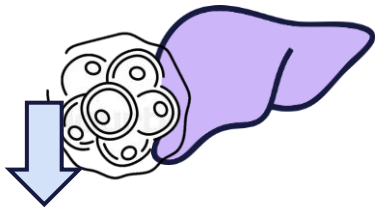
Improvement and Restoration of Glycemic Control



Reduced fasting insulin and improved glucose control

03

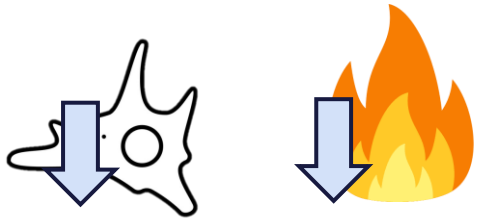
Enhanced Lipid Metabolism



Decreased steatosis and serum cholesterol

04

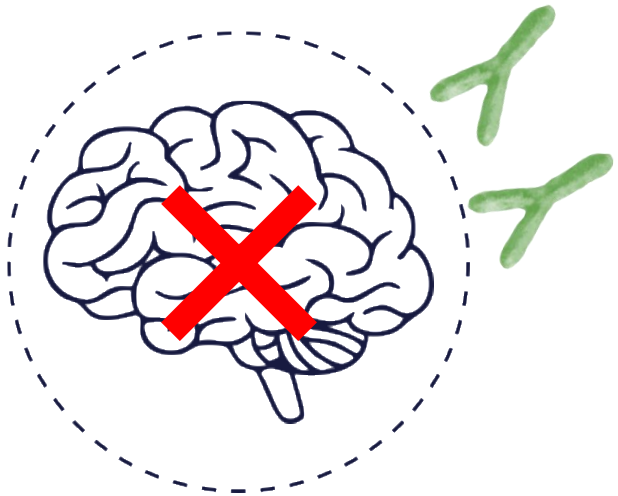
Reduction of Obesity-Induced Inflammation



Decreased inflammation and fibrosis markers

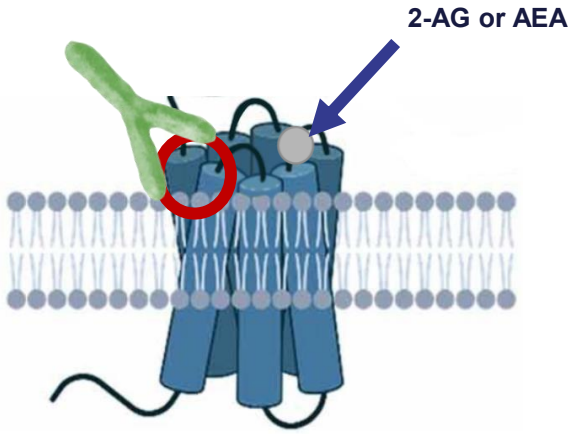
Nimacimab is Differentiated from Small Molecule CB1 Inhibitors

Peripheral Restriction



Significantly less brain penetration than small molecules currently in development

Negative Allosteric Modulator



Unlike small molecules currently in development, **nimacimab** retains potency even in the presence of competition

Nimacimab: Peripherally-restricted CB1-inhibiting Antibody

Long Half-life

- 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

Exclusion from Brain

- Multiple NHP studies: background levels 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

Differentiated Inhibitor

- Functions as both an **antagonist** and an **inverse agonist**
- Binds allosteric site and non-competitively inhibits CB1, independent of agonist

Safe & Effective Drug

- Achieve ~8x peripheral CB1 inhibition while ~600x below CB1 inhibition in brain
- Allosteric binding maintains peripheral CB1 inhibition with increased endocannabinoids
- Supports a favorable therapeutic index to safely and effectively treat obesity

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

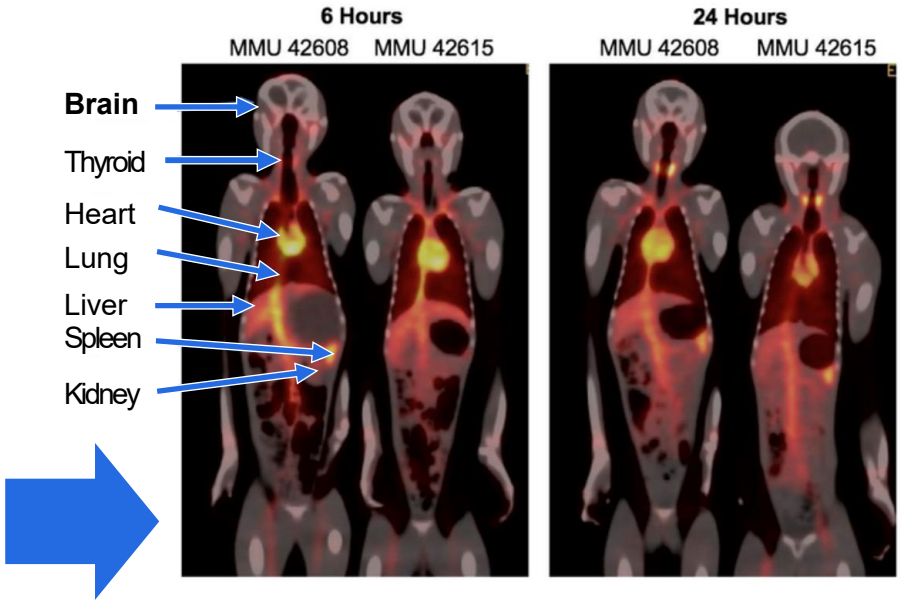
Cyno	9 hours
CSF/Serum 40 mg/kg IV	0.01%

— 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

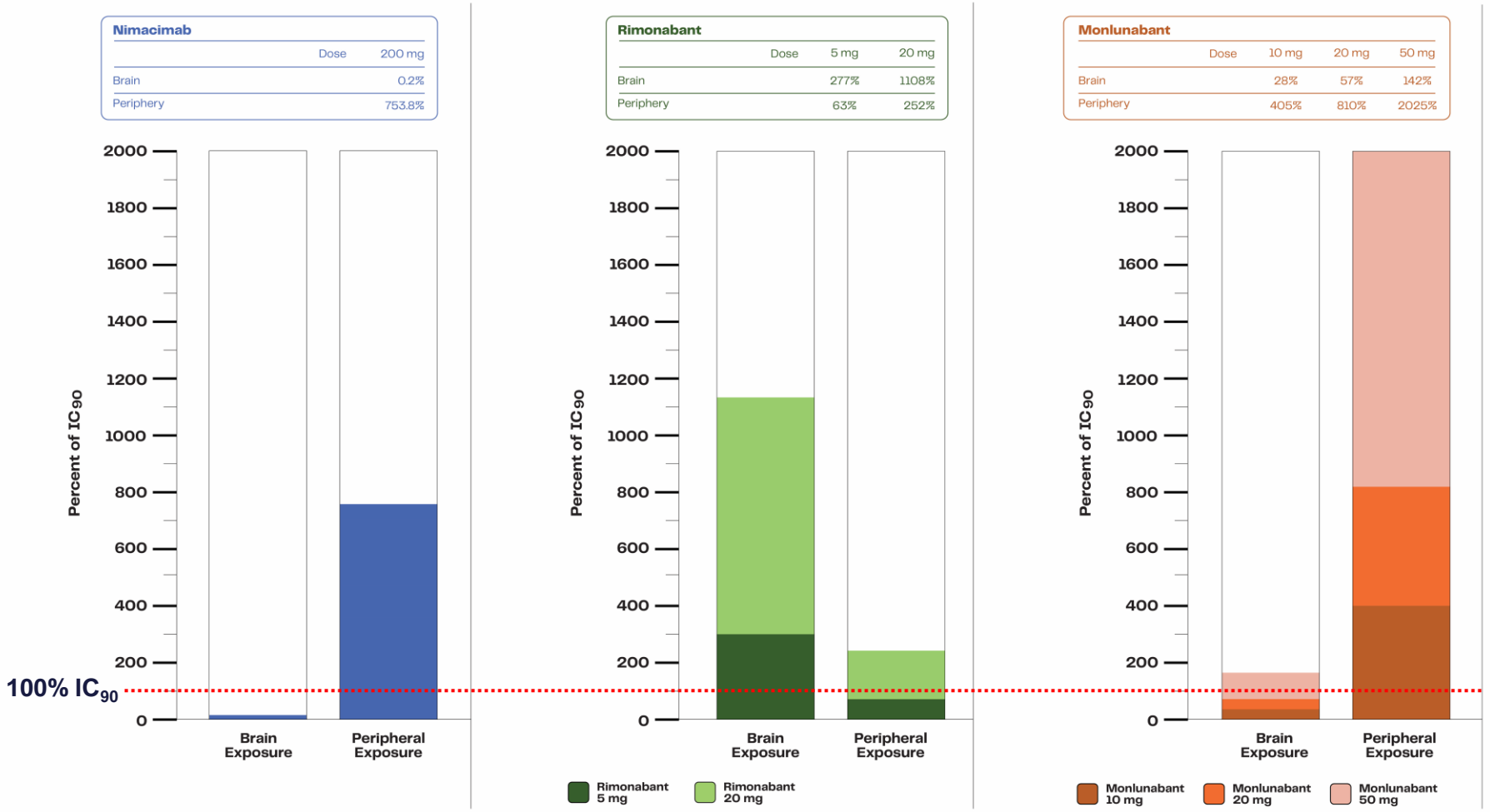
PET imaging also confirmed broad antibody distribution in tissues having upregulated CB1 expression, with no accumulation in the brain



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

Nimacimab Achieves Peripheral CB1 Inhibition Without CNS Risk

Superior peripheral restriction vs. small molecules: over 750% of IC_{90} in periphery, with <1% CNS exposure



Rimonabant:

- 5mg and 20mg doses have significant brain exposure, resulting in neuropsychiatric effects at both doses.
- Only 20mg exceeds IC_{90} in the periphery, resulting in significant weight loss.

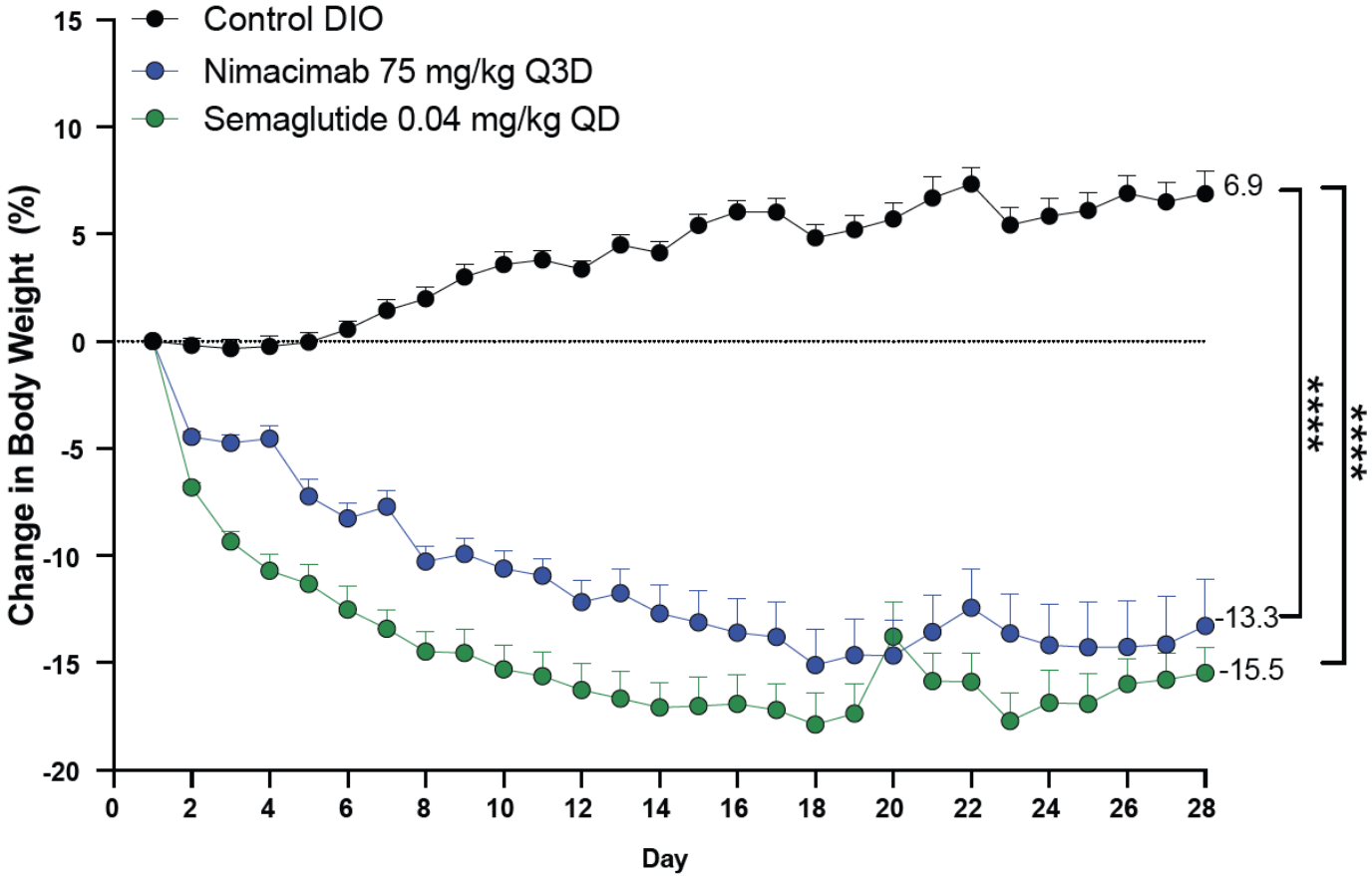
Monlunabant:

- 10mg, 20mg, and 50mg doses all exceed IC_{90} in the periphery, resulting in significant, but not dose-dependent, weight loss.
- Increasing doses result in increasing exposure in the brain which leads to dose-dependent increase in neuropsychiatric effects without additional weight loss benefit.

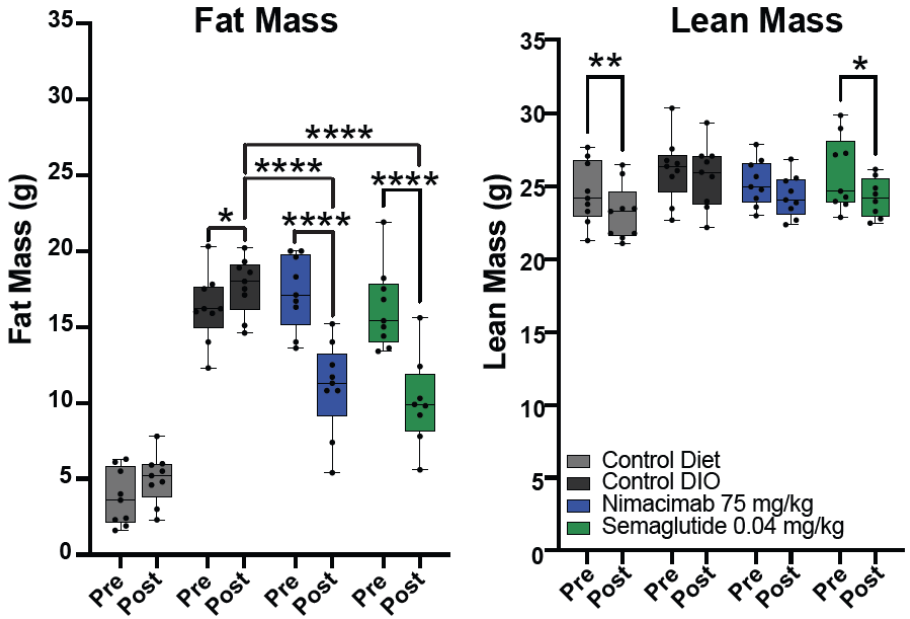
Source: Braga et al., Demonstrating the sufficiency of peripheral CB1 inhibition to promote weight loss using clinical pharmacokinetic and pharmacodynamic. European Congress on Obesity PO4.148. https://eco2025.org/assets/docs/programme-book.pdf?a=5678

Repeat DIO Study with Independent Lab: Similar Weight Loss with Reduced Fat Mass

Body Weight



Body Composition

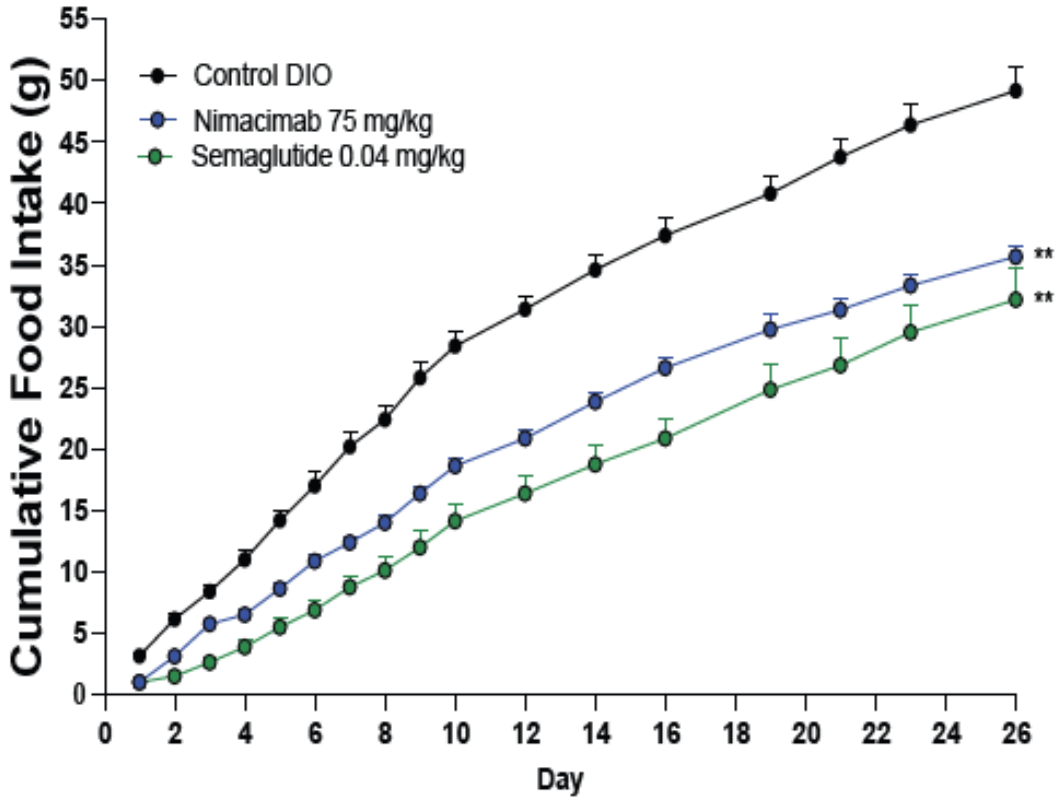


Body weight and composition analyses were performed with two-way ANOVA repeated measurements. Tukey multiple comparison test was then performed for all pairwise comparisons. Body weight reporting through 28 days of treatment. Body composition measured with echo MRI on day 26

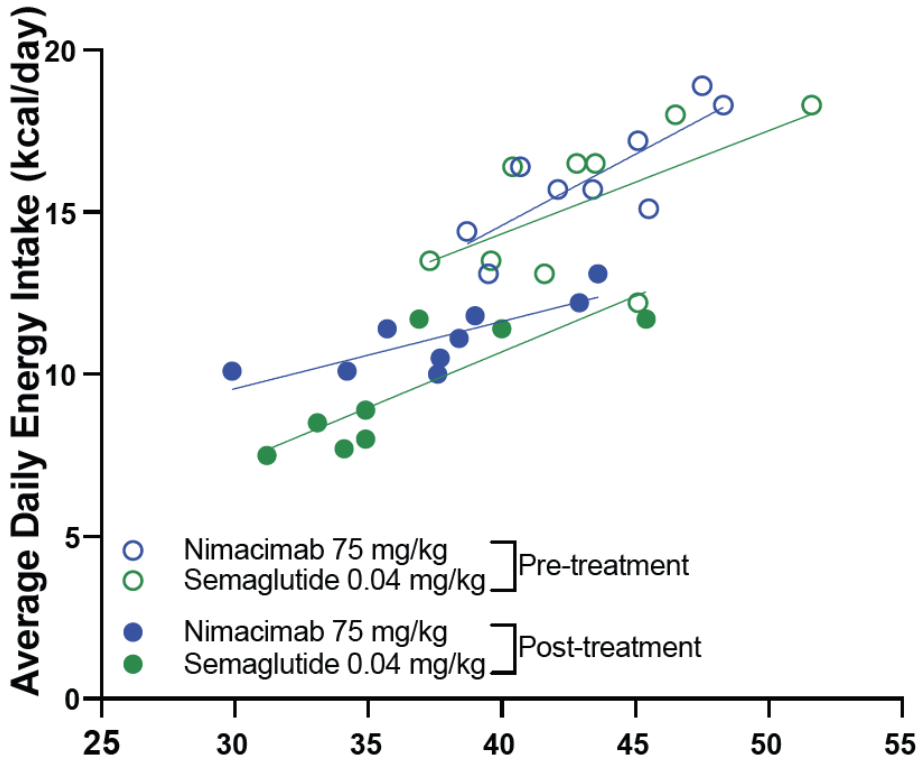
Nimacimab Led to Reduced Food Intake

Reduced caloric intake with nimacimab comparable to semaglutide – supporting centrally mediated appetite suppression without CNS penetration

Cumulative Food Intake



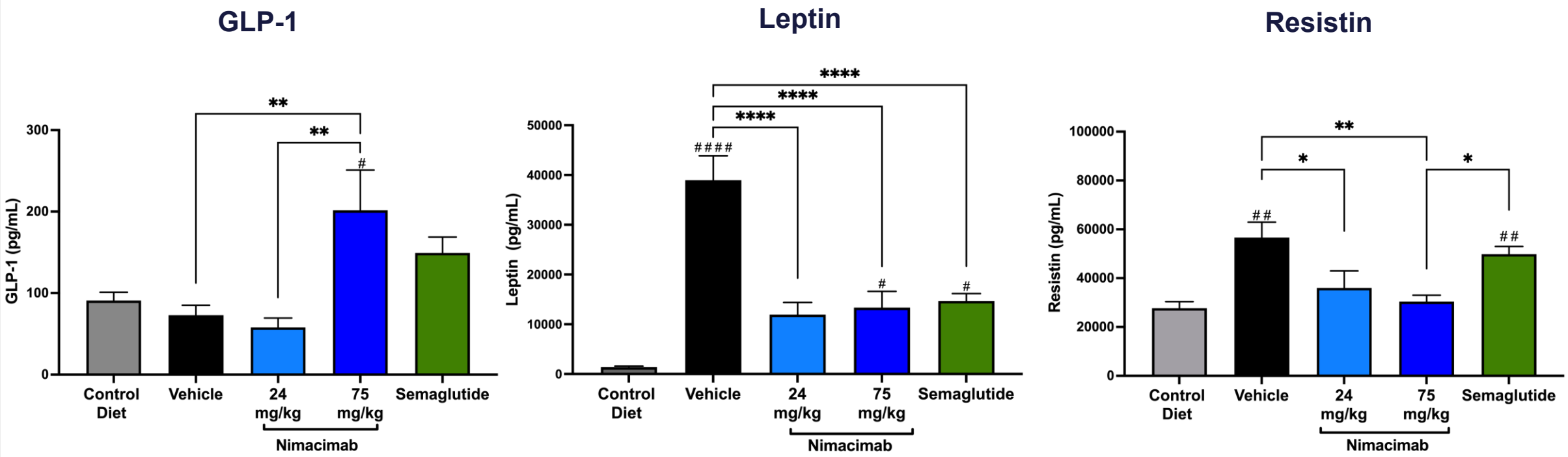
Caloric Intake vs Body Weight



*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*

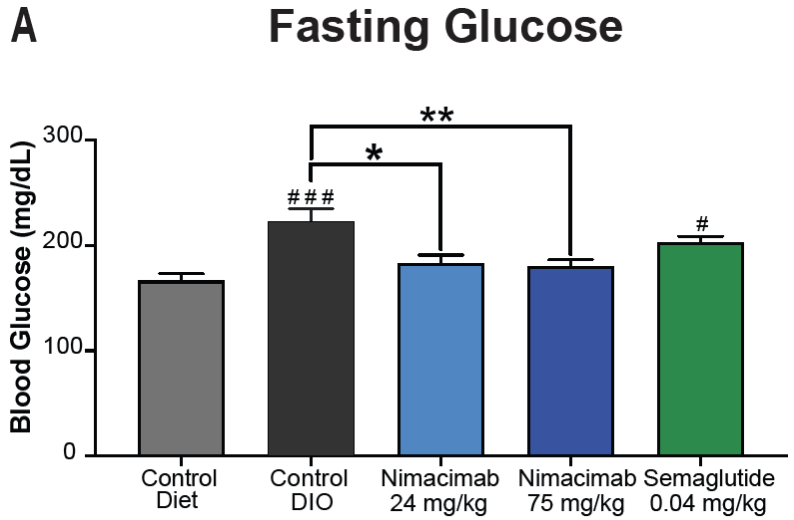
Productive Modulation of Key Hormones with Nimacimab

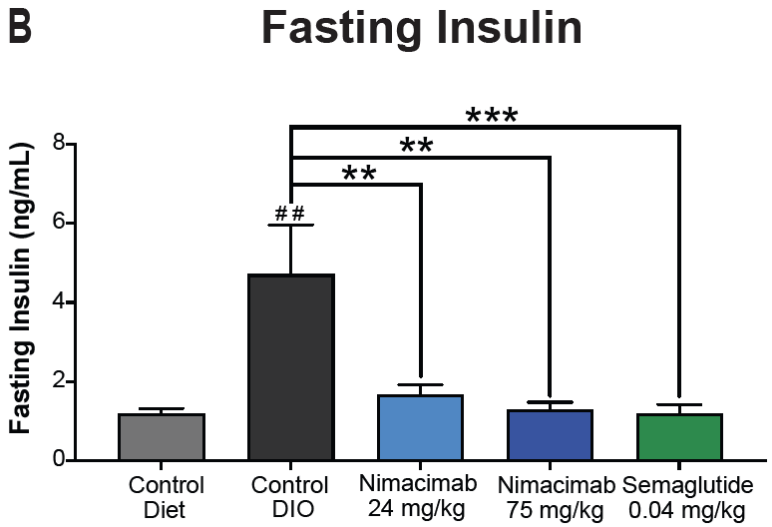
Peripheral CB1 inhibition modulates gut and adipose tissue hormones important for central control of appetite

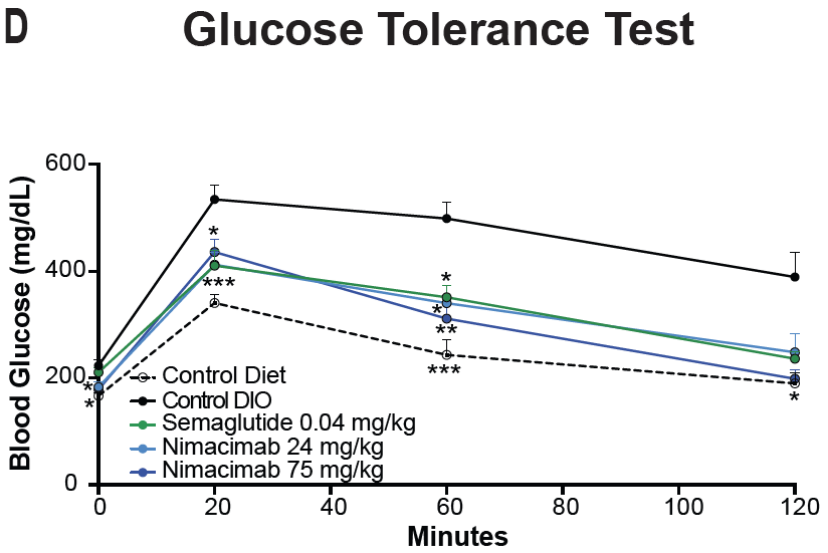


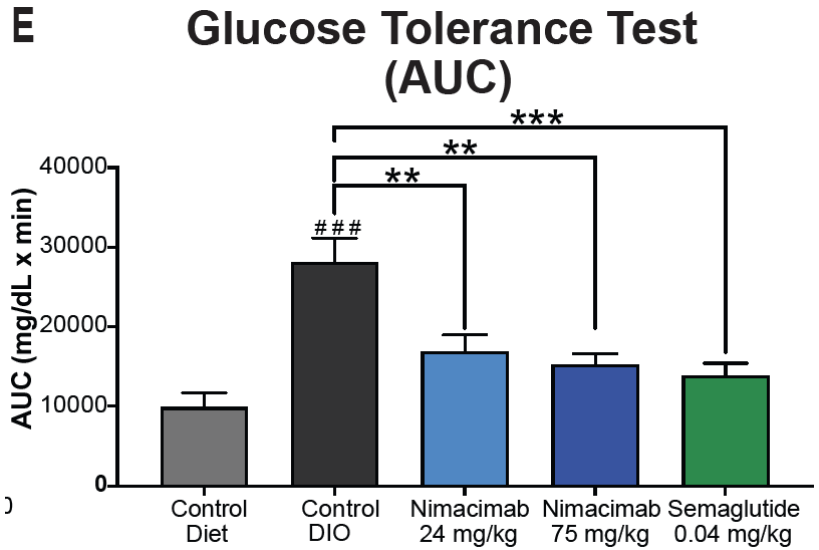
Serum was collected on day 36 and hormone levels were determined with a Bio Plex Multiplex immunoassay. For all analyses: one-way ANOVA repeated measurements (Tukey multiple comparison test). # denotes significance to the control diet group.

Nimacimab Improves Glycemic Control









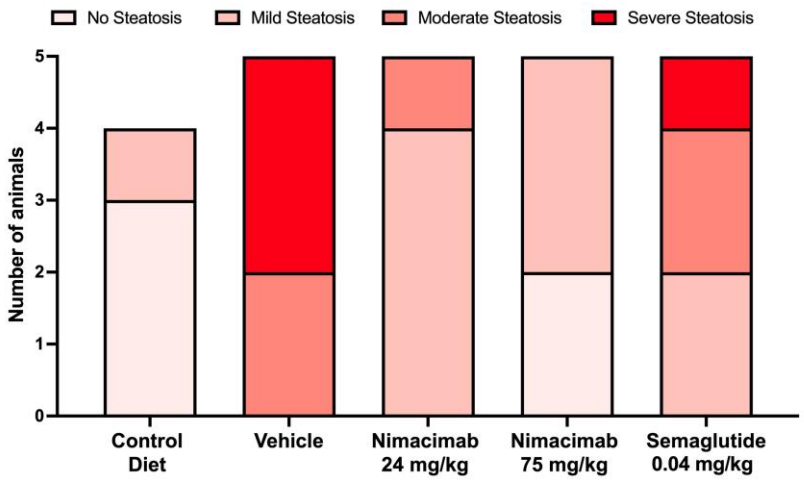
Day 27 mice were fasted for 4h before collecting serum to measure glucose and insulin levels. Day 27 mice were fasted for 4h before ip injection of 2g/kg glucose. GTT analyses: 2-way ANOVA repeated measurements (Tukey multiple comparison test); baseline subtracted AUC analysis was performed with a one-way ANOVA with Tukey multiple comparison test.

Nimacimab Treatment Promotes Lipid Metabolism

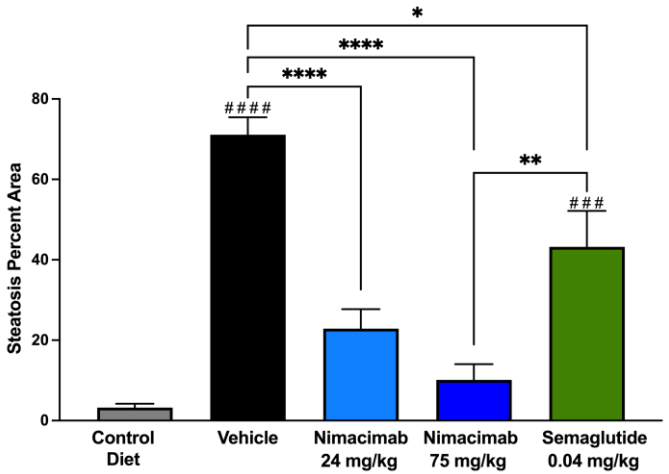
Dose-dependent reduction in steatosis and serum cholesterol

Steatosis Analysis (Liver)

Steatosis Score

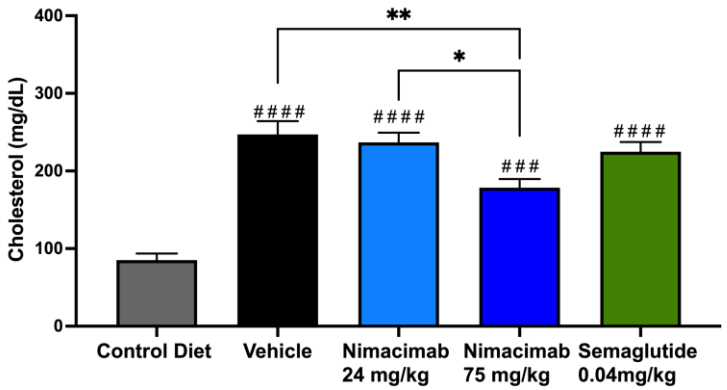


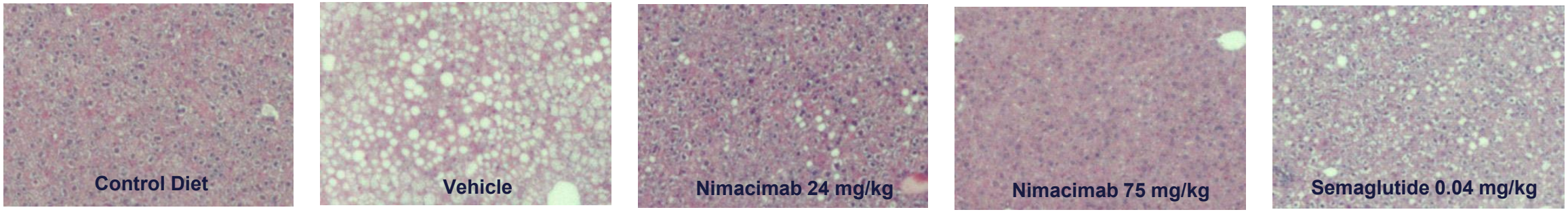
Steatosis Percent Area



Serum

Cholesterol





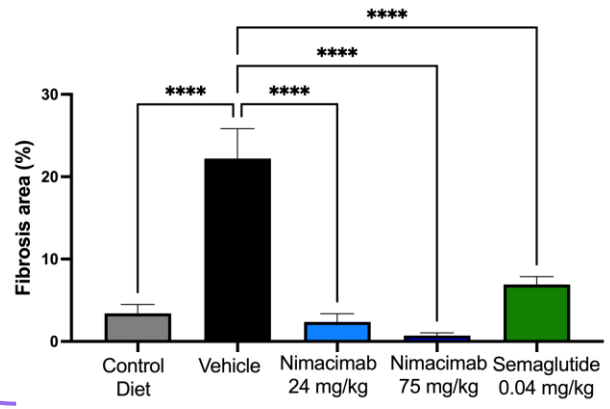
*Liver sections scored by a pathologist using computer-aided analysis. A score of 0-3 was assigned based on % of hepatocytes with fat. 0 = no steatosis (<5%), 1=mild (5-33%), 2=moderate (>33-66%), 3=severe steatosis (>66%). (B) steatosis percent area was analyzed using computer-aided analysis with Cellprofiler. (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<0.001 vs control diet.*

Nimacimab Improves Obesity-related Inflammation

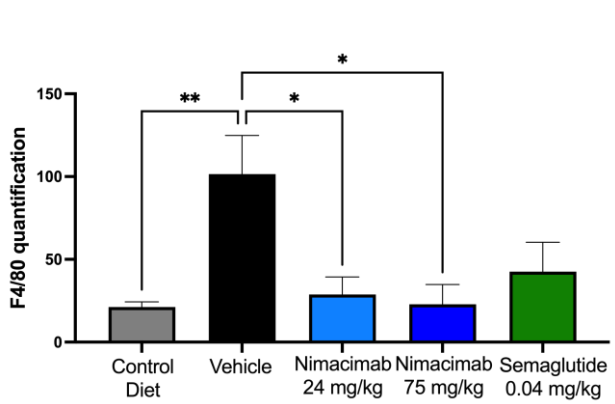
Reduced Inflammation, Fibrosis, and Adipocyte Area

Liver

Fibrosis Area

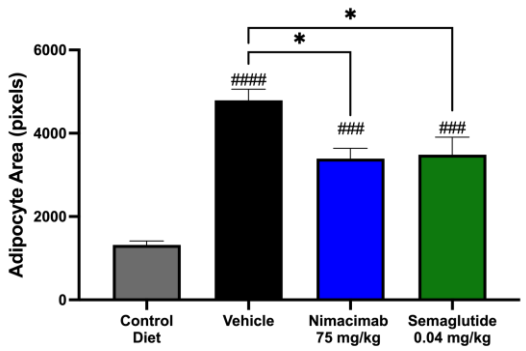


Macrophage (F4/80) Density

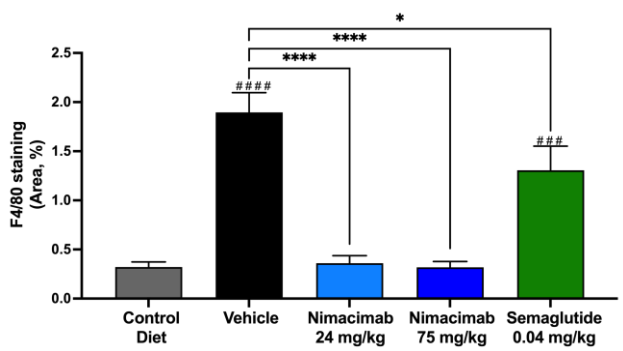


iWAT

Adipocyte Area

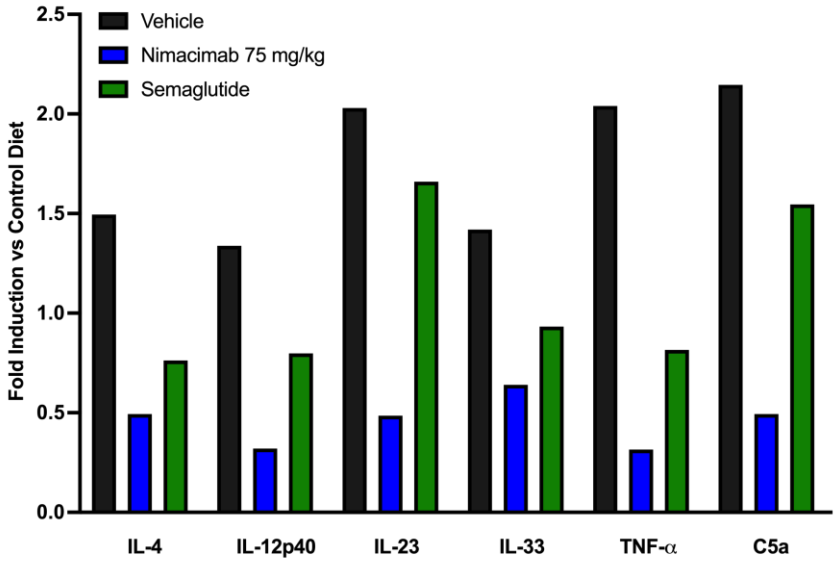


Macrophage (F4/80) Density



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.

*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 (fibrosis). Three fields per slide were quantified for adipocyte area in iWAT. Analysis was performed using a one-way ANOVA with a Tukey multiple comparison test. # denotes significance to the control diet group. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.*

Study Design: Measuring Efficacy and Rebound Dynamics of Monlunabant and Nimacimab at Active Doses

male hCB1
N=8

8 weeks

HFD initiated (60 kcal% fat)

16.3 weeks on HFD

Phase A: Nimacimab and Monlunabant Monotherapy

Phase B: Assess Rebound or Maintenance with Nimacimab

Days -10 0 23 2 47 48

MRI MRI MRI

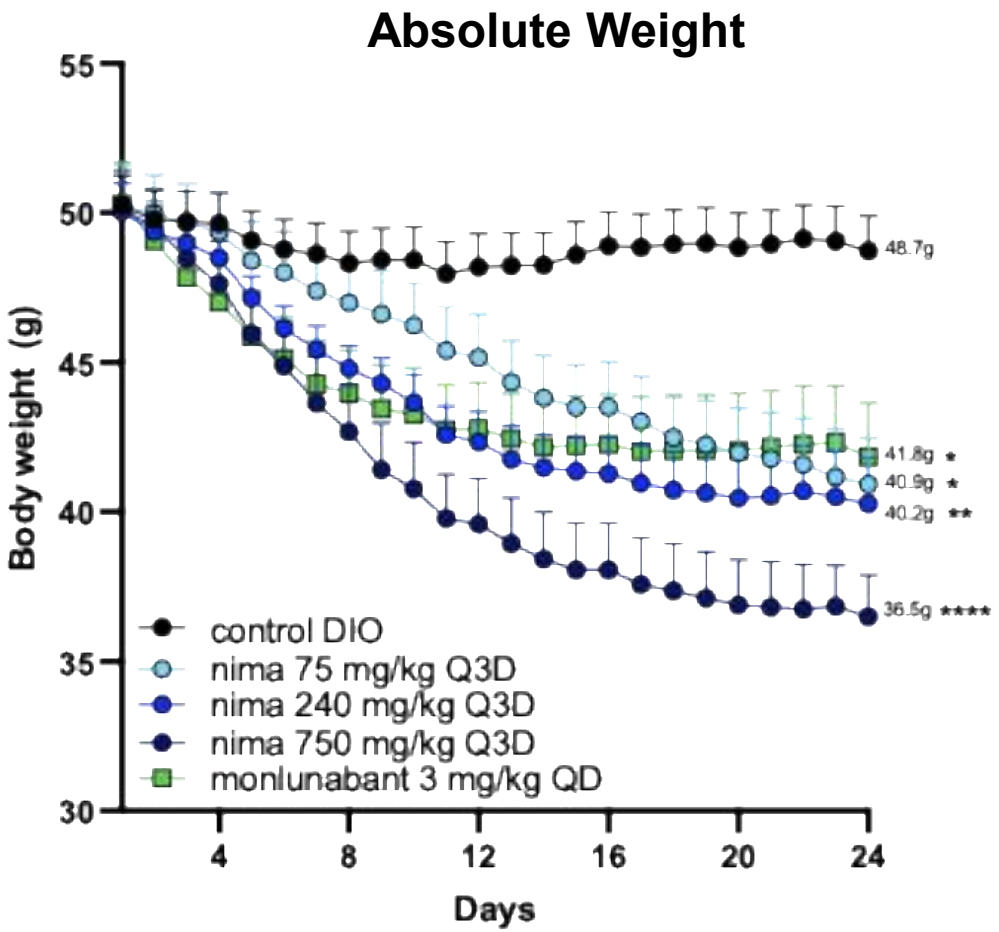
Tissue collection

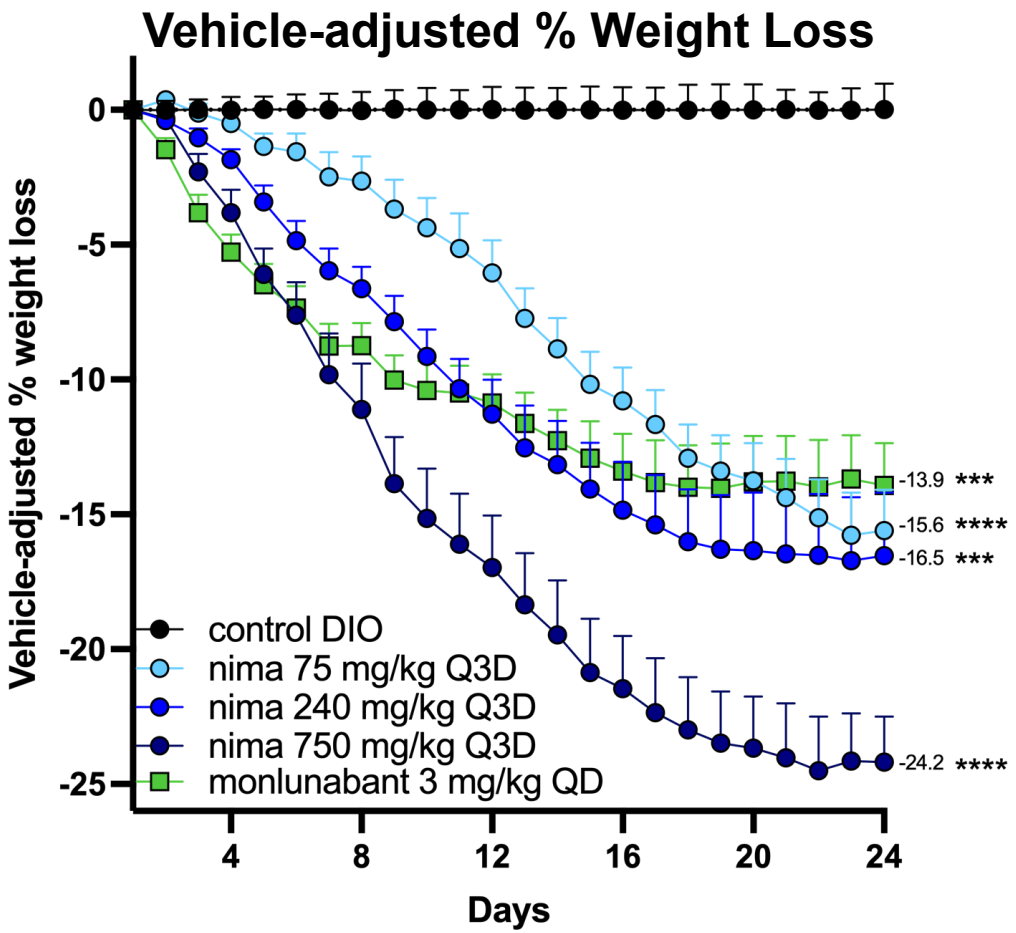
- vehicle (control DIO) → no intervention
- nimacimab 75 mg/kg Q3D → no intervention
- nimacimab 240 mg/kg Q3D → no intervention
- nimacimab 750 mg/kg Q3D → no intervention
- monlunabant 3 mg/kg QD → no intervention

Endpoints:

- Daily body weight
- Daily food consumption
- EchoMRI (Body composition)
- Biomarkers for MOA

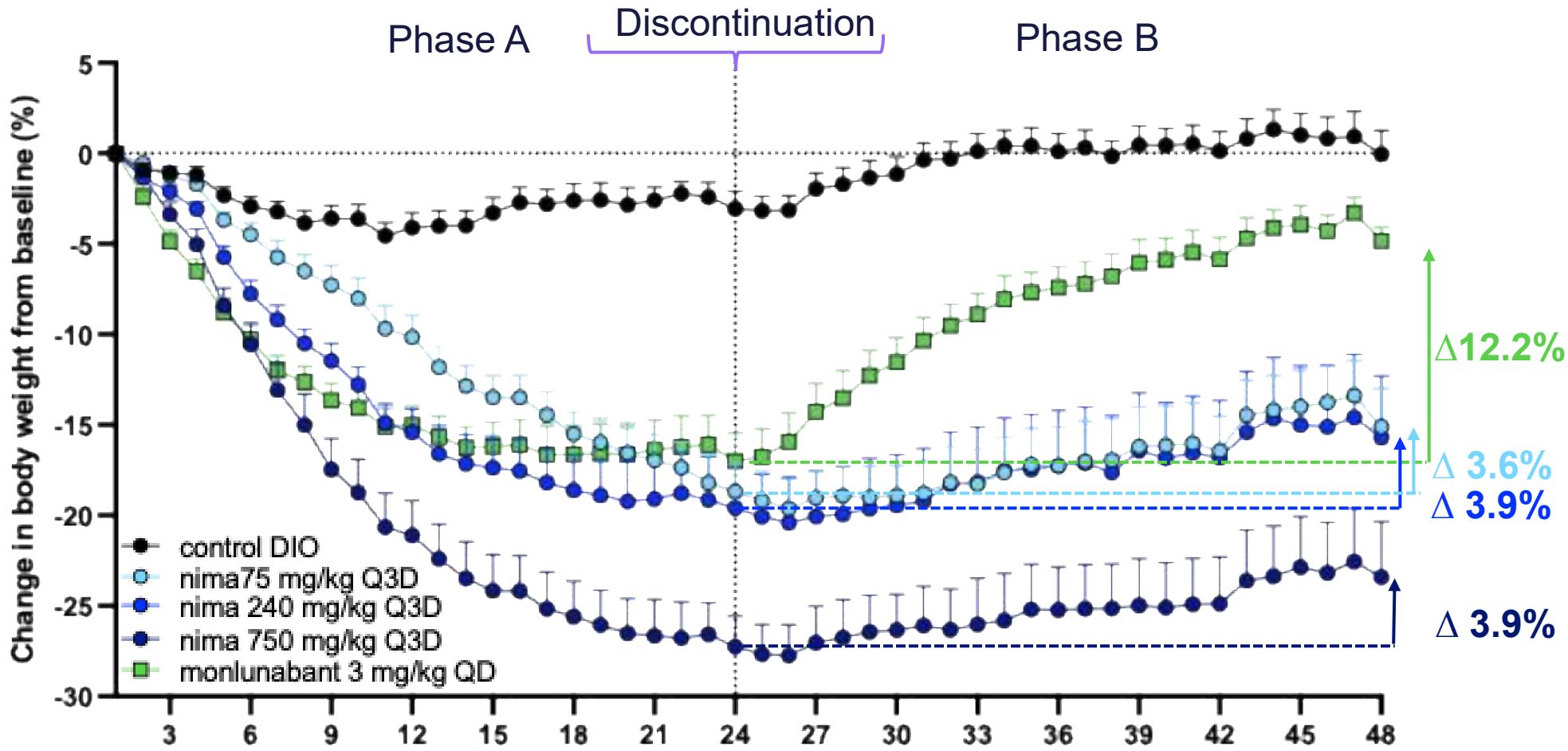
Nimacimab Compares Favorably to Monlunabant at All Doses





The daily average change in body weight from day 1 of treatment from the control DIO group was subtracted from the individual change in body weight per animal to calculate % change in body weight from baseline, vehicle adjusted. 2-way ANOVA, followed by Tukey's multiple comparisons test. *p<0.05, **p<0.01 ***p<0.001, ****p<0.0001. Reporting significance on day 24. Data are expressed as mean ± SEM.N=8 per group.

Nimacimab Drives Durable Weight Loss and Minimal Rebound Compared to Monlunabant Treatment



Data are expressed as mean ± SEM. N=7-8 per group. At day 48, all nimacimab treated groups were significantly different to control DIO (nima 75, ***p<0.001, nima 240 *p<0.05, nima 750 ***p< 0.001, monlunabant not significant).

Study Design: Nima/TZP/Combo with Rebound/Maintenance #1

male hCB1
N=8

8 weeks

HFD initiated (60 kcal% fat)

Phase A

Monotherapy and Combo with Suboptimal TZP

Phase B

Assess Rebound or Maintenance with Nimacimab

Days: -7 (MRI) -4 (GTT) -2 (ITT) 0 24 (MRI) 25 45 (MRI) 50 Tissue collection

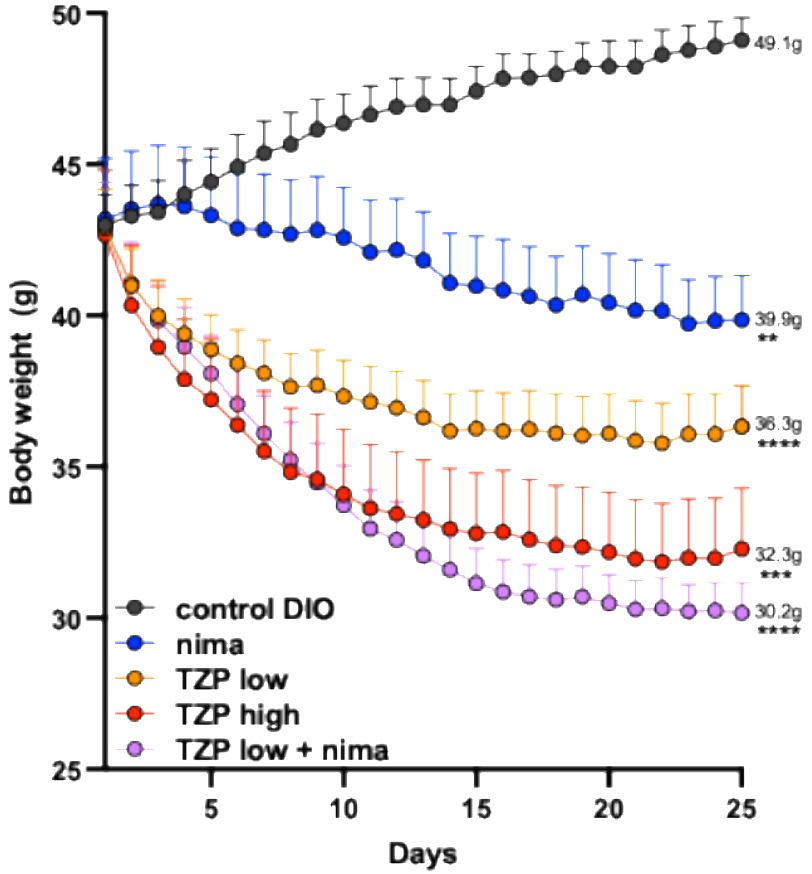
	Phase A	Phase B
vehicle	vehicle	vehicle
nimacimab 240 mg/kg Q3D	vehicle	vehicle
tirzepatide 3 nmol/kg QD	vehicle	nimacimab 240 mg/kg Q3D
tirzepatide 10 nmol/kg QD	nimacimab 240 mg/kg Q3D	nimacimab 240 mg/kg Q3D
tirzepatide 3 nmol/kg QD + nimacimab 240 mg/kg Q3D	nimacimab 240 mg/kg Q3D	nimacimab 240 mg/kg Q3D

Endpoints:

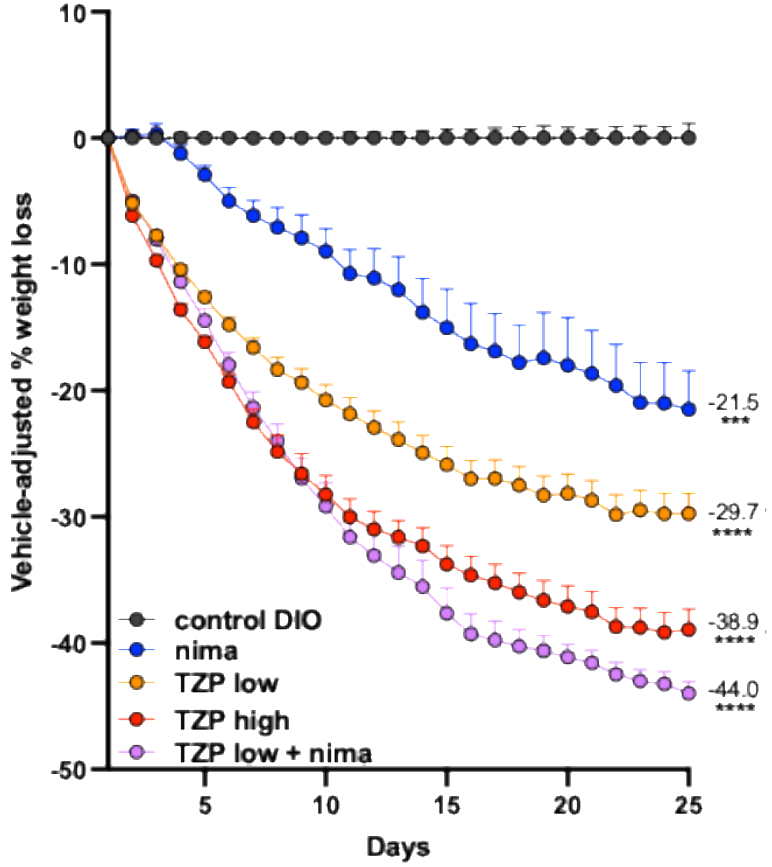
- Daily body weight
- Daily food consumption
- EchoMRI (Body composition)
- Biomarkers for MOA

Nimacimab Significantly Enhances Weight Loss as Monotherapy or Combined with Low-Dose Tirzepatide

Absolute Weight

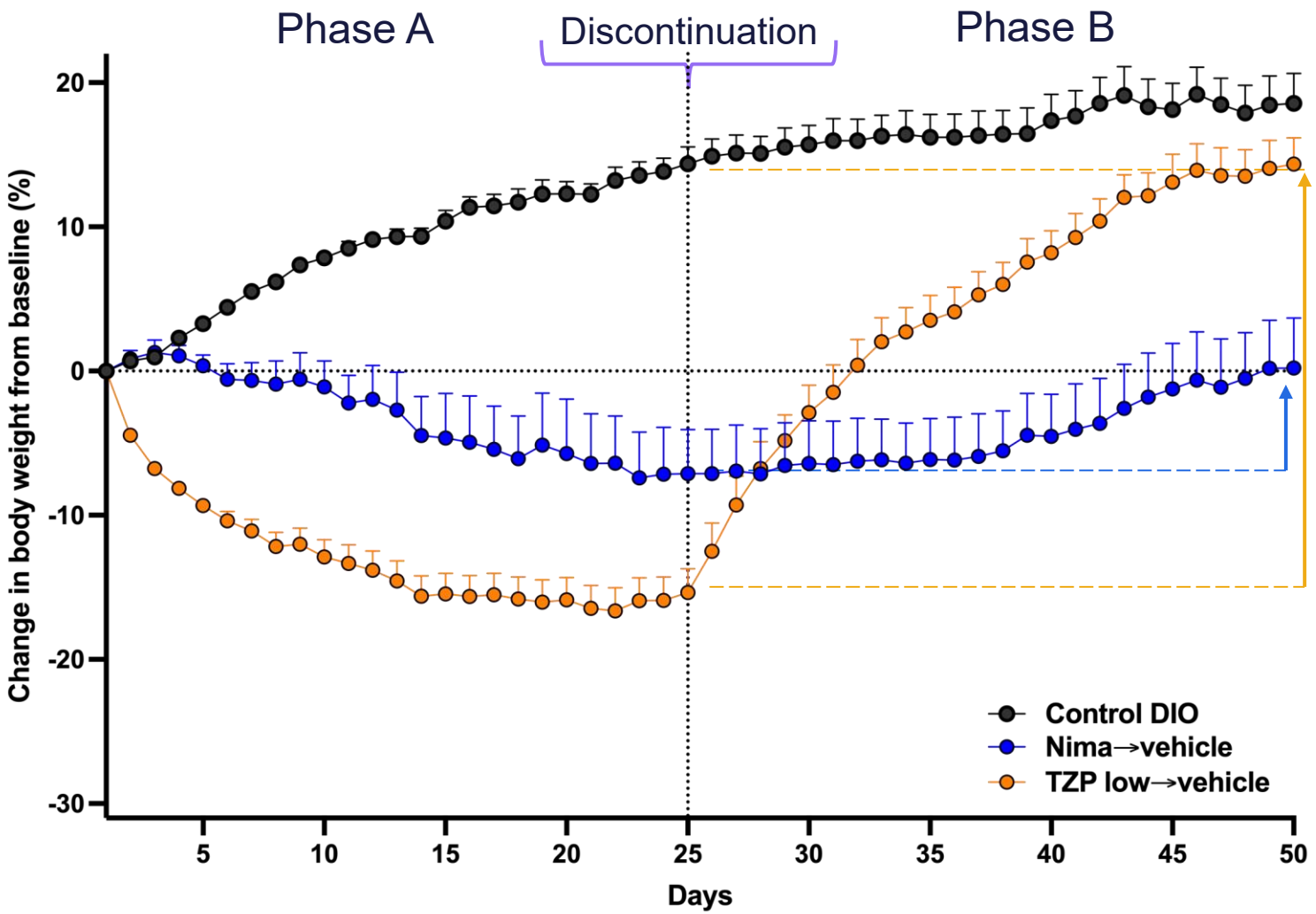


Vehicle-adjusted %Weight Loss



The daily average change in body weight from day 1 of treatment from the vehicle group was subtracted from the individual change in body weight per animal to calculate % change in body weight from baseline, vehicle adjusted. The combination of nimacimab with tirzepatide significantly outperformed either agent alone. 2-way ANOVA, followed by Tukey's multiple comparisons test. *p<0.05, **p<0.01 ***p<0.001, ****p<0.0001. Reporting significance on day 25. Data are expressed as mean ± SEM.N=8 per group.

Nimacimab Drives Durable Weight Loss with Minimal Rebound Compared to Tirzepatide Treatment

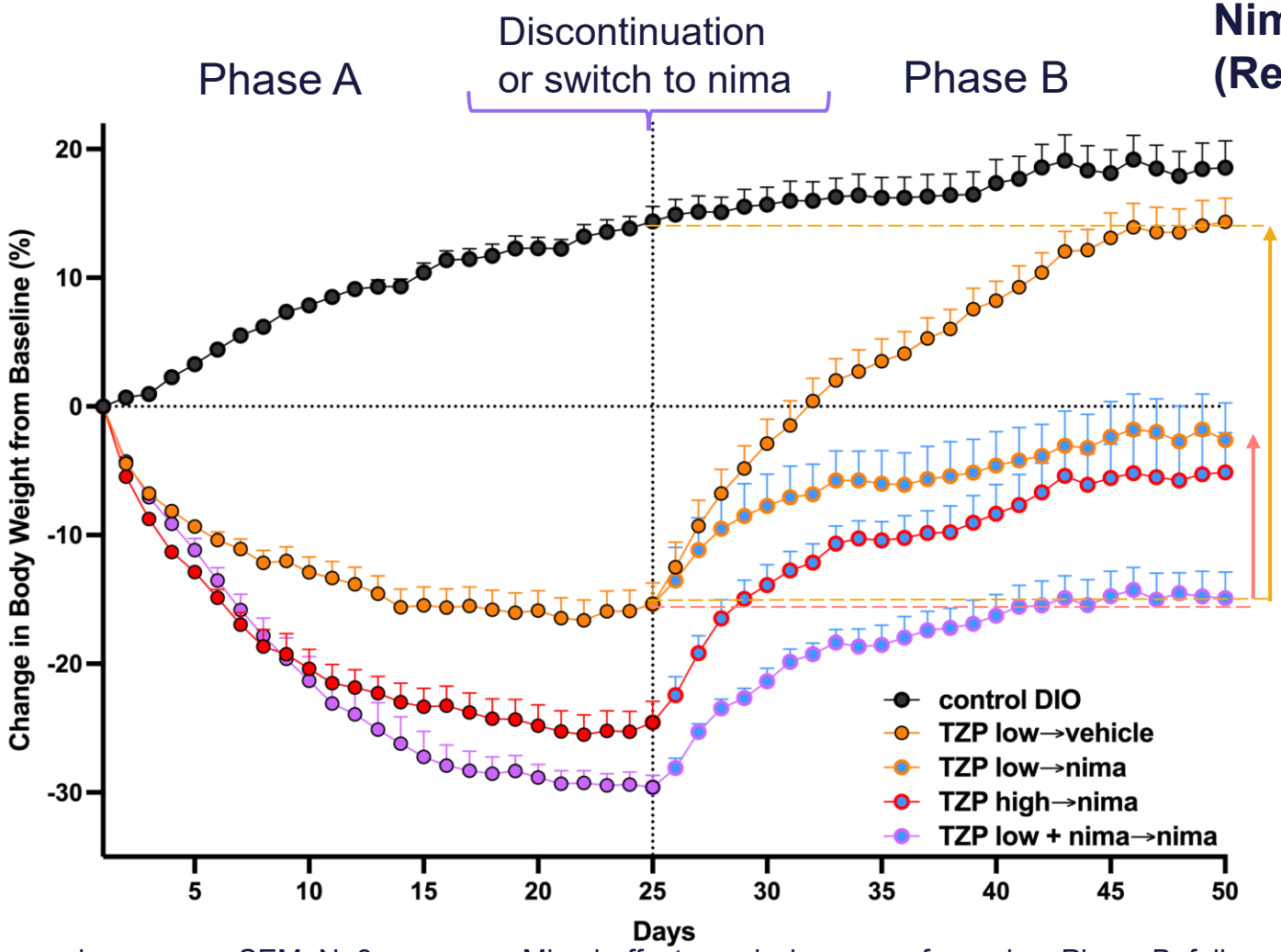


Δ29.7% tirzepatide 'rebound'

Δ7.3% nimacimab 'rebound'

Data are expressed as mean ± SEM. N=8 per group. A mixed-effects analysis was performed on Phase B, followed by Tukey's multiple comparisons test. At day 50, nima→vehicle **p<0.01, TZP low→vehicle ns.

Switching to Nimacimab Treatment Limits Rebound and Shows Significant Potential as Maintenance Therapy



Nimacimab maintenance = 17%
(Rebound – Switch % Weigh Loss)

Δ29.7% tirzepatide 'rebound'

Δ12.8% nimacimab 'switch'

Data are expressed as mean ± SEM. N=8 per group. Mixed-effects analysis was performed on Phase B, followed by Tukey's multiple comparisons test. At day 50, TZP low→vehicle ns, TZP low → nima ** p<0.01, TZP high→nima ***p<0.001, TZP low + nima →combo ****p<0.0001.

Study Design: Nima/TZP/Combo with Rebound/Maintenance #2

male hCB1
N=8

8 weeks

HFD initiated (60 kcal% fat)

Phase A: Monotherapy and Combo with Sub-optimal TZP

Phase B: Assess Rebound or Maintenance with Nimacimab

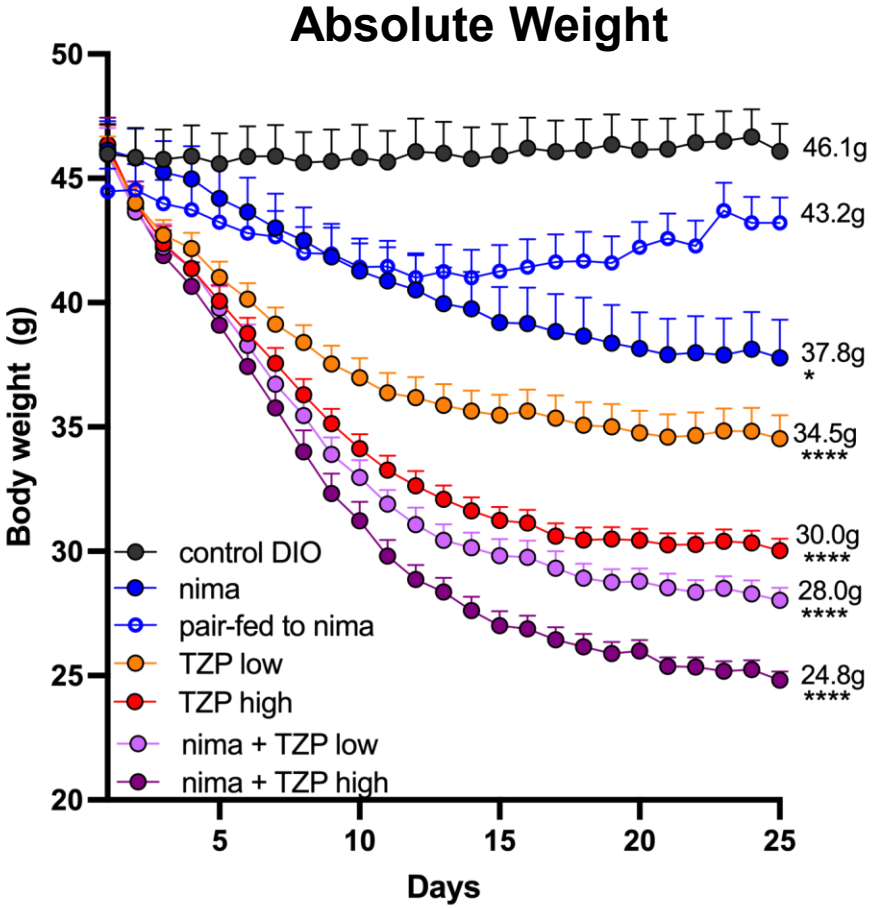
Days: -7 (MRI) | 0 | 24 (MRI) | 25 | 45 (MRI) | 50 Tissue collection

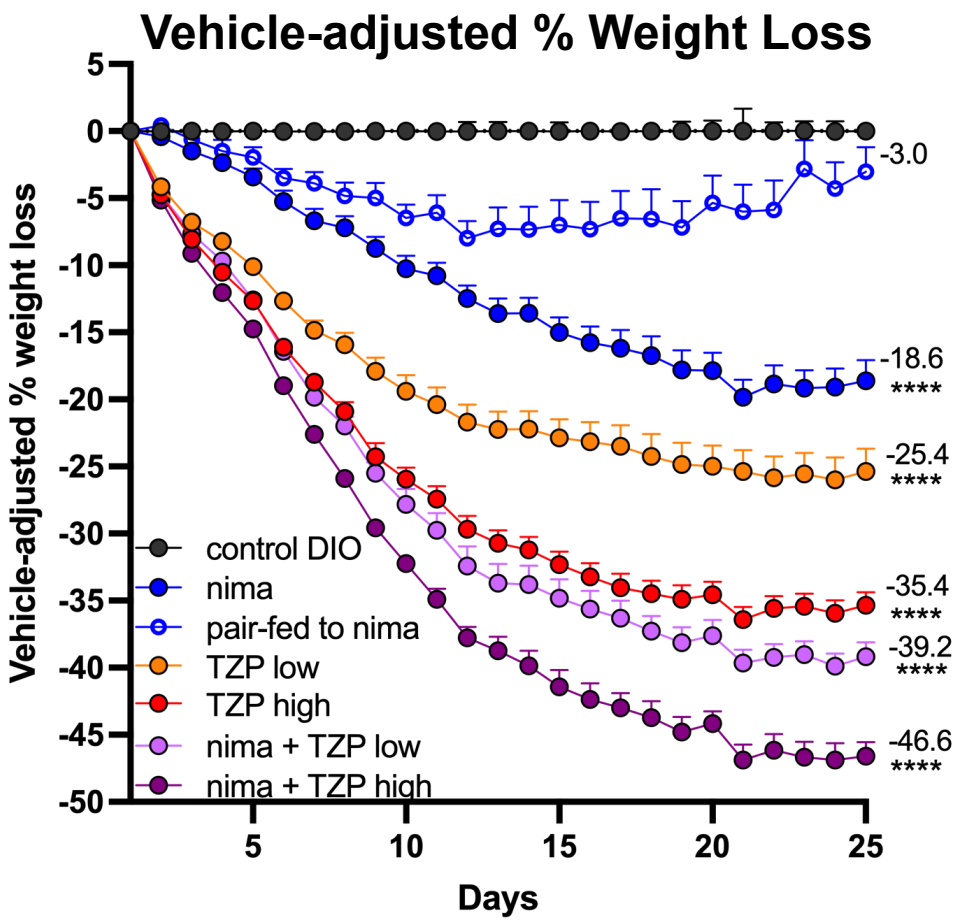
- vehicle → vehicle
- pair-fed to nimacimab → pair-fed to nimacimab
- nimacimab 240 mg/kg Q3D → vehicle
- tirzepatide 3 nmol/kg QD → vehicle / nimacimab 240 mg/kg Q3D
- tirzepatide 10 nmol/kg QD → vehicle / nimacimab 240 mg/kg Q3D
- tirzepatide 3 nmol/kg QD + nimacimab 240 mg/kg Q3D → vehicle
- tirzepatide 10 nmol/kg QD + nimacimab 240 mg/kg Q3D → vehicle

Endpoints:

- Daily body weight
- Daily food consumption
- EchoMRI (Body composition)
- Biomarkers for MOA

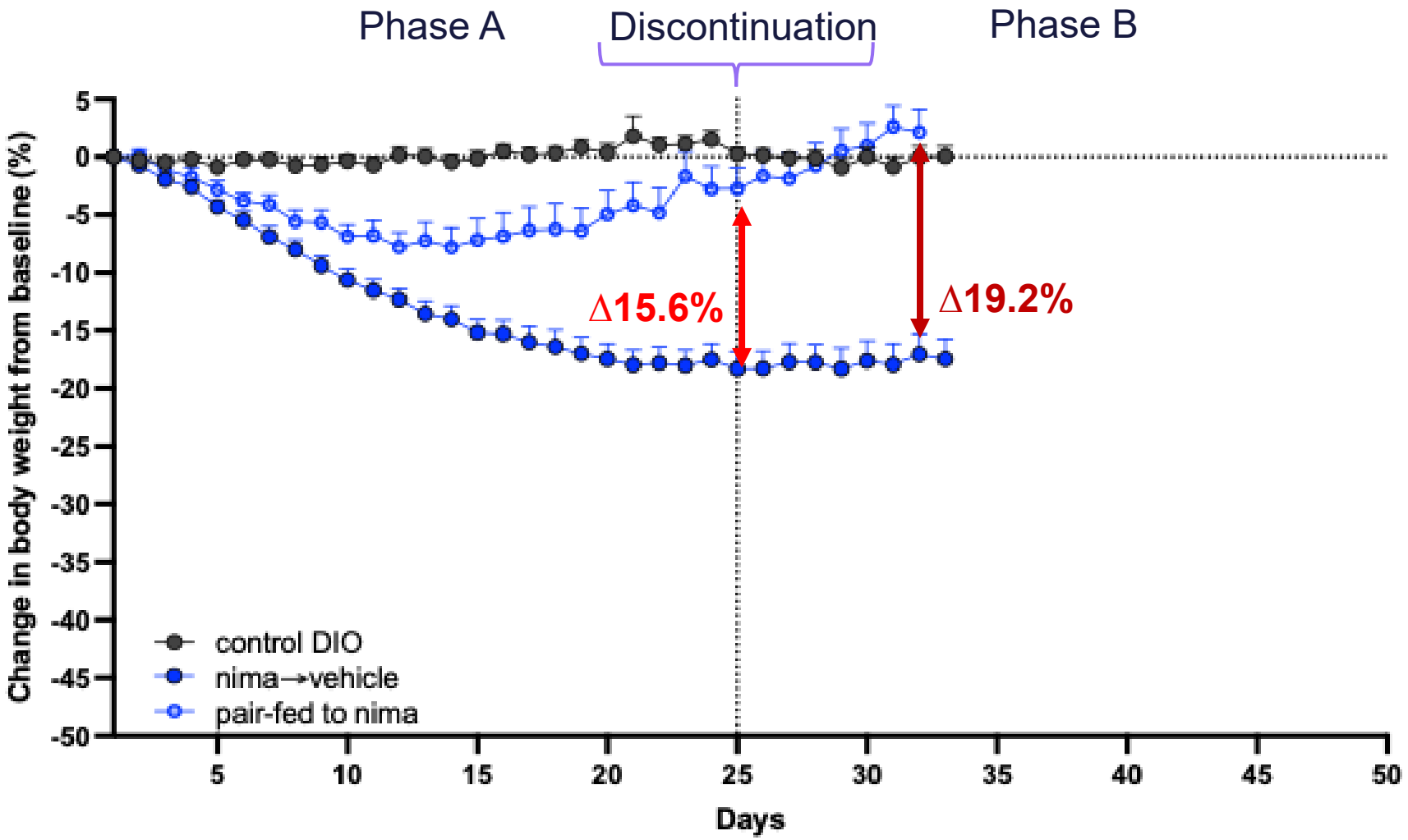
Nimacimab Enhances Weight Loss when Combined with both Low-Dose and High-Dose Tirzepatide





The daily average change in body weight from day 1 of treatment from the vehicle group was subtracted from the individual change in body weight per animal to calculate % change in body weight from baseline, vehicle adjusted. 2-way ANOVA, followed by Tukey's multiple comparisons test. *p<0.05, **p<0.01 ***p<0.001, ****p<0.0001. Reporting significance on day 25. Data are expressed as mean ± SEM.N=8 per group. TZP combination therapies differ significantly from their respective monotherapy at high and low doses (p<0.0001).

Pair-fed Control Highlights that Nimacimab-Driven Weight Loss is not a Result of Caloric Deficit Alone



To determine how much of nimacimab-driven weight loss is due to reduced food intake, we performed a pair-feeding experiment.

Animals were randomized based on body weight and body composition and placed into individual housing for daily food intake measurements. Mice with comparable body weight in the pair-fed group had their calories restricted to match the daily calories consumed by the nimacimab group the day before.

Data are expressed as mean ± SEM. N=8 per group. Mixed-effects analysis was performed on Phase B, followed by Tukey's multiple comparisons test. At day 32, pair-fed group ns, nima→vehicle ***p< 0.001 compared to control DIO.

Nimacimab Preclinical Profile

A differentiated mechanism with broad potential across treatment settings

✓ **Durable and Clinically Relevant Weight Loss**

- Nimacimab consistently reduces fat mass while **preserving lean mass** in DIO models.
- Weight loss is durable, with **minimal rebound after treatment withdrawal**.

✓ **Additive & Orthogonal to Incretins**

- In combination with tirzepatide, nimacimab achieved **>40% weight loss (vehicle-adjusted)** with minimal rebound, supporting its role in **combination and maintenance therapy**.

✓ **Favorable vs. CB1 Small Molecule Benchmarks**

- All nimacimab dose levels compared **favorably to monlunabant** both during treatment and in post-withdrawal rebound models.
- Maintains potency despite endocannabinoid competition and exhibits **peripheral restriction**, avoiding CNS liabilities.

✓ **Broader Metabolic Benefits**

- Improves glycemic control, reduces hepatic steatosis and serum cholesterol, and decreases obesity-induced inflammation and fibrosis.

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.

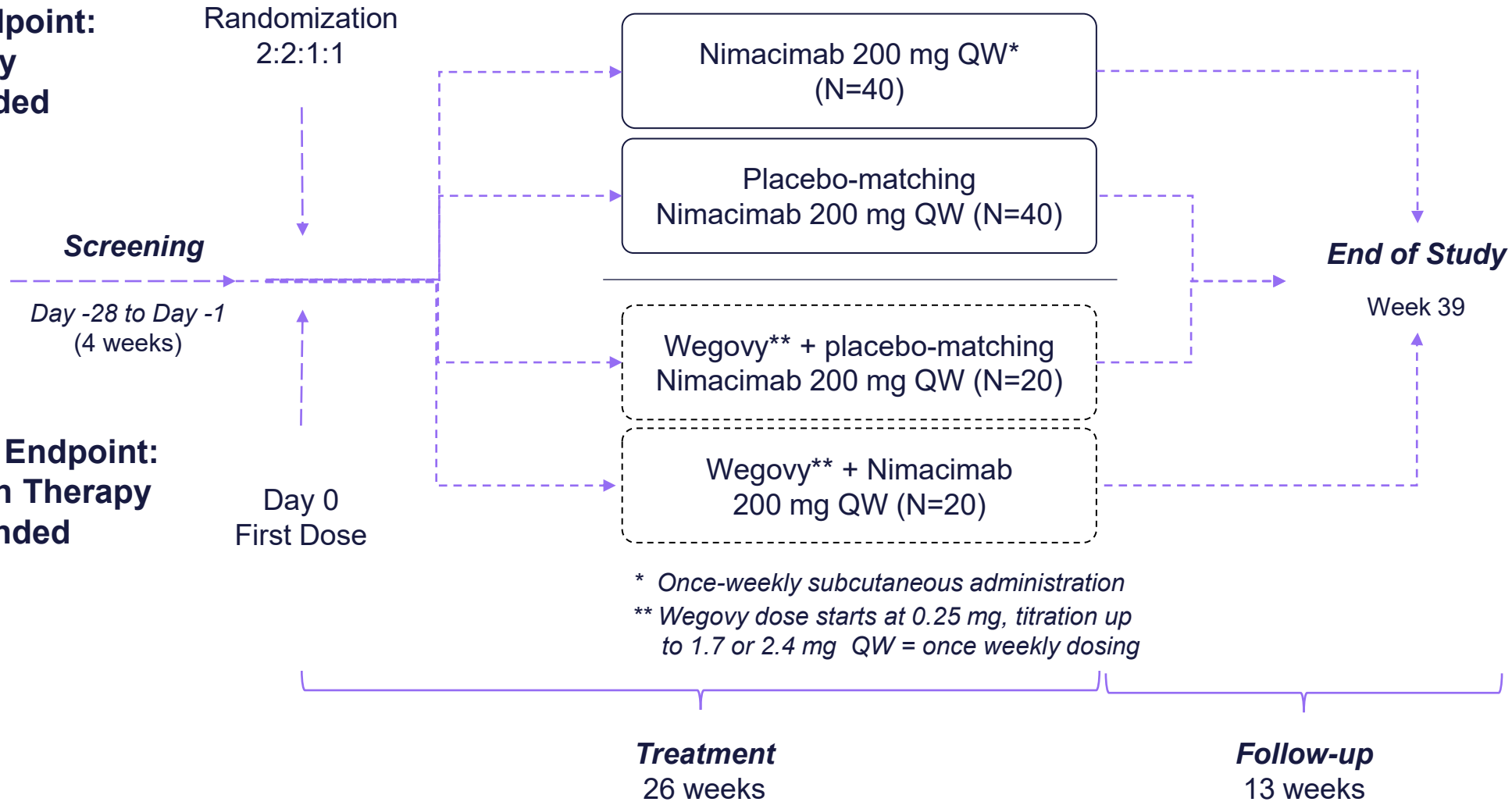
Clinical & Regulatory

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



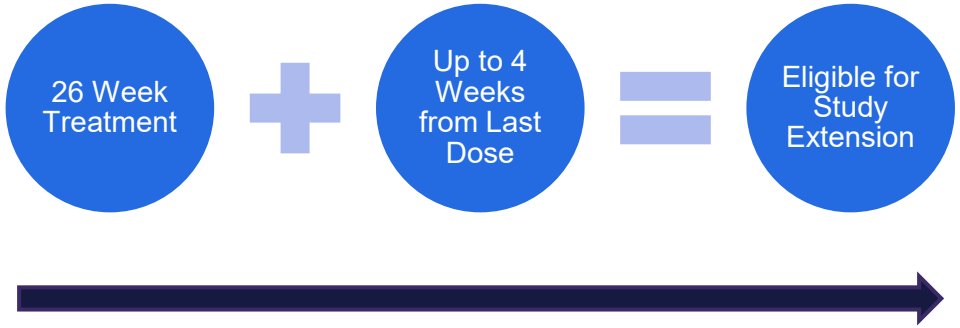
Nimacimab and Adverse Events of Interest

- 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.

CBeyond™ Phase 2 Study Extension

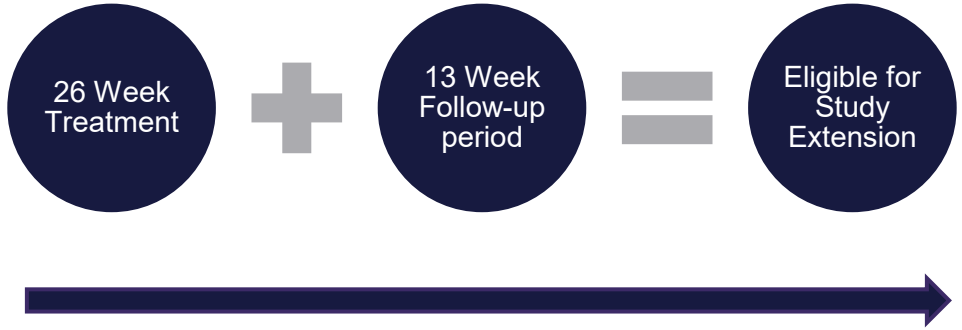
Continuing Combination Arms (52 Weeks)



- ✓ 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).

Enrollment Completed N=19

Monotherapy Arms (~July 2025)

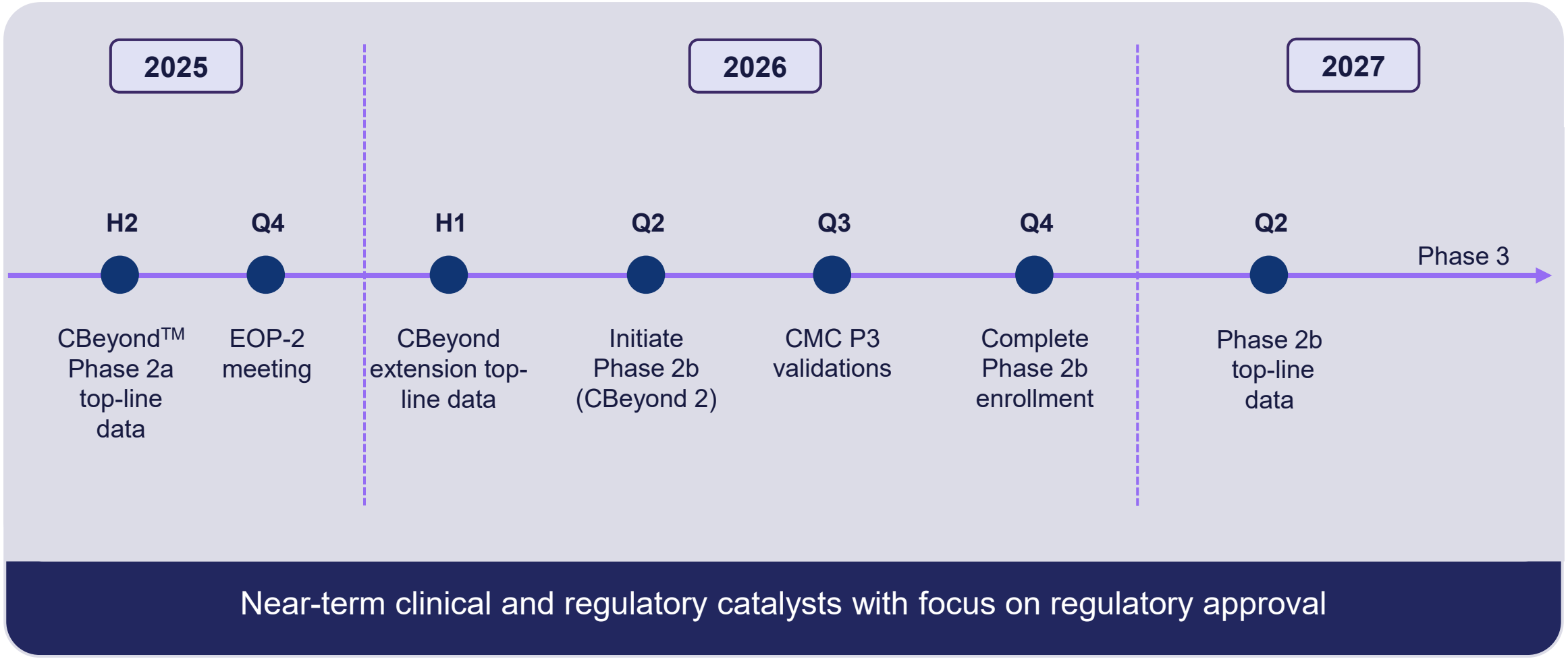


- ✓ Participants who have completed 26 weeks of treatment and are still enrolled in the study (even if in the follow up period and not currently on drug) are eligible to enroll into the open-label study extension at the beginning of August 2025
- ✓ Will provide 52-week data, new 26-week cohort, and also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

Enrollment Completed N=24

****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.*

Anticipated Clinical and Regulatory Milestones



CBeyond Topline: What You May See and How We'll Read it

Efficacy success band (26-wks): 5 - 8%; ≥8% = upside **if** safety/tolerability preserved and slope continues

	Endpoint *(Topline Read)*	Expectations to support TPP	Why it Matters
1	**Efficacy: % Weight Loss Mono** *Absolute and placebo-adjusted weight loss at 26 weeks*	5-8% (placebo-adjusted)	**5 – 8%** → **PoC support**; informs 52-week view; dose/duration & **Phase 2b planning**. **≥8% (pbo-adjusted)** → Represents **high-end PoC outcome**
2	**Combo Efficacy: % Weight Loss** (GLP-1 Combination) *Absolute and placebo-adjusted weight loss at 26 weeks* *Directional additivity vs GLP-1 alone*	CB1 + GLP-1: PoC (Look for additivity signals)	Supports path to **double-digit WL** with improved **tolerability** (hypothesis-building).
3	**GI Tolerability** (Mono & Combo) *Nausea/vomiting/diarrhea; discontinuations related to GI*	Lower GI Burden	**Lower GI burden** → better **adherence** and **combo usability** vs incretin classes.
4	**Safety** (incl. neuropsychiatric) *26-week summary; Looking for any neuropsychiatric signals and other safety concerns*	No Neuropsychiatric	**Clean safety** is the **gate** to Phase 2b for a **peripheral CB1** antibody.
5	**Body Composition** *Fat vs. lean mass (DXA/MRI or descriptive signal)*	Preferential fat loss	**Preferential fat loss** strengthens real-world value and durability/maintenance positioning.
6	**Metabolic Biomarkers** *Directionality in insulin resistance, lipids, ALT, adiponectin (exploratory)*	Support peripheral CB1 biology	**Metabolic quality** of WL reinforces **peripheral CB1 biology** and payer-relevant benefits.

Why Better Tolerability Matters

The Value of Better Tolerability and the Translation to CBeyond Topline Data

Case for Better Tolerability

1. **Monotherapy differentiation:** Semaglutide-like efficacy profile **with materially better tolerability** would be attractive on its own; we don't believe it is commercially necessary to exceed GLP-1 weight-loss magnitude.

2. **Combination potential:** A peripheral CB1 mechanism with better tolerability makes **GLP-1 combinations feasible** to reach higher weight-loss and/or improve body composition **without adding burden.**
   (This has been challenging for other non-incretin add-ons historically.)

3. **Persistence & maintenance:** We believe better tolerability supports adherence and long-term use – **the foundation for maintenance therapy** (e.g., post-GLP-1 discontinuation or dose minimization).

Topline Data Priorities

- Safety first: overall profile including absence of neuropsychiatric signals.
- GI tolerability: nausea/vomiting/diarrhea & discontinuations; key to real-world use and combinations.
- Mechanistic quality (CB1 pathway): directionality in insulin resistance, lipids, ALT, adiponectin.
- Efficacy & trajectory: semaglutide-like band is sufficient if safety is preserved; continued slope adds value.
- Combination lens: Additive WL with a clean GI profile supports combo strategy.

* From KOL interviews

Nimacimab – Market Opportunity

Review of target product profile and primary research insights

How Obesity Clinicians View Nimacimab Target Product Profile

Opportunity across multiple treatment settings

	Monotherapy	Maintenance	Combination
Addressable Population	Patients who are contraindicated, intolerant, and/or suboptimal response/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 POTENTIAL MULTI-BILLION DOLLAR OPPORTUNITY

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

Obesity Treatment Paradigm

Following lifestyle interventions, overweight and obese individuals are eligible for GLP-1 receptor agonists prior to bariatric procedures for patients with morbid obesity

Treatment Paradigm

Lifestyle Interventions
(e.g., reduced / low energy diet, increased physical activity)

GLP-1 Receptor Agonists
(e.g., Zepbound, Wegovy, Saxenda)

Alternative Agents
(e.g., alpha-glucose inhibitors, antilipemic agents, orlistat)

Surgical Bariatric Procedures*

Key Considerations

- **Inability to Reach Target Weight Loss Goal**: Patients unable to achieve a 2.5% weight loss within 1 month of initiating lifestyle interventions can be prescribed a pharmacotherapy[1,2]
  - Weight loss goals differ by obesity class; severe obesity patients will target a weight loss goal of >15%[1]
- **Common Initial Pharmacologic Therapies:** Patients initially receive a GLP-1 receptor agonist; those unable to tolerate these may receive alternative options[1,2,3]
- **Associated Comorbidities Drive Treatment**: The choice of pharmacotherapy is heavily dependent on the presence of comorbidities
  - Wegovy is the preferred option for patients with established CVD to combat their comorbidity while simultaneously inducing weight loss[1,2]
- **Limited Use of Bariatric Surgery:** Only about 1% of qualified patients underwent bariatric surgery in the U.S. in 2022 (~280 K patients)[4], largely due to its invasive and irreversible nature
  - Surgical bariatric procedures* are recommended for severe patients with a BMI ≥40 kg/m^2, or for those with a BMI ≥35 kg/m^2 not achieving weight loss goals by lifestyle interventions and pharmacotherapies[2,3]

*Inclusive of laparoscopic adjustable gastric banding, sleeve gastrectomy, Roux-en-Y or one-anastamosis gastric bypass, biliopancreatic diversion with duodenal switch, single anastomosis duodeno-ileal bypass with sleeve gastrectomy, intragastric balloon, transpyloric bulb, aspiration therapy, and vagal nerve blocking therapy. Abbreviations: CVD: Cardiovascular diseases.
Sources: 1. UpToDate; 2. Cornier et al., 2022 (link). 3. Garvey et al., 2016 (link); 4. Clapp et al, 2024 (link)

Obesity Unmet Needs

Despite approvals of Zepbound and Wegovy, significant unmet needs remain for alternative treatments that preserve muscle, minimize side effects, offer a more convenient RoA, or provide easier access

Efficacy Limits and Adverse Events

- **Increased Loss of Lean Mass**: While approved therapies are adequately effective, incretin-induced weight loss may involve a notable contribution form lean mass loss, highlighting the need for a therapy that preserves muscle
- **Association with Serious Side Effects**: Existing pharmacologics have both short- and long-term safety concerns; nausea, diarrhea, constipation, or vomiting can lead to treatment discontinuation

Inconvenient Administration and Frequency

- **No Oral GLP-1 Receptor Agonists Available:** While multiple pharmacologics are available, all require frequent once-weekly subcutaneous administration with no alternatives for needle-phobic patients[1,2]
- **Hard-To-Titrate Dosing Forms**: Current injections are difficult to titrate (3 - 6-month titration period) and are restricted to available dosage forms

Accessibility and Coverage Issues

- **Significant Out of Pocket Costs**: Only 10% of qualified patients with obesity can access a prescribed GLP-1 receptor agonist through insurance plans, with strict step edits and restrictions further limiting access[3]
- **GLP-1 Supply Delays Limit Availability:** Marketed GLP-1s have experienced supply delays, driven by limited manufacturing capacity*, shifting physician prescription behavior and habits

*The FDA announced the end of the Wegovy and Zepbound shortage, ongoing since 2022, in Q4 2024. Abbreviation: MoA: Route of administration; SubQ: Subcutaneous; OOP: Out-of-pocket; Sources: 1. UpToDate; 2. Tak et al., 2021 (link); 3. Market Landscape for Obesity Drugs (link)

Summarized Primary Research Insights

KOLs believe CB1 inhibitors are well-positioned to provide benefit to select patients given the favorable safety profile and acceptable efficacy

Current Management Paradigm

KOLs indicate that most pharmacologically-treated patients are prescribed a GLP-1 RA; ~15% of patients discontinue treatment due to intolerable side effects while an additional ~10% discontinue due to an inadequate response

Perspectives on Pipeline

KOLs expect that novel mechanisms will support individualized treatment approaches in the near future (e.g., Class II / III patients requiring more weight loss, those with fatty liver disease, needle averse patients)

Unmet Needs

Despite satisfaction with GLP-1 RAs, KOLs identify the need for 1) enhanced access to pharmacological therapies, 2) treatments with improved GI tolerability, and 3) more sustainable and healthier therapeutic options

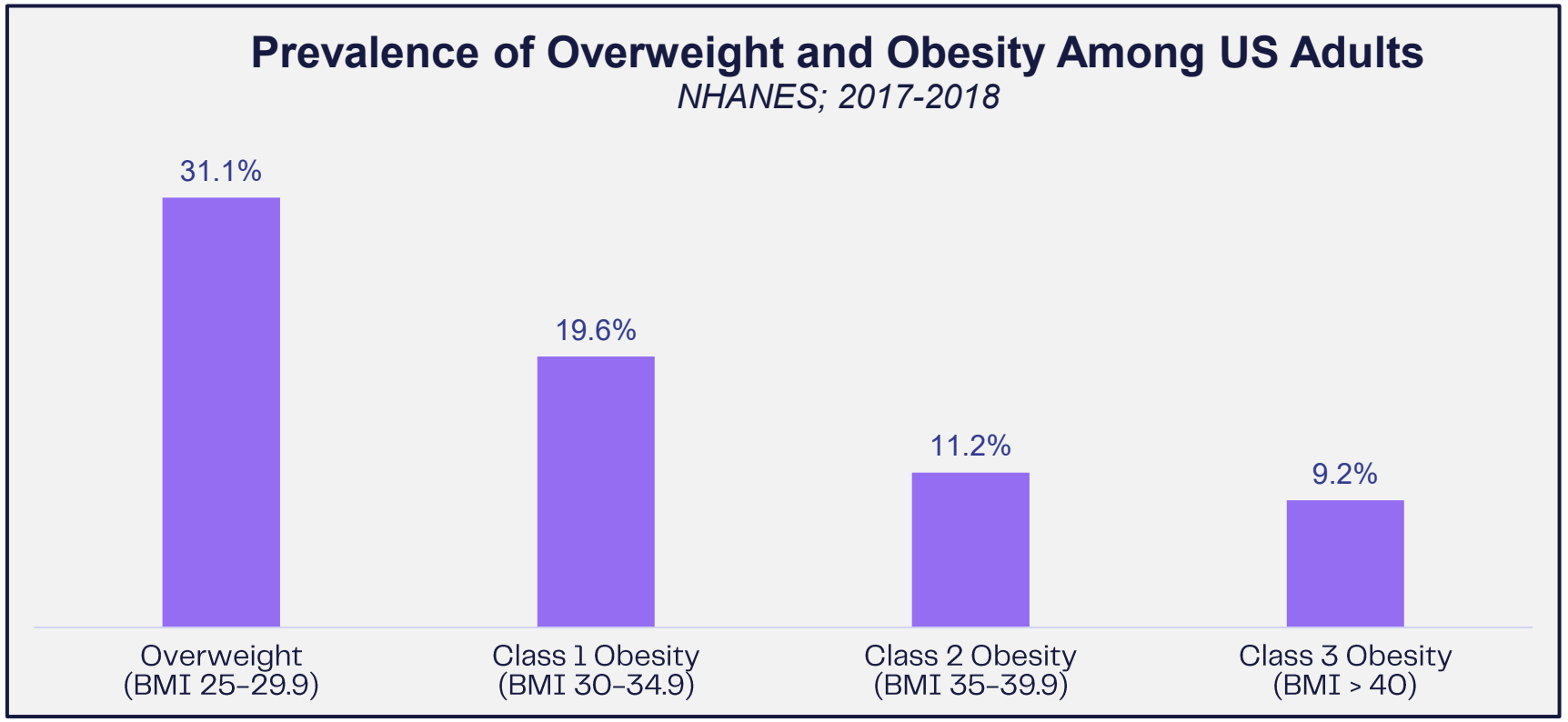
Potential Skye Positioning

Select KOLs believe CB1 inhibitors can be utilized in patients with sarcopenia, as well as patients with overweight / Class I obesity who are receiving the highest GLP-1 dose in long-term maintenance or have tolerability issues

RA: Receptor agonist; CB1: Cannabinod-1 receptor type; KOL: Key opinion leader
Source: LifeSci Q1 2025 Primary Market Research (N=10 KOLs)

Heterogeneous Overweight Population Requires Different Treatment Options

Significant (20%+) weight reduction demonstrated by GLP-1s is not therapeutically appropriate for all obese patients



Obesity is Highly Heterogeneous; Many Sub-Types

Nimacimab Opportunity

~8% reduction + enhanced safety and improved body composition to achieve market establishment

Source: LifeSci Primary Market Research (N=10 Endocrinologists, N=14 PCPs)

HCP-reported Nimacimab Addressable Pt Segments *(1 of 2)*

Physicians identify numerous additional nimacimab use cases across treatment settings; HCPs believe nimacimab may address select unmet needs that current and future agents may not

Most Relevant Patient Characteristics for Monotherapy

- **GLP non-responders, particularly those unable to lose ≥5% weight loss at 3 – 6 months on a GLP**
- **GLP intolerable who are at risk of CV disease** (prescribers of alt. agents would replace with Nimacimab)
- **Class 1 or 2 obesity with mild-moderate GI side effects on GLP (may switch to more tolerable agent)**
- **Prior history or at risk of pancreatitis and thyroid cancer (contraindicated for GLP)**
- **Elderly (65+ years of age) who have or at risk of sarcopenia**
- **Any patient at risk of sarcopenia** (e.g., women with osteoporosis)
- **Patients with concerns about muscle loss** (e.g., middle-aged men)
- **Patients concerned about or apprehensive towards GLP-1 side effects** (e.g., optical neuropathy)

"[nimacimab] would be limited to those who couldn't tolerate or take incretins... I would use combo in patients who need additional weight loss to see if it super charges the patient."

"This is a good option for patients with a lower BMI who didn't feel great on Zepbound. There are patients with side effects even at low doses. I would offer this to patients who should try a safer option."

"Wegovy and Zepbound work well, but there are limitations. I would use a product with a novel MOA in those who have a history of pancreatitis or thyroid cancer who shouldn't be on a GLP-1."

Source: LifeSci Primary Market Research (N=10 Endocrinologists, N=14 PCPs)

HCP-reported Nimacimab Addressable Pt Segments *(2 of 2)*

In combination with incretin-based therapies, HCPs believe Nimacimab will be most appropriate for patients requiring significant weight loss

Most Likely Candidate for Nimacimab Combination

- **Class 3 patients who require significant weight loss (≥ 20% weight loss)**
- **Initial GLP users who:**
  - **Have Class 3 obesity and require additional weight loss once they reach a weight plateau**
  - **Are unable to achieve weight loss goals due to tolerability issues at the highest dose**
  - **Are unable to achieve their weight loss goals due to a limited response (0 – 10% weight loss) with a GLP alone**
- **Add on agent after exhausting multiple options** (e.g., GLPs alone, alternative agents, such as Qsymia)

"I would use [nimacimab] in combination with an incretin-based agent in patients who need additional weight loss to see if it super charges the patient."

"I think the combo approach is good for patients who have reached a plateau. I would add another agent like [nimacimab] to see if it can help achieve greater weight loss, especially because Wegovy would be a better option than switching to a future incretin agent."

"Based on the data, [nimacimab's] combination approach could be used in the people who are not reaching their weight loss goals on a GLP-1. They would be strong candidates as well as others who have no other options to try, where [nimacimab] would be good to use as an add on."

Source: LifeSci Primary Market Research (N=10 Endocrinologists, N=14 PCPs)

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)*

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]	**$4.00**
Shares Outstanding[2]	**31.0M**
Shares Fully Diluted[2]	**47.8M**
Cash, Cash Equivalents & Short-term Investments [3]	**$48.6M**
Market Cap[1]	**$124.0M**
Avg. 3-Mo. Daily Trading Volume[1]	**911.4K**

[1] Sep 5/25 [2] Aug 5/25 [3] June 30/25

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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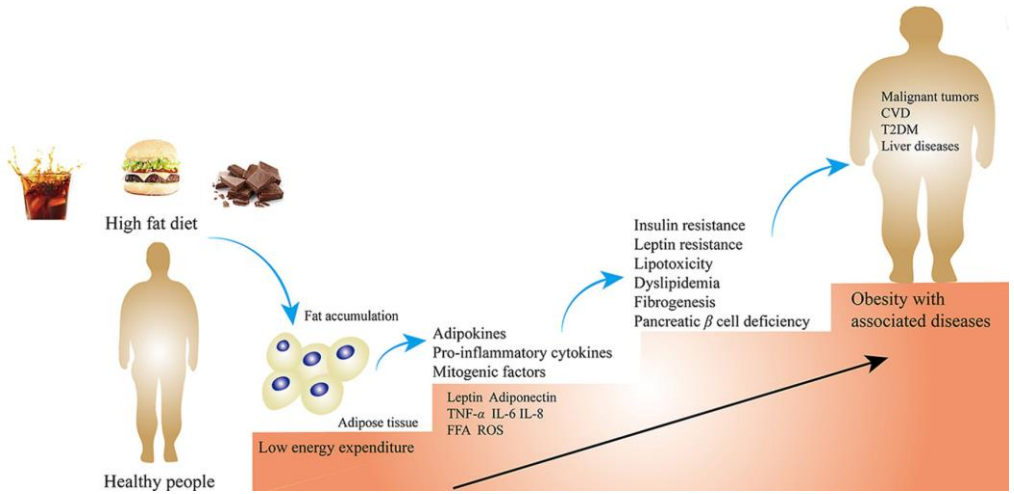
Obesity Disease Overview

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]

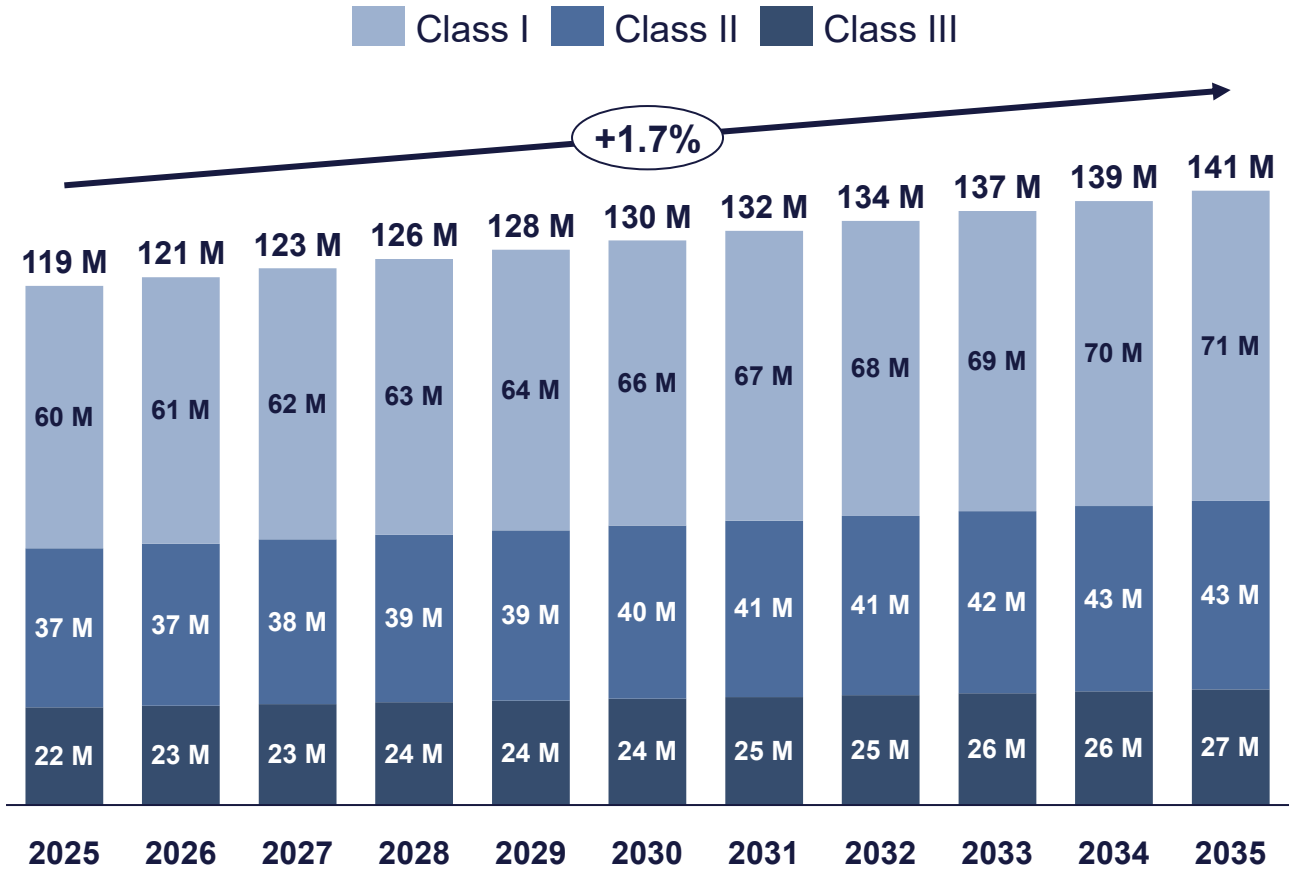
Genetic Underpinning

- **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]

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).

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%

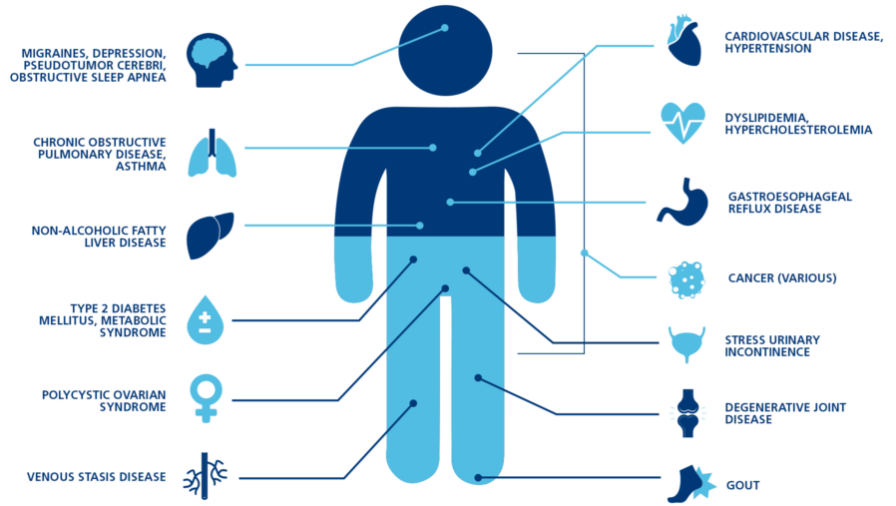
Osteoarthritis: 22%

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.

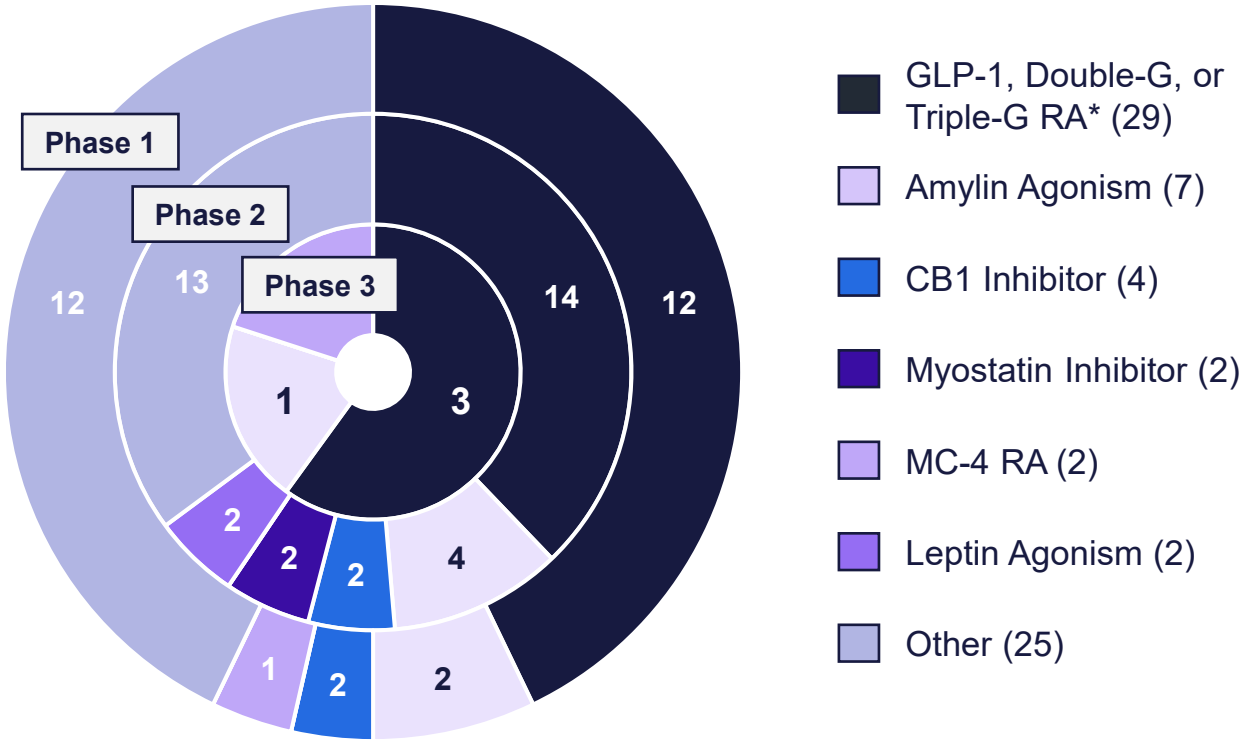
Concurrent comorbidities are also strongly associated with obesity, demonstrating a **33% *(Class I)* – 44% *(Class III)* prevalence** in obese individuals vs. 23% in normal-weight comparators

- 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.

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