Developing Innovative Medicines to Treat Obesity and Other Metabolic Diseases

November 2025

Nasdaq: SKYE

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Investment Thesis

Nimacimab: a complement, not a competitor – scalable add-on to extend and enhance incretin therapy

- **Additive efficacy on top of GLP-1s:** ~3% additional weight loss vs. semaglutide alone at 26 weeks, with continued separation.
- **Durability & "quality" weight loss:** Lower post-treatment rebound (~18% combo vs. ~50% sema-alone) and a favorable body-composition profile support use for maintenance after incretins.
- **Combo-friendly safety, titration-free:** No additive GI burden and 0% neuropsychiatric AEs in the combo arm; enables straightforward combination use across the incretin class.
- **Built to ride (not fight) the GLP-1 wave:** Peripheral CB1 mechanism provides complementary differentiation in a crowded incretin market, positioning it as a combination with potential payer alignment with its prospect of optimizing long-term maintenance, dosing, health, and cost.
- **De-risked path & catalysts:** Clear PK data and exposure-response understanding from Phase 2a supports higher-dose exploration; combination-first development; cash runway into 2027

Nimacimab: Building a Differentiated Profile

Evidence built to date and near-term milestones

Data Established to Date

- Combination efficacy with differentiated MOA
- Durable weight loss and restoration of metabolic homeostasis
- Improves glycemic control
- Modulates lipid metabolism
- Reduces obesity-induced inflammation and fibrosis
- Additive with incretin therapies + maintenance
- Potency, PK modeling vs. small molecules
- No CNS penetration in NHP study
- Comparison of nimacimab versus monlunabant in DIO model

Key Takeaways

- **Differentiated Mechanism:** first peripheral CB1 mAb that complements incretins; ~30% increase in weight loss vs semaglutide alone at 26 weeks; greater fat loss with lean-mass preservation.
- **Durability & maintenance:** lower post-treatment rebound and a favorable body-composition profile support use for maintenance after incretins.
- **Safety-first profile:** peripheral action potentially avoids CNS penetration; clean tolerability at tested doses enables combination use; no added GI burden and no neuropsychiatric signals at tested doses.
- **Clear next step; higher dose:** plan to test higher doses for optimal efficacy in both monotherapy and combination; 52-week extension informs long-term safety/durability.
- **CMC & access:** potentially progressing to high-concentration SC formulation, payer-aligned COGs to support chronic dosing.
- **Market fit:** Complementary MOA; serves GLP-1 non-responders/intolerant patients and augments weight loss in responders.

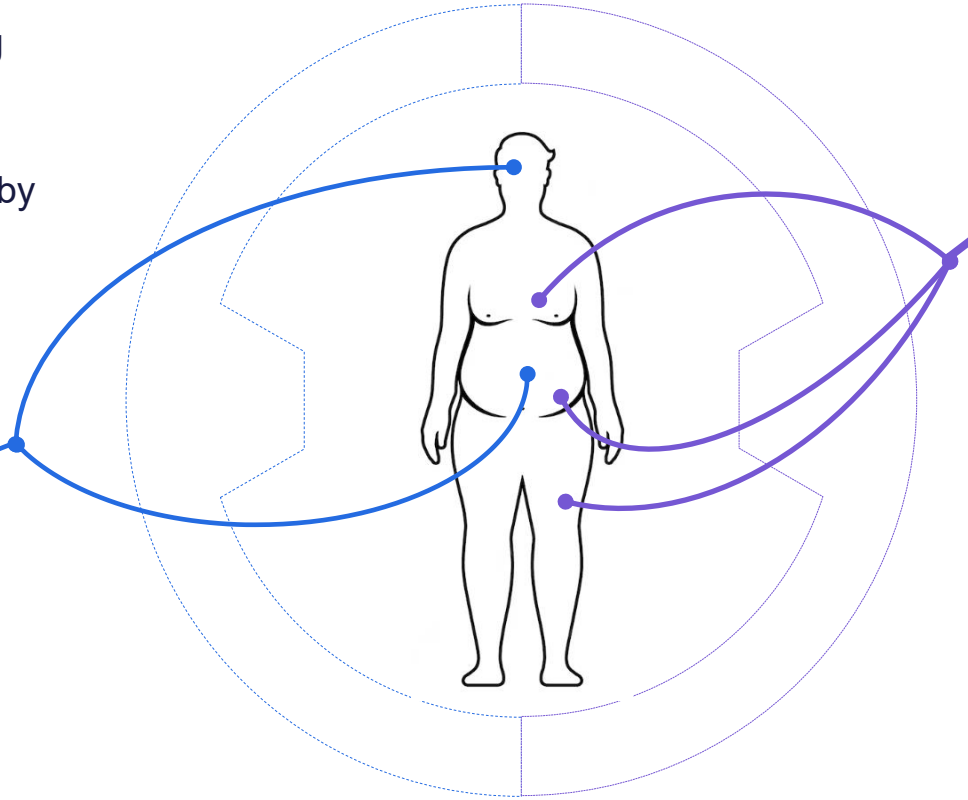
CB1: Differentiated Non-incretin Target to Tackle Weight Loss

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 pathways, including 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

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

A POTENTIAL MULTI-BILLION DOLLAR OPPORTUNITY

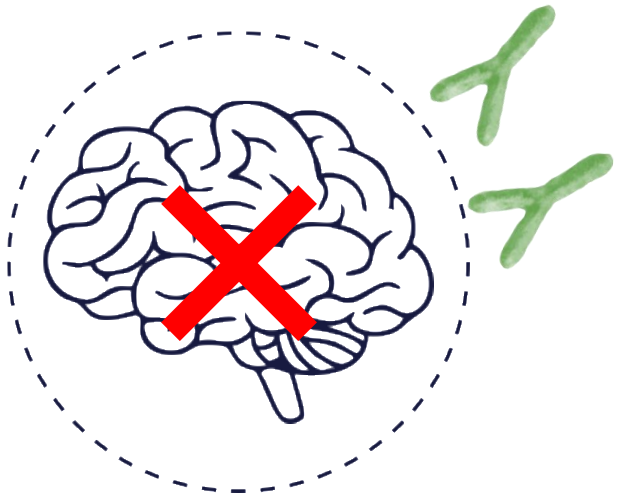
AOM: Anti-obesity Medication
Source: Primary Market Research (N=10 Endocrinologists, N=14 PCPs)

Nimacimab

A Highly Peripherally-restricted CB1-inhibiting Antibody that Stands Apart from Small–molecule CB1 Inhibitors

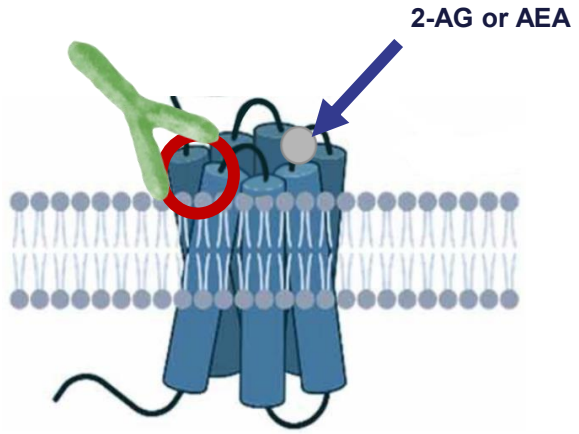
Nimacimab is Differentiated from Small Molecule CB1 Inhibitors

Peripheral Restriction



Significantly less brain penetration than small molecules currently in development

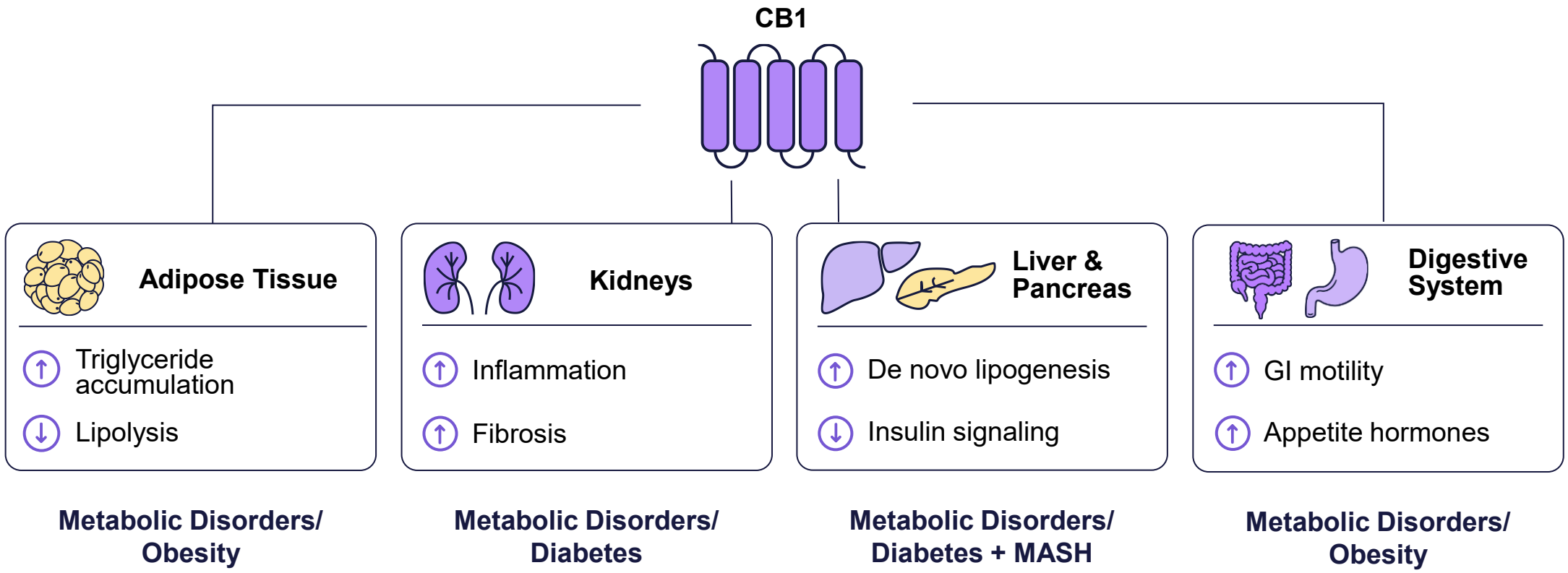
Negative Allosteric Modulator



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

Peripheral CB1 Signaling: Metabolic-focused Targets

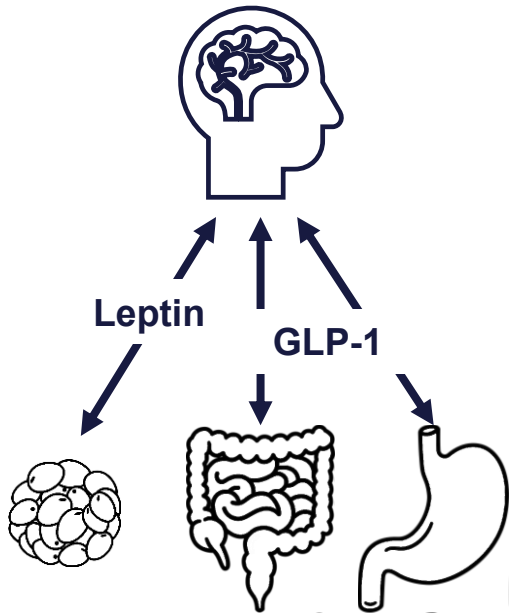
Active CB1 engagement promotes inflammation, fibrosis, and metabolic dysfunction;
blocking peripheral CB1 can reverse negatively-trending pathologies



Four Mechanistic Pillars of Nimacimab

01

Peripheral Modulation of Appetite Regulating Hormones



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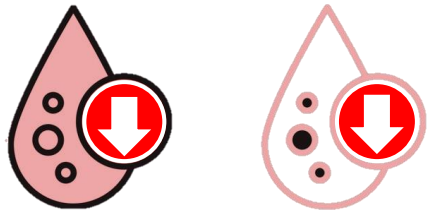
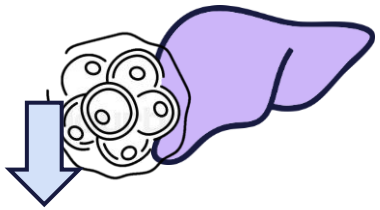
Improvement and Restoration of Glycemic Control



Reduced fasting insulin and improved glucose control

03

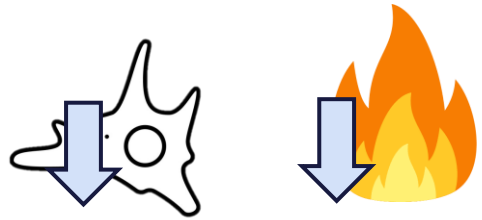
Enhanced Lipid Metabolism



Decreased steatosis and serum cholesterol

04

Reduction of Obesity-Induced Inflammation



Decreased inflammation and fibrosis markers

Nimacimab: 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 ~7x 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

Nimacimab

Deeper Look at Extensive Preclinical Data Validating the Potential Significant Outcomes of Peripheral CB1 Inhibition

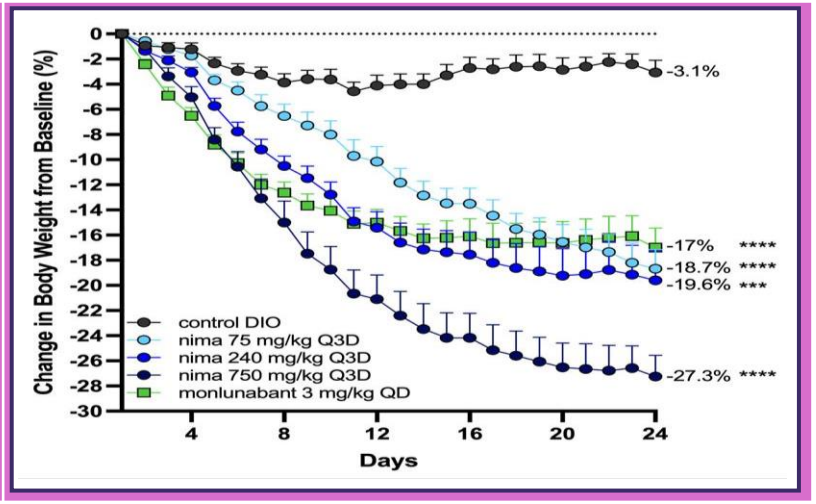
Diet-induced Obesity Model Data Characterizes the Ability of Nimacimab to Induce Meaningful Weight Loss and Other Pertinent Outcomes as a Monotherapy and Combination Therapeutic

Preclinical Data: Vital Insights & Validation of Nimacimab

DIO model highlights peripherally-restricted CB1-inhibiting antibody outcomes within class + relative to GLP1s

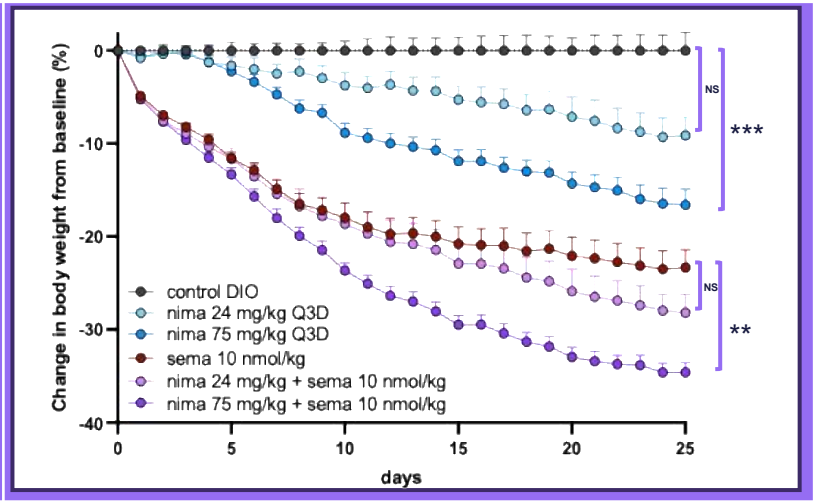
Potential Efficacy Advantage vs Small-Molecule CB1 Inhibitor

Dose-dependent weight loss of nimacimab validates utility of peripheral CB1 inhibition (with no evidence of neuro AEs)



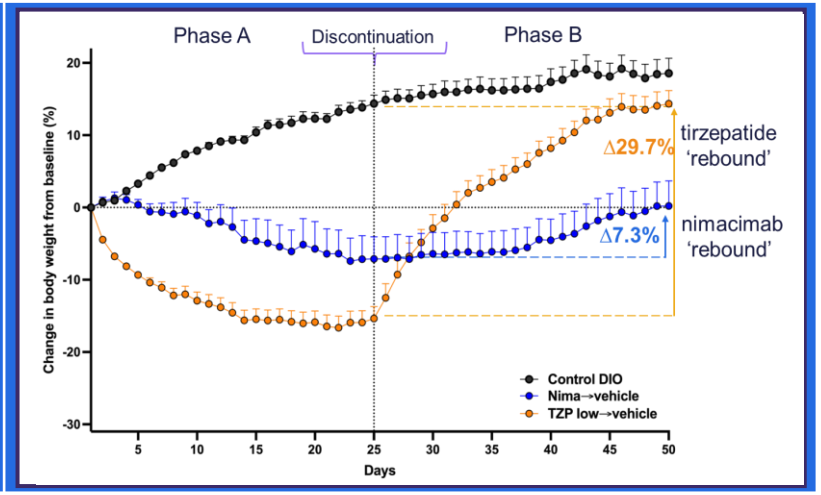
Increasing Nimacimab Unlocks Combination with Incretin

Preclinical DIO study models combination with a suboptimal CBeyond dose (24mg/kg) vs an active clinical dose (75mg/kg)



Complementary/Additive Mechanism to Incretins

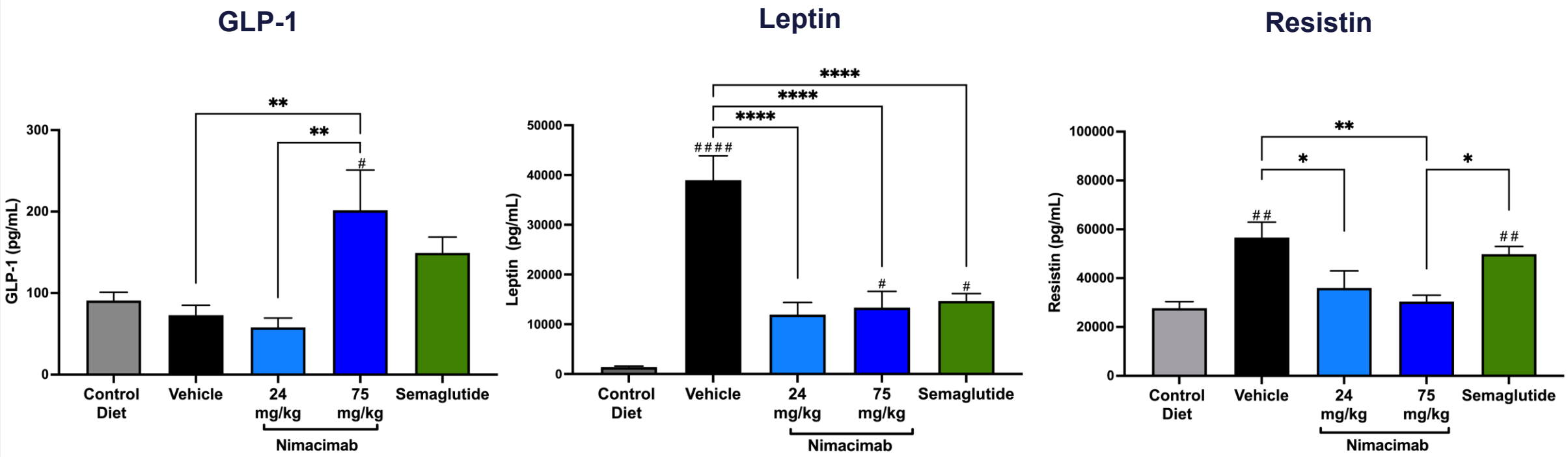
Nimacimab drives meaningful weight loss with more durable outcome vs incretin therapy



Nimacimab, a highly-restricted CB1-inhibiting antibody, displays attributes that indicate superiority within the class and characterize its potential for a broad TPP encompassing mono, maintenance, and combination therapies

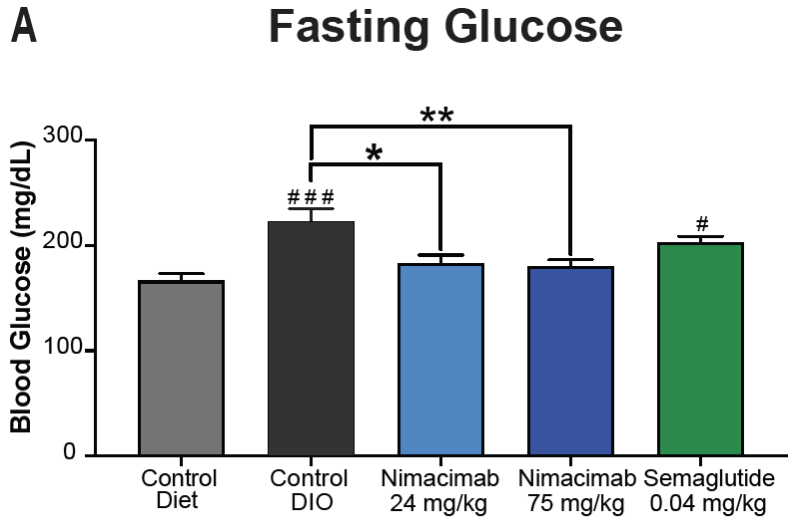
Productive Modulation of Key Hormones with Nimacimab

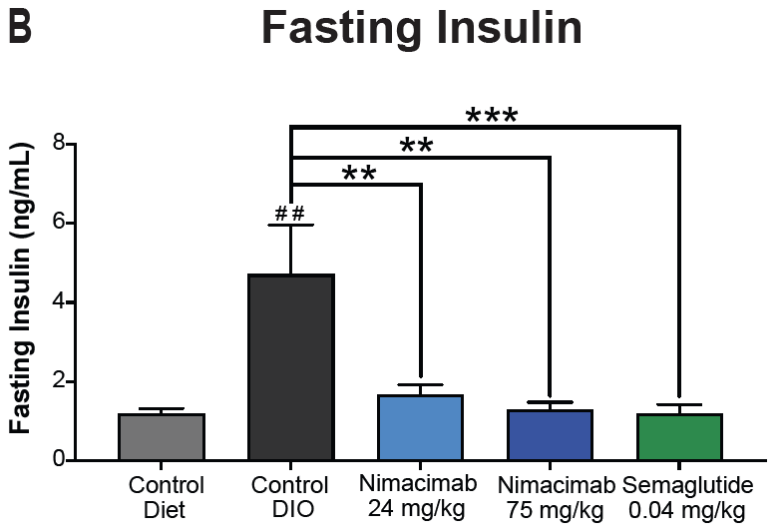
Peripheral CB1 inhibition modulates gut and adipose tissue hormones important for central control of appetite

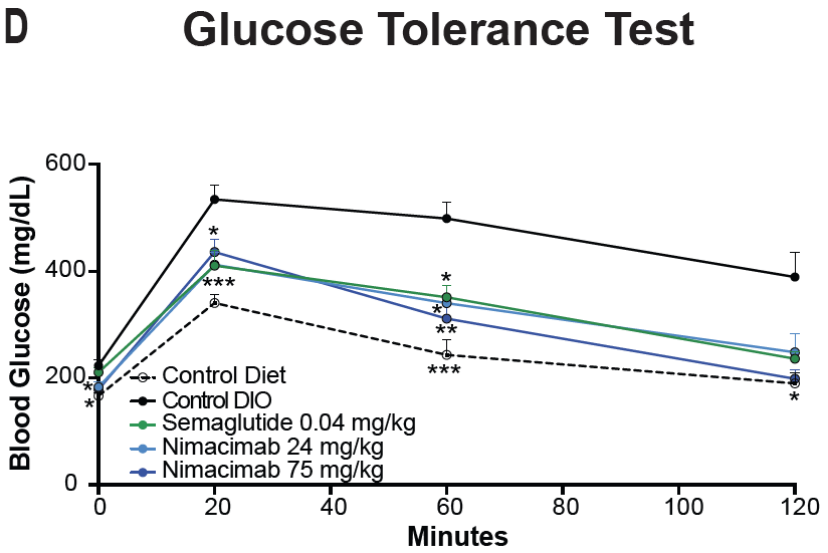


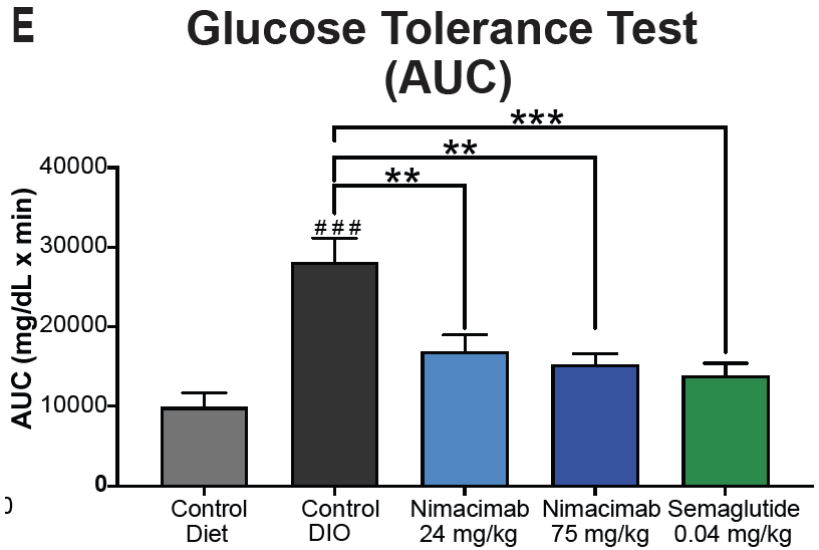
Serum was collected on day 36 and hormone levels were determined with a Bio Plex Multiplex immunoassay. For all analyses: one-way ANOVA repeated measurements (Tukey multiple comparison test). # denotes significance to the control diet group.

Nimacimab Improves Glycemic Control









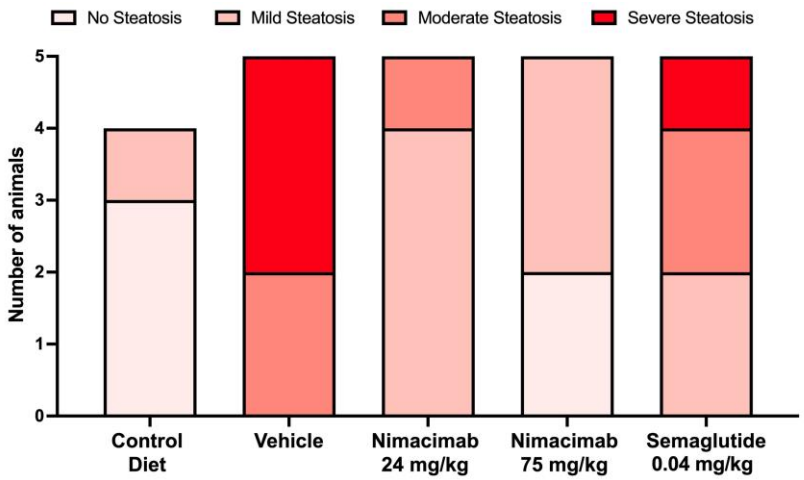
Day 27 mice were fasted for 4h before collecting serum to measure glucose and insulin levels. Day 27 mice were fasted for 4h before ip injection of 2g/kg glucose. GTT analyses: 2-way ANOVA repeated measurements (Tukey multiple comparison test); baseline subtracted AUC analysis was performed with a one-way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

Nimacimab Treatment Promotes Lipid Metabolism

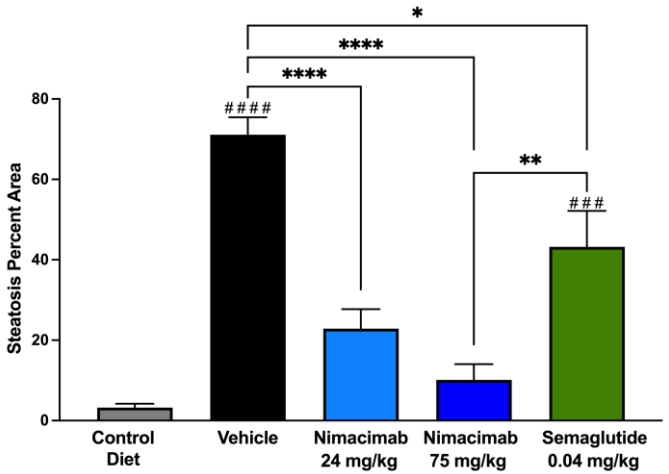
Dose-dependent reduction in steatosis and serum cholesterol

Steatosis Analysis (Liver)

Steatosis Score

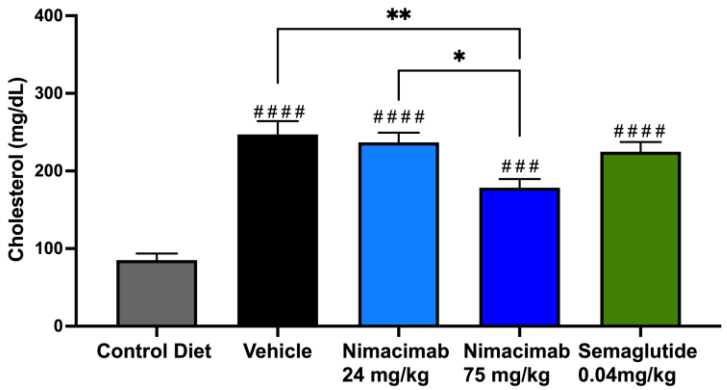


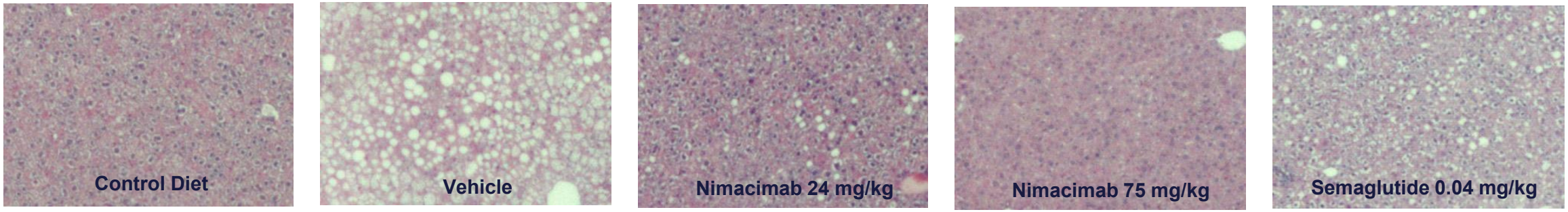
Steatosis Percent Area



Serum

Cholesterol





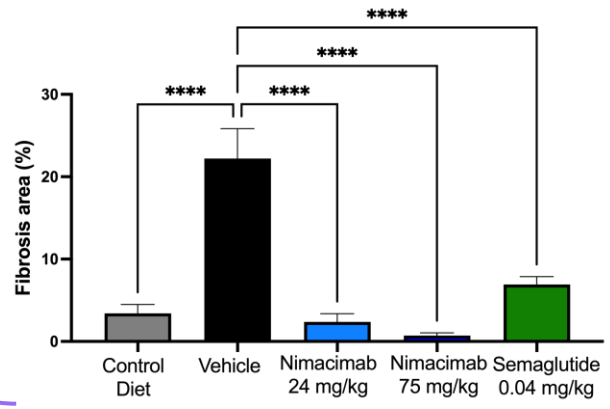
Liver sections scored by a pathologist using computer-aided analysis. A score of 0-3 was assigned based on % of hepatocytes with fat. 0 = no steatosis (<5%), 1=mild (5-33%), 2=moderate (>33-66%), 3=severe steatosis (>66%). (B) steatosis percent area was analyzed using computer-aided analysis with Cellprofiler.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

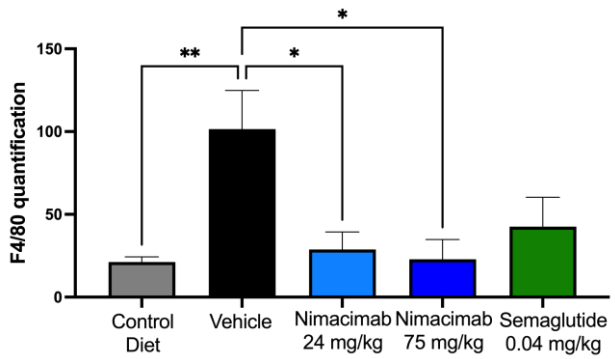
Reduced Inflammation, Fibrosis, and Adipocyte Area

Liver

Fibrosis Area

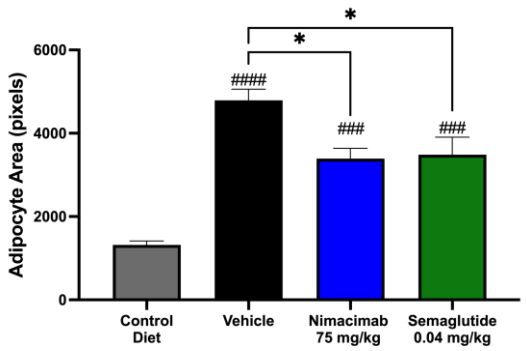


Macrophage (F4/80) Density

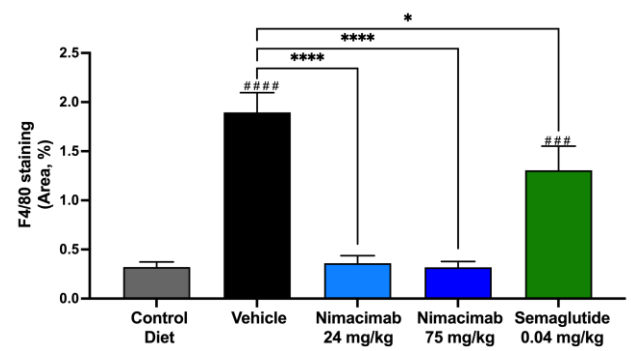


iWAT

Adipocyte Area

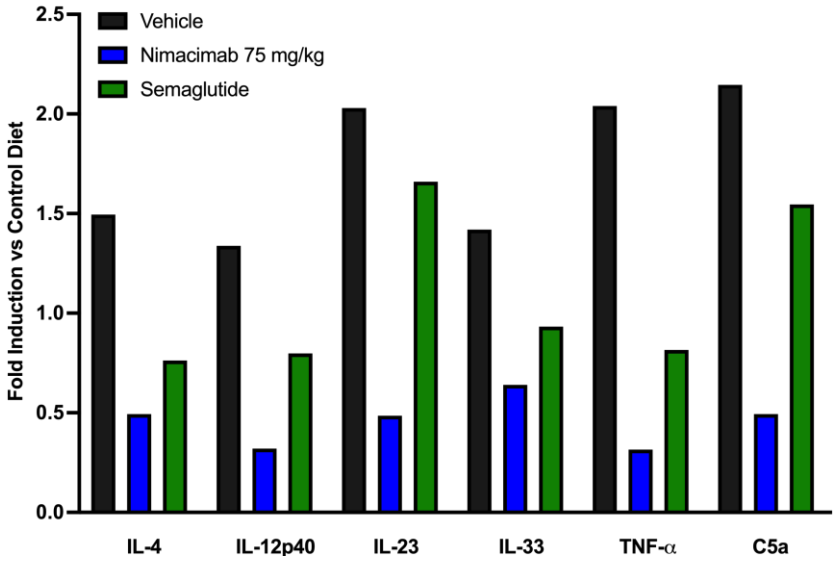


Macrophage (F4/80) Density



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.

Nimacimab Peripheral CB1 Inhibitor: Preclinical Profile

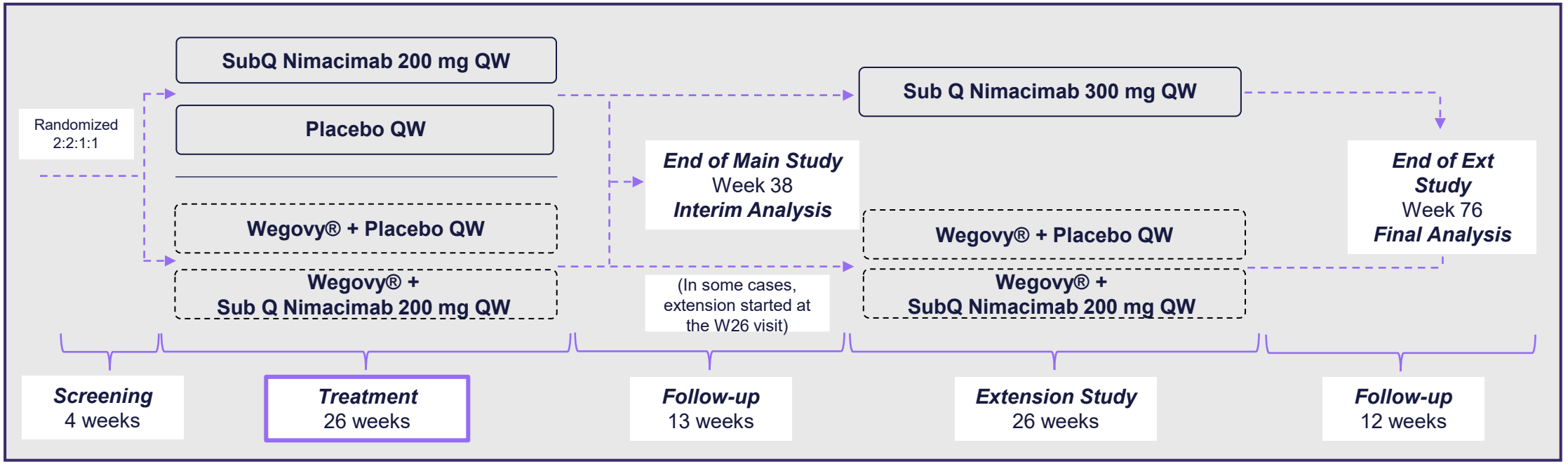
A differentiated mechanism with broad potential across treatment settings

- ✓ **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 in DIO models, supporting its role in **combination and maintenance therapy**.
- ✓ **Favorable Outcomes vs. CB1 Small Molecule Benchmarks**
  - All nimacimab dose levels compared **favorably to monlunabant** both during treatment and in post-withdrawal rebound models in DIO models.
  - Maintains potency despite endocannabinoid competition and exhibits **peripheral restriction**, potentially avoiding CNS liabilities.
- ✓ **Broader Metabolic Benefits**
  - Improves glycemic control, reduces hepatic steatosis and serum cholesterol, and decreases obesity-induced inflammation and fibrosis.

Detailed Review of Nimacimab's Outcomes in Phase 2a Clinical Trial

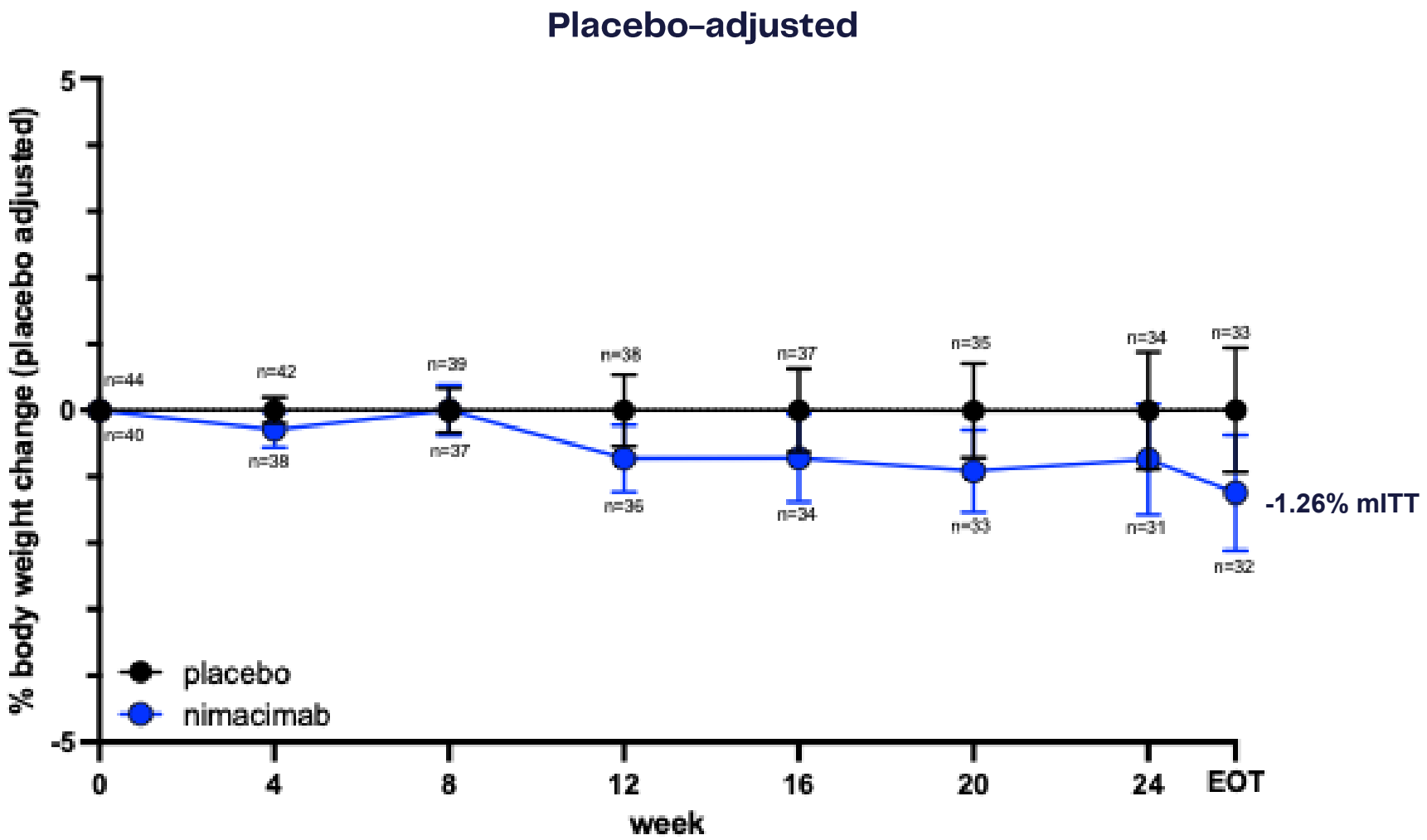
CBeyond Phase 2a Clinical Trial Design for Proof of Concept

Monotherapy and combination arms: weight loss, safety/tolerability, body composition, biomarkers



Initial 26-week treatment period completed; 26-week extension study ongoing

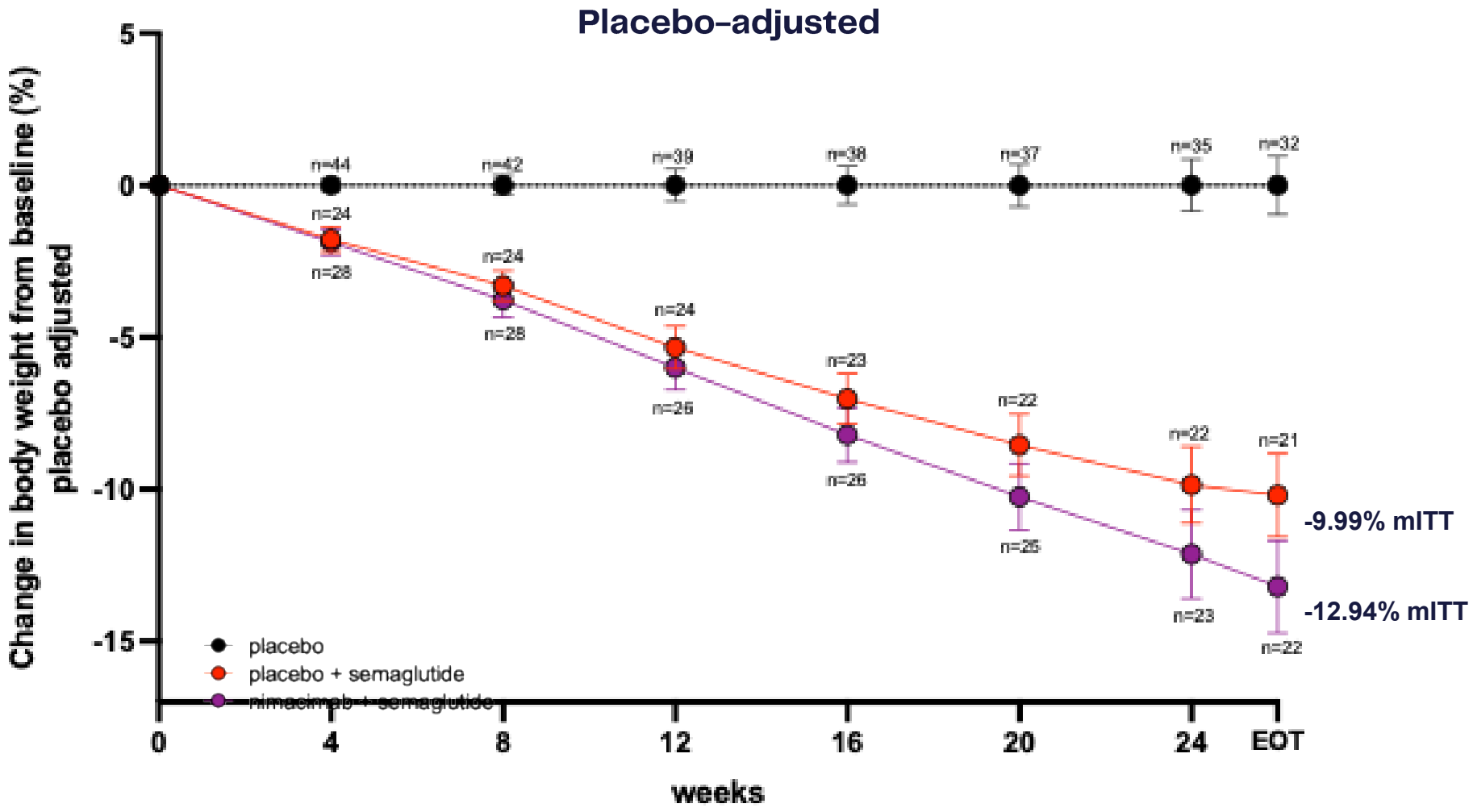
Weight Loss with Nimacimab Monotherapy



PP change in body weight from baseline placebo: 0.53
PP change in body weight from baseline nimacimab: -0.44
mITT LS mean difference: -1.26 (1.136); CI (-3.5, 1.0); p = 0.2699
PP LS mean difference: -1.33 (1.246); CI (-3.8, 1.1); p=0.2578

Data is plotted as mean ± SEM.

Increased Weight Loss in Combination with Semaglutide

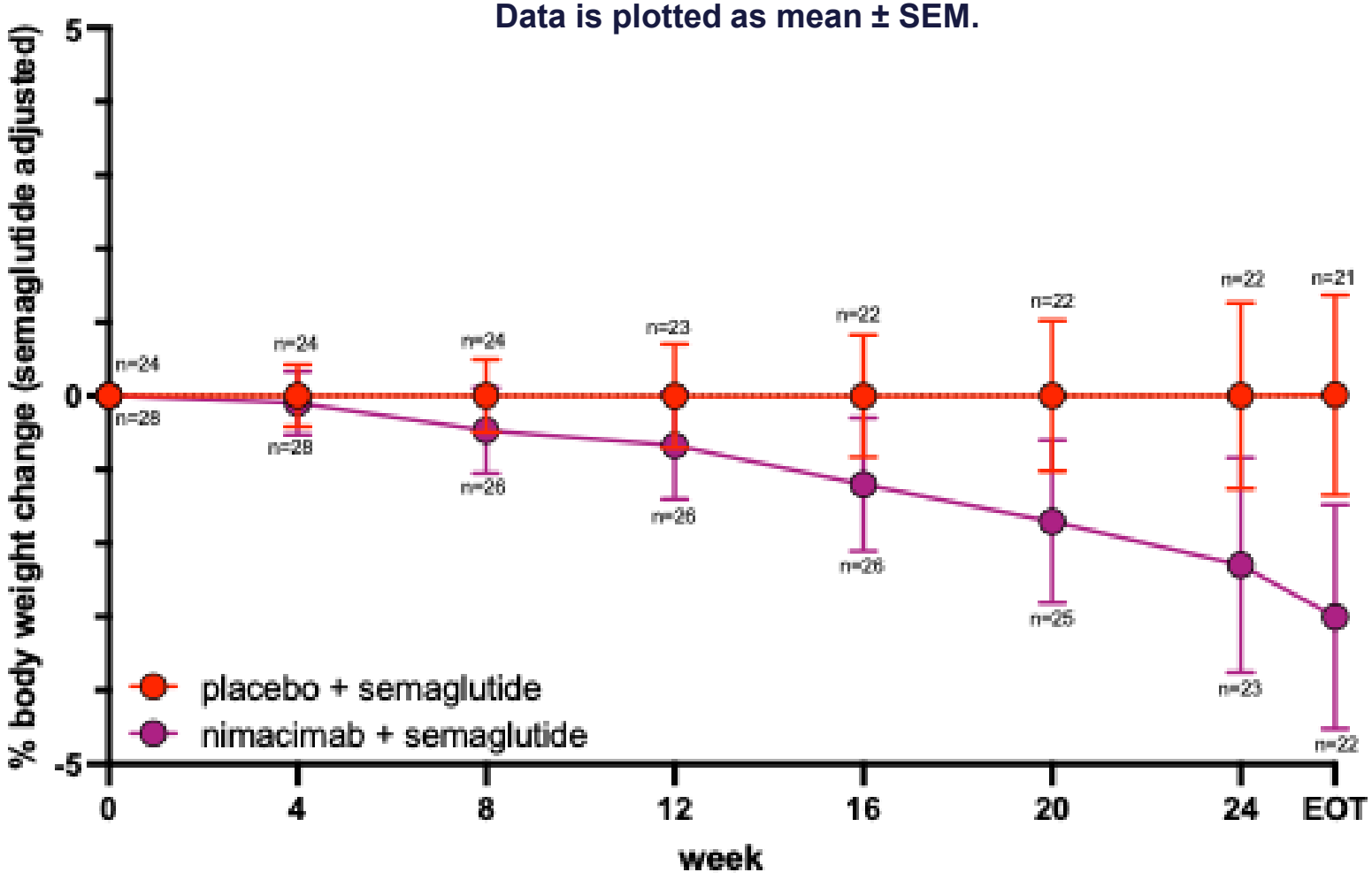


PP change in body weight from baseline placebo + semaglutide: -10.38
PP change in body weight from baseline nimacimab + semaglutide: -13.65
mITT LS mean difference: -2.95 (1.405) (-5.7, -0.2), 0.0372
PP LS mean difference: -3.51 (1.460) (-6.4, -0.6), 0.0178

Data is plotted as mean ± SEM.

Semaglutide-adjusted Weight Loss with Combo Treatment

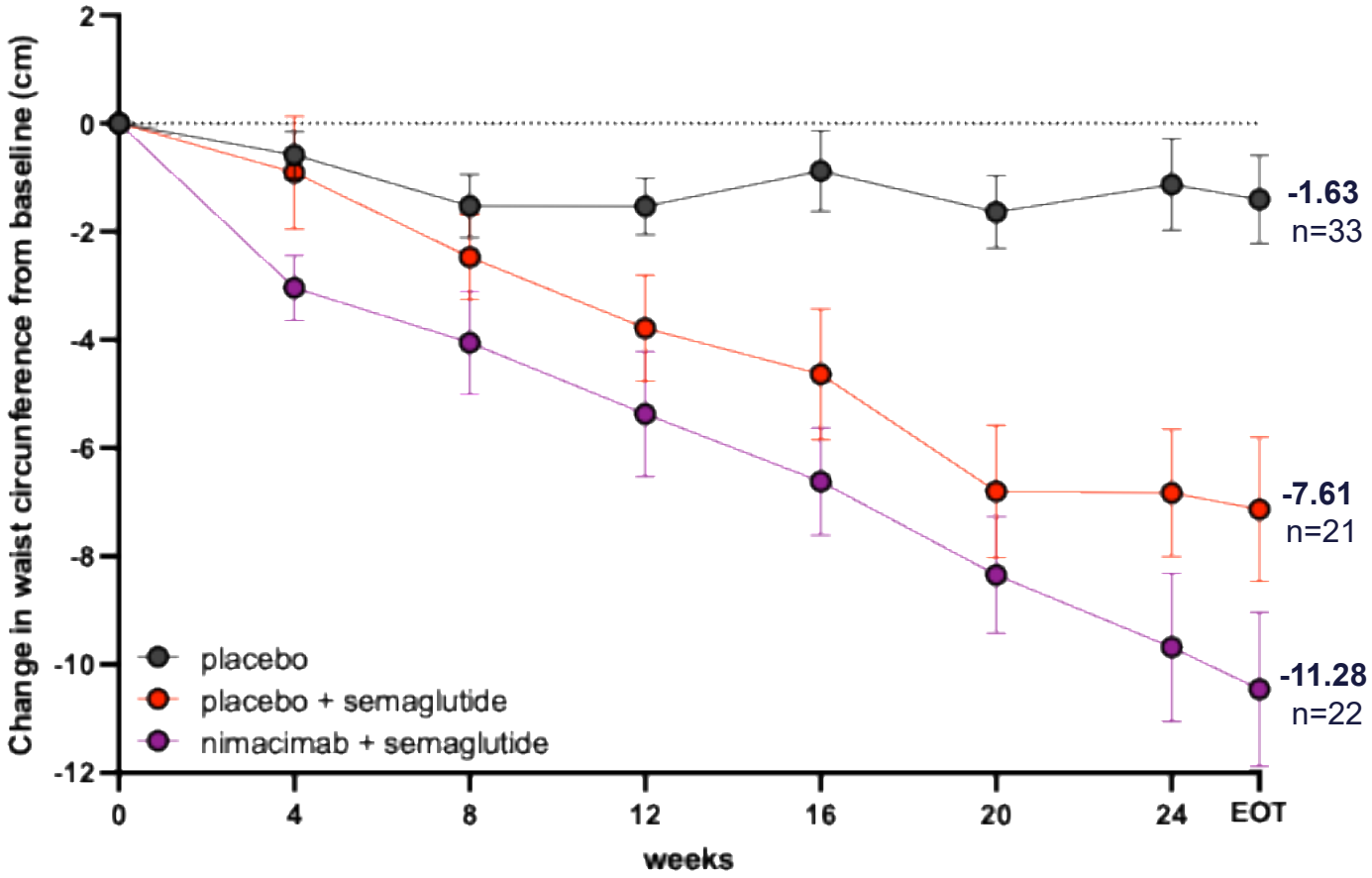
Data is plotted as mean ± SEM.



-2.95% mITT

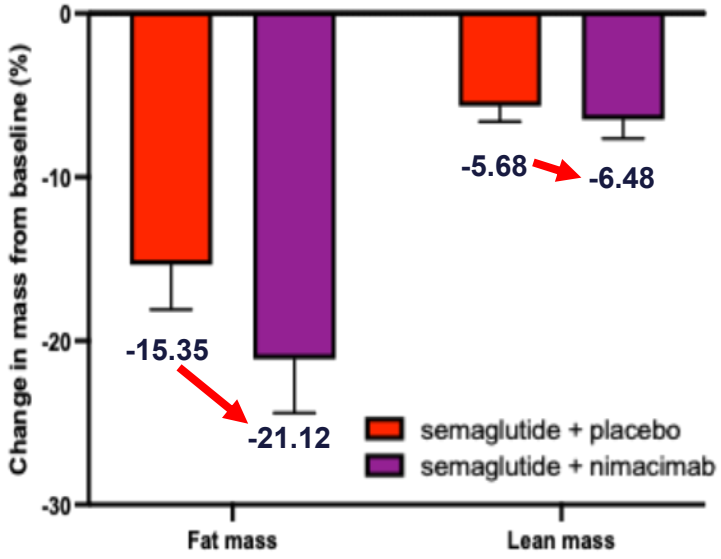
mITT LS mean difference: -2.95 (1.405) (-5.7, -0.2), 0.0372
PP LS mean difference: -3.51 (1.460) (-6.4, -0.6), 0.0178

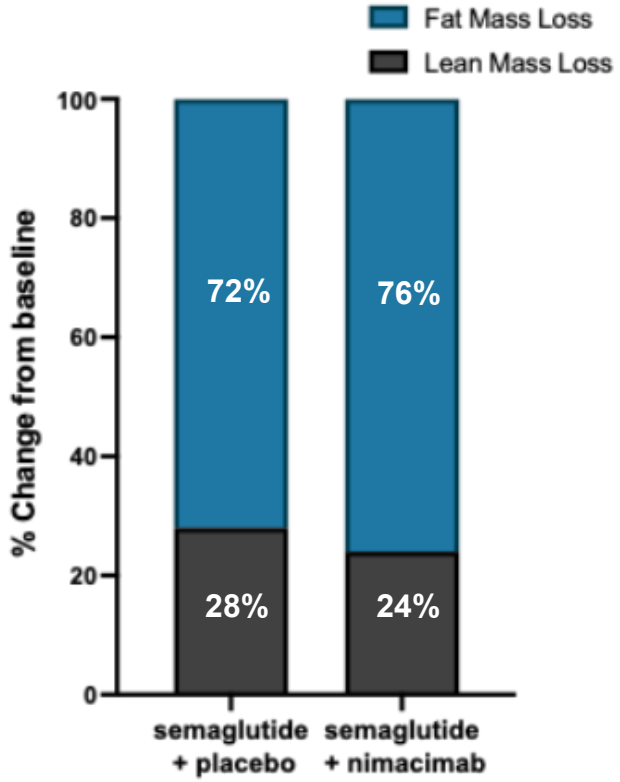
Reduction in Waist Circumference



LS Means (SE) placebo -2.25 (1.00), semaglutide+placebo -8.09 (1.25), semaglutide+nimacimab -11.26 (1.16)
LS Means Difference (SE) semaglutide+placebo vs semaglutide+nimacimab -3.17 (1.59) p=0.0492

Lean to Fat Mass Ratio Improves with Nimacimab-Semaglutide Combination



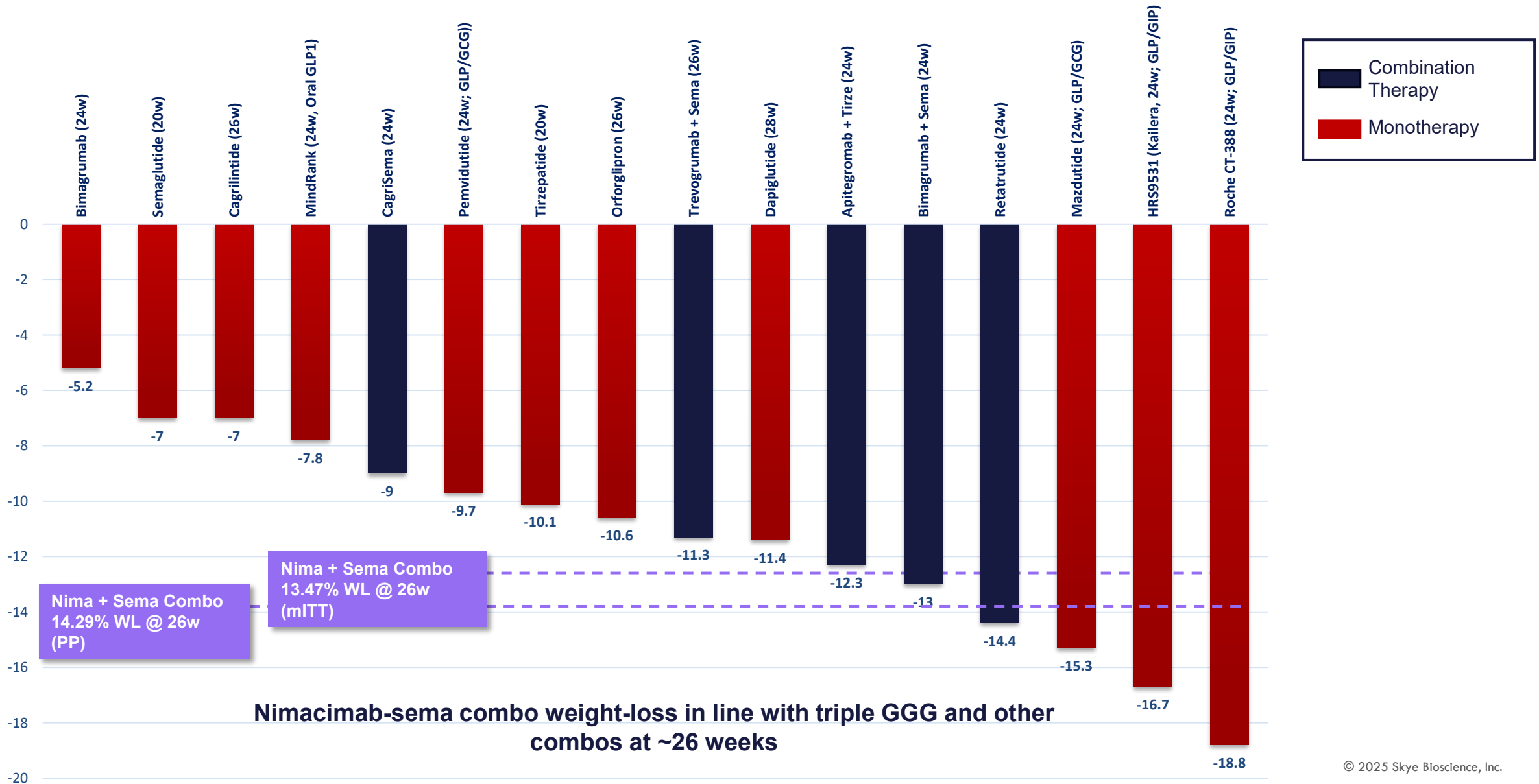


Change in Lean to Fat Mass Ratio with Weight Loss

	Placebo + Semaglutide	Nimacimab 200 mg + Semaglutide
	n=20	n=25
Mean baseline lean to fat mass ratio (SD)	1.15 (0.296)	1.06 (0.216)
Mean Week 26 lean to fat mass ratio (SD)	1.32 (0.312)	1.30 (0.463)
Least-squares mean change from baseline (SE)* (95% CI)	**0.13 (0.038) (0.1, 0.2)**	**0.26 (0.037) (0.2, 0.3)**
Least-squares mean difference from semaglutide (SE) (95% CI), P-value		**0.13 (0.051) (0.0, 0.2), p= 0.0126**

Nimacimab + semaglutide increases weight loss by ~30% & fat loss by 37% compared to semaglutide alone

Weight-Loss Benchmark at ~26-Weeks (Placebo-Adjusted)



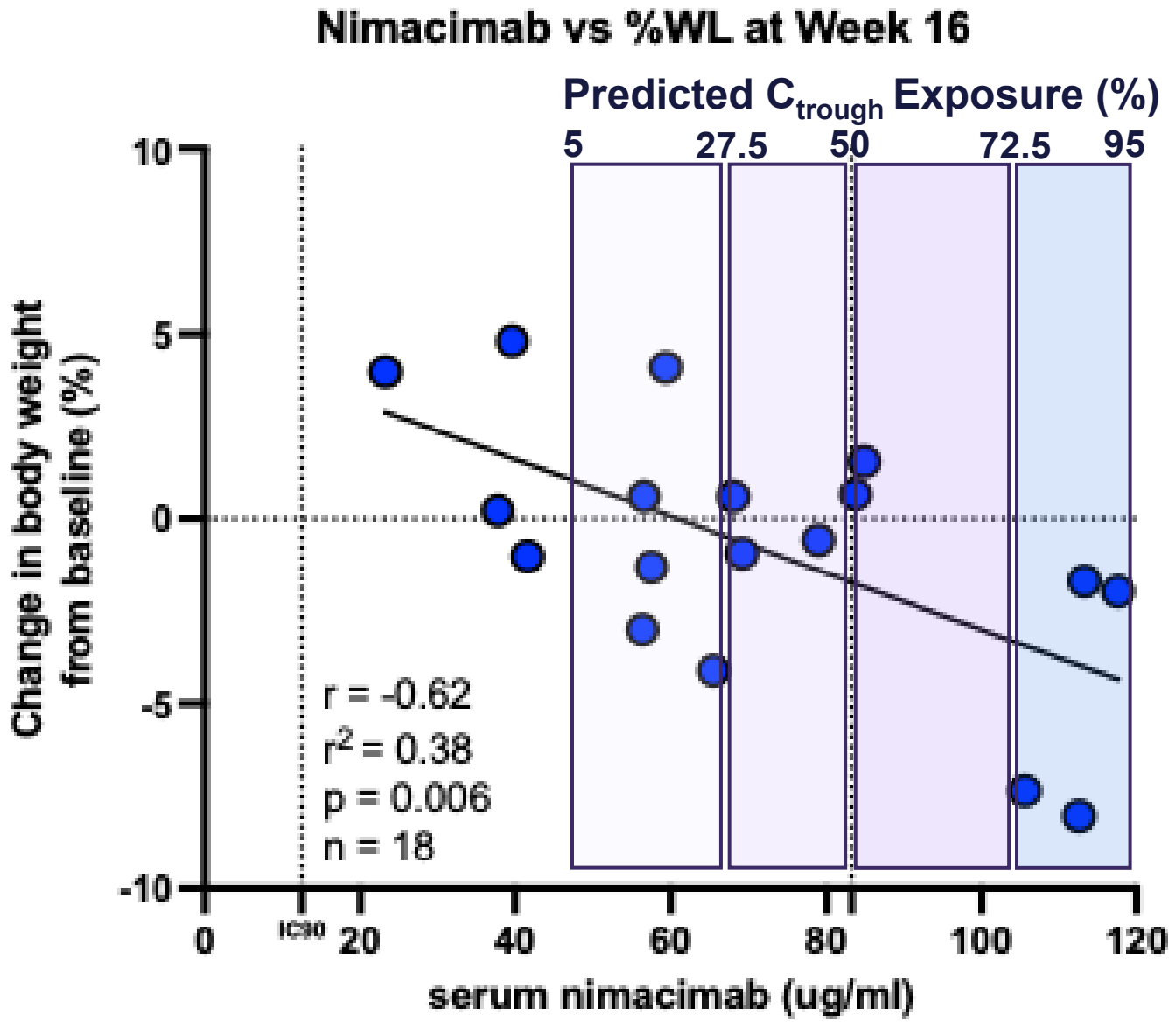
Nimacimab-sema combo weight-loss in line with triple GGG and other combos at ~26 weeks

Association of Weight Loss and Exposure of Nimacimab

Initial observed Week 16 Ctrough values from nimacimab-treated subjects

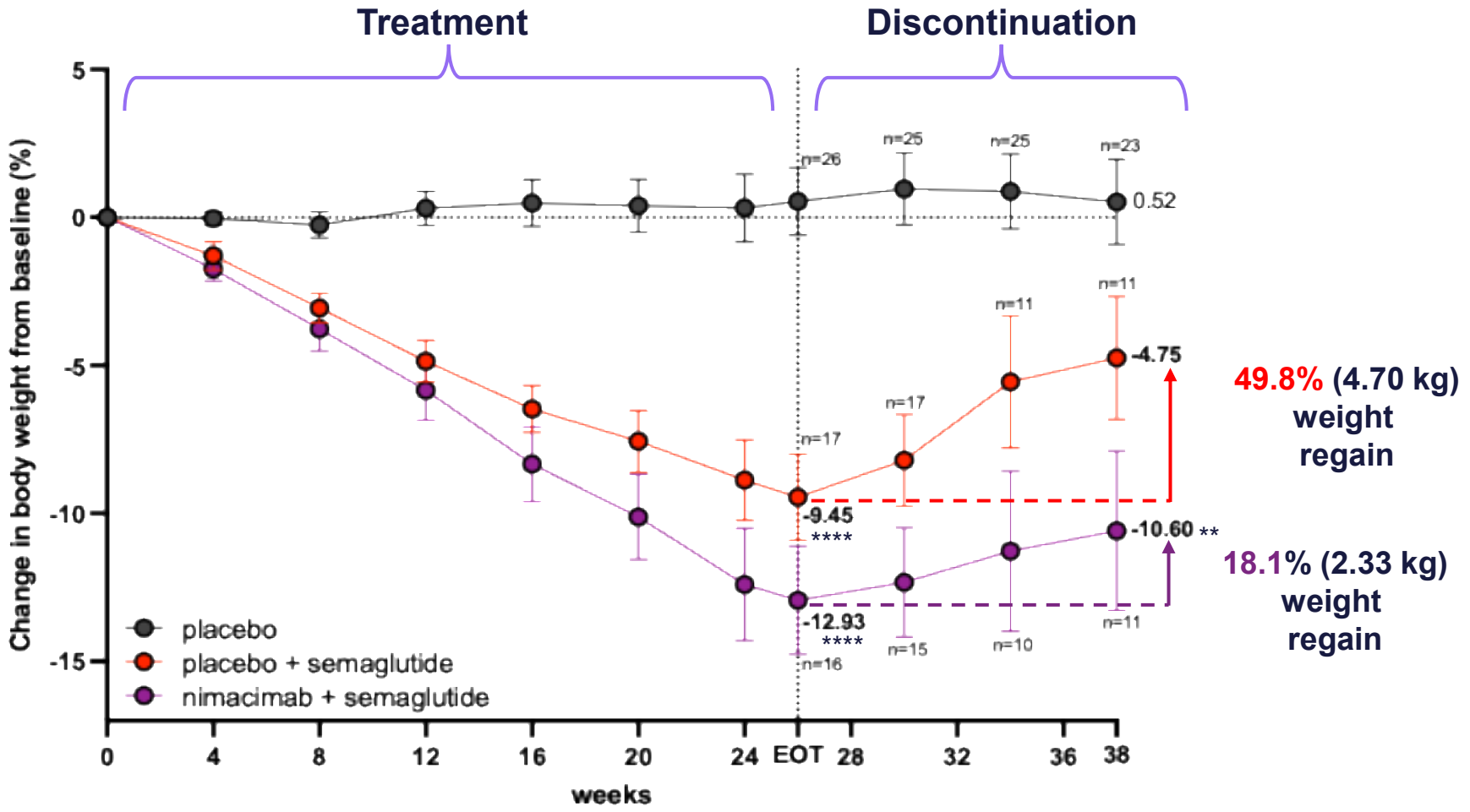
- Additional evidence of less than expected nimacimab exposure
  - Expected W16 Ctrough = 83ug/mL
  - Actual W16 Ctrough = 67ug/mL

- Highlights a preliminary dose-response



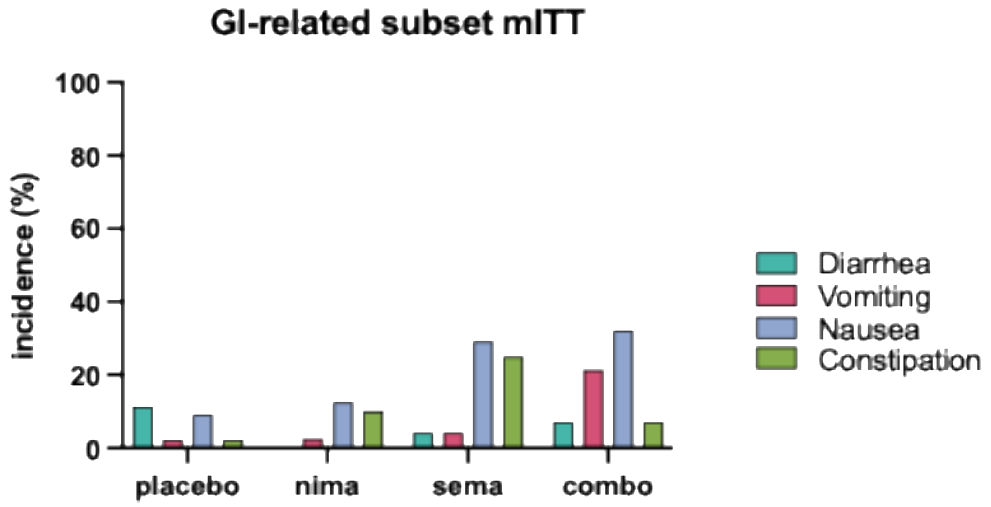
* Removed (1) patient who discontinued nimacimab and switched to tirzepatide therapy at week 12

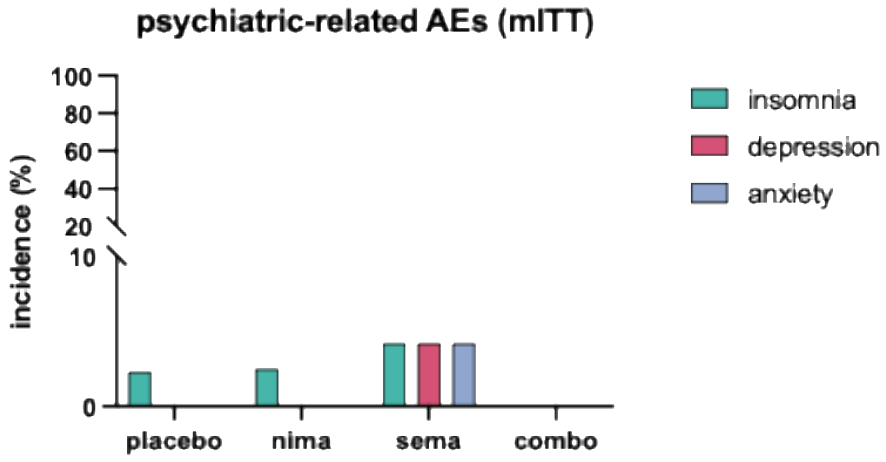
Nimacimab Reduces Weight Regain



Inclusion criteria: patients must have completed at least 75% of treatment and have at least one follow-up visit three or more weeks after week 26/EOT. Data is reported as mean ± SEM. 2-way ANOVA followed by Tukey's multiple comparison tests, reporting significance vs placebo at week 38 and EOT. Rebound data is interim data from off-therapy follow-up.

Nimacimab Demonstrates Potential Best-in-Class Safety and Tolerability





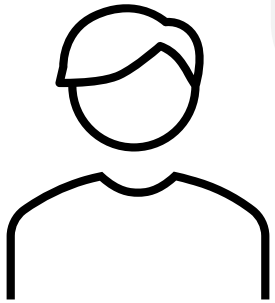
4 patients reported psychiatric-related AEs
(insomnia n=3 events, anxiety n=1 events, depression n=1 events)

- No severe AEs or SAEs attributed to nimacimab.
- Combination of nimacimab + semaglutide did not increase number of observed AEs.
- GI adverse events were very low and consistent with profile observed in Phase 1 study.
- Neuropsychiatric adverse events were minimal and not associated with nimacimab.

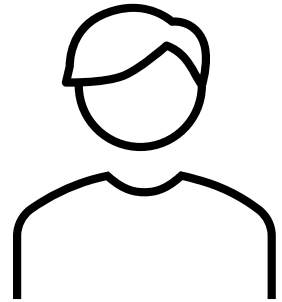
Benchmark Milestones Shape CB1 Inhibitor Next Steps

Skye's CBeyond Phase 2a study of its nimacimab peripheral CB1 inhibitor shows first-ever additive efficacy with GLP-1 combo and favorable tolerability/safety profile

"This is the first clinical study to show that the **combination of a CB1 inhibitor and a GLP-1 therapeutic can drive clinically meaningful additional weight loss** beyond a GLP-1 drug alone. Equally important, although the sample size is small, nimacimab achieved this **without neuropsychiatric or additive gastrointestinal adverse events**. I believe these results warrant further evaluation of the therapeutic potential of this novel CB1 inhibitor."



Louis Aronne, MD
Past President, The Obesity Society; past Chairman, American Board of Obesity Medicine; and clinical advisor to Skye



Sean Wharton, MD
Director, Wharton Medical Clinic and clinical advisor to Skye

"Gastrointestinal side effects remain a leading cause of discontinuation with obesity therapies. It was notable that **nimacimab did not increase GI adverse events while adding clinically meaningful weight loss in combination with semaglutide**. In my view, a next study with higher nimacimab dosing is the logical step to fully define its role in clinical practice."

CBeyond Phase 2a Topline Data – Key Takeaways

Nimacimab demonstrated additive efficacy, clean safety, and mechanistic clarity — providing a defined path to higher-dose validation and Phase 2b execution

- ✓ **Interpretation of Monotherapy Weight Loss**
  - The 200 mg dose was below the therapeutic range; weight loss was potentially limited by sub-optimal exposure.
  - **Signal of activity** observed in high-exposure patients supports **mechanism validity**.
  - Safety profile confirms **headroom to move higher on dose**.

- ✓ **Implications of Combination Therapy Weight Loss**
  - **~30% (35% PP) greater weight loss** versus semaglutide alone at 26 weeks (*p = 0.0372*).
  - **Improved body composition** (higher lean-to-fat mass ratio, reduced waist circumference).
  - Supports **synergistic benefit** of peripheral CB1 blockade plus GLP-1 pathway.
  - **Mitigated rebound weight gain** post-discontinuation shows potential for **durable benefit**.

- ✓ **Significance of Favorable Gastrointestinal and Neuropsychiatric Profiles**
  - **No neuropsychiatric adverse events** observed across any arm.
  - **No additive GI burden**
  - Differentiates nimacimab as a **combination-friendly, titration-free antibody** suitable for chronic use.

- ✓ **Next Clinical Steps**
  - **Phase 2b study** – evaluate **optimized monotherapy and combination doses**, confirm safety, efficacy and durability, and position nimacimab for pivotal development.

Select Financial Figures & Metrics

- $107M in equity capital raised since August 2023
- Supported by top-tier specialist life science investors
- Funded into 2027, runway excludes clinical cost of Phase 2b
- Ongoing strategic investments in scaling manufacturing, operations, R&D, and advancing clinical pipeline

Stock Information

Listed: Nasdaq	**SKYE**
Stock Price[1]	**$1.52**
Shares Outstanding[2]	**32.1M**
Shares Fully Diluted[2]	**51.0M**
Cash, Cash Equivalents & Short-term Investments [3]	**$35.3M**
Market Cap (inclusive of PFWs)[1]	**$45M**
Avg. 3-Mo. Daily Trading Volume[3]	**814K**

[1] Nov 12/11 [2] Nov 8/25 [3] Sep 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

THANK YOU!

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San Diego, CA 92130

Please learn more or contact us at:

ir@skyebioscience.com

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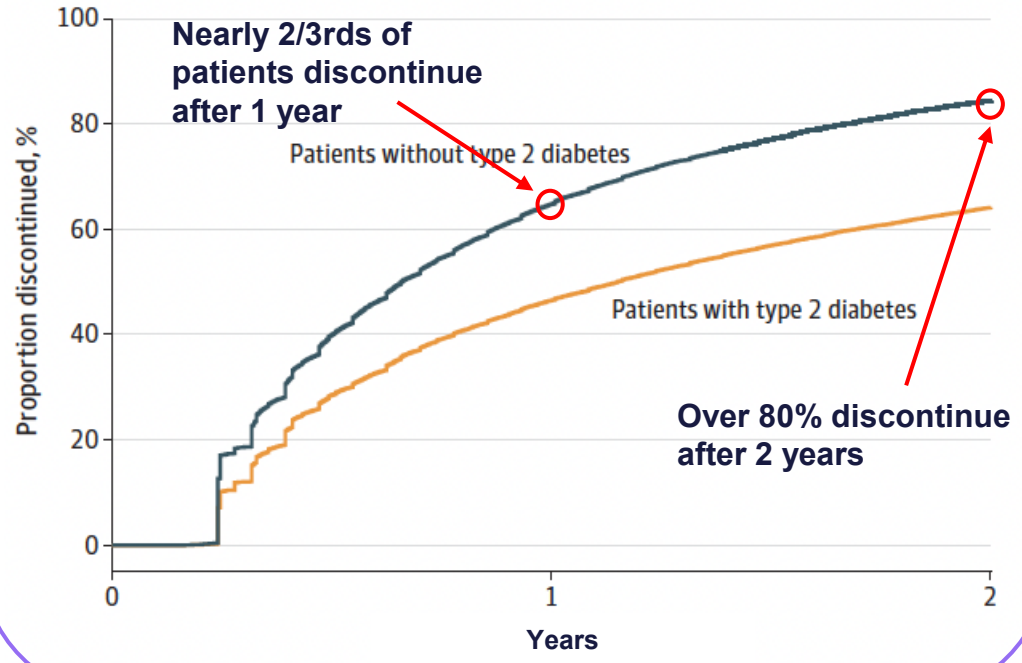
APPENDIX

Back-up Slides

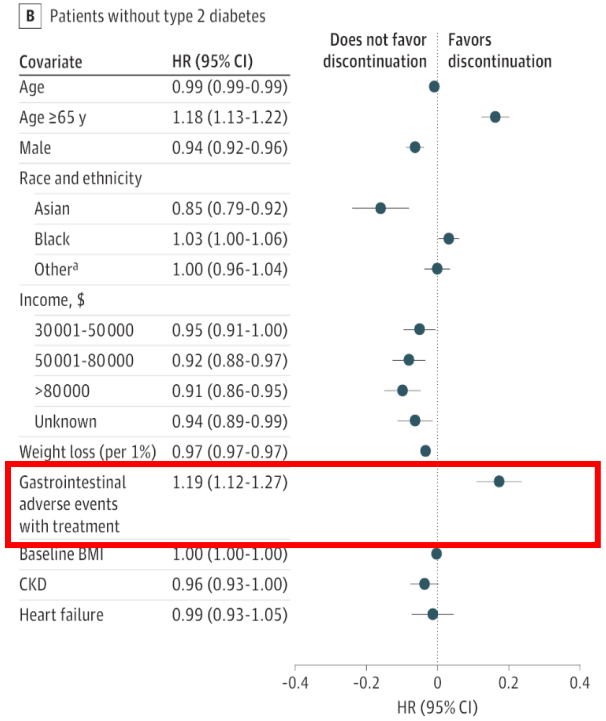
Pattern of GLP-1 Discontinuation

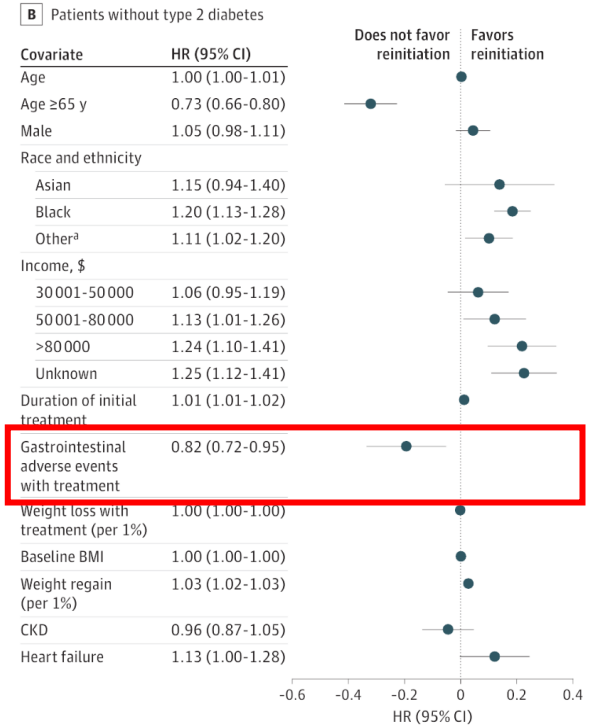
Most adults with overweight or obesity discontinue GLP-1 RA therapy within one year

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

Significant Opportunity 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

Nimacimab

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

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

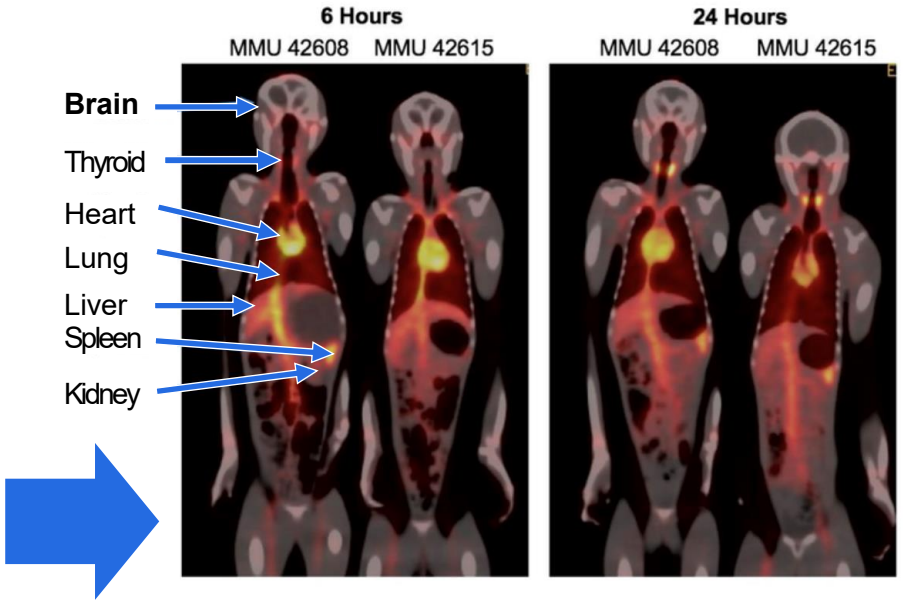
Cyno	9 hours
CSF/Serum 40 mg/kg IV	0.01%

— 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

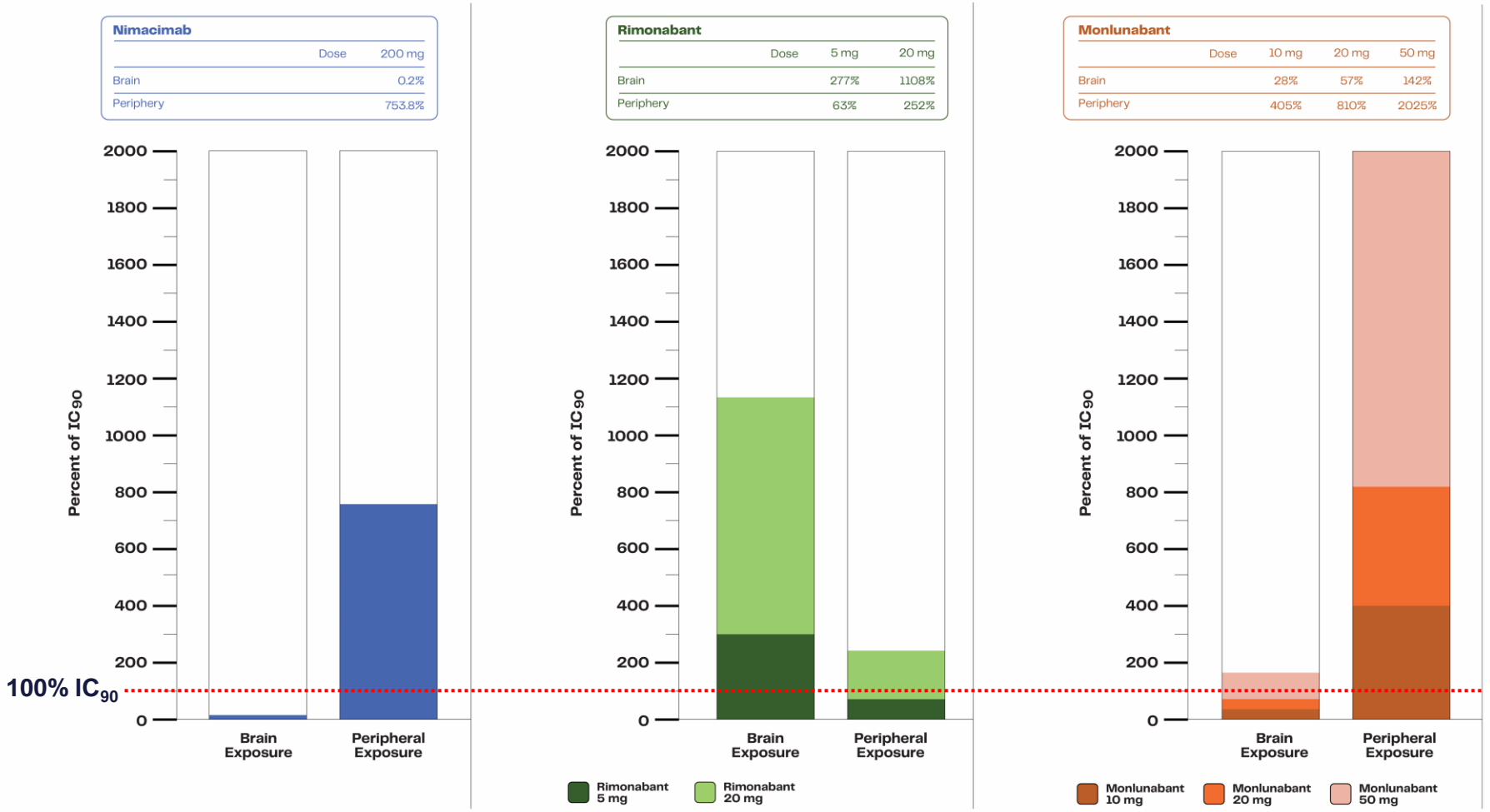
PET imaging also confirmed broad antibody distribution in tissues having upregulated CB1 expression, with no accumulation in the brain



- *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.

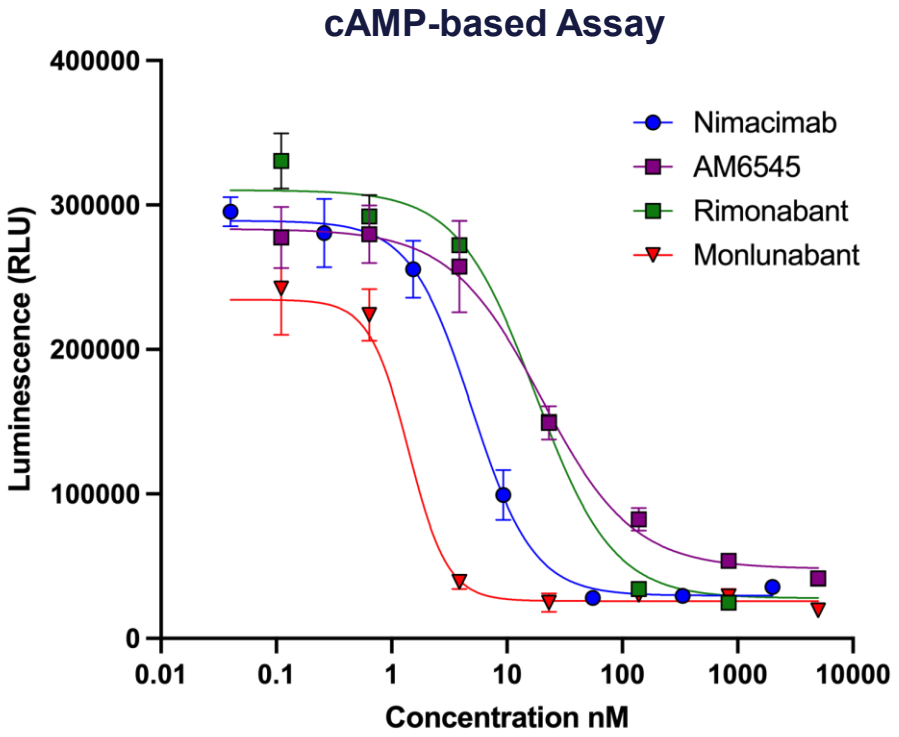
Monlunabant:

- 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.

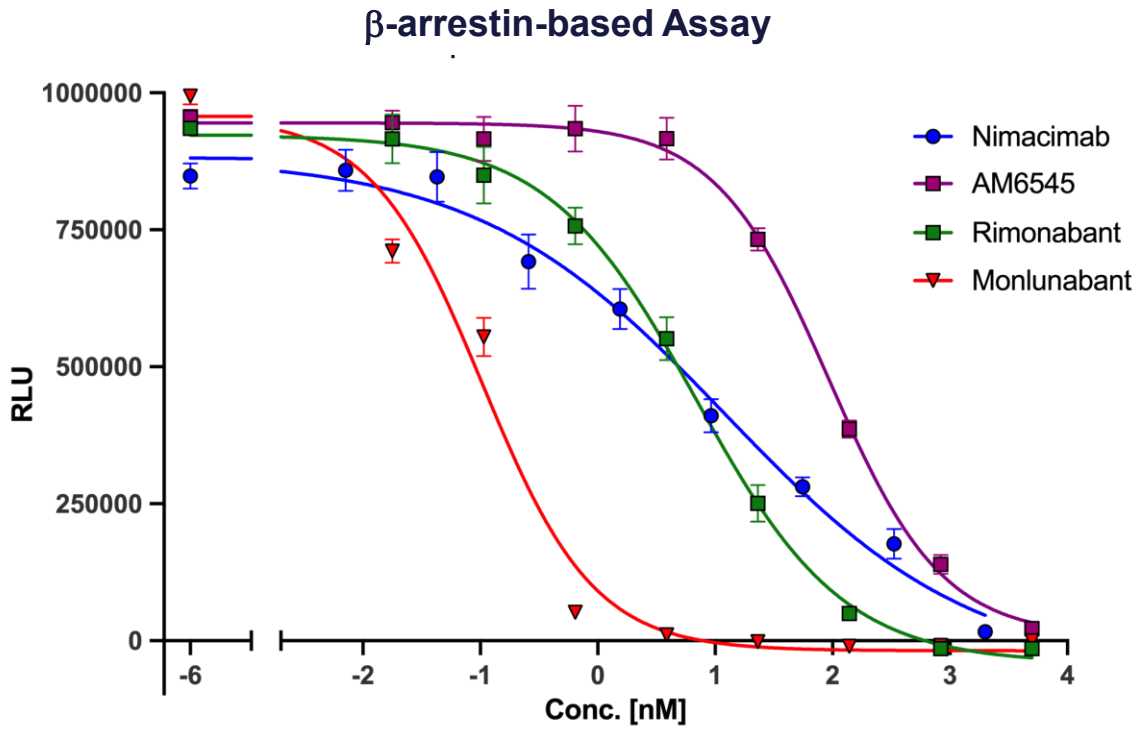
Source: Braga et al., Demonstrating the sufficiency of peripheral CB1 inhibition to promote weight loss using clinical pharmacokinetic and pharmacodynamic. European Congress on Obesity PO4.148. https://eco2025.org/assets/docs/programme-book.pdf?a=5678

Nimacimab Potency Similar to Small Molecule Inhibitors

Based on both cAMP and β-arrestin assays



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

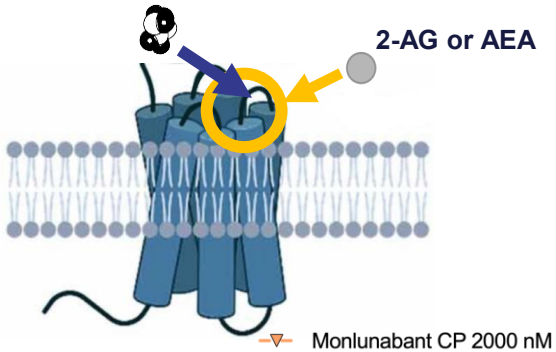


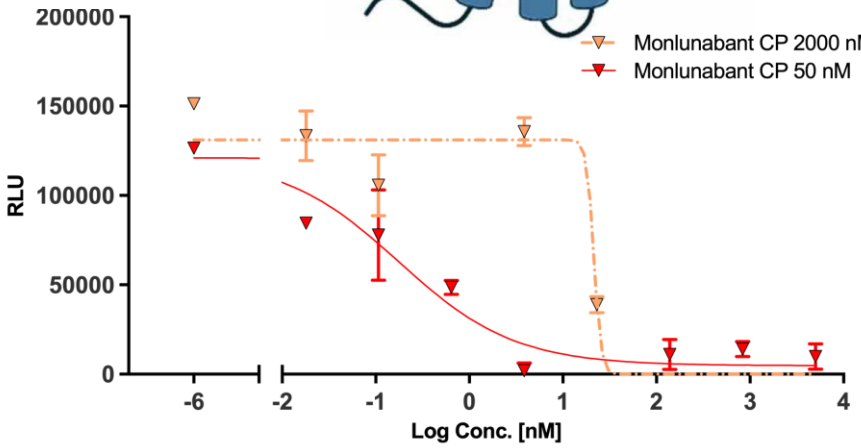
CB1 Inhibitor	IC_{50} (nM)
Nimacimab	10.83
AM6545 (neutral antagonist)	47.62
Rimonabant	5.36
Monlunabant	0.07

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

Monlunabant

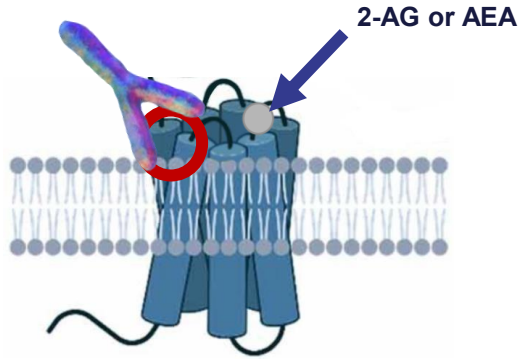
Monlunabant **competes** with AEA/2-AG for binding to the orthosteric site

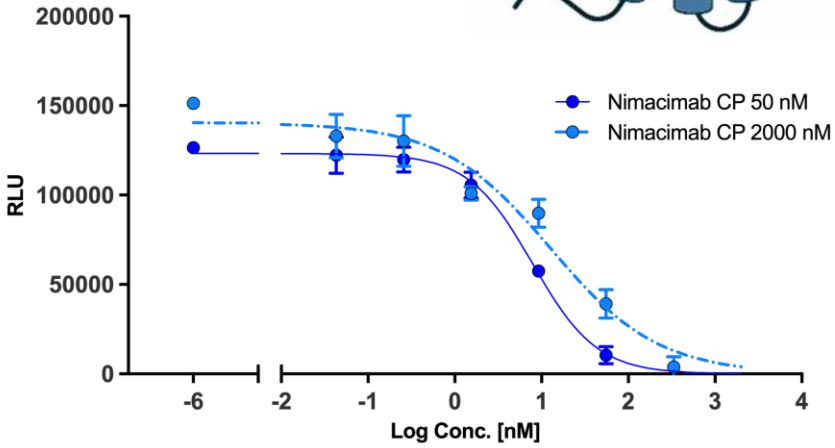




Nimacimab

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

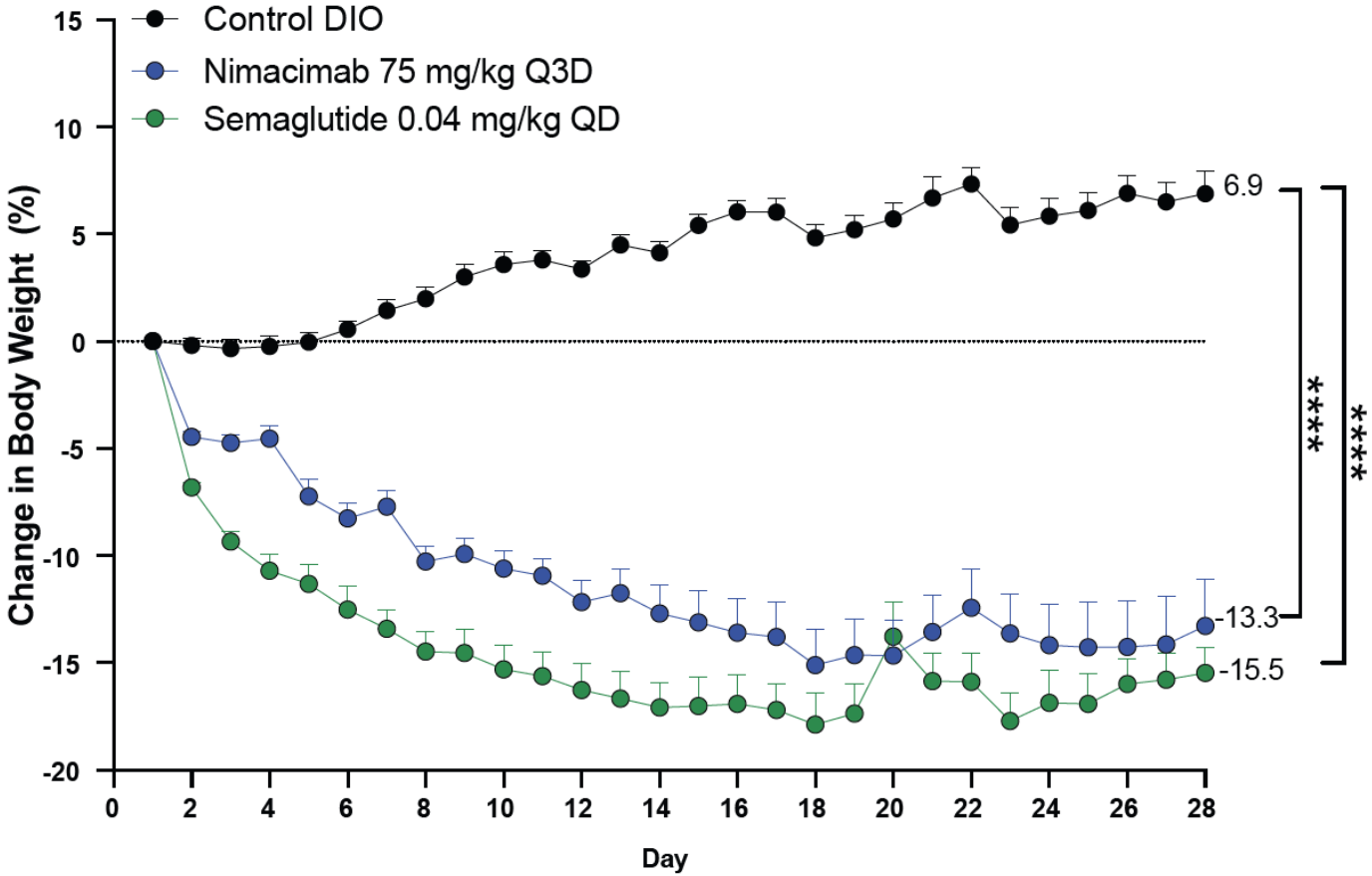




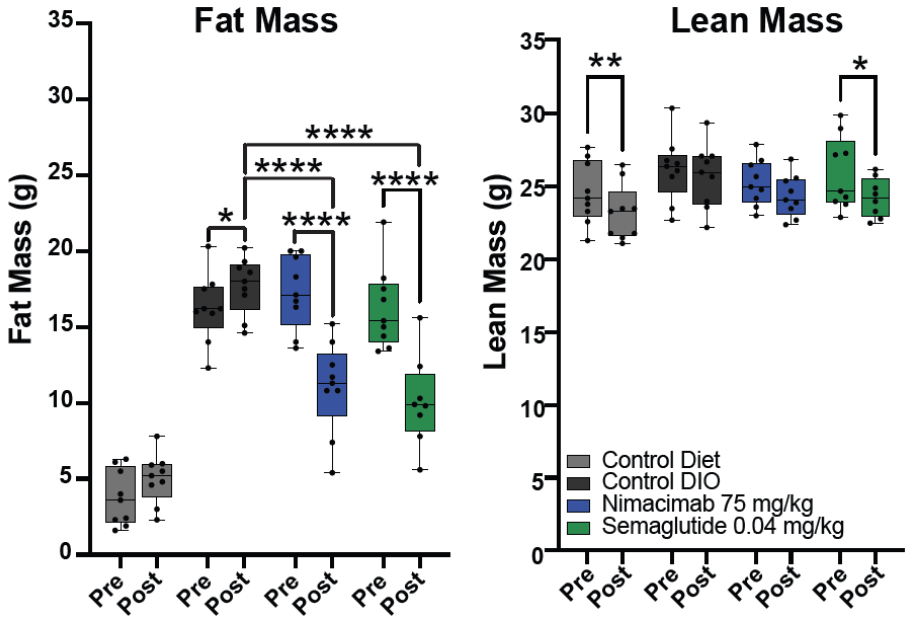
CB1 Inhibitor	Agonist: CP55940		Reduction in Fold Potency
	EC_{80} (50 nM)	40x EC_{80} (2000 nM)	
Nimacimab IC_{50} (nM)	7.9	12.7	**1.6**
Monlunabant IC_{50} (nM)	0.2	21.44	**107**

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

Body Weight



Body Composition

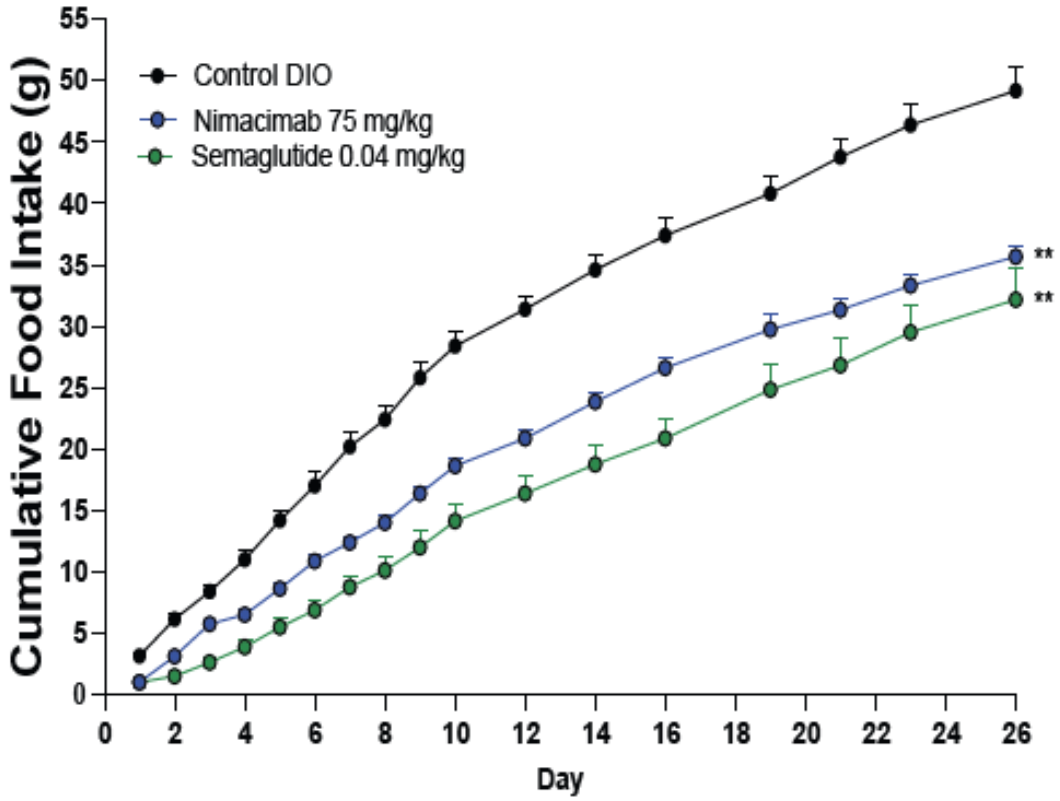


Body weight and composition analyses were performed with two-way ANOVA repeated measurements. Tukey multiple comparison test was then performed for all pairwise comparisons. Body weight reporting through 28 days of treatment. Body composition measured with echo MRI on day 26

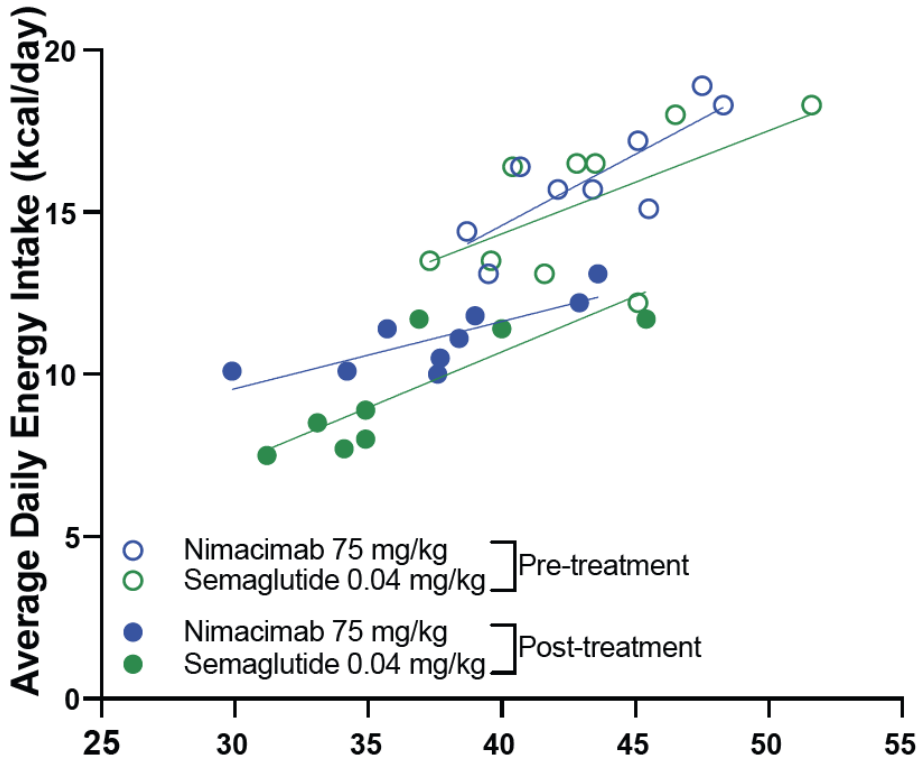
Nimacimab Led to Reduced Food Intake

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*

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

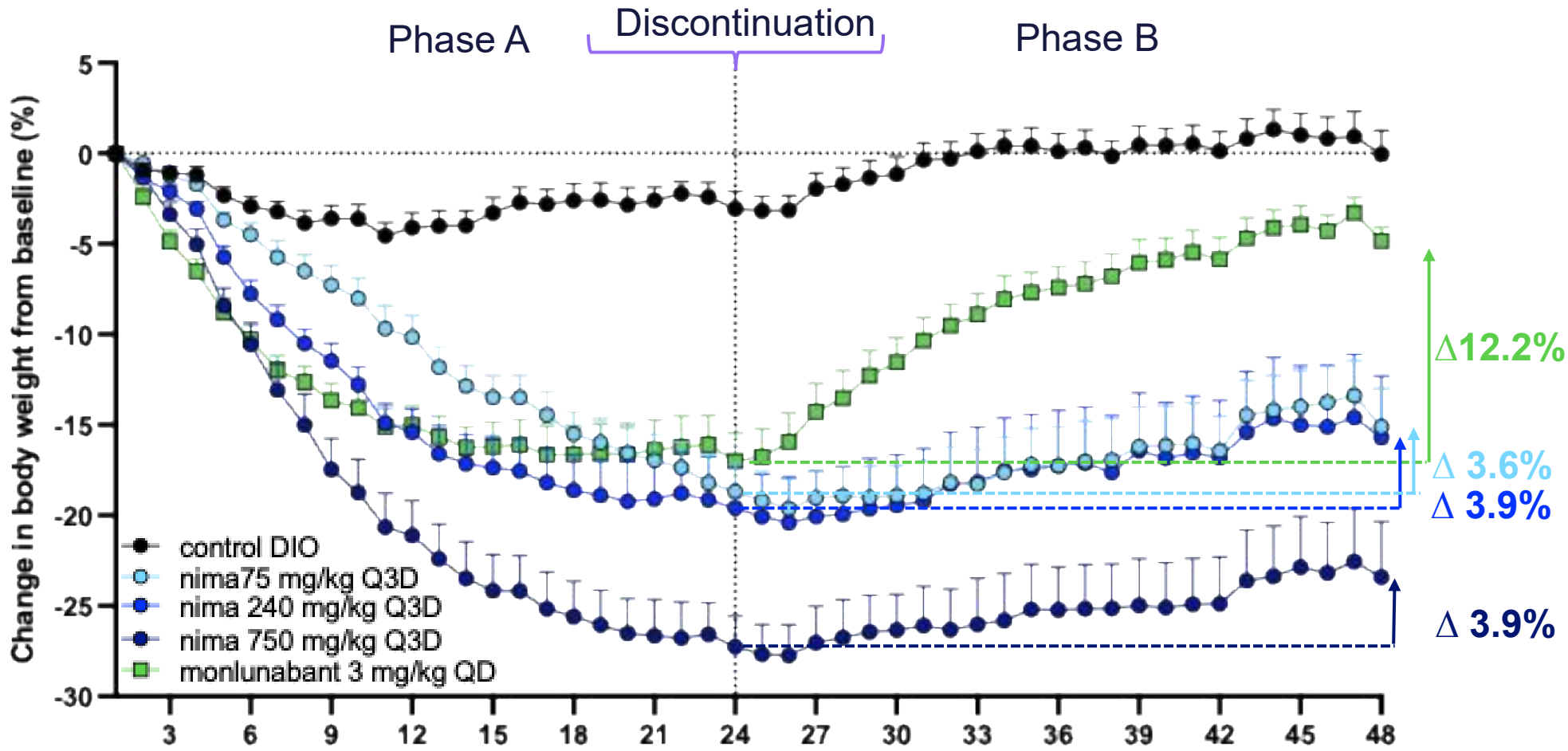
Tissue collection

- 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:

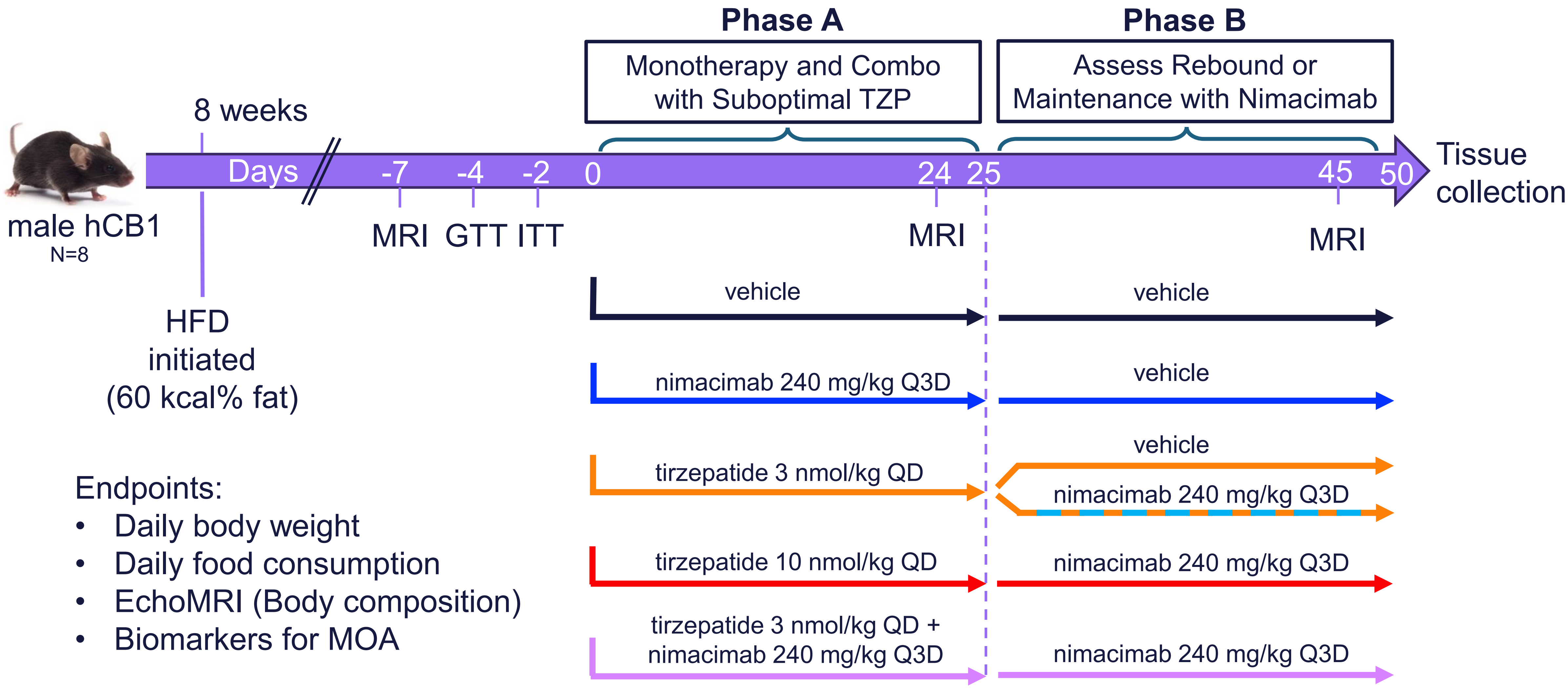
- Daily body weight
- Daily food consumption
- EchoMRI (Body composition)
- Biomarkers for MOA

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



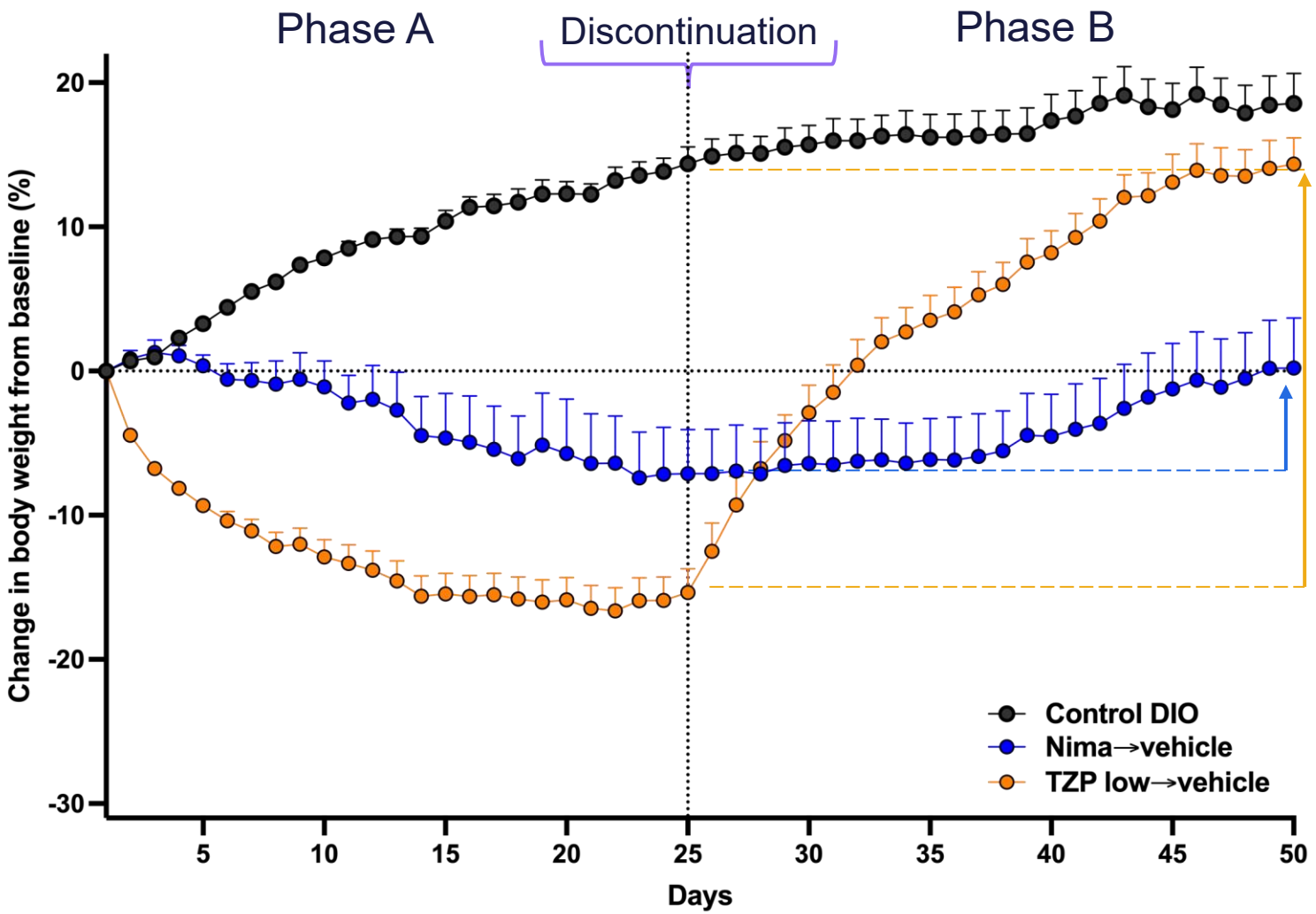
Data are expressed as mean ± SEM. N=7-8 per group. At day 48, all nimacimab treated groups were significantly different to control DIO (nima 75, ***p<0.001, nima 240 *p<0.05, nima 750 ***p< 0.001, monlunabant not significant).

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



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

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

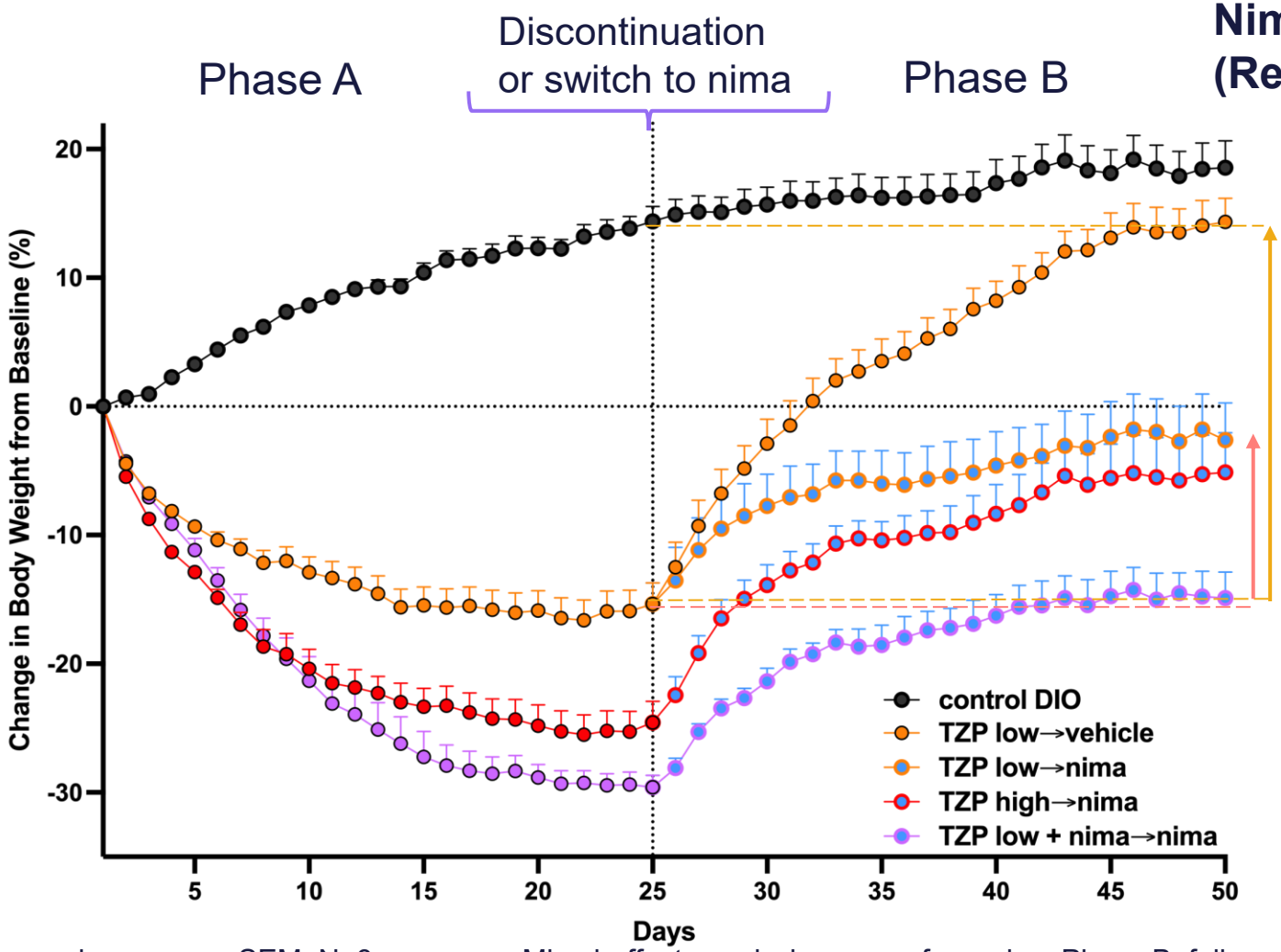


Δ29.7% tirzepatide 'rebound'

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

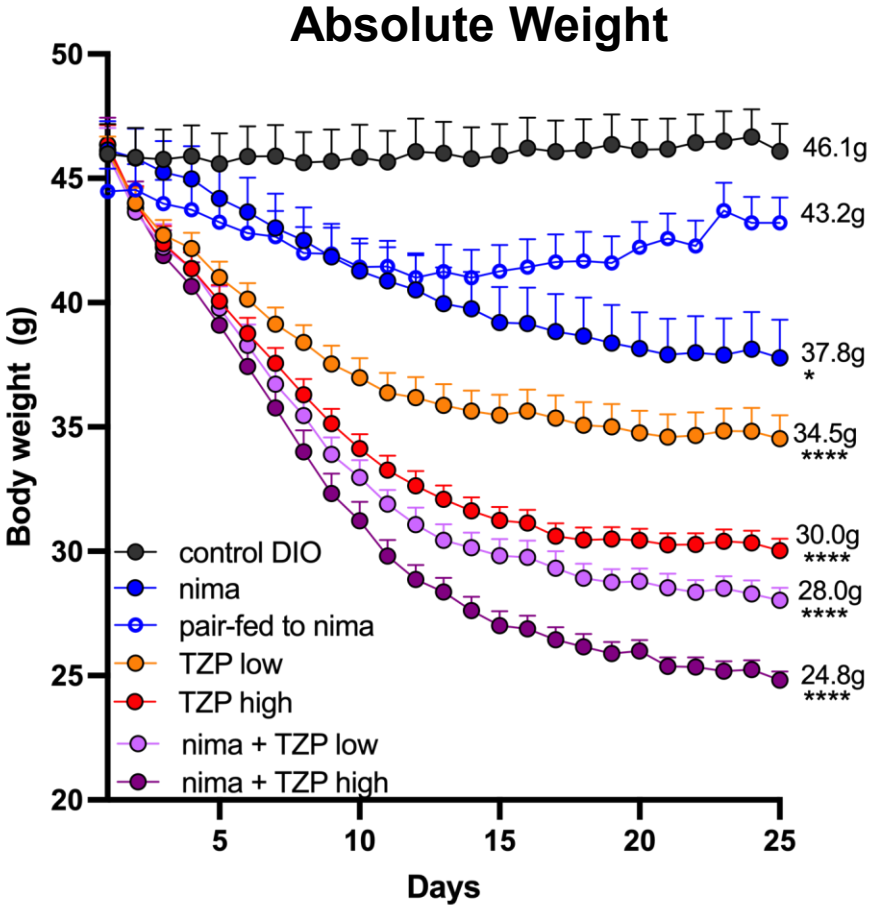
Days: -7 (MRI) | 0 | 24 (MRI) | 25 | 45 (MRI) | 50 Tissue collection

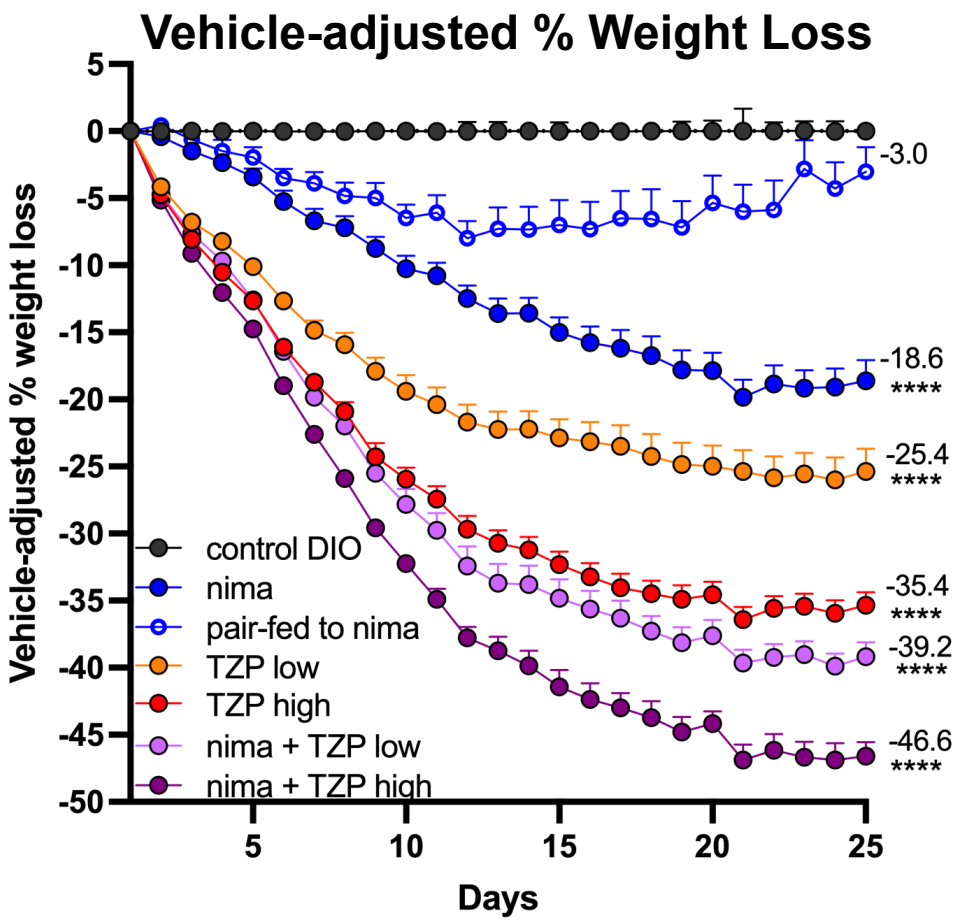
- vehicle → vehicle
- pair-fed to nimacimab → pair-fed to nimacimab
- nimacimab 240 mg/kg Q3D → vehicle
- tirzepatide 3 nmol/kg QD → vehicle / nimacimab 240 mg/kg Q3D
- tirzepatide 10 nmol/kg QD → vehicle / nimacimab 240 mg/kg Q3D
- tirzepatide 3 nmol/kg QD + nimacimab 240 mg/kg Q3D → vehicle
- tirzepatide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

Endpoints:

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

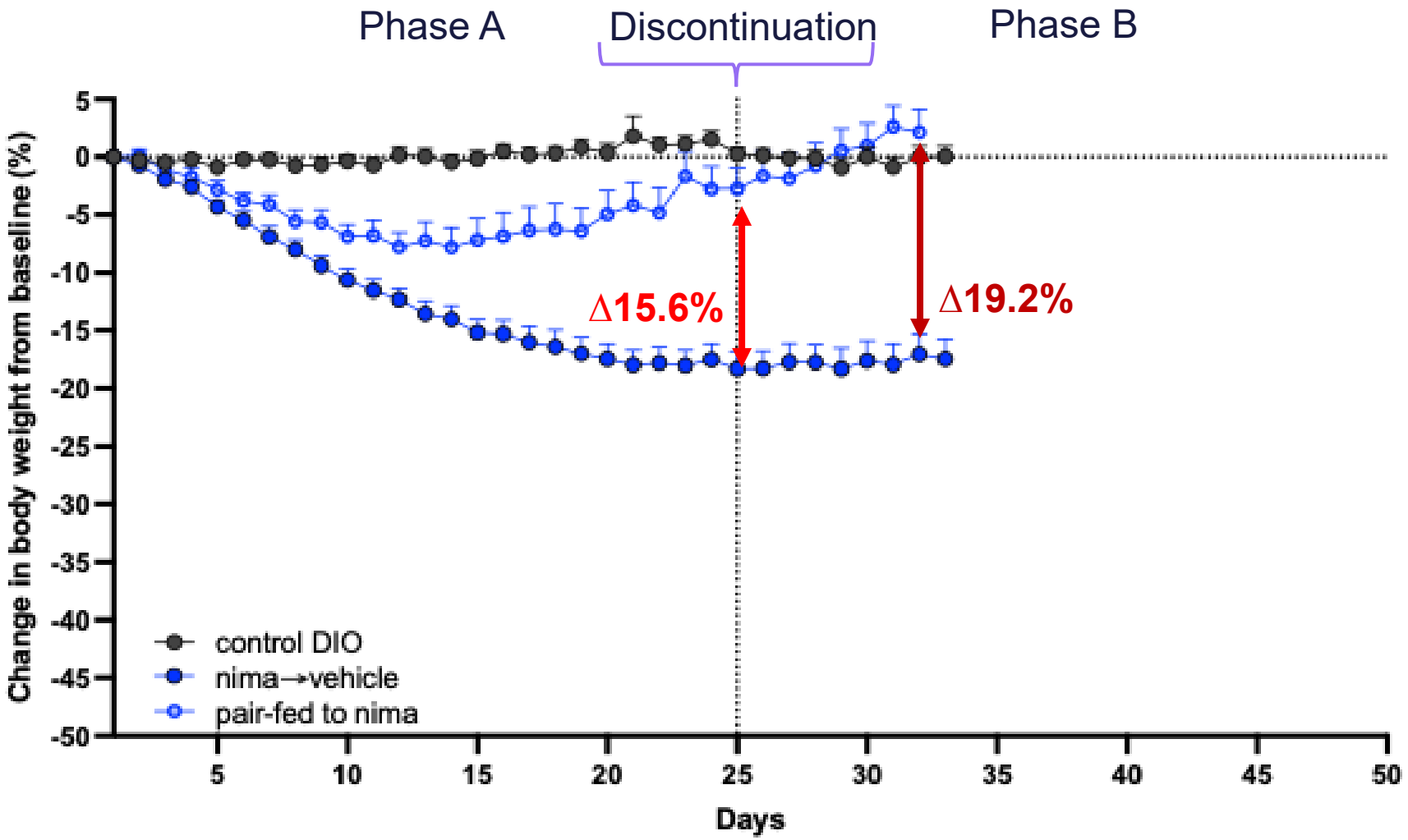
Nimacimab Enhances Weight Loss when Combined with both Low-Dose and High-Dose Tirzepatide





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



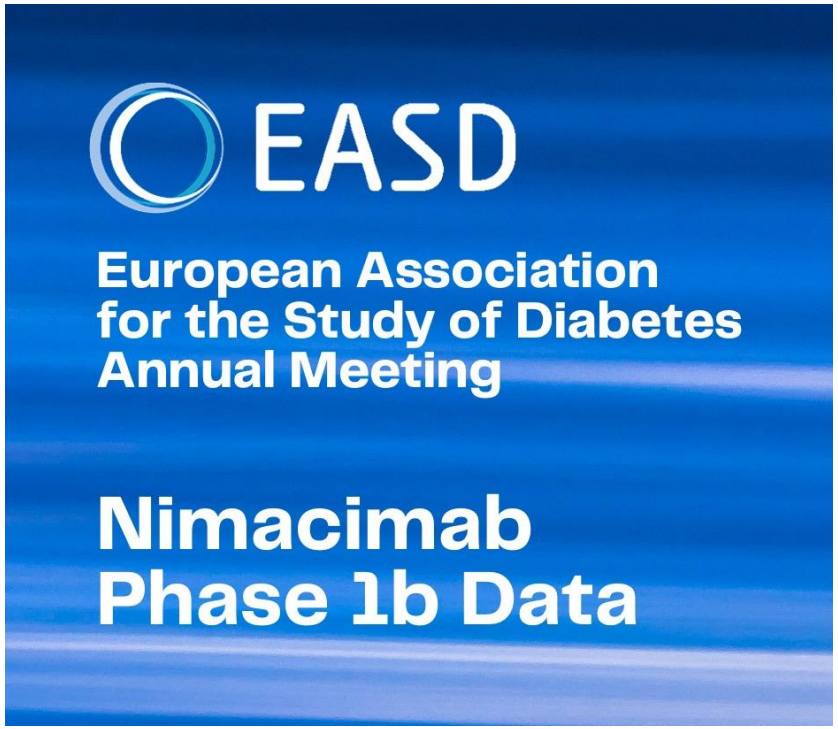
To determine how much of nimacimab-driven weight loss is due to reduced food intake, we performed a pair-feeding experiment.

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 Phase 1 Profile

Safety and tolerability outcomes supportive of distinctive, complementary role in therapeutic landscape



Oral category: "New medications on the horizon?"

Session: "A multiple dose study to evaluate the safety and tolerability of nimacimab, a peripherally-restricted, inhibitory CB1 receptor antibody in subjects with metabolic associated fatty liver disease (MAFLD)"

- ✓ **Safe, Well-tolerated**
  - No serious adverse events
  - No discontinuations due to adverse events
  - No evidence of neuropsychiatric safety signals
  - Gastrointestinal side effects were infrequent and mild
- ✓ **Predictable Pharmacokinetics**
- ✓ **Low immunogenicity** across multiple ascending dose cohorts.

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

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.

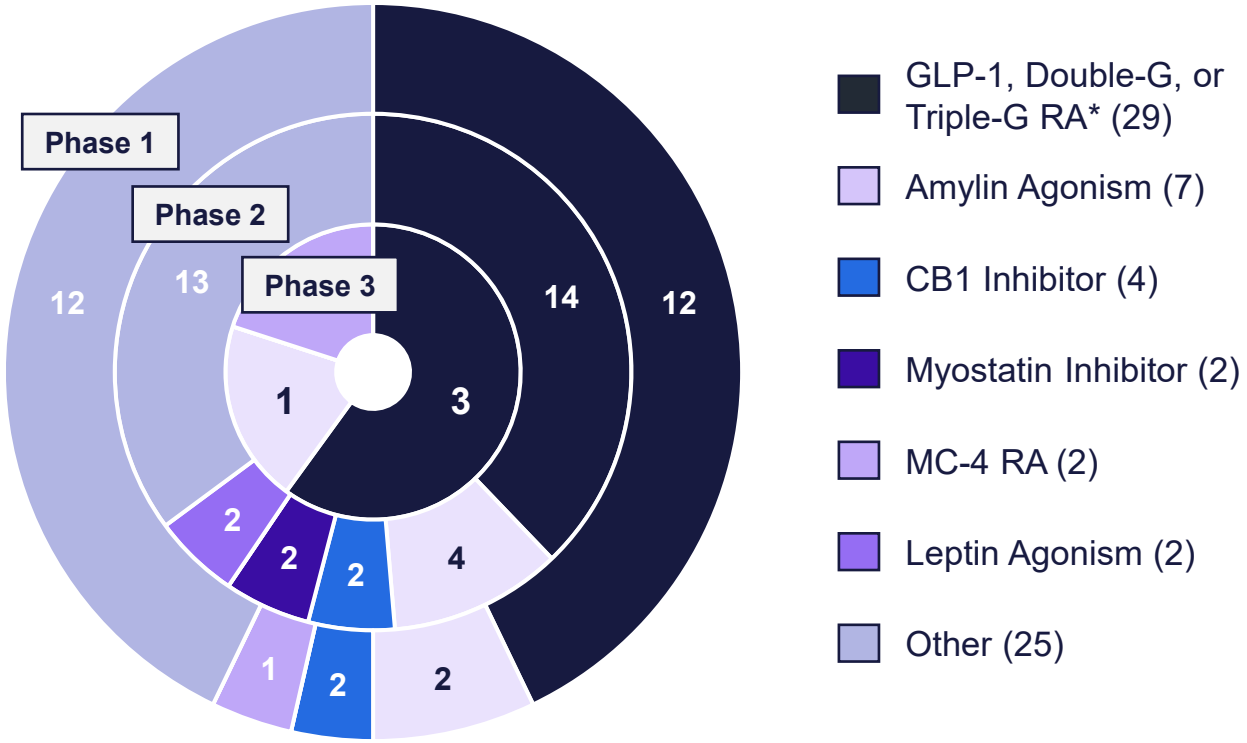
Nimacimab – Market Opportunity

Review of target product profile and primary research insights

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

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)

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)

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)