Nasdaq: SKYE

JANUARY 2026

Developing Innovative Medicines to Treat Obesity and Other Metabolic Diseases

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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:**
  13% weight-loss at 26-weeks which was significantly better than semaglutide alone (p=0.03) and no plateau at 26-weeks in Phase 2a study. 52-week data available in Q1, with potential for >20% weight loss representing a meaningful outcome.

- **Durable & quality weight loss:**
  Lower post-treatment rebound (~18.1% combo vs. ~49.8% sema-alone) and a favorable body-composition profile in Phase 2a study support use for maintenance after incretins and minimizing impact of weight regain.

- **Safe combo, titration-free:**
  No additive GI burden and 0% neuropsychiatric AEs in the combo arm in Phase 2a study; enables potential straightforward combination use across the incretin class.

- **Built to ride (not fight) the GLP-1 wave:**
  In a crowded incretin landscape, peripheral CB1 mechanism provides potential differentiation that is complementary to incretins.

- **Near term catalysts:**
  Additional 26-week data in combination setting from CBeyond; Additional clinical data & catalysts through 2026 including potential launch of Phase 2b combination study

Nimacimab Target Product Profile (TPP)

Opportunity across multiple treatment settings that adds clinically meaningful weight loss on top of GLP-1 therapy without adding tolerability burden and designed for chronic use.

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

Highest-priority candidates for combo nimacimab (with GLP-1 based therapy)

- **Severe obesity** (e.g., BMI ≥40 kg/m² or BMI ≥35 kg/m² with comorbidities) requiring greater total weight reduction (often ≥20% goal)
- **Incretin "plateau":** patients with attenuated incremental weight loss after sustained therapy where further dose escalation of incretin alone yields diminishing benefit
- **Inadequate response to incretin alone:** patients not meeting treatment goals despite adherence (e.g., ≤10% weight loss on GLP-1 therapy)
- **Dose-limiting tolerability:** patients unable to reach/maintain maximal incretin dose due to GI intolerance or other adverse effects

Target TPP

- **Target Efficacy:** +5-8% weight loss on top of incretin-based therapy.
- **Target Safety/Tolerability:** No meaningful increase in GI burden when combined with incretin-based therapy; No neuropsychiatric signal
- **Target Dosing & Delivery:** Ideally subcutaneous QM dosing, or QW dosing of nimacimab with co-administration of incretin-based therapy.
- **Target Durability:** Minimal weight regain following treatment discontinuation allowing for potential treatment cycling.

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

Presentation Overview

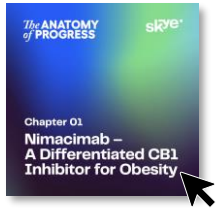
1.0

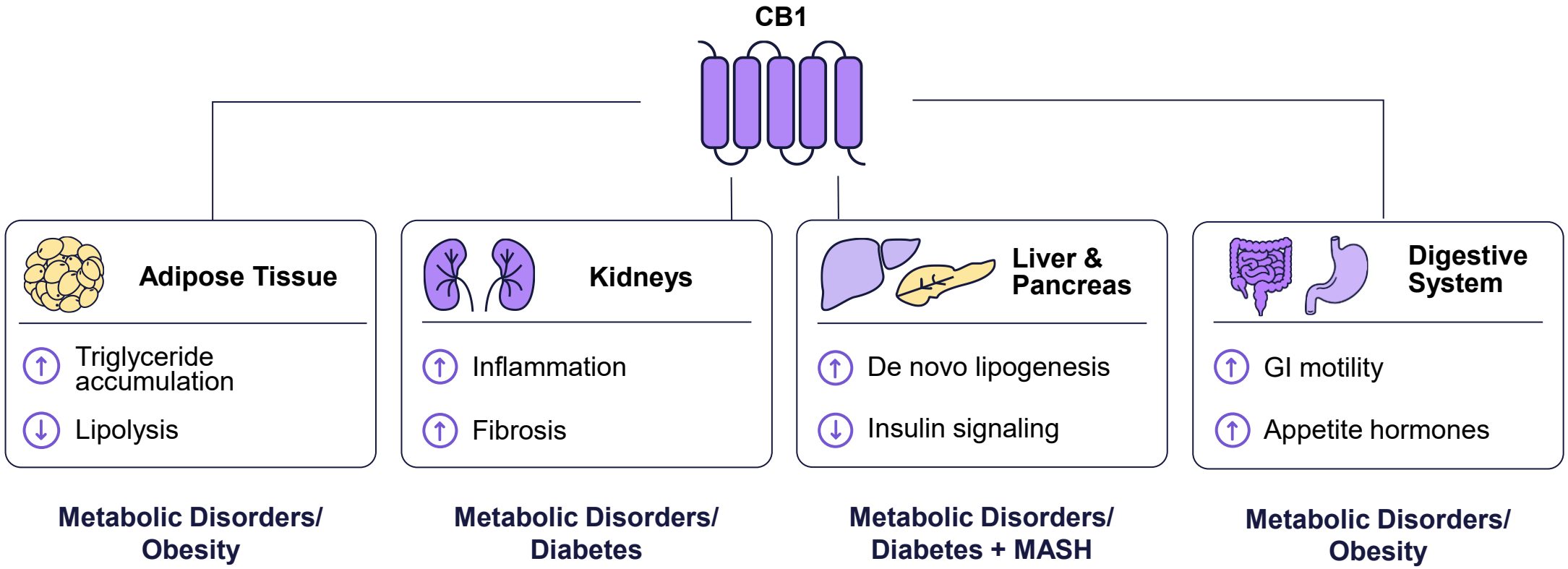
Nimacimab

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

Peripheral CB1 Signaling: Metabolic-focused Targets

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





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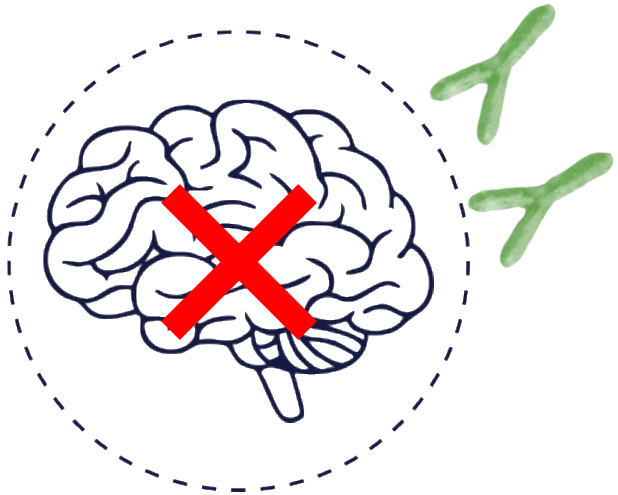
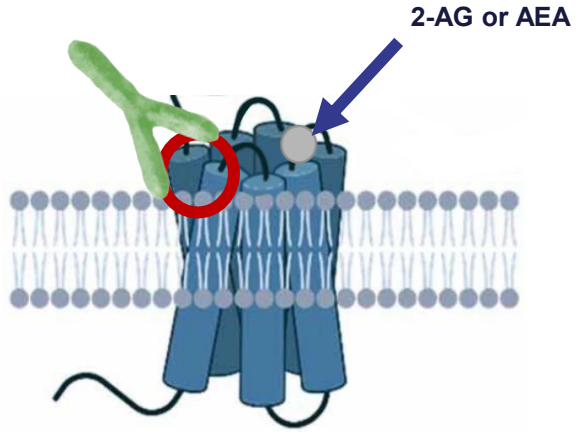
Nimacimab is Differentiated from Small Molecule CB1 Inhibitors

Peripheral Restriction



Significantly less brain penetration than small molecules currently in development

Negative Allosteric Modulator

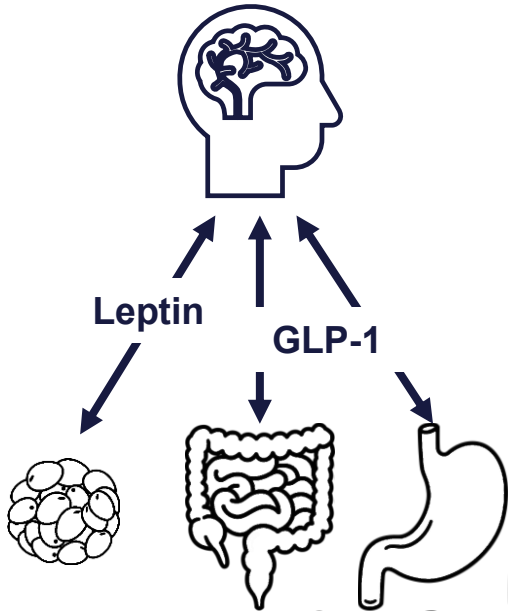


Unlike small molecules currently in development, **nimacimab retains potency** even in the presence of competition

Four Mechanistic Pillars of Nimacimab

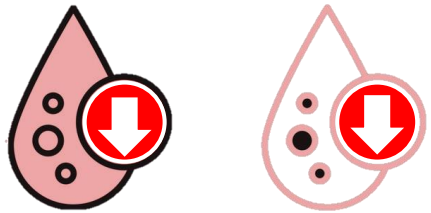
01

Peripheral Modulation of Appetite Regulating Hormones



02

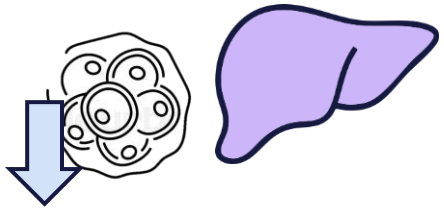
Improvement and Restoration of Glycemic Control



Reduced fasting insulin and improved glucose control

03

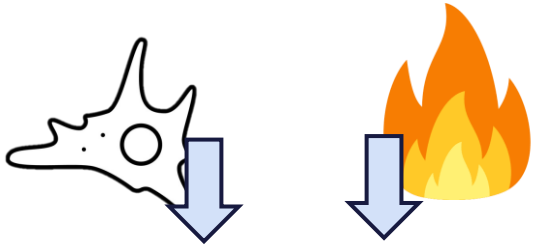
Enhanced Lipid Metabolism



Decreased steatosis and serum cholesterol

04

Reduction of Obesity-Induced Inflammation



Decreased inflammation and fibrosis markers

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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

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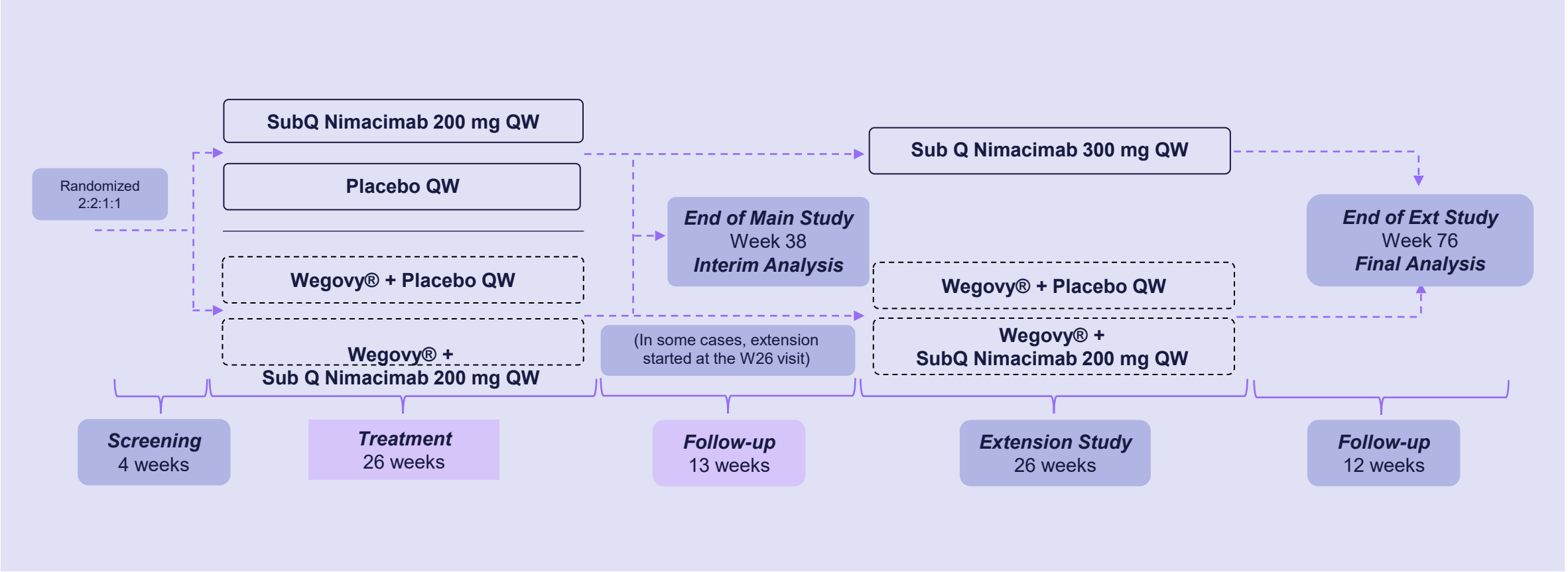
2.0

Review of Outcomes in Phase 2a Clinical Trial

CBeyond

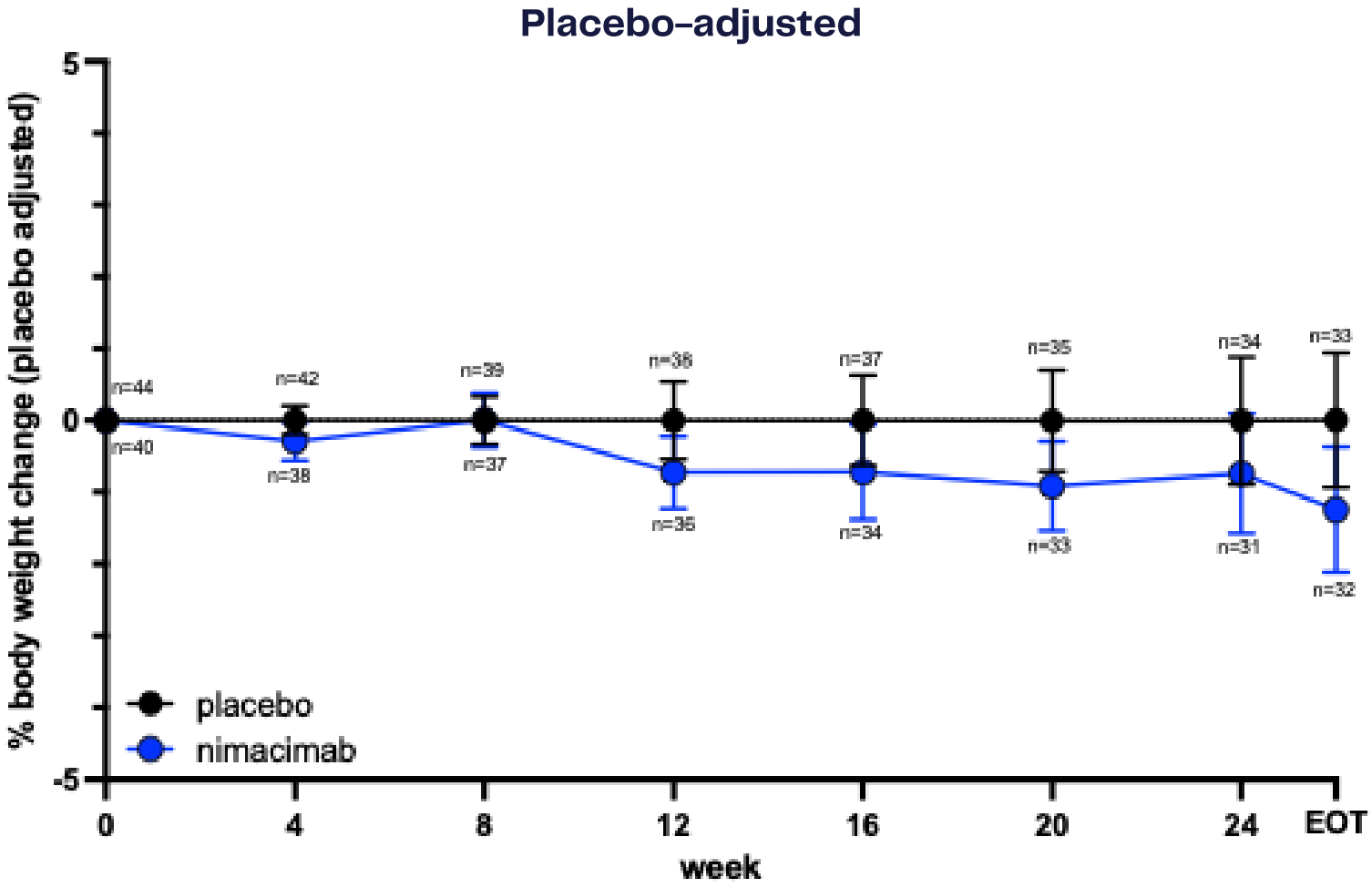
CBeyond Phase 2a Clinical Trial Design for Proof of Concept

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

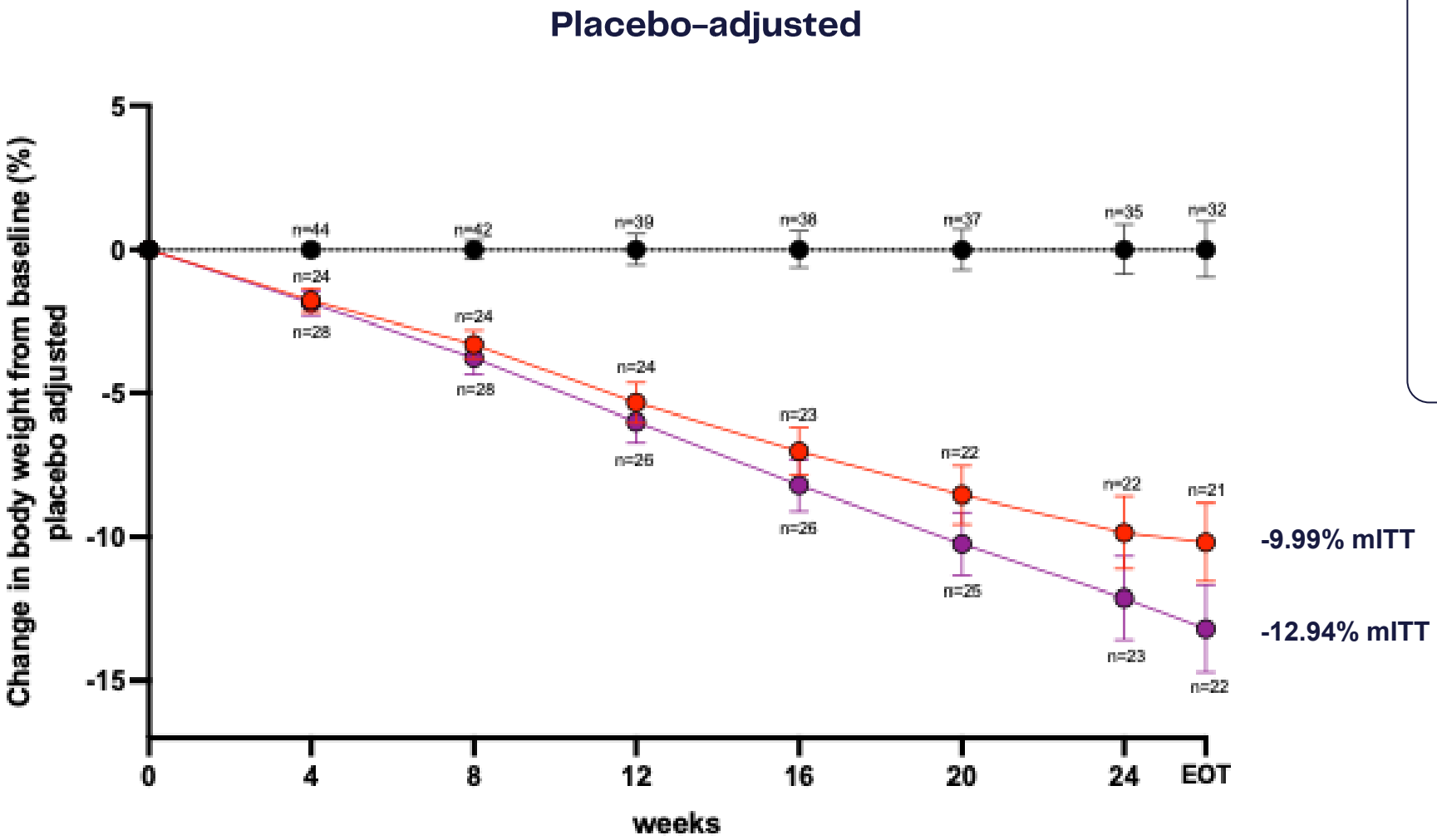


-1.26% mITT

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.

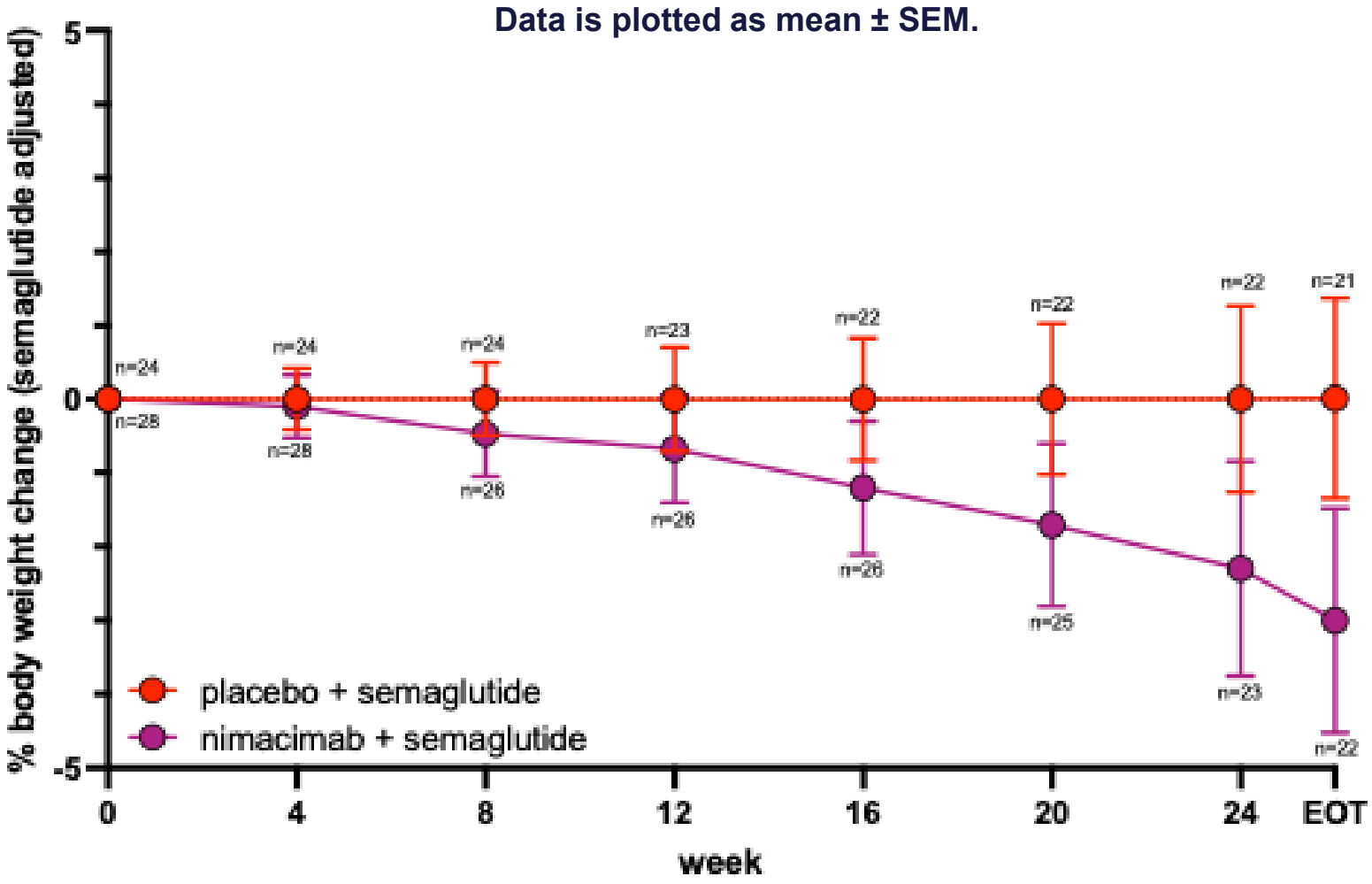
Increased Weight Loss in Combination with Semaglutide



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



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

-2.95% mITT

CBeyond

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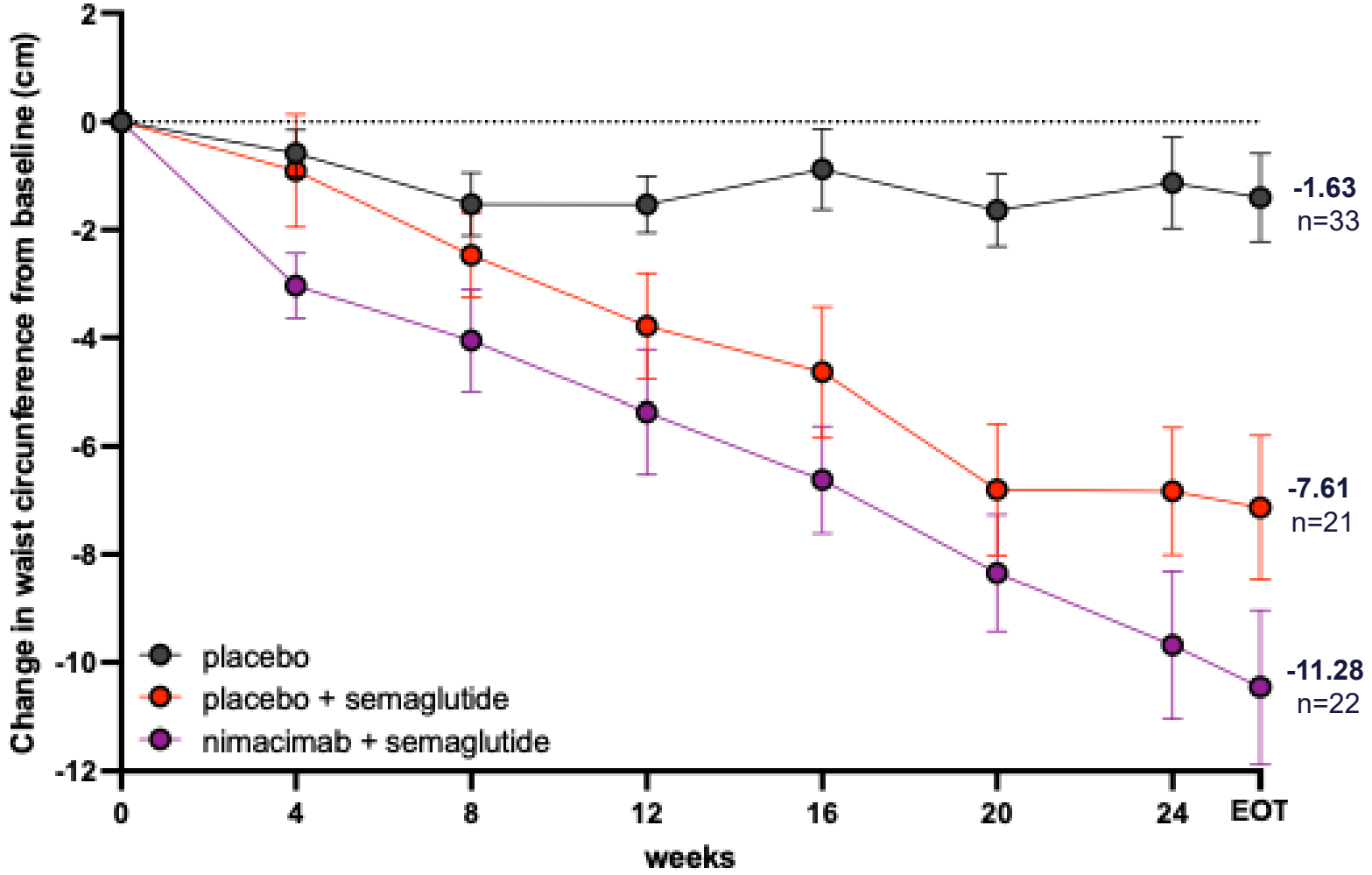
Change in Waist Circumference with Combo Treatment



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

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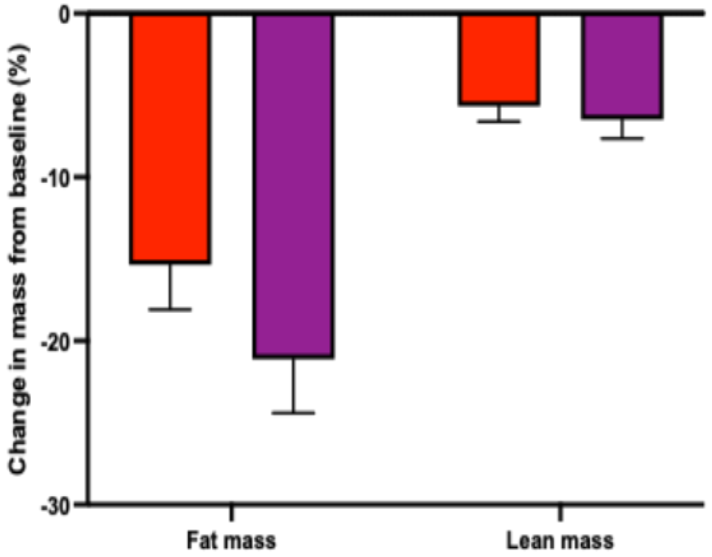
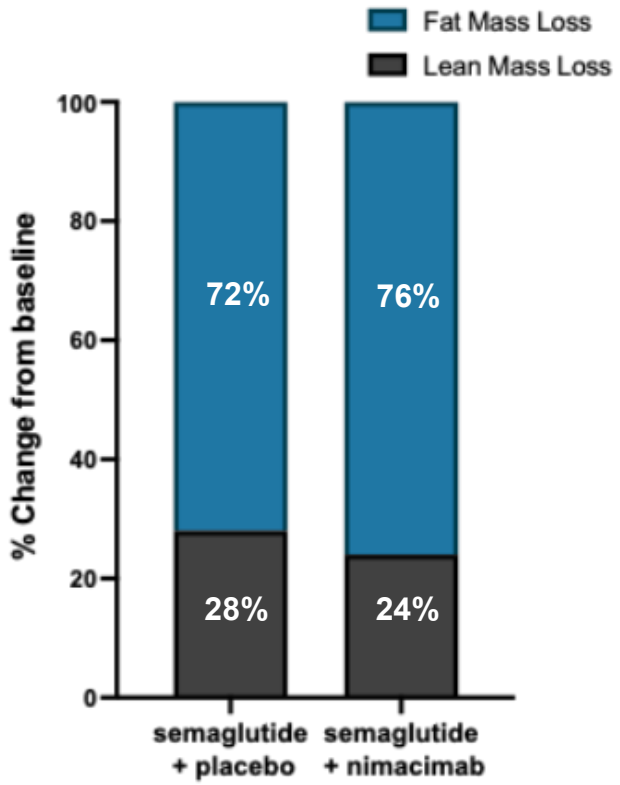
Lean to Fat Mass Ratio Improves with Nimacimab-Semaglutide Combination



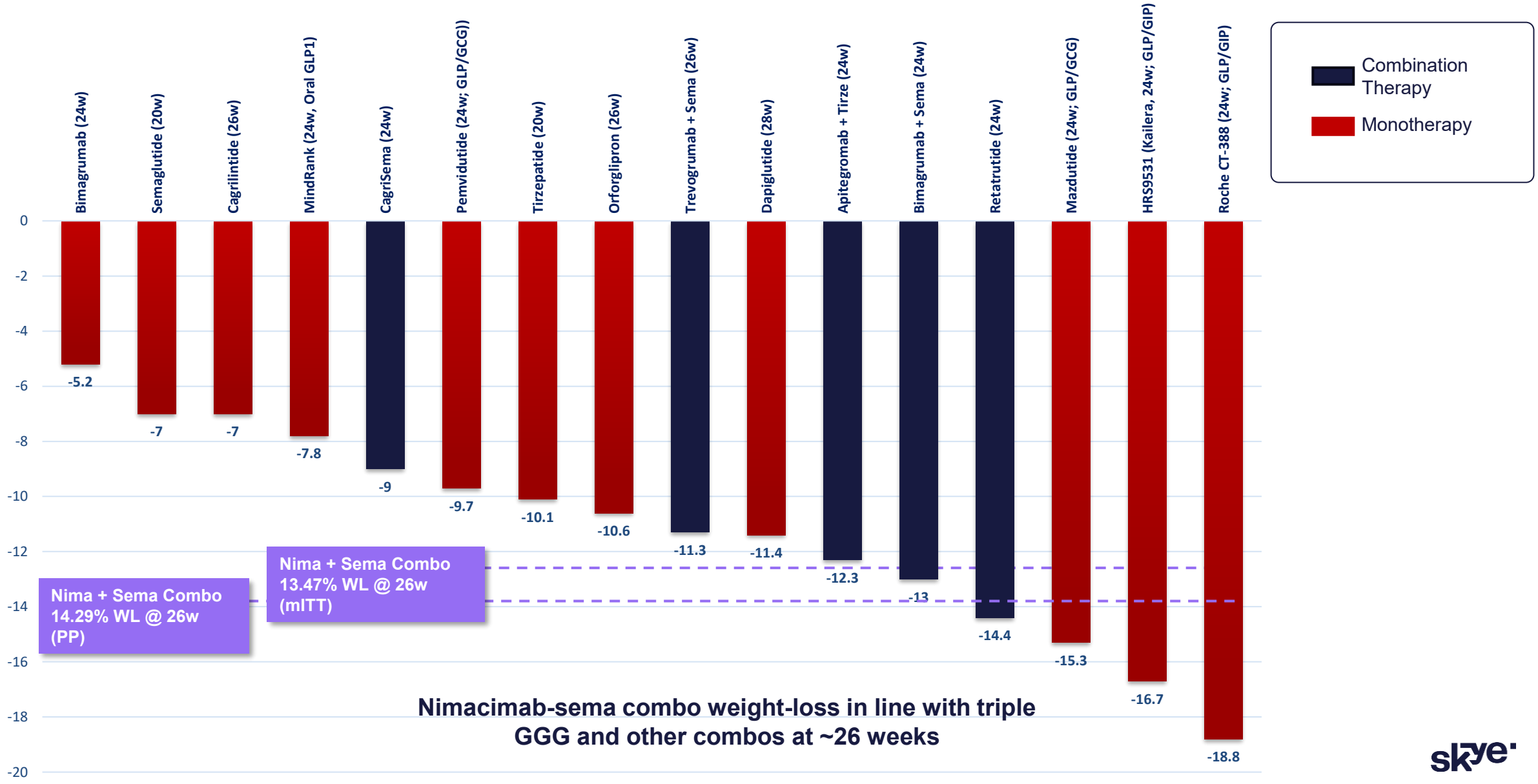


Change in Lean to Fat Mass Ratio with Weight Loss

	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**

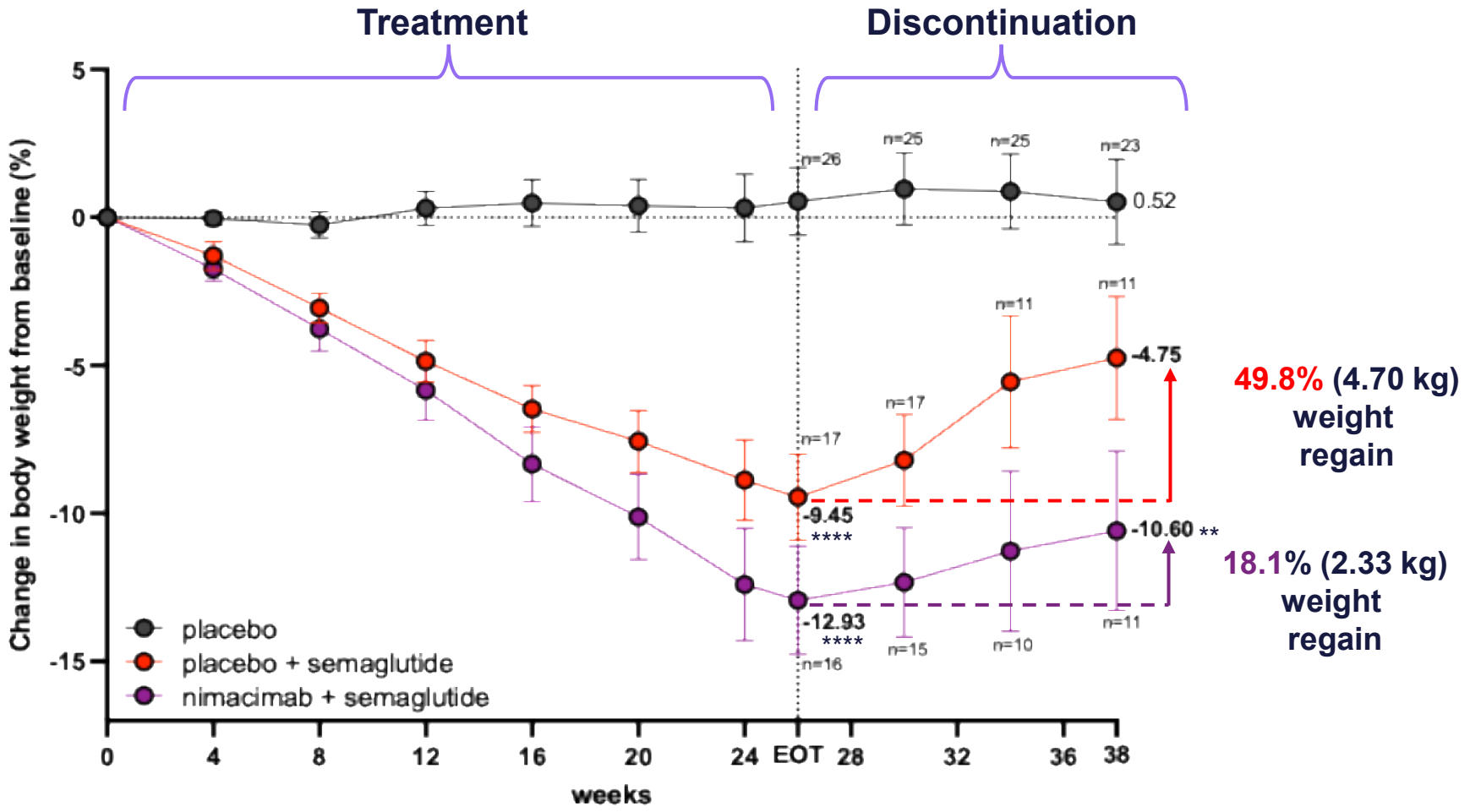
Nimacimab + semaglutide increases weight loss by ~30% & fat loss by 37% compared to semaglutide alone

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



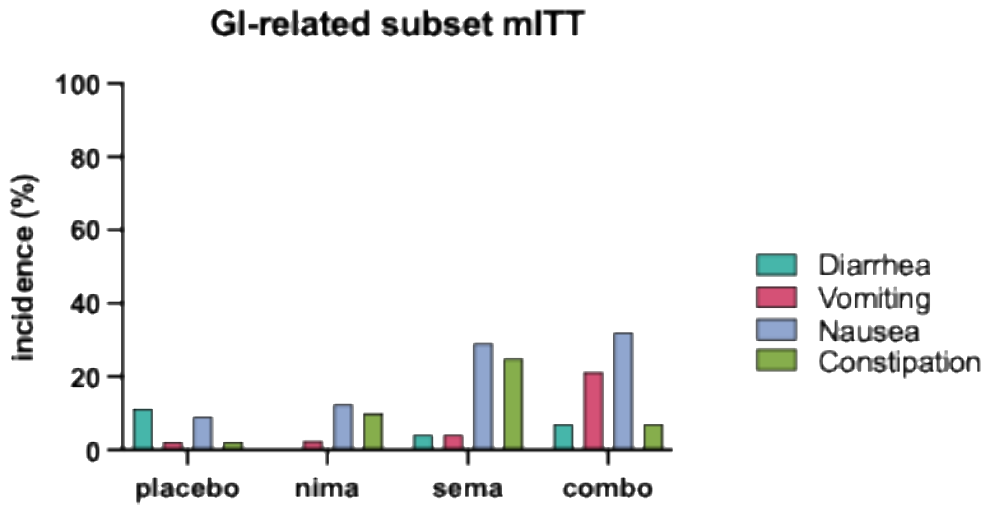
Nimacimab-sema combo weight-loss in line with triple GGG and other combos at ~26 weeks

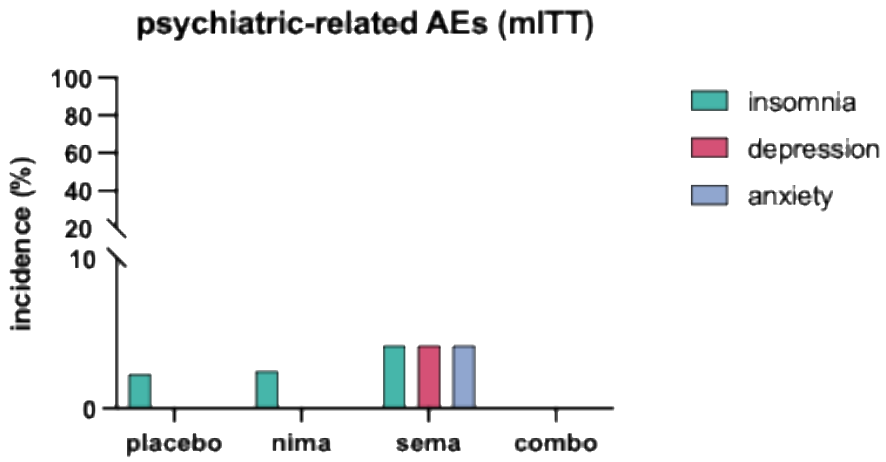
Nimacimab Reduces Weight Regain



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.

CBeyond Phase 2a Topline Data – Key Takeaways

Nimacimab demonstrated additive efficacy in combination, 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 potential **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.

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2.1

What We Learned From

What We Learned from CBeyond

Data from CBeyond, together with our preclinical models, suggest:

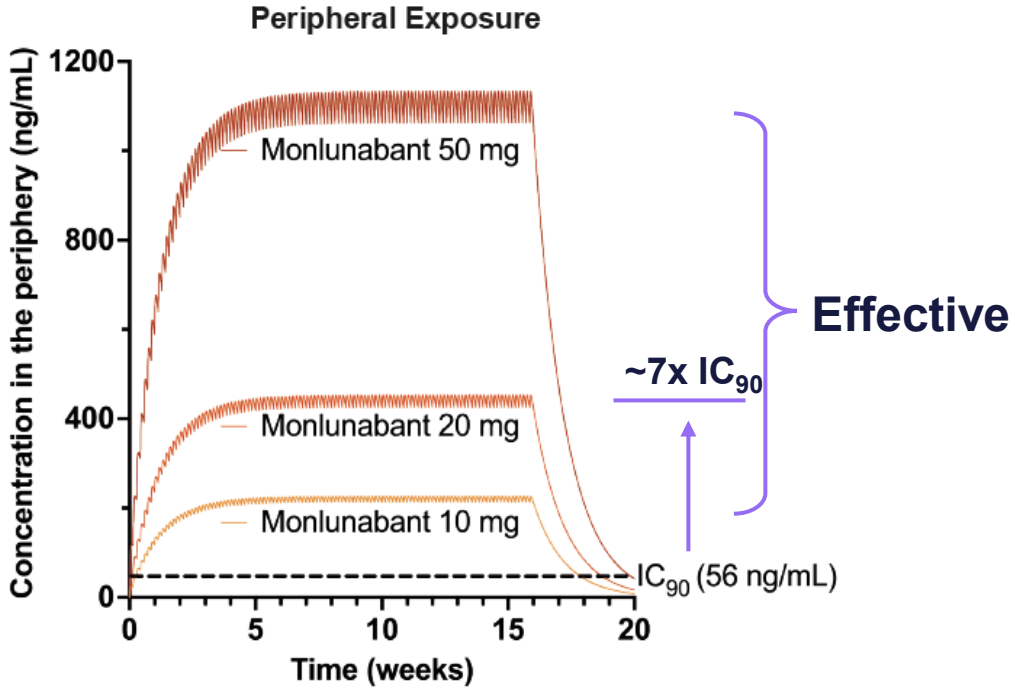
1. Concentration in the serum does not equal concentration in the tissues, and achieving a higher serum concentration and steady-state sooner through a loading dose can potentially improve response.

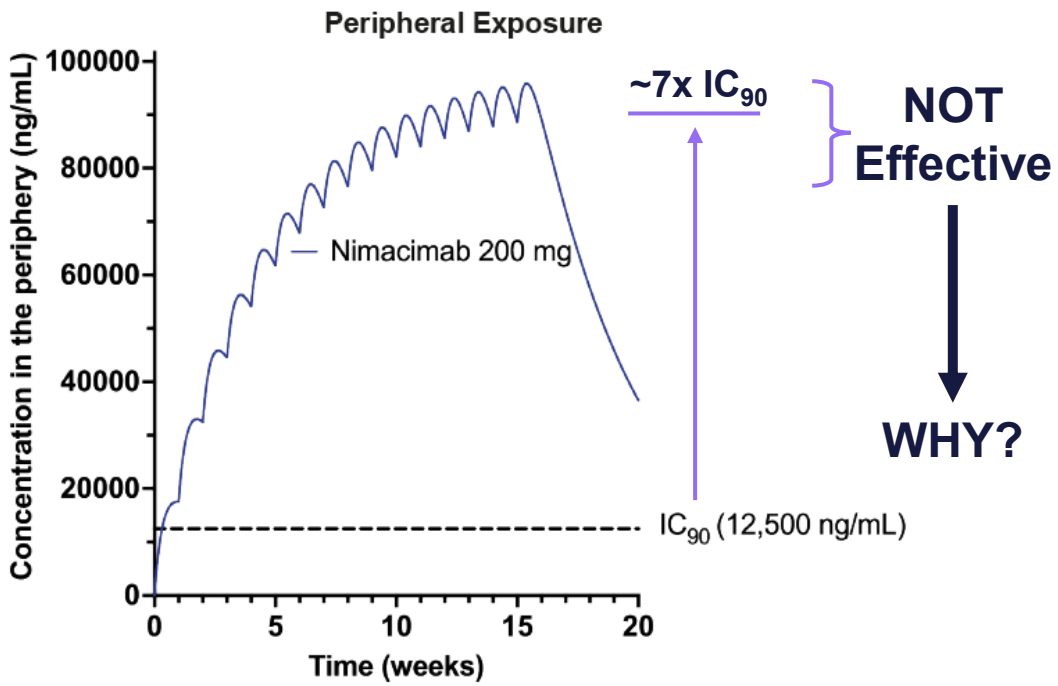
2. Nimacimab can be dosed significantly higher and drive additional weight loss as both a monotherapy and in combination with semaglutide.

3. Compliance and retention are priorities for the success of the next study. We will budget to include weekly on-site visits for dosing and implement highly competitive retention programs.

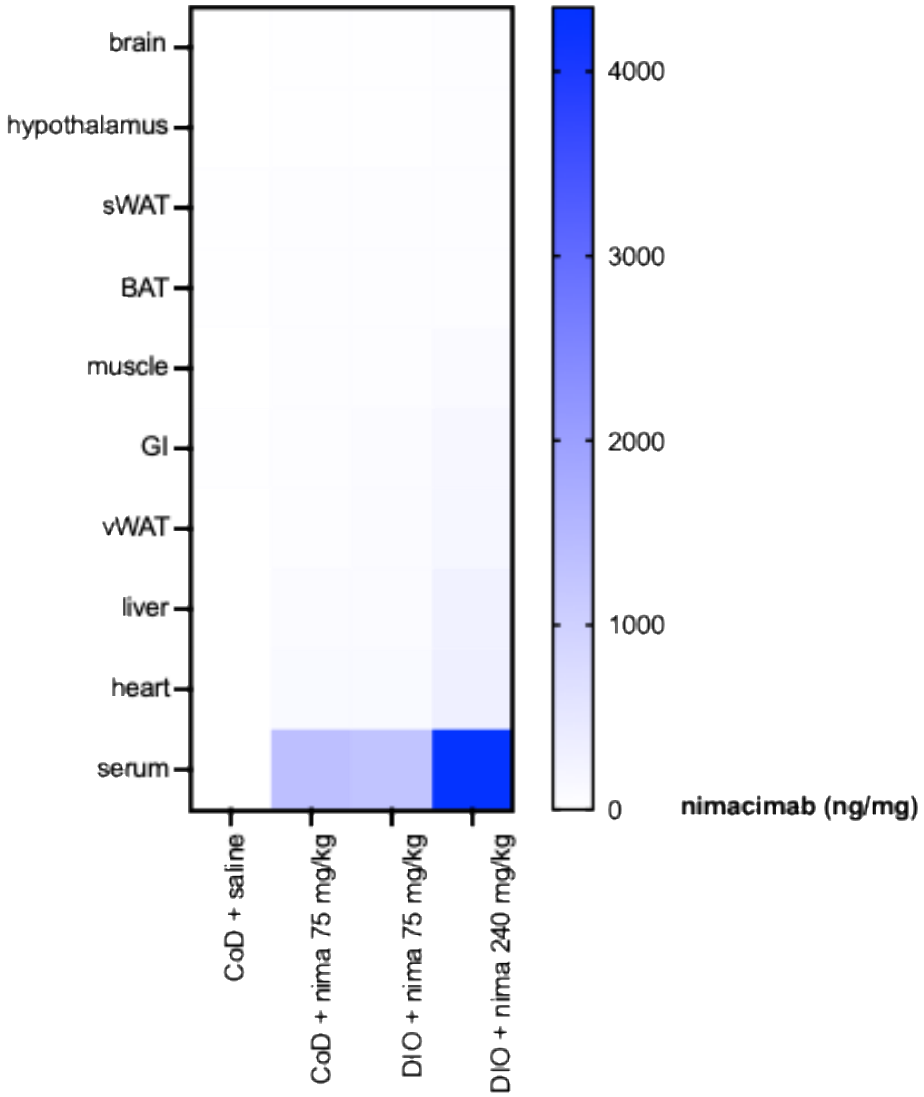
Initial rationale for CBeyond Dosing

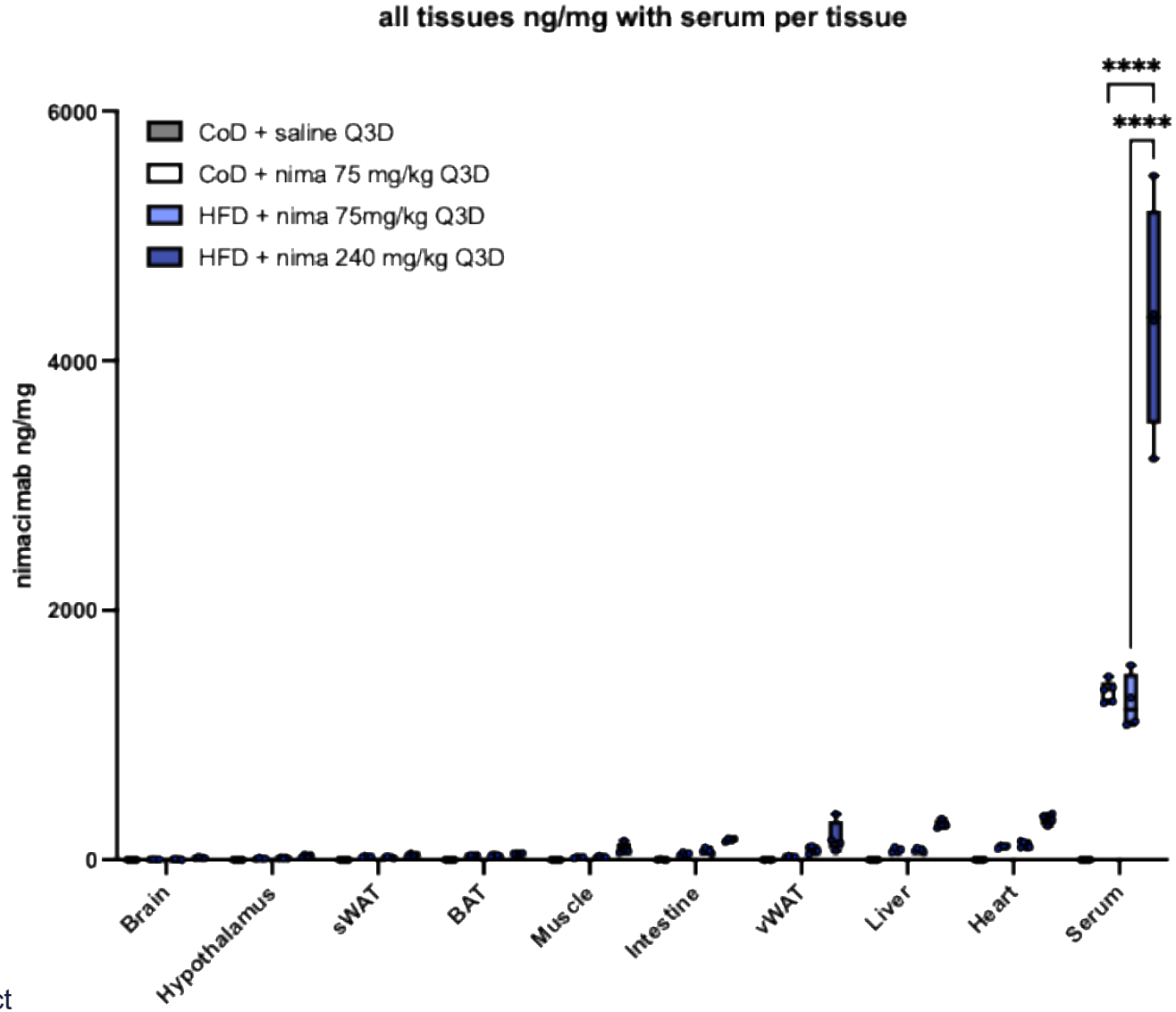
- Before pharmacodynamic data (clinical weight loss or DIO model), Skye developed clinical PK models (Ph1 data) to understand dosing options
- IC_{90} (serum) was used as a surrogate for target engagement
- Similar IC_{90} at $C_{max, ss}$ with 20mg monlunabant and 200mg nimacimab





Nimacimab biodistribution in lean and obese mice

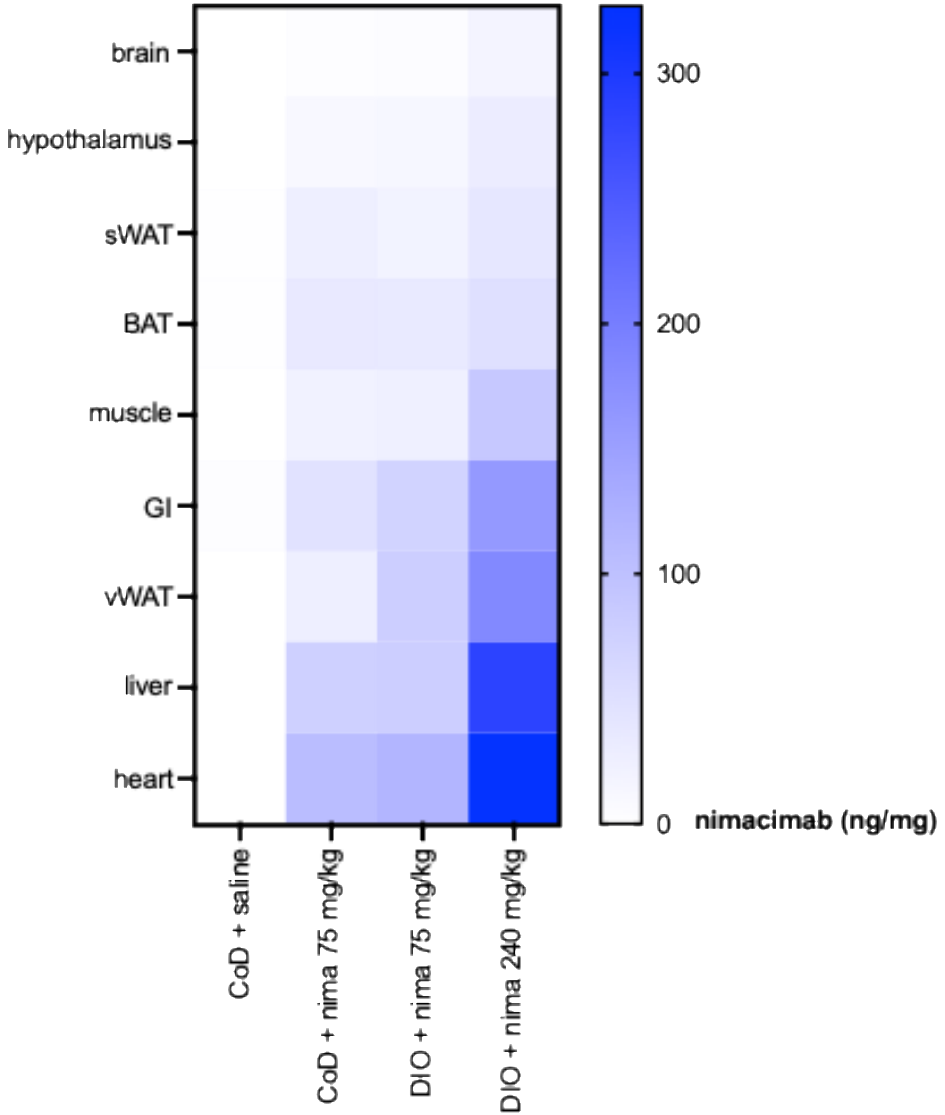


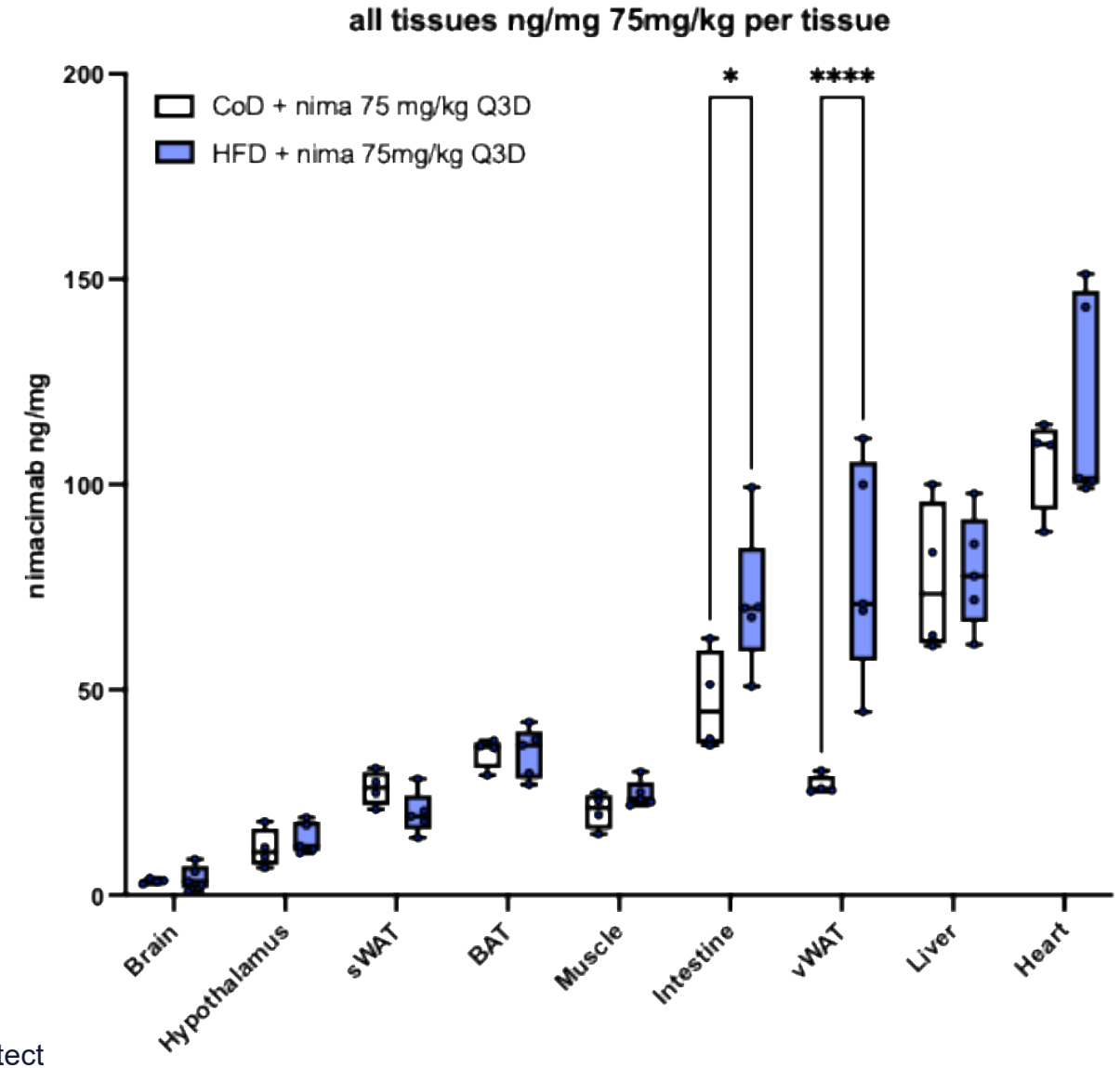


Human IgG ELISA kit (Ray Biotech, catalog# ELH-IGG) was used to detect nimacimab in tissue homogenates. Results are reported as ng of nimacimab/mg of tissue. N=4-5 per group.

2-way ANOVA followed by Tukey's multiple comparison tests per tissue.

Nimacimab tissue biodistribution in lean and obese mice





Human IgG ELISA kit (Ray Biotech, catalog# ELH-IGG) was used to detect nimacimab in tissue homogenates. Results are reported as ng of nimacimab/mg of tissue. N=4-5 per group.

2-way ANOVA followed by Tukey's multiple comparison tests per tissue.

Beyond the Serum: CB1 Inhibition in Peripheral Tissues

Small molecule vs antibody-based CB1 inhibitors demonstrate differential distribution in peripheral tissues

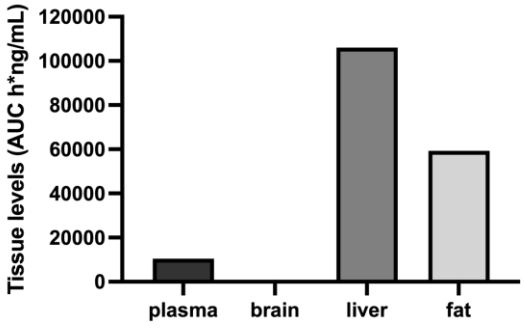
Small molecule

"S-MRI-1867 exhibited high exposure in most tissues, with concentrations ranging from 2 to 31 times greater than in plasma"

Adapted from Padilha EC. et. al. Biomed Pharmacother. 2023 Dec;168:115178

"Tissue distribution of Rimonabant preferentially accumulated in the liver and the adipose tissue"

Muller T. et. al. Int J Mol Sci. 2022 Mar 8;23(6):2923

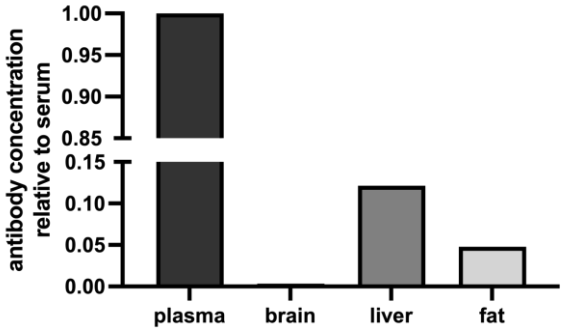


Parameter	Plasma	Brain	Liver	Fat
Tissue/Plasma AUC_{0-last} Ratio	-	0.05	10	6

Antibody

Antibody distribution into tissues is ~4–16% of the plasma concentration for most tissues

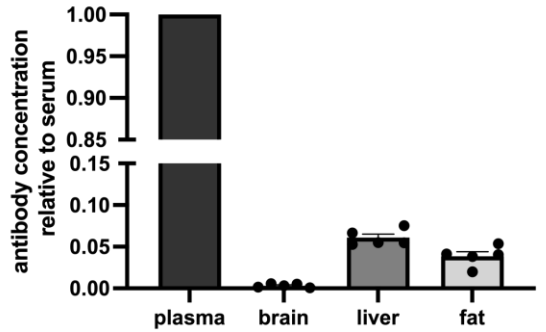
Shah, D. K., & Betts, A. M. *mAbs*, 2013 *5*(2), 297–305



Parameter	Plasma	Brain	Liver	Fat
Tissue/Plasma Ratio	1	0.0035	0.12	0.048

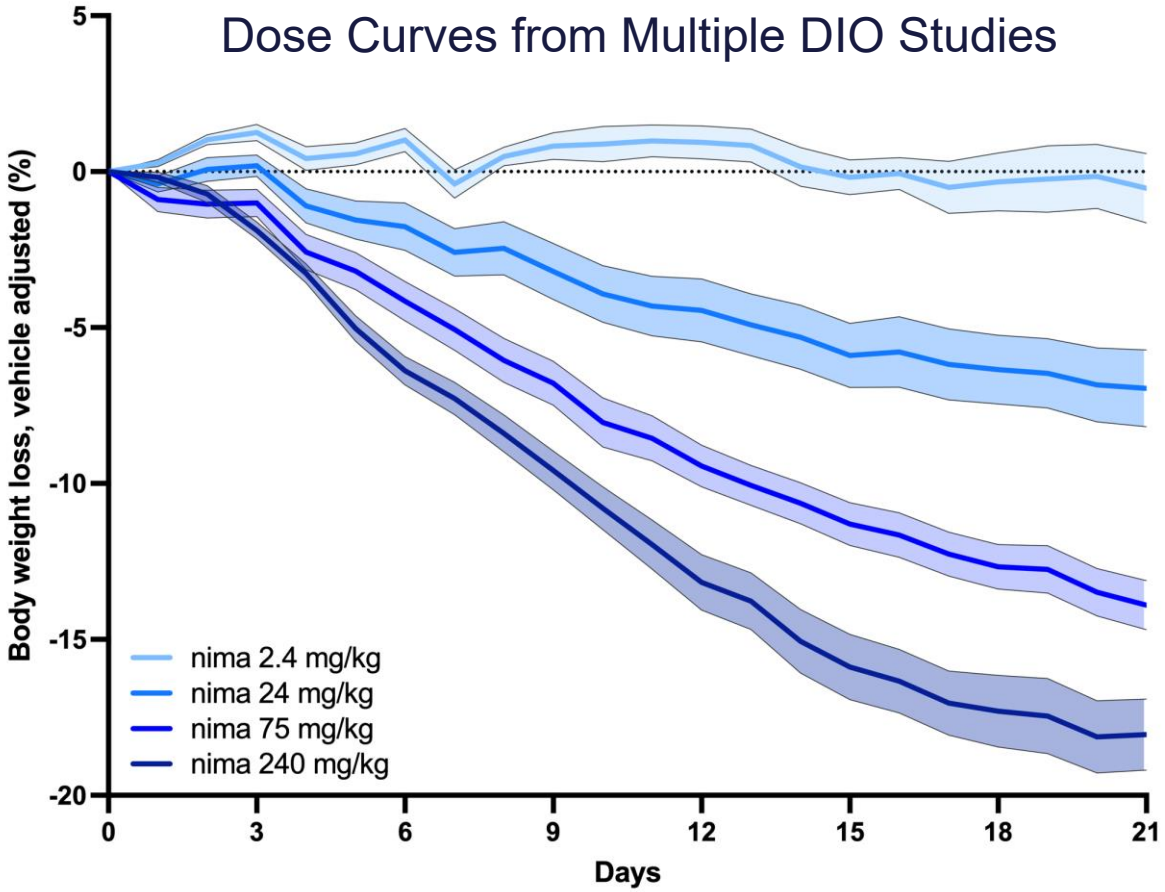
Skye BioD mouse data*

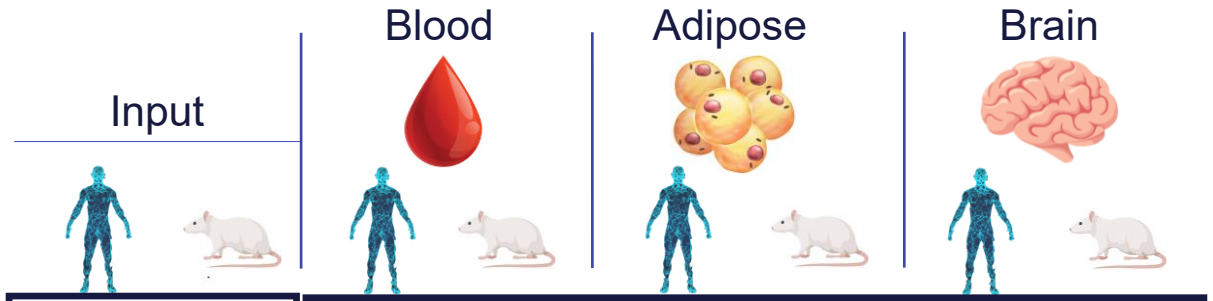
*this is data from the previous slide – ratios are derived tissue vs serum



Parameter	Plasma	Brain	Liver	Fat
Tissue/Plasma Ratio	1	0.003	0.06	0.04

Compartmental Analysis: Activity associated with CB1 inhibition in peripheral tissue





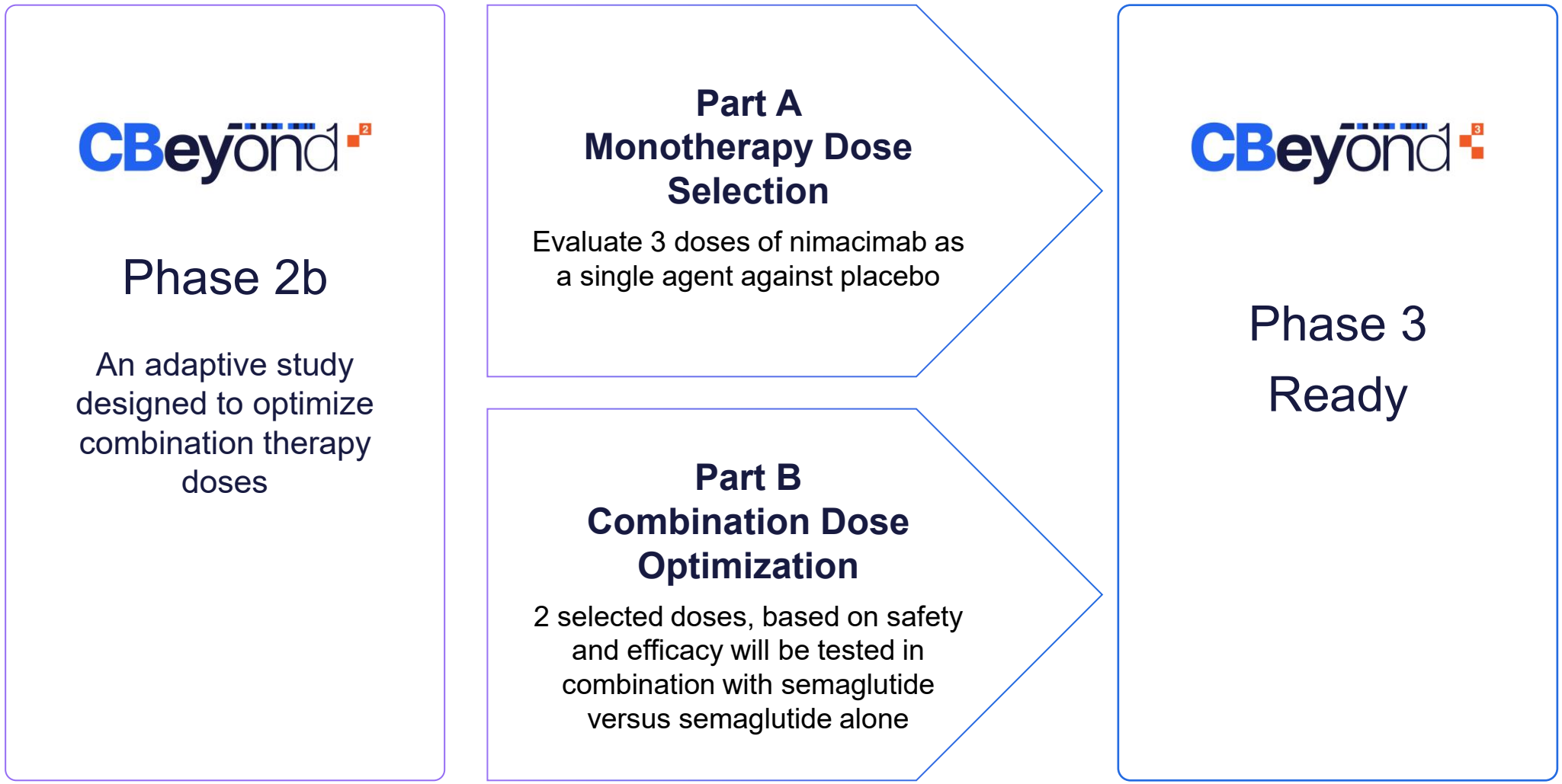
dose		nimacimab concentration (relative to IC_{90})					
200 mg dose	24 mg/kg	7.3x	6.4x	0.4x	0.3x	0.03x	0.02x
600 mg dose	75 mg/kg	22x	20x	1.1x	0.9x	0.1x	0.1x

Nimacimab concentration in serum based on Ctrough at week 26 (human Ph1) and day 24 (DIO mouse). Concentration in adipose tissue used serum:adipose ratio derived from NHP bioD study and published human data (human) and Skye bioD DIO data (mouse). Concentration in brain used serum:brain ratio derived from more conservative published human data (human) and Skye bioD DIO data (mouse).

3.0

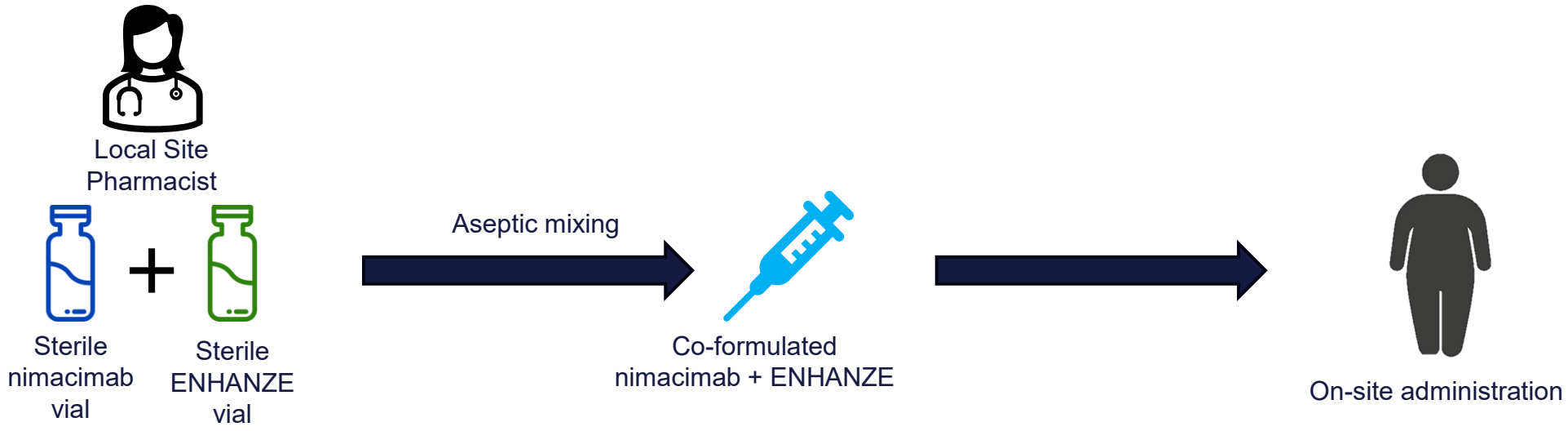
Clinical Strategy
Phase 2 Adaptive Design Dose-Ranging Study

Path to the Phase 3 Pivotal Study



“Mix-and-Deliver” Approach – Ensuring Compliance

- In the potential Phase 2b study, all patients will visit the site for their weekly injections.
- These mandatory weekly visits will ensure compliance, while also allowing for ENHANZE and nimacimab to be co-formulated on-site prior to injection.
- This “mix-and-deliver” approach reduces need for co-formulation development prior to Phase 2b study start.
- Compatibility and in-use stability (CIUS) studies will be completed to support ‘mix-and-deliver’ approach to use the co-formulated product as a Category 1 Compounded Sterile Preparation.



3.1

Regulatory Strategy **Combination Approval, Monotherapy Opportunity**

Combination Regulatory Strategy

- Phase 2b adaptive design is meant to satisfy the agency need to evaluate contribution of parts between nimacimab and semaglutide.
- If acceptable, we believe the pivotal Phase 3 design would only require a two-arm study comparing combination of nimacimab+semaglutide versus placebo.
- There is precedent for this approach as QSYMIA was approved on the basis of studies evaluating the combination of phentermine+topiramate versus placebo.

Monotherapy Opportunities

- Nimacimab has opportunity to fill gaps in the 2nd line therapy space after patients fail NuSH therapies (i.e. GLP1, GLP1/GIP, or amylin).
- If nimacimab alone can demonstrate at least +8% pbo-adjusted weight loss then it could be an ideal 2nd line therapy
- Alternatively, nimacimab has the potential as a maintenance therapy, using a similar regulatory path to orlistat (Xenical).
- Xenical Label:

----------INDICATIONS AND USAGE ----------

- XENICAL is a reversible inhibitor of gastrointestinal lipases indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. (1)
- XENICAL is also indicated to reduce the risk for weight regain after prior weight loss. (1)

4.0

Financial Overview

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 and cost to complete the manufacturing for the Phase 2b
- Ongoing strategic investments in scaling manufacturing, operations, R&D, and advancing the clinical pipeline

Stock Information

Listed: Nasdaq	**SKYE**
Stock Price[1]	**$0.98**
Shares Outstanding[2]	**32.1M**
Shares Fully Diluted[2]	**47.9M**
Cash, Cash Equivalents & Short-term Investments [3]	**$35.3M**
Market Cap (inclusive of PFWs)[1]	**$37.6M**
Avg. 3-Mo. Daily Trading Volume[3]	**858K**

[1] Jan 9/26 [2] Nov 11/25 [3] Sep 30/25

Multiple Anticipated Catalysts Over the Next 12 Months

Q1 2026	Q2 2026	H2 2026	Q1 2027
❑ CBeyond Interim Extension Data	❑ CBeyond Topline Extension Data	❑ CBeyond^2 Phase 2b Study Initiation	❑ CBeyond^2 Part 1 Study Enrollment Complete
❑ FDA Type C Meeting			

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!

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

Please learn more or contact us at:

ir@skyebioscience.com

+1 (858) 410-0266

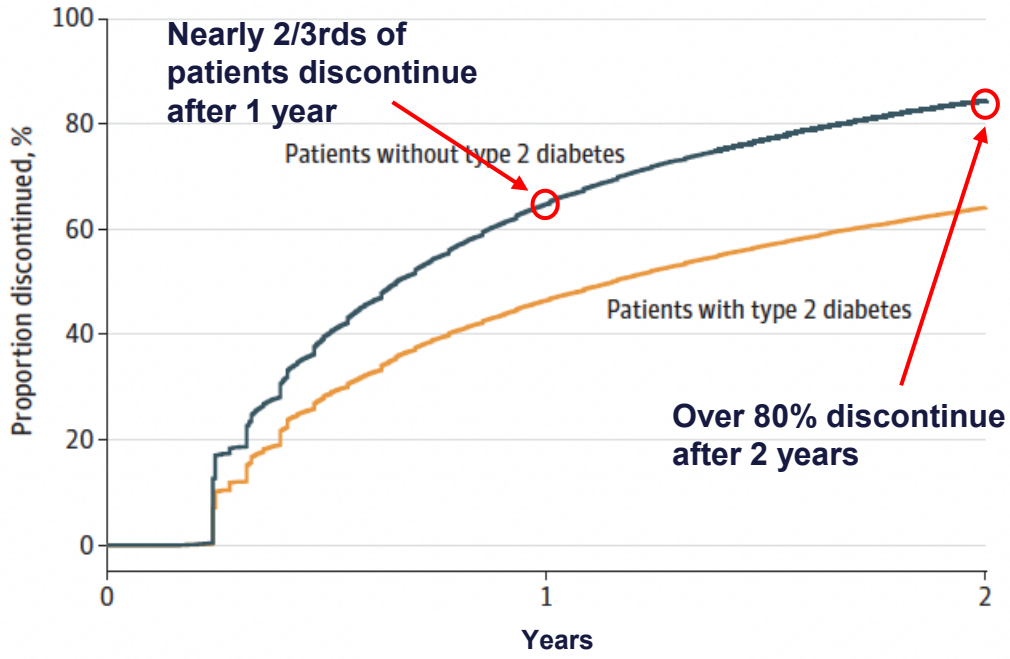
5.0

Appendix

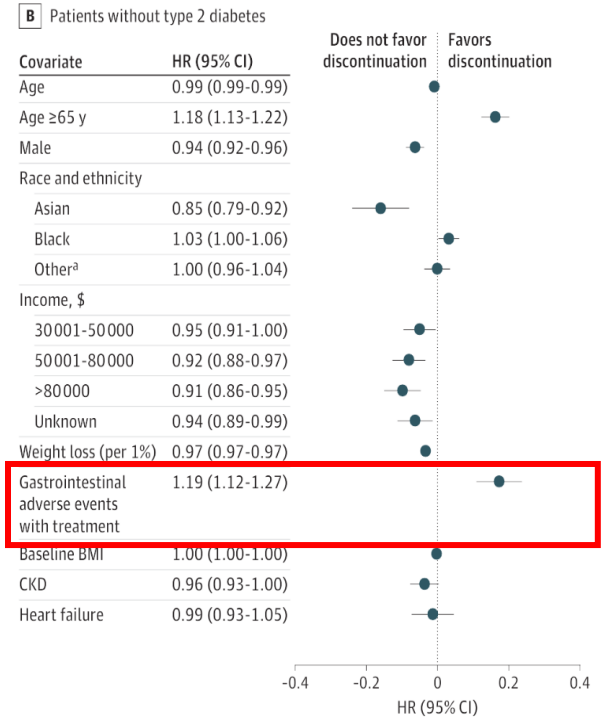
Pattern of GLP-1 Discontinuation

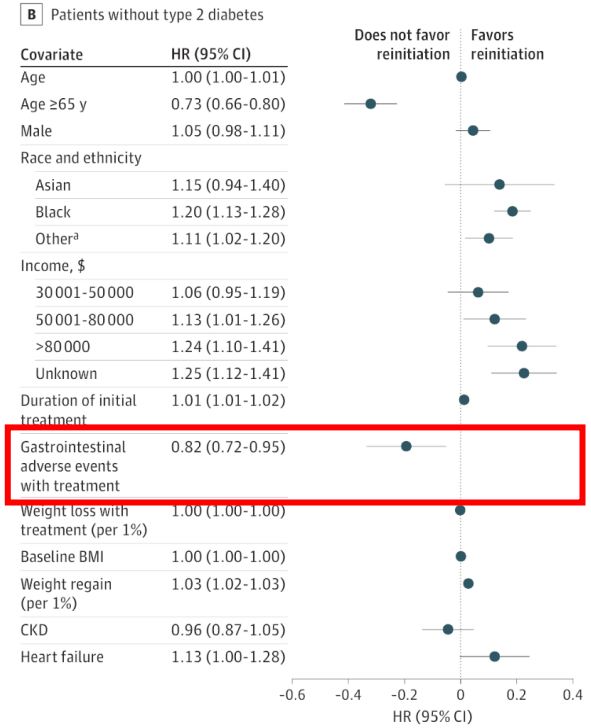
Most adults with overweight or obesity discontinue GLP–1 RA therapy within one year

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

5.1

Nimacimab – Preclinical

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

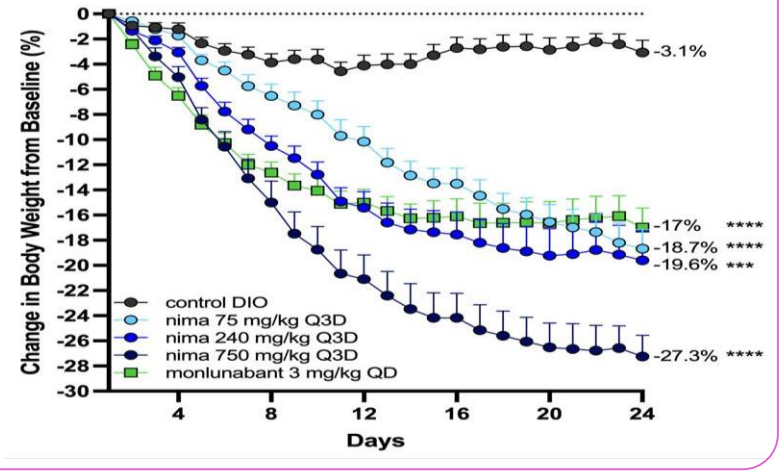
Diet-induced Obesity Model Data Characterizes the Ability of Nimacimab to Induce Meaningful Weight Loss and Other Pertinent Outcomes as a Monotherapy and Combination Therapeutic

Preclinical Data: Vital Insights & Validation of Nimacimab

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

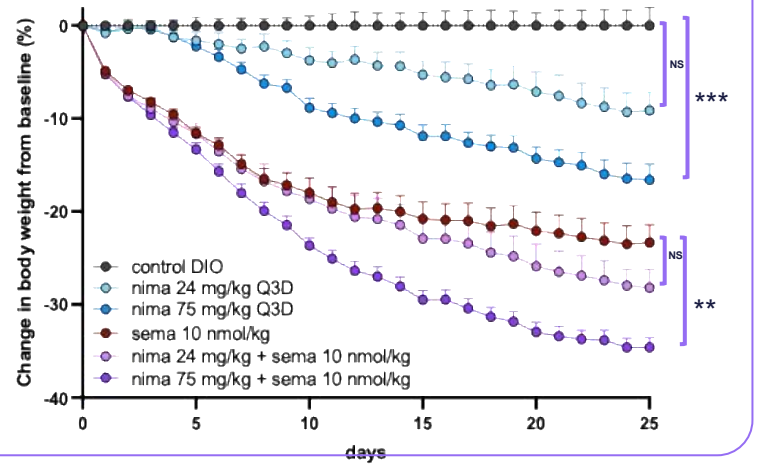
Potential Efficacy Advantage vs Small-Molecule CB1 Inhibitor

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



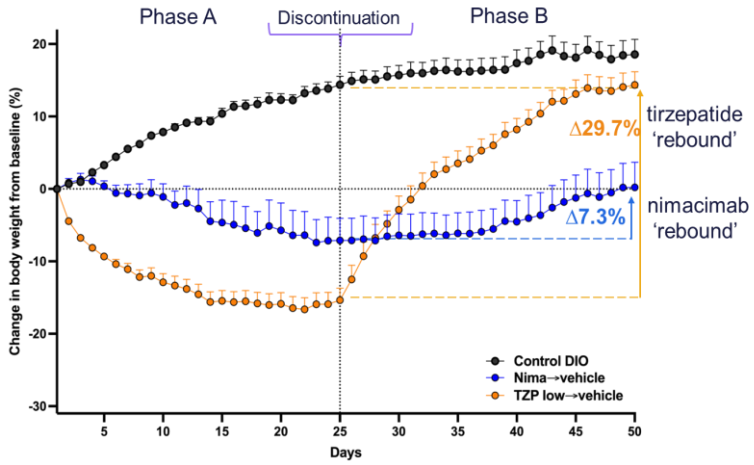
Increasing Nimacimab Unlocks Combination with Incretin

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



Potential Efficacy Advantage vs Small-Molecule CB1 Inhibitor

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

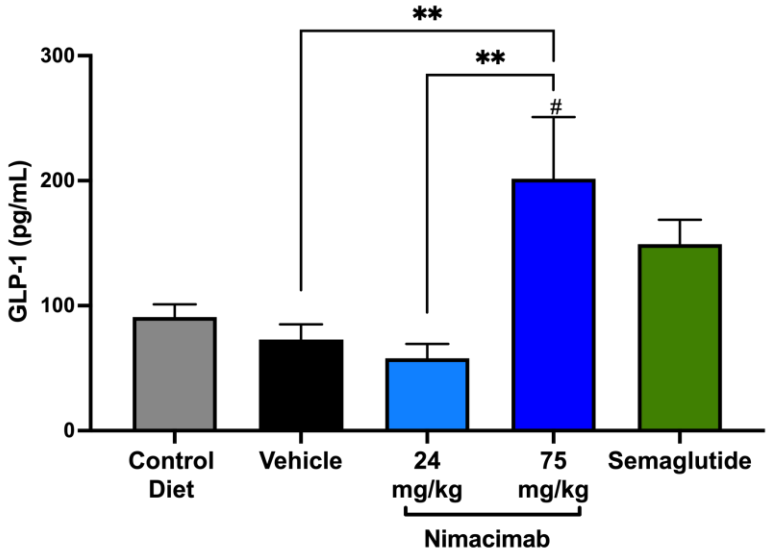


Nimacimab, a highly-restricted CB1-inhibiting antibody, displays attributes that indicate superiority within the class and characterize its potential for a broad TPP encompassing mono, maintenance, and combination therapies

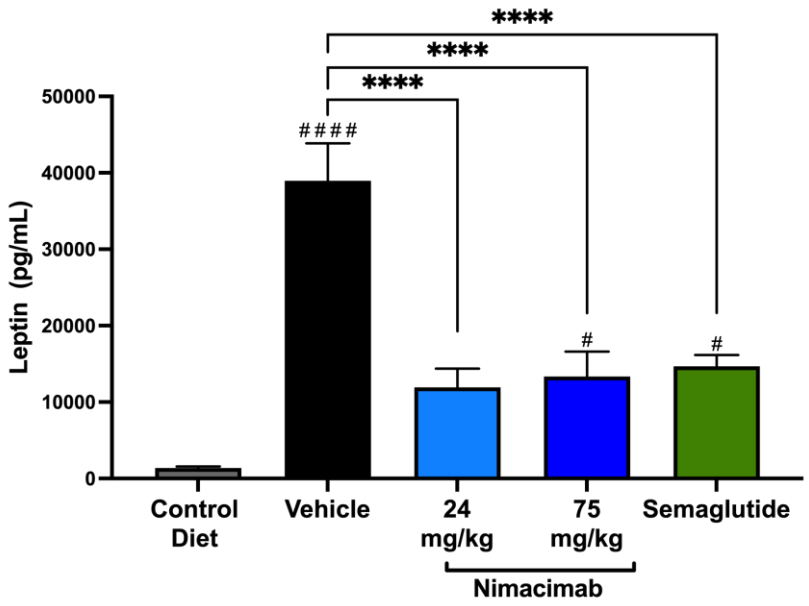
Productive Modulation of Key Hormones with Nimacimab

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

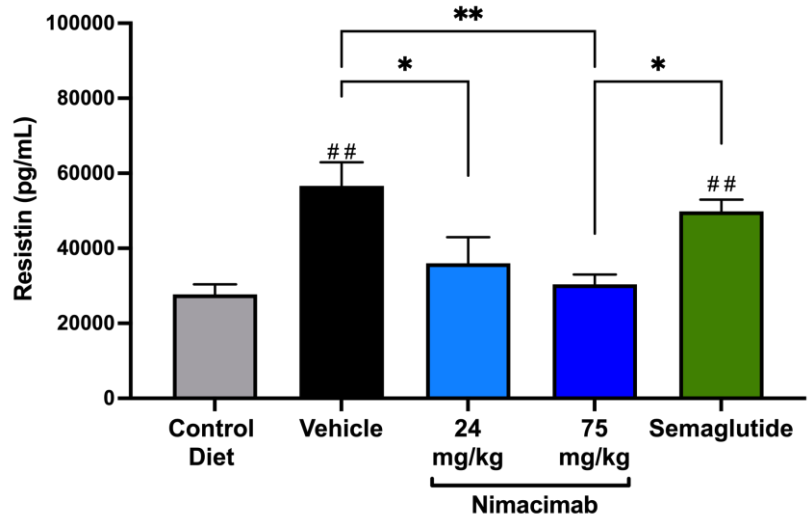
GLP-1



Leptin

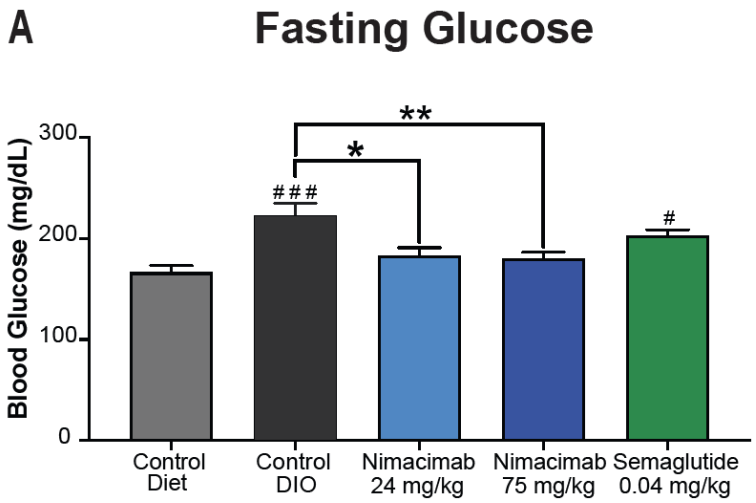


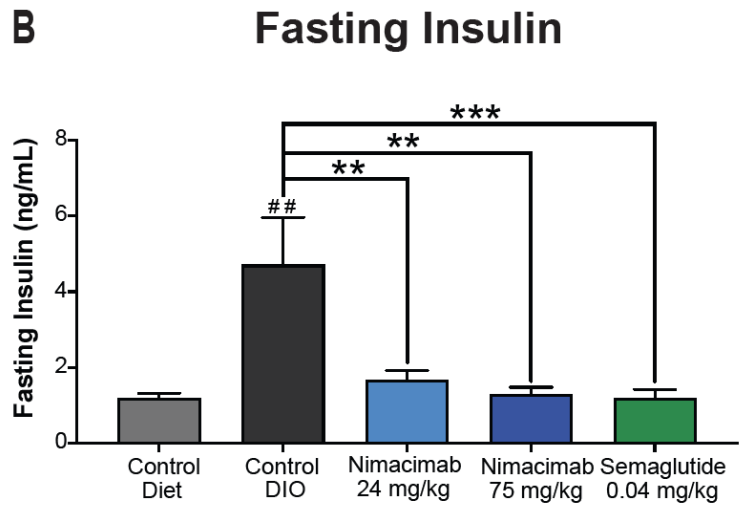
Resistin

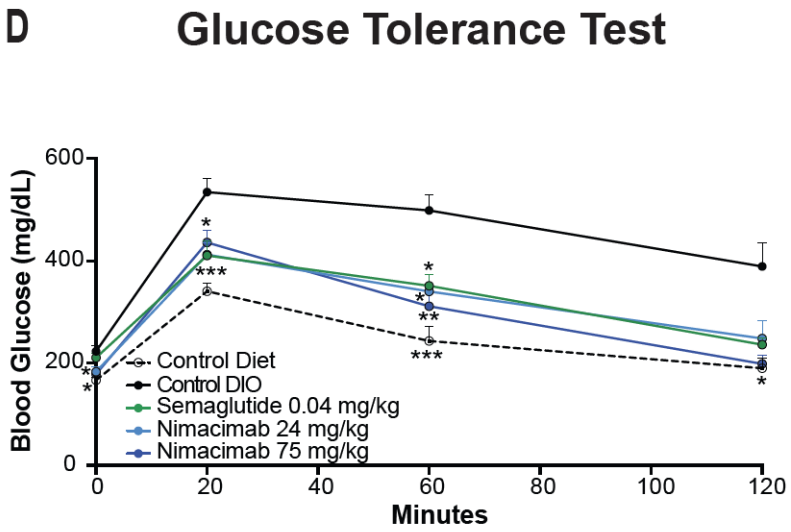


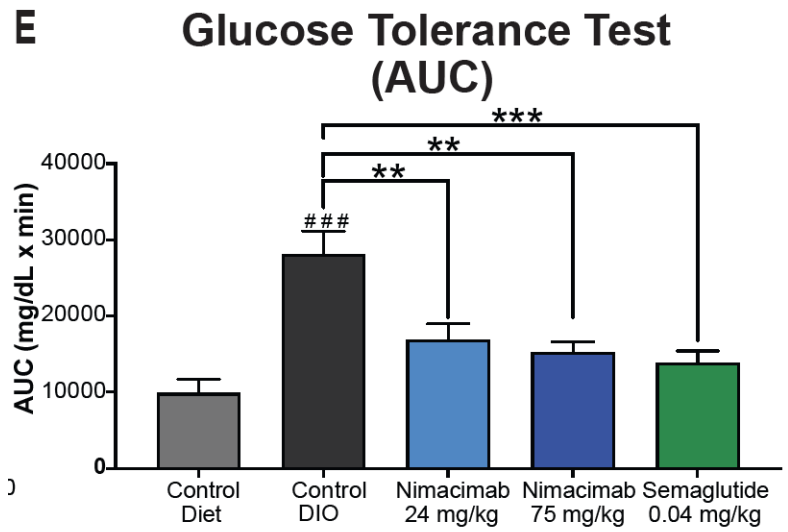
Serum was collected on day 36 and hormone levels were determined with a Bio Plex Multiplex immunoassay. For all analyses: one-way ANOVA repeated measurements (Tukey multiple comparison test). # denotes significance to the control diet group.

Nimacimab Improves Glycemic Control









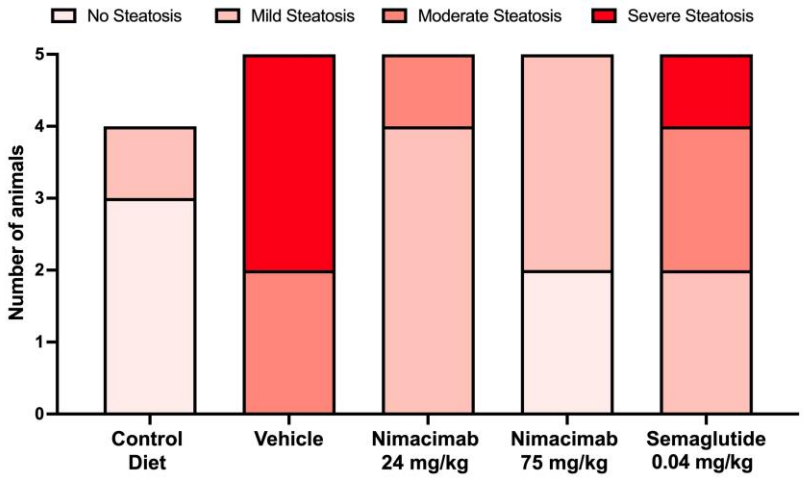
Day 27 mice were fasted for 4h before collecting serum to measure glucose and insulin levels. Day 27 mice were fasted for 4h before ip injection of 2g/kg glucose. GTT analyses: 2-way ANOVA repeated measurements (Tukey multiple comparison test); baseline subtracted AUC analysis was performed with a one-way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

Nimacimab Treatment Promotes Lipid Metabolism

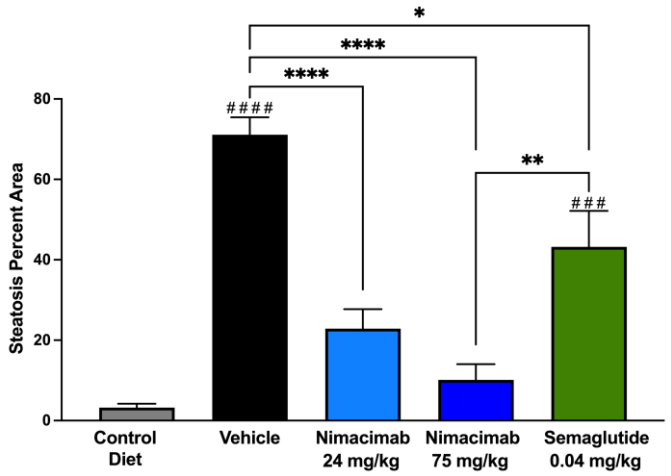
Dose-dependent reduction in steatosis and serum cholesterol

Steatosis Analysis (Liver)

Steatosis Score

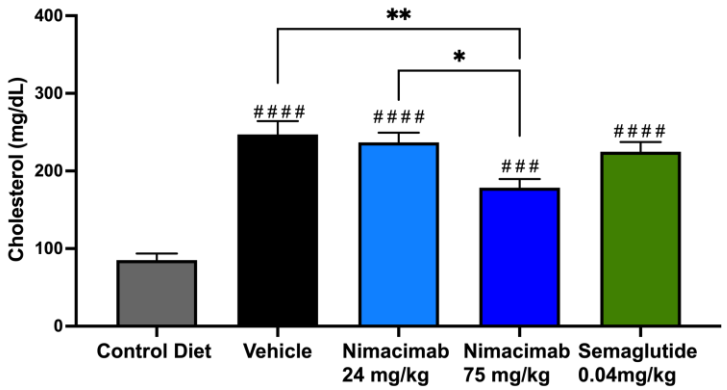


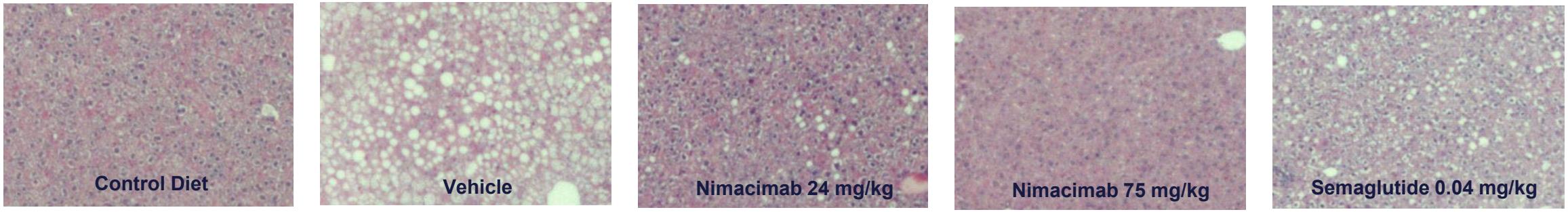
Steatosis Percent Area



Serum

Cholesterol





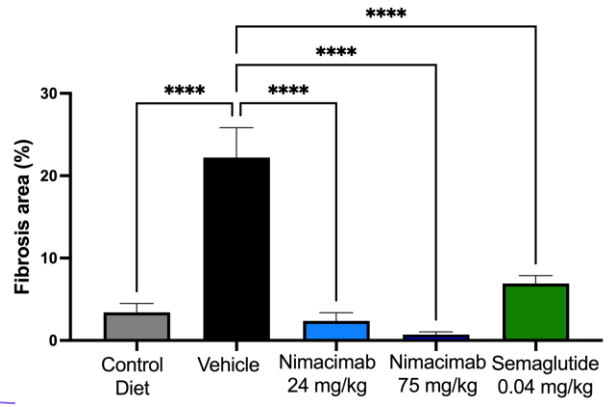
Liver sections scored by a pathologist using computer-aided analysis. A score of 0-3 was assigned based on % of hepatocytes with fat. 0 = no steatosis (<5%), 1=mild (5-33%), 2=moderate (>33-66%), 3=severe steatosis (>66%). (B) steatosis percent area was analyzed using computer-aided analysis with Cellprofiler.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

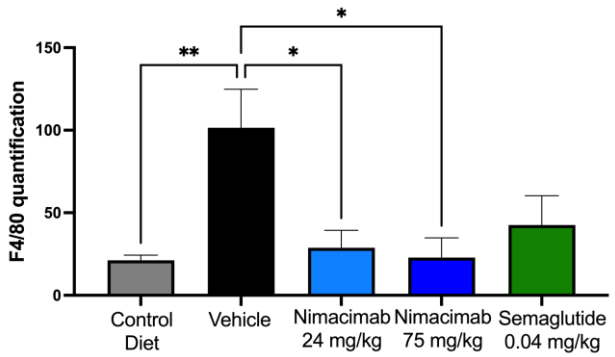
Reduced Inflammation, Fibrosis, and Adipocyte Area

Liver

Fibrosis Area

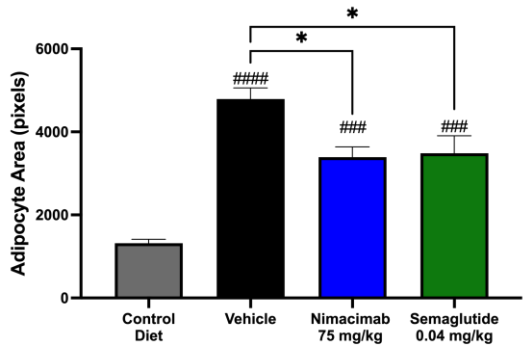


Macrophage (F4/80) Density

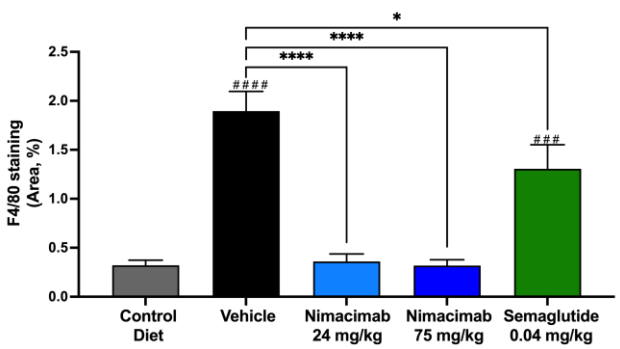


iWAT

Adipocyte Area

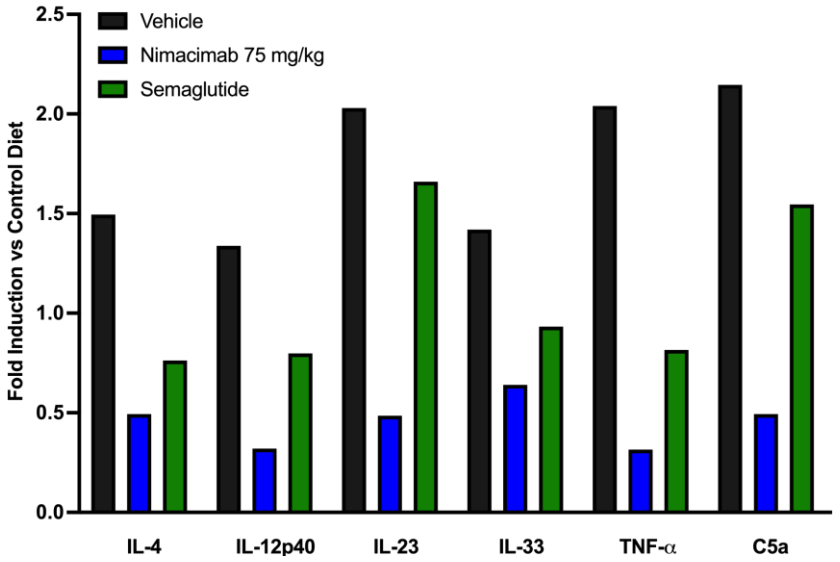


Macrophage (F4/80) Density



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.

skye

5.2

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%

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

— Level in CSF determined using quantitative ELISA

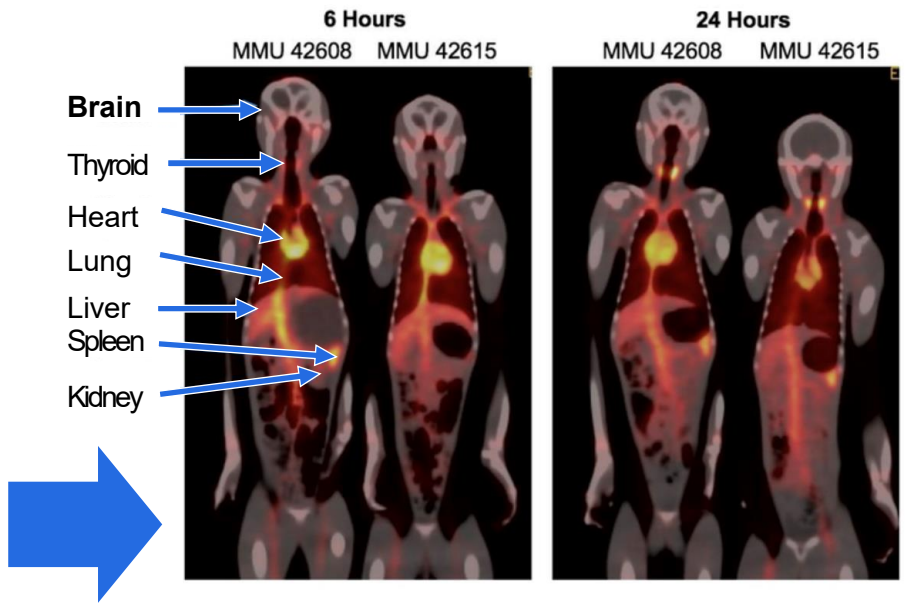
Rhesus	48 hours
CSF/Plasma	0.05%
Prefrontal Cortex/Plasma	0.83%
Cerebellum/Plasma	0.84%
Liver/Plasma	16.44%

— 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

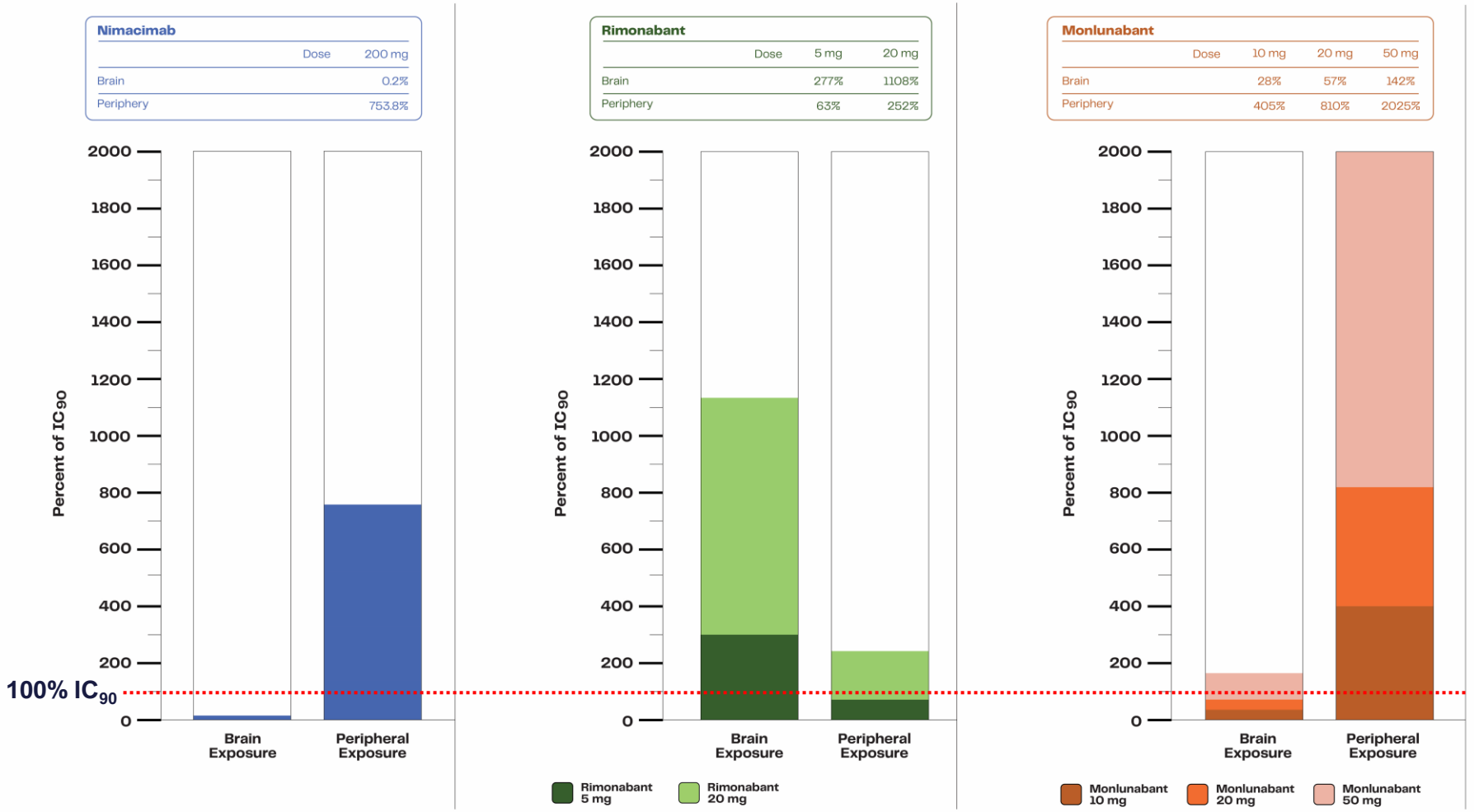
- *Tissues harvested without perfusion*
- *Tissue to plasma assuming 1 mL = 1 g*

Phase 1 data showed absence of negative neuropsychiatric effects in humans



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.

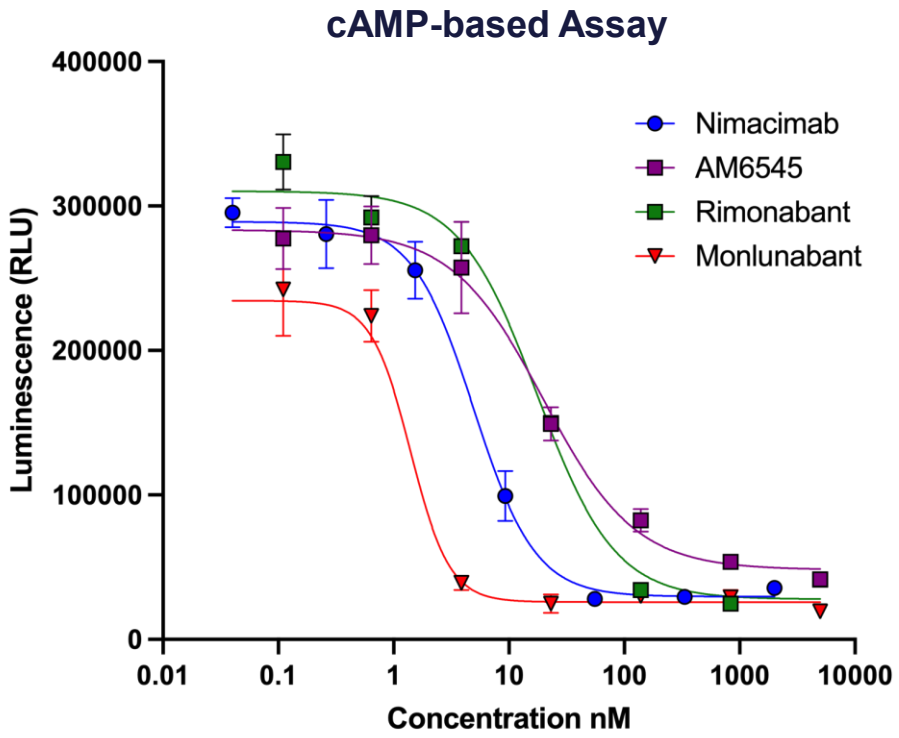
Monlunabant:

- 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.

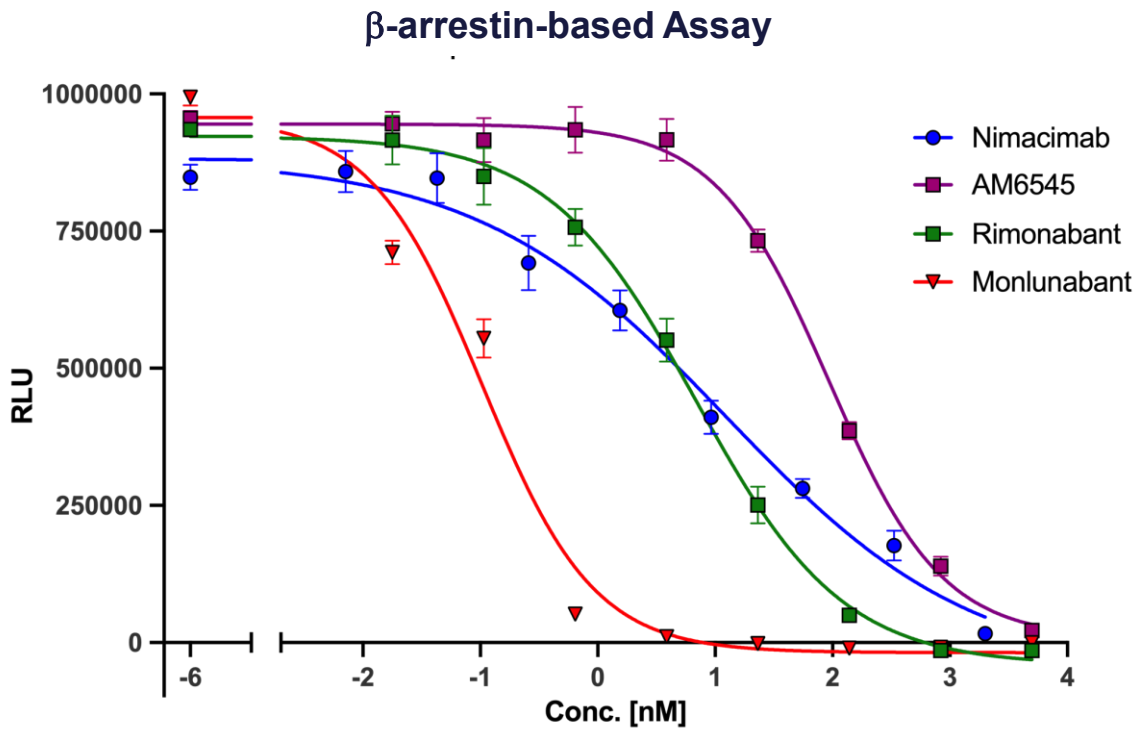
Source: Braga et al., Demonstrating the sufficiency of peripheral CB1 inhibition to promote weight loss using clinical pharmacokinetic and pharmacodynamic. European Congress on Obesity PO4.148. https://eco2025.org/assets/docs/programme-book.pdf?a=5678

Nimacimab Achieves Peripheral CB1 Inhibition Without CNS Risk

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



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

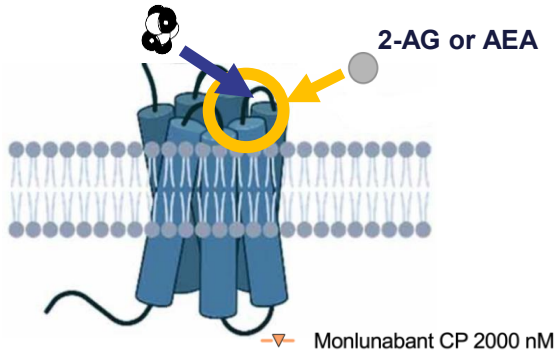


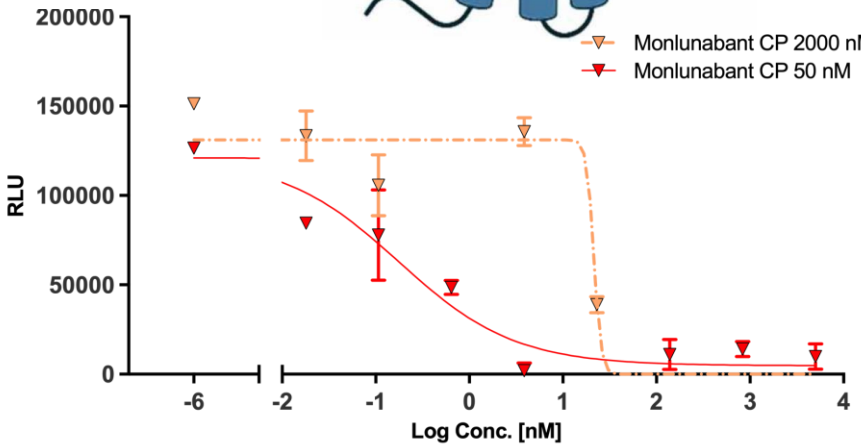
CB1 Inhibitor	IC_{50} (nM)
Nimacimab	10.83
AM6545 (neutral antagonist)	47.62
Rimonabant	5.36
Monlunabant	0.07

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

Monlunabant

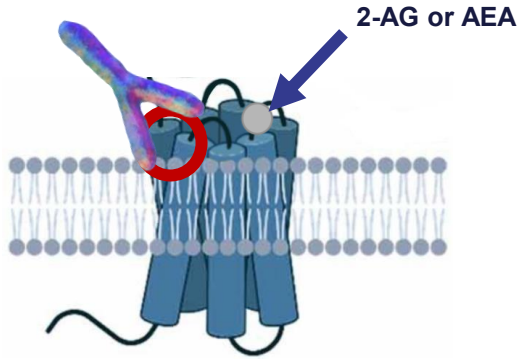
Monlunabant **competes** with AEA/2-AG for binding to the orthosteric site

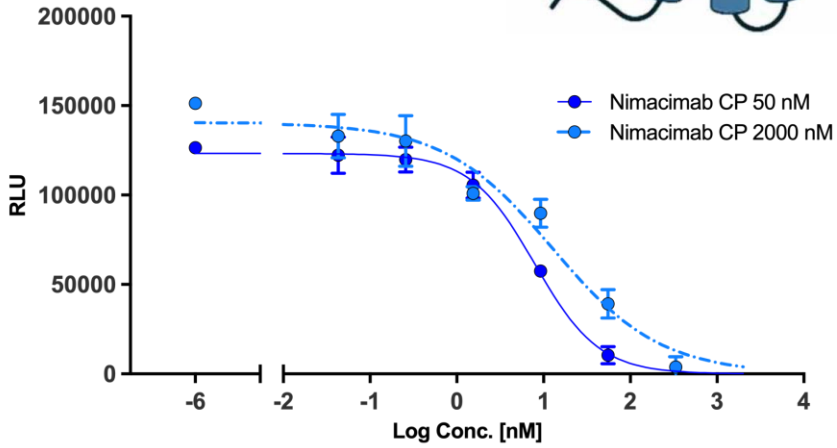




Nimacimab

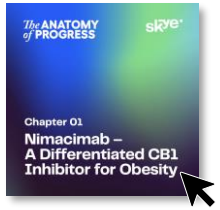
Nimacimab **non-competitively** binds allosteric site; AEA/2-AG binds the orthosteric site



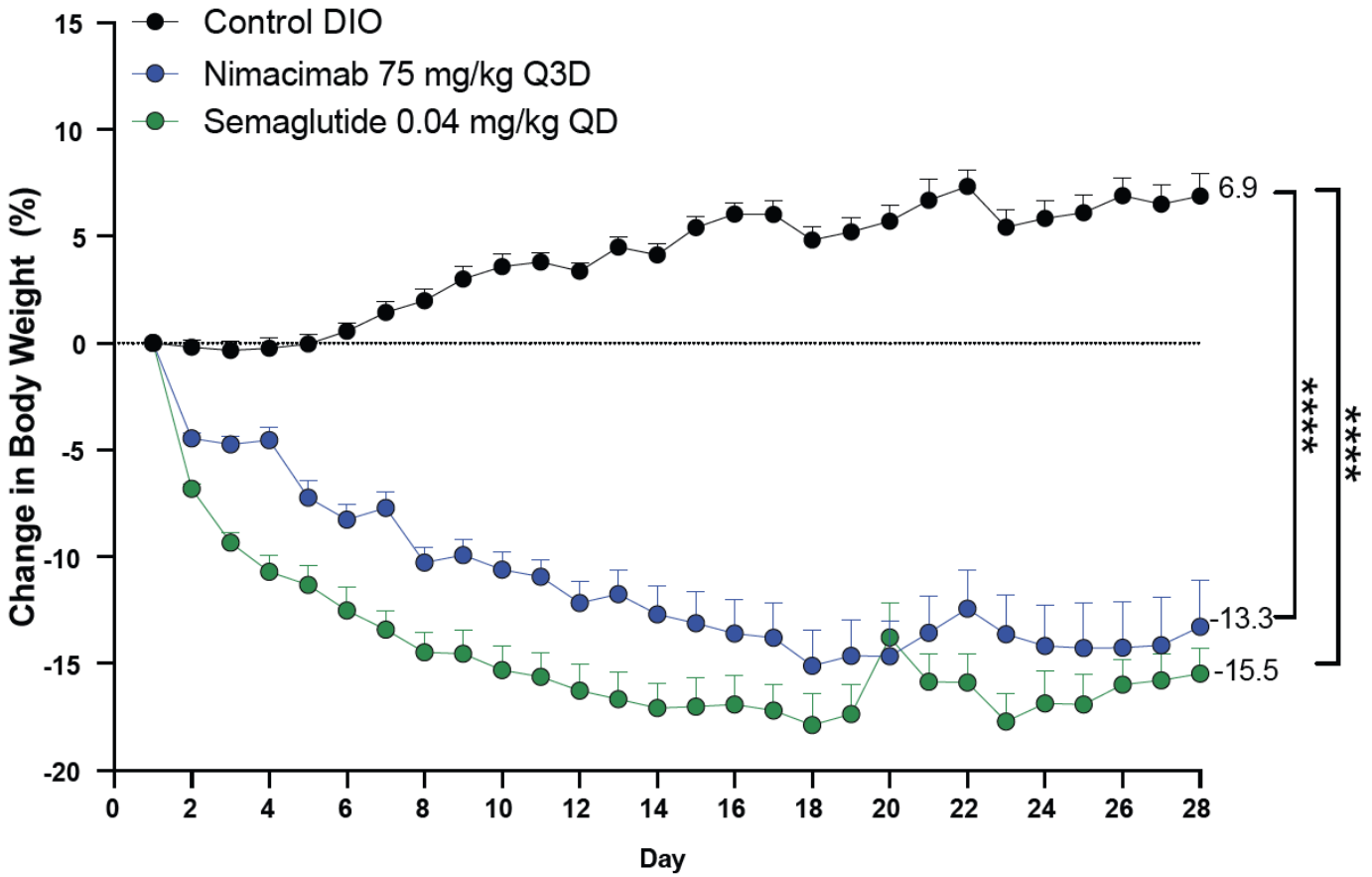


CB1 Inhibitor	Agonist: CP55940		Reduction in Fold Potency
	EC_{80} (50 nM)	40x EC_{80} (2000 nM)	
Nimacimab IC_{50} (nM)	7.9	12.7	**1.6**
Monlunabant IC_{50} (nM)	0.2	21.44	**107**

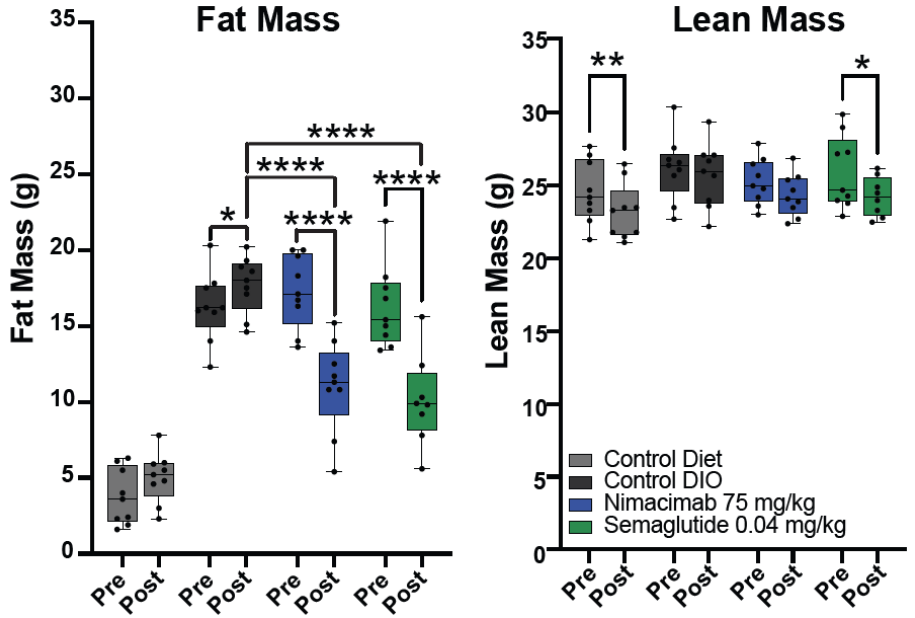
Repeat DIO Study with Independent Lab: Similar Weight Loss with Reduced Fat Mass



Body Weight



Body Composition

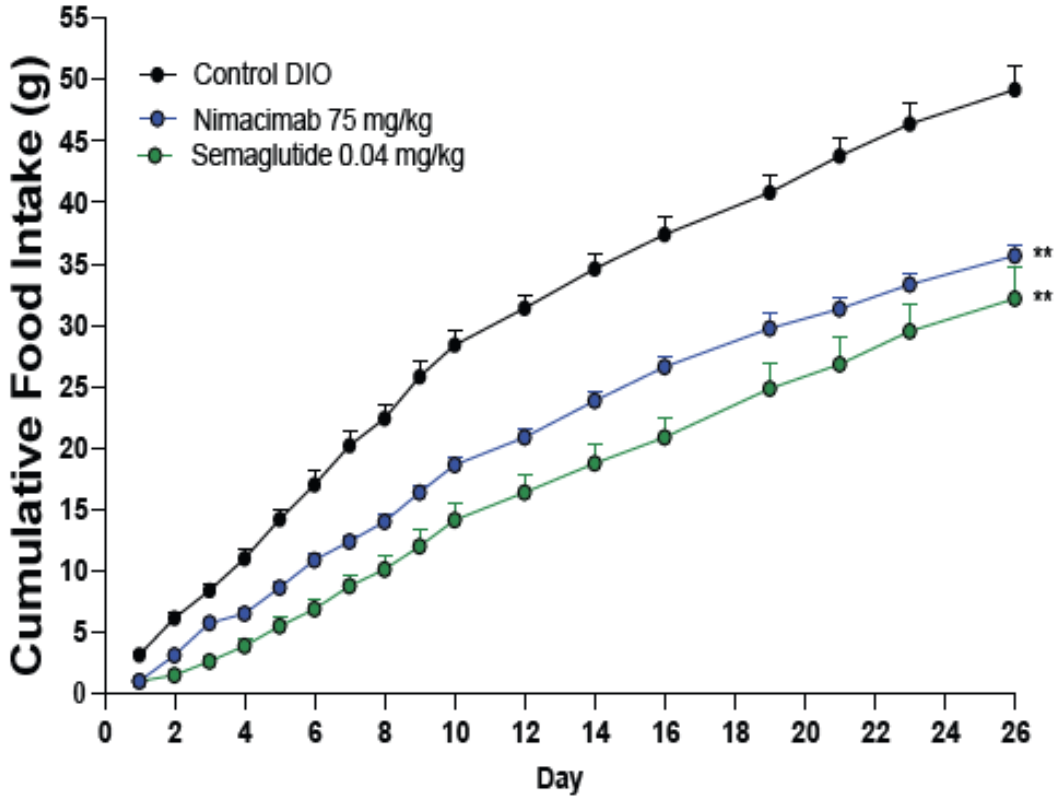


Body weight and composition analyses were performed with two-way ANOVA repeated measurements. Tukey multiple comparison test was then performed for all pairwise comparisons. Body weight reporting through 28 days of treatment. Body composition measured with echo MRI on day 26

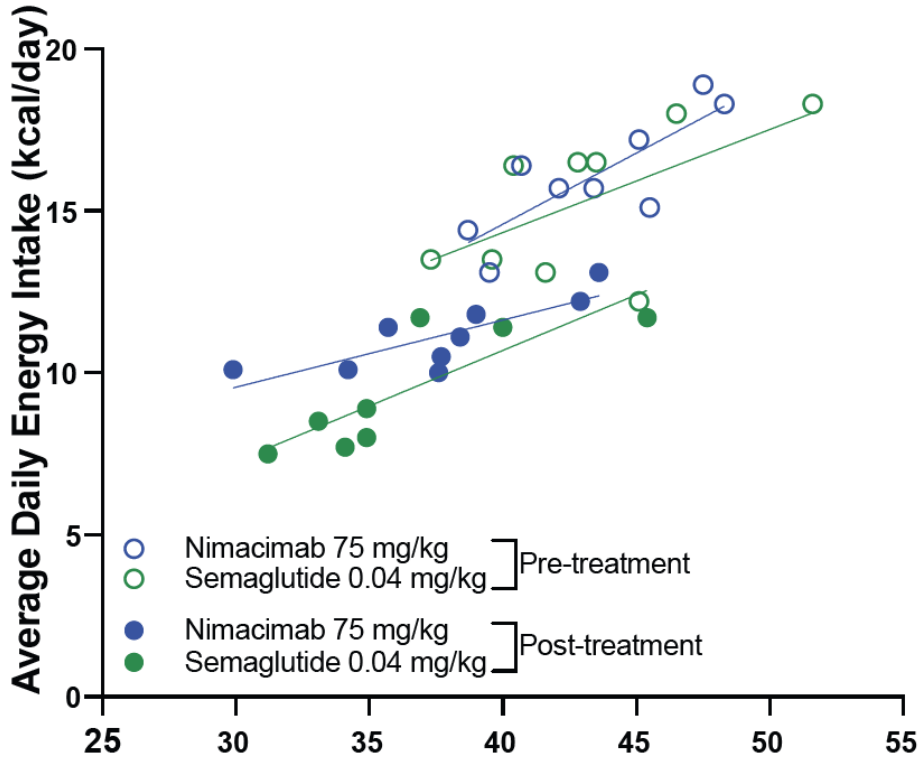
Nimacimab Led to Reduced Food Intake

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

Cumulative Food Intake

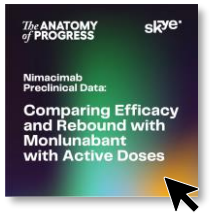


Caloric Intake vs Body Weight



*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

Tissue collection

MRI MRI MRI

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

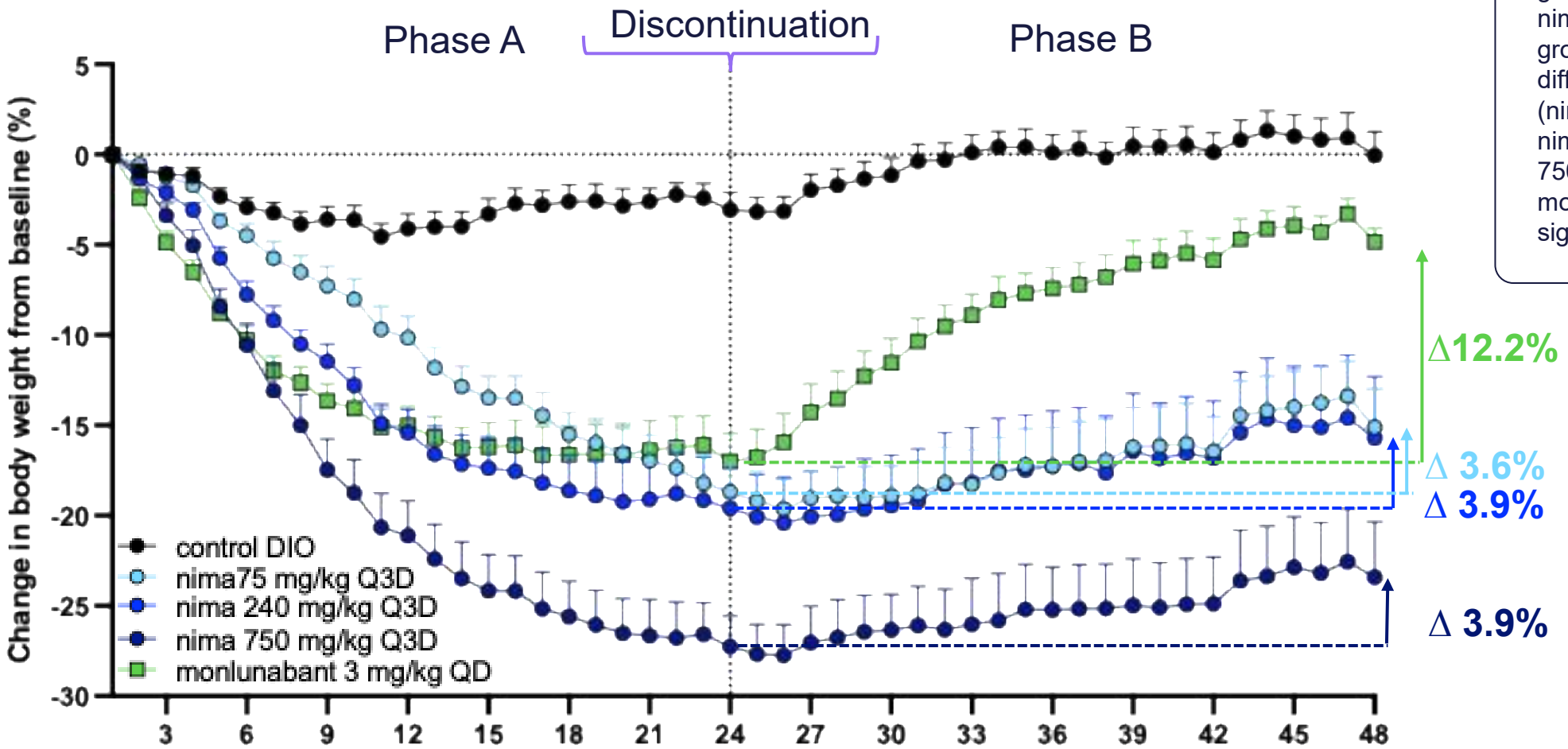
monlunabant 3 mg/kg QD → no intervention

Endpoints:

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

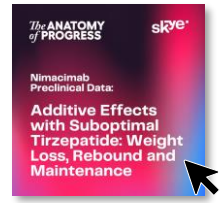
skye

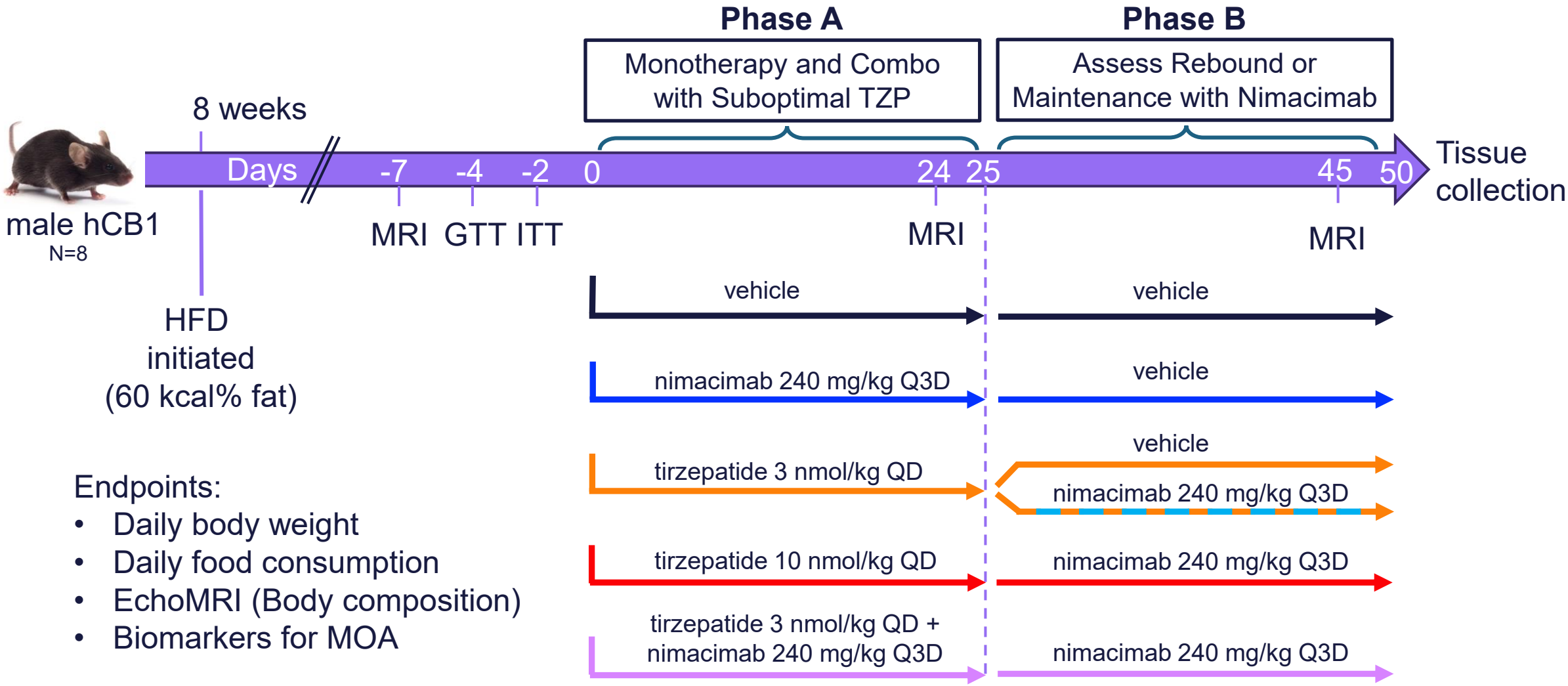
Nimacimab Drives Durable Weight Loss and Minimal Rebound Compared to Monlunabant Treatment



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

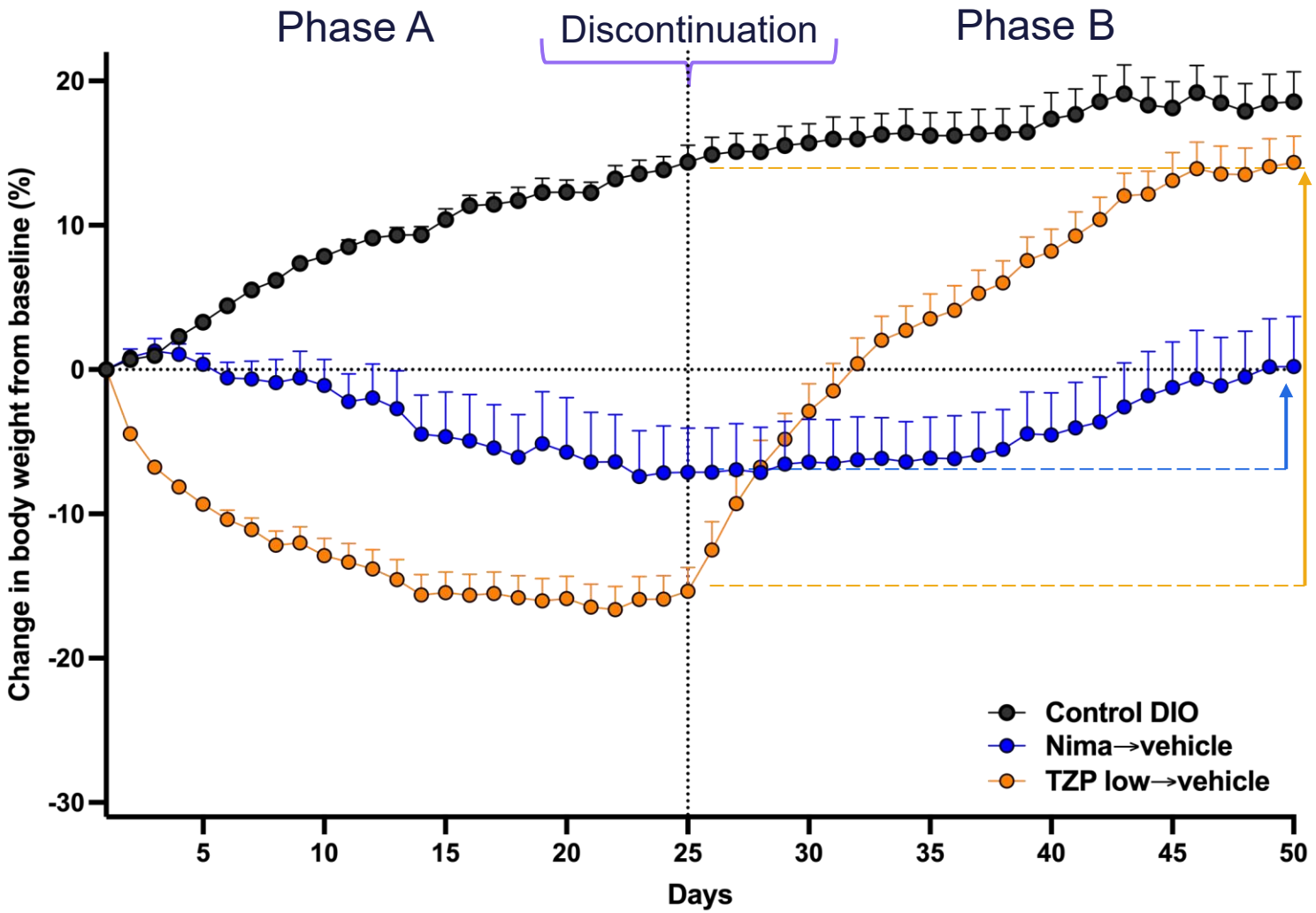




Endpoints:

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

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

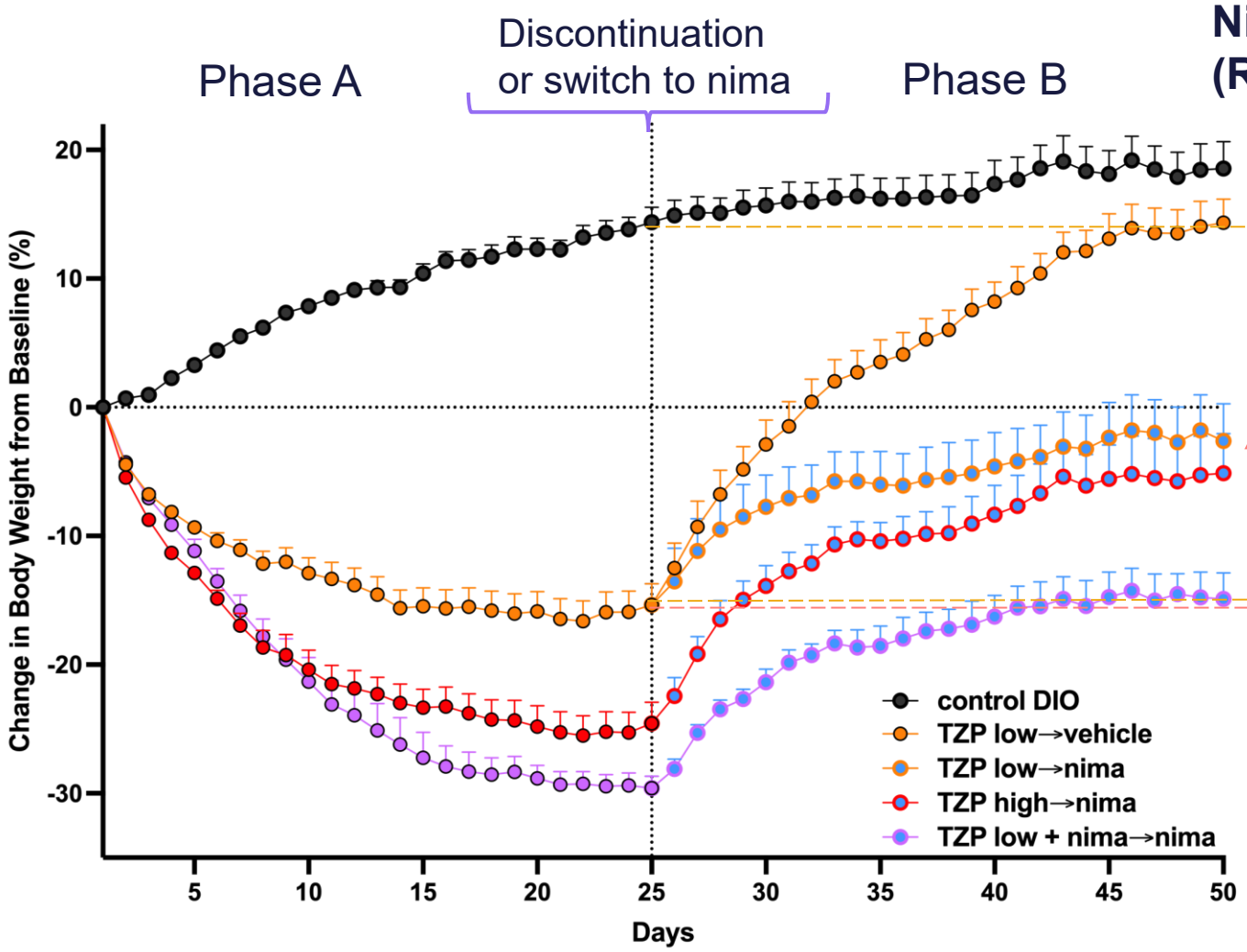


Δ29.7% tirzepatide 'rebound'

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)

Days -7 0 24 25 45 50

Tissue collection

MRI MRI MRI

Phase A: Monotherapy and Combo with Sub-optimal TZP

Phase B: Assess Rebound or Maintenance with Nimacimab

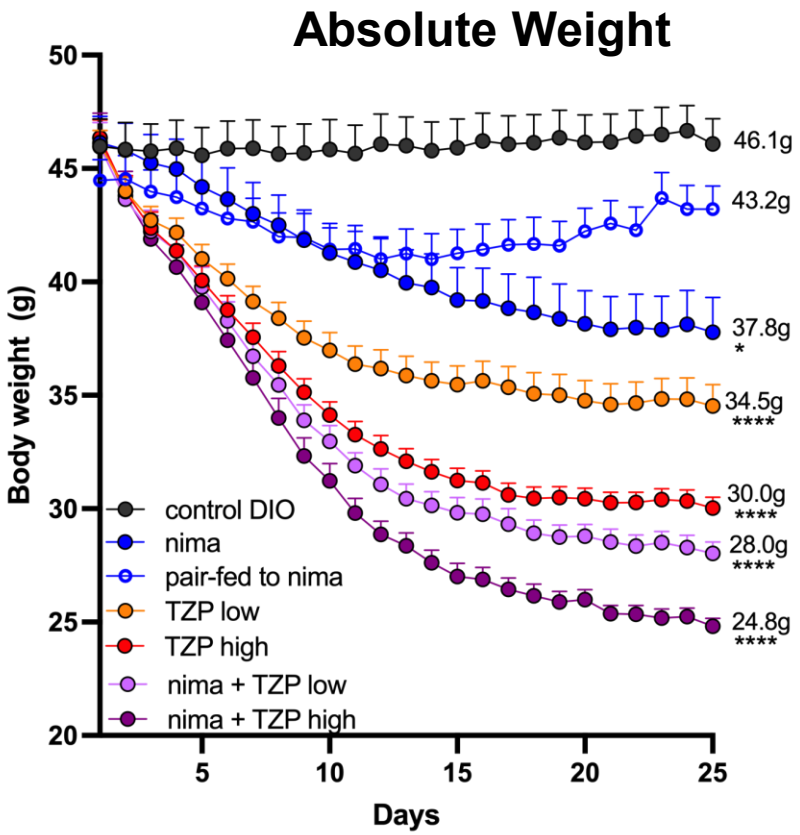
	Phase A	Phase B
vehicle	vehicle	vehicle
pair-fed to nimacimab	pair-fed to nimacimab	pair-fed to nimacimab
nimacimab 240 mg/kg Q3D	nimacimab 240 mg/kg Q3D	vehicle
tirzepatide 3 nmol/kg QD	tirzepatide 3 nmol/kg QD	vehicle nimacimab 240 mg/kg Q3D
tirzepatide 10 nmol/kg QD	tirzepatide 10 nmol/kg QD	vehicle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

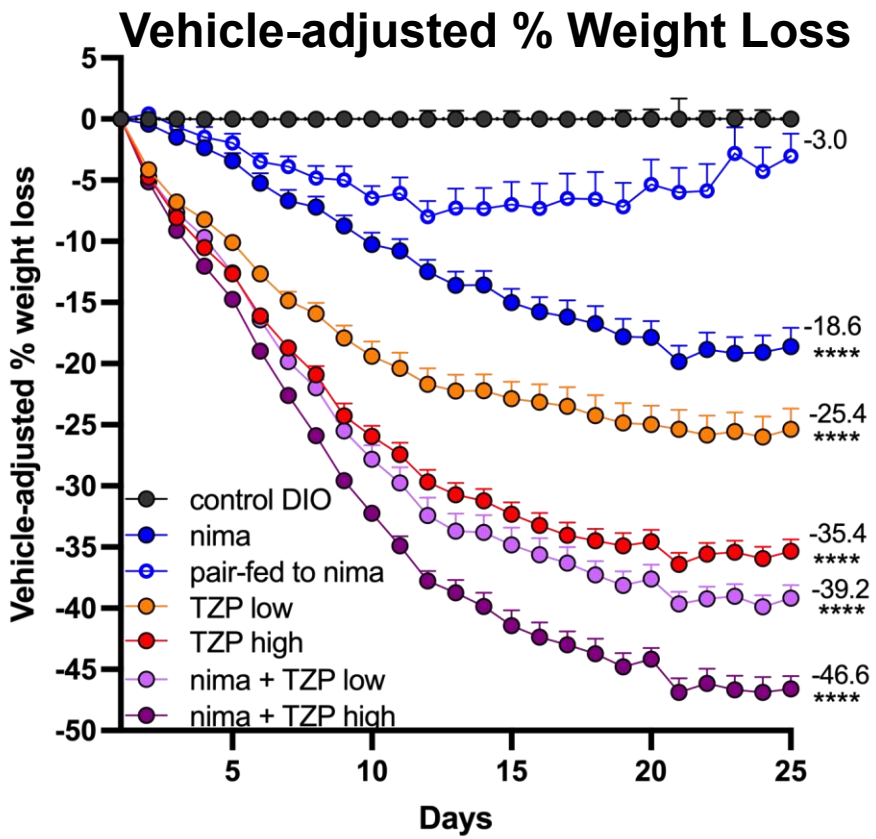
Endpoints:

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

skye

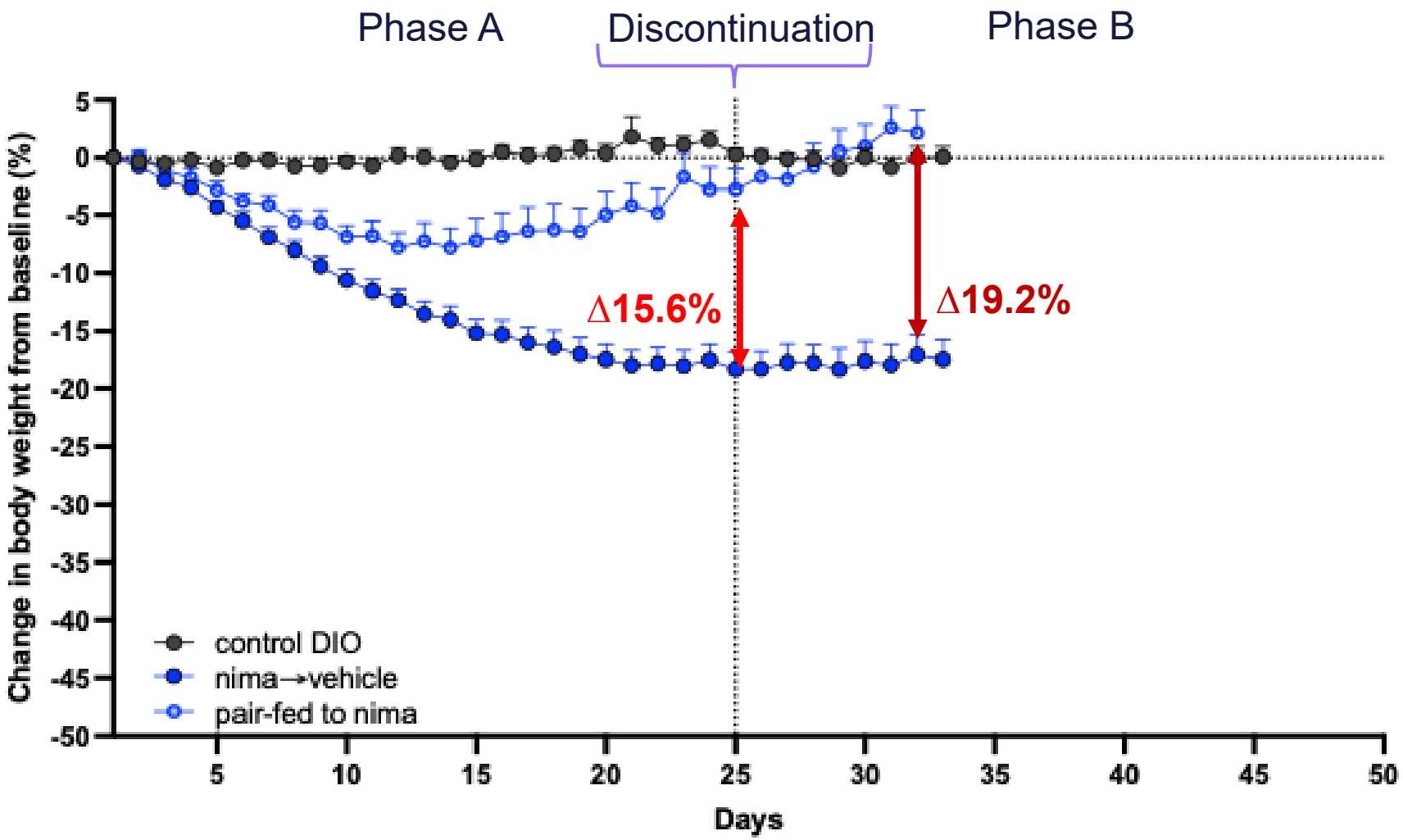
Nimacimab Enhances Weight Loss when Combined with both Low-Dose and High-Dose Tirzepatide





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.