Nasdaq: SKYE

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Developing Innovative Medicines to Treat Obesity and Other Metabolic Diseases

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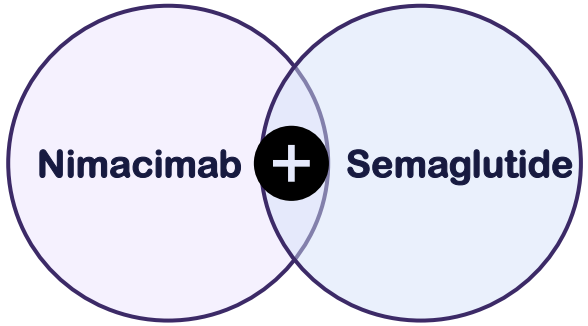
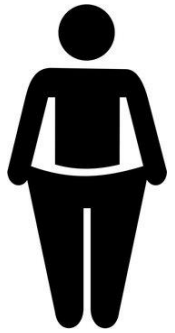
Executive Summary

CBeyond data established potential path for combination strategy with existing incretin therapies



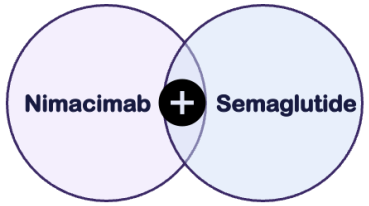
Additive Weight Loss



Improved Durability of Weight Loss

Favorable Tolerability Profile

Skye has developed a combination strategy for nimacimab + semaglutide that has the potential to provide a compelling new therapeutic option for patients.



52-Week Combination Data

High-Dose Rationale

High-Dose Feasibility

Regulatory Alignment

Commercial Scalability

Attractive Target Product Profile

What has Objectively Changed in the CB1 Field

Since launching nimacimab in obesity, Skye has delivered a series of field-firsts for peripheral CB1

1 FIELD FIRST

First-in-class modality

Allosteric GPCR antibody designed for peripheral CB1 inhibition to improve energy metabolism while minimizing brain exposure.

2 CLINICAL FIRST

First human obesity program with clean safety

First clinical obesity program to evaluate a CB1 monoclonal antibody and create a direct readout for the mechanism without any neuropsychiatric events.

3 COMBINATION FIRST

First CB1 + GLP-1 dataset

First reported clinical test of a CB1 mechanism in combination with a GLP-1, establishing proof of combination activity.

INFRASTRUCTURE **Human-CB1 knock-in DIO workflow + quantitative biodistribution + APC Platform**

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CBeyond: Three Primary Learnings

Meaningful combo efficacy, clean safety, and a clear dosing path

CBeyond

LEARNING 1

Meaningful combination signal

+3.0%

incremental weight loss vs semaglutide alone at 26 weeks

22.3%

mean weight loss at 52 weeks, with no plateau observed

- Significant waist circumference improvement
- Improved lean-to-fat mass ratio

LEARNING 2

Clean safety and tolerability

0

nimacimab-associated neuropsychiatric signal through 52 weeks

No additive GI burden

with semaglutide

- Combination-ready at tested exposure

LEARNING 3

Solvable development variable

200 mg

weekly monotherapy underexposed peripheral tissues

Next step: higher exposure

- Higher-dose expansion study underway
- ENHANZE supports higher-exposure SC delivery

Meaningful combination efficacy. Clean safety. Clear dosing path.

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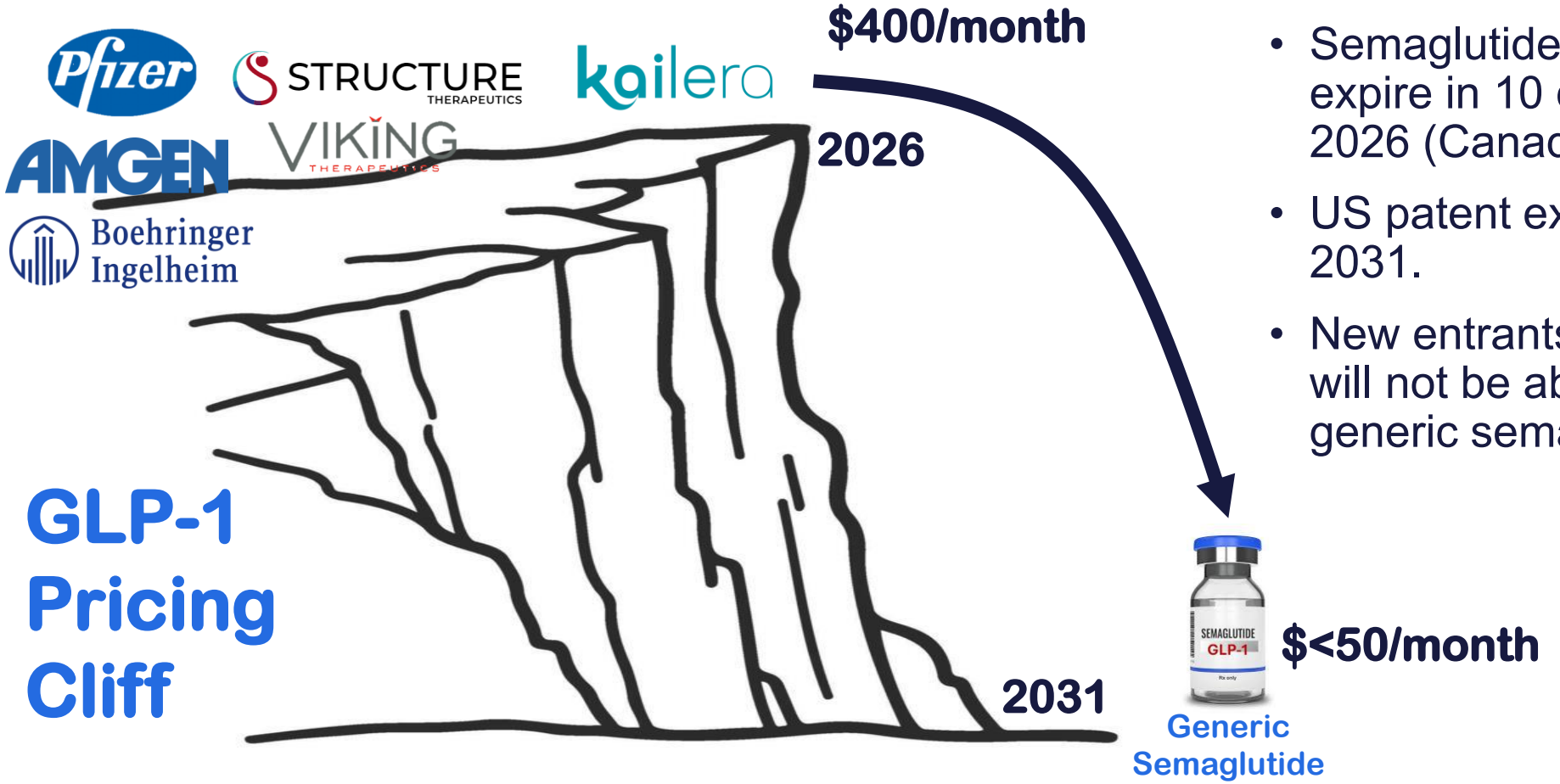
Investment Thesis – GLP-1s Are Facing a Pricing Cliff

Nimacimab: complementary, not competitive – potential scalable add-on to enhance incretin therapy



- Semaglutide patents due to expire in 10 countries globally in 2026 (Canada, India, Brazil, etc.).
- US patent expiry expected in 2031.
- New entrants to the GLP-1 space will not be able to compete with generic semaglutide.

Investment Thesis – Nimacimab Target Product Profile

Nimacimab: complementary, not competitive – potential scalable add-on to enhance incretin therapy

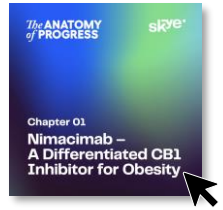
Obesity is becoming a chronic, multi-line treatment market — and a meaningful proportion of patients already exposed to incretins will need a safer, mechanistically distinct therapy that can deepen response, improve quality of weight loss, or sustain control when the current standard of care leaves clinically important residual disease. Nimacimab is being developed to be that product.

Patient Demographic	Current Treatment Options	Dosing Regimen	Pricing Structure
GLP-1 Experienced patients who: • Lose <10% WL • Intolerant to GLP-1 • Plateaued WL • Need >20% WL	• Naltrexone/ bupropion (Contrave) • Phentermine/ topiramate (Qysmia) • Orlistat (Xenical/Alli)	• Once-weekly (QW) • Potentially once-monthly as maintenance dose	• $274/month after projected 60% discount • Combined with generic semaglutide • Total combination cost less than $300/month

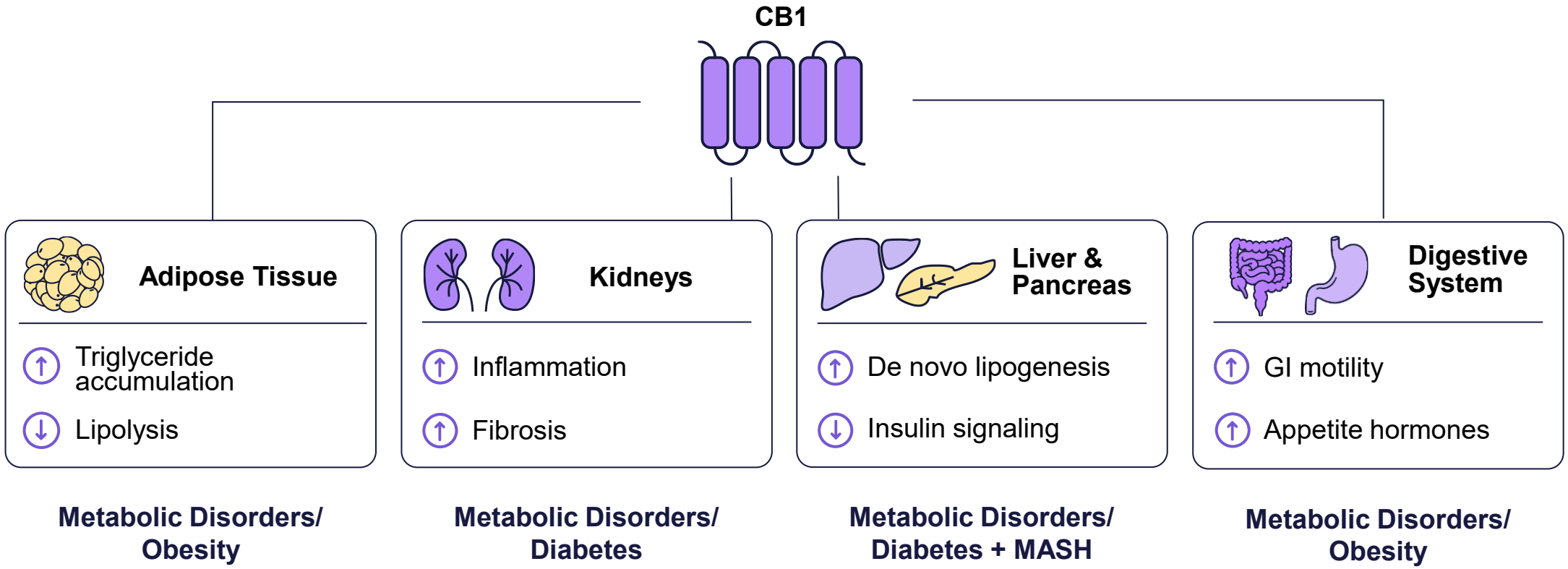
Nimacimab

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 potentially reverse negatively-trending pathologies



Nimacimab: Peripherally-restricted CB1-inhibiting Antibody

Long Half-life

- Stable antibody with half-life of 18-21 days (potential Q2W 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

Potential 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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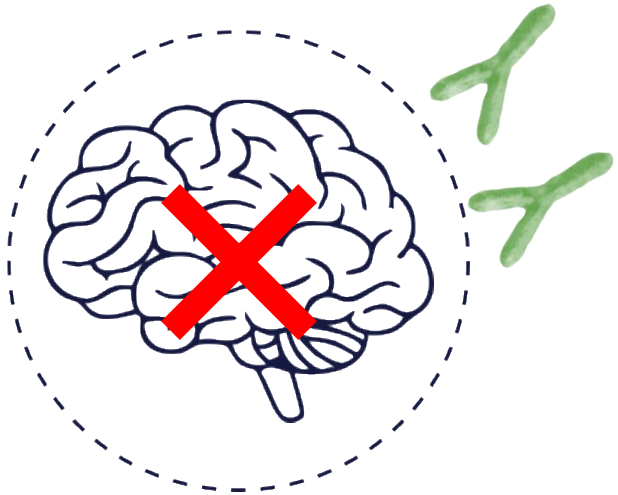
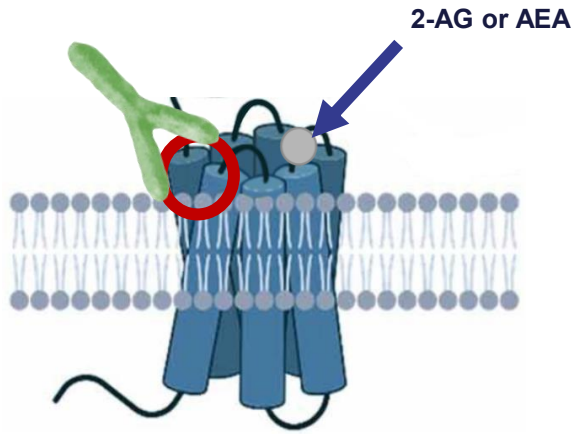
Nimacimab's Potential Differentiation from Small Molecule CB1 Inhibitors

Peripheral Restriction



Significantly less brain penetration than small molecules currently in development

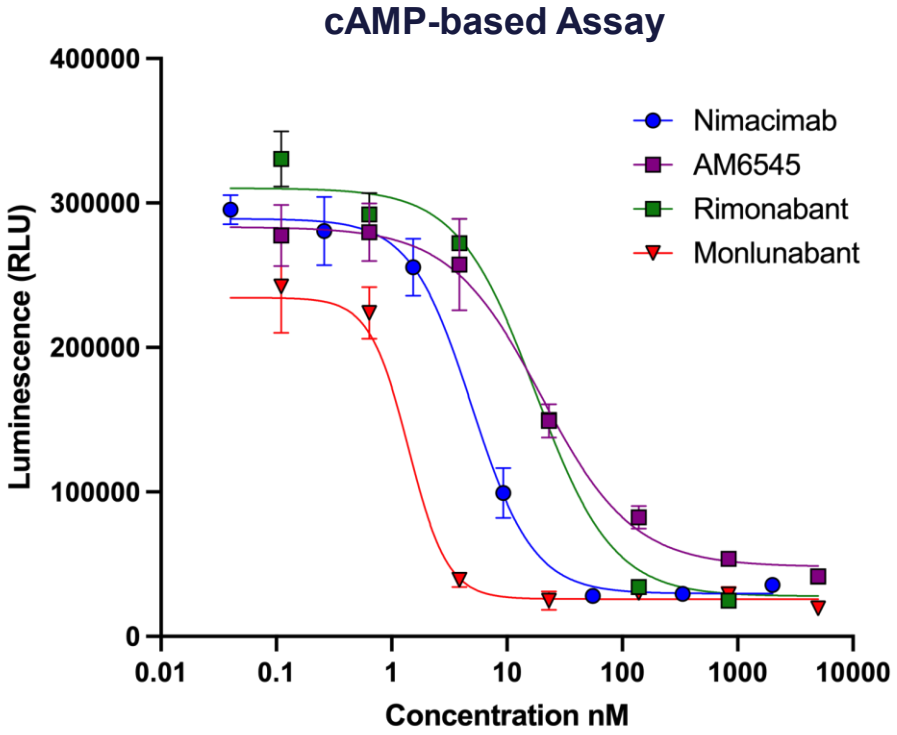
Negative Allosteric Modulator



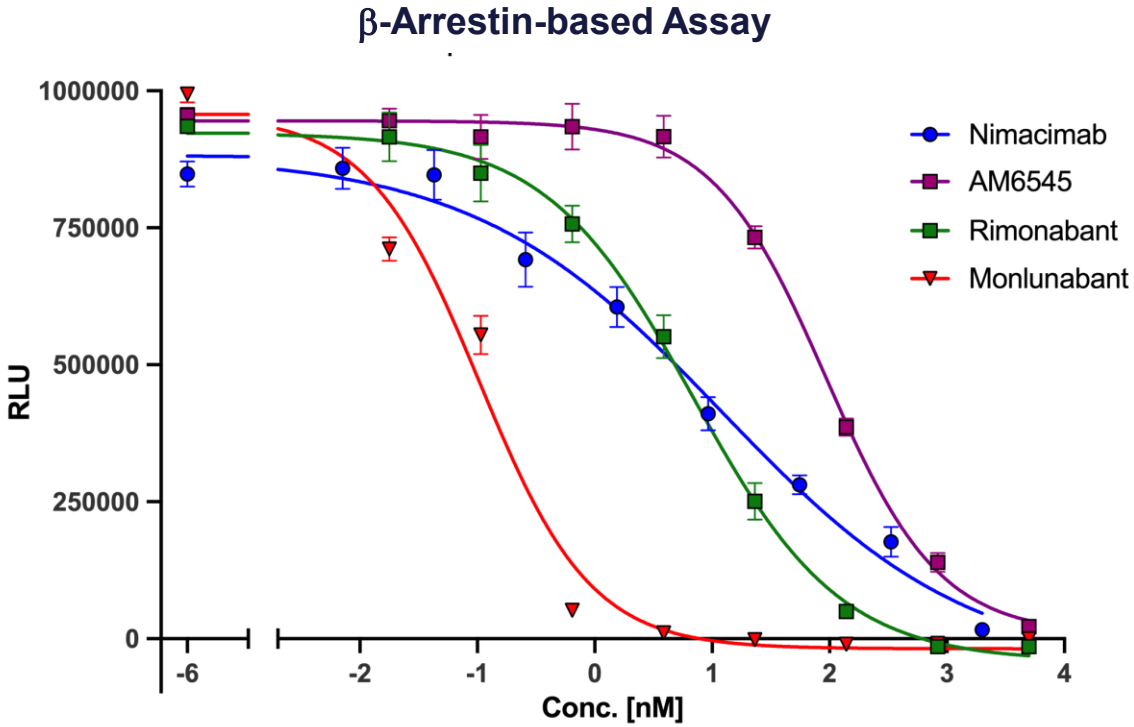
Unlike small molecules currently in development, **nimacimab retains potency** even in the presence of competition

Nimacimab Potency Similar to Small Molecule Inhibitors

Based on both cAMP and b-arrestin assays



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

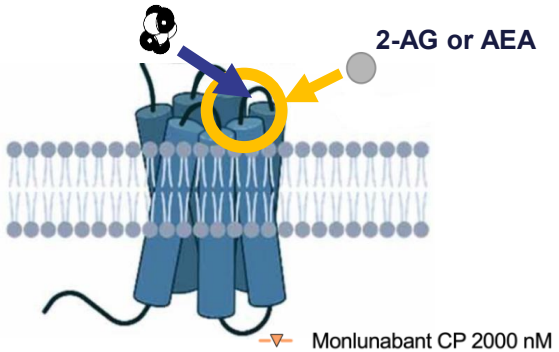


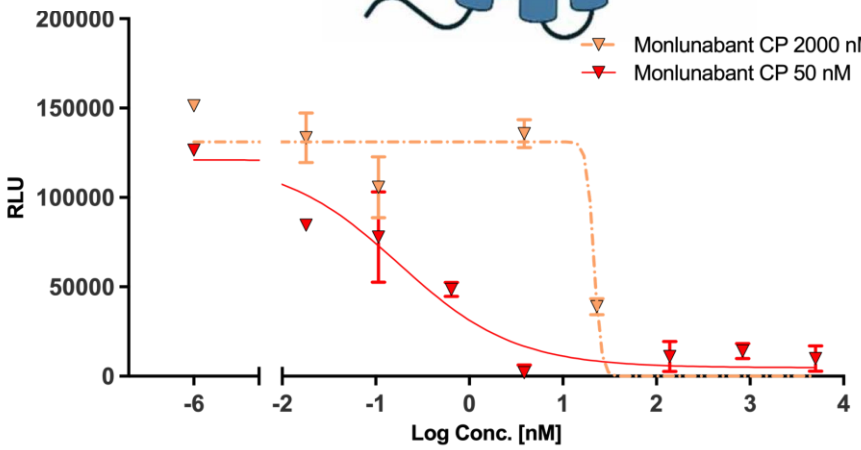
CB1 Inhibitor	IC_{50} (nM)
Nimacimab	10.83
AM6545 (neutral antagonist)	47.62
Rimonabant	5.36
Monlunabant	0.07

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

Monlunabant

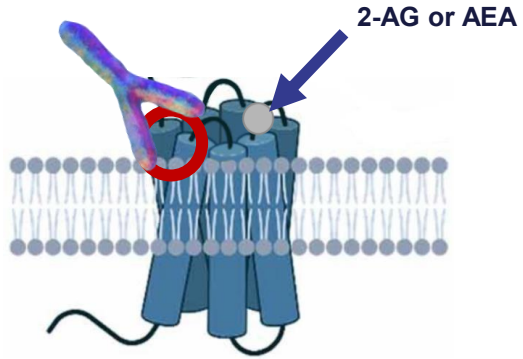
Monlunabant **competes** with AEA/2-AG for binding to the orthosteric site

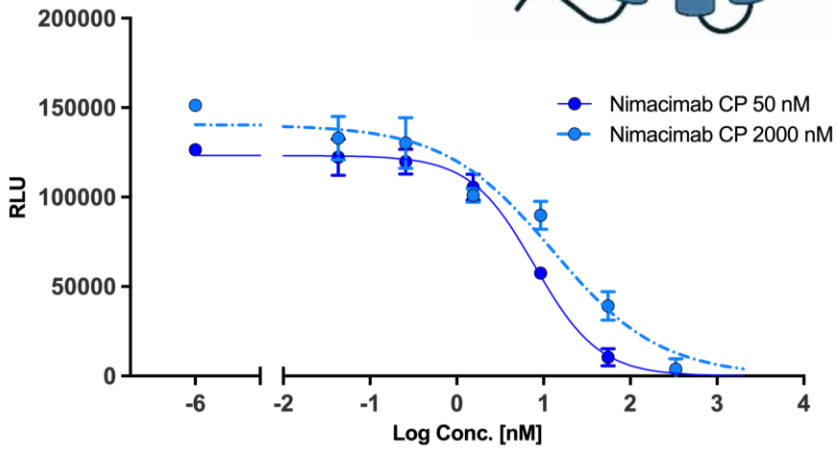




Nimacimab

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



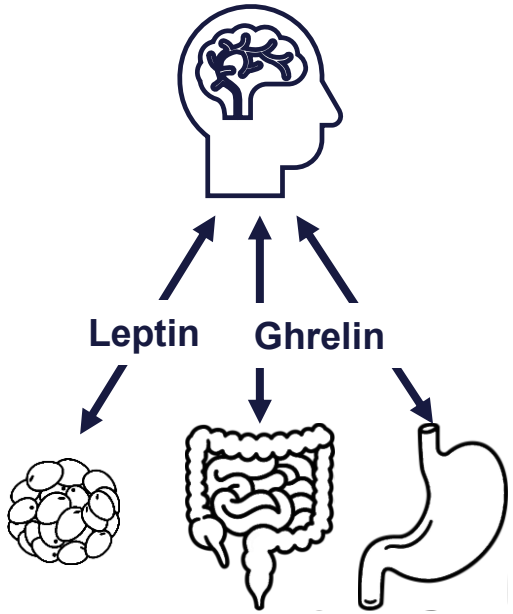


CB1 Inhibitor	Agonist: CP55940		Reduction in Fold Potency
	EC_{80} (50 nM)	40x EC_{80} (2000 nM)	
Nimacimab IC_{50} (nM)	7.9	12.7	**1.6**
Monlunabant IC_{50} (nM)	0.2	21.44	**107**

Four Mechanistic Pillars of Nimacimab

01

Peripheral Modulation of Appetite Regulating Hormones



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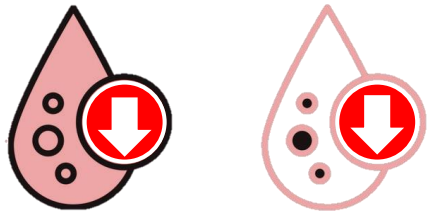
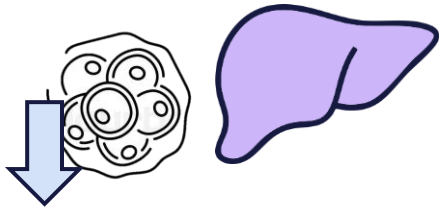
Improvement and Restoration of Glycemic Control



Reduced fasting insulin and glucose tolerance

03

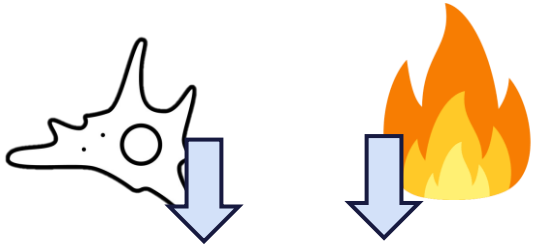
Enhanced Lipid Metabolism



Decreased steatosis and serum cholesterol

04

Reduction of Obesity-Induced Inflammation



Decreased inflammation and fibrotic markers

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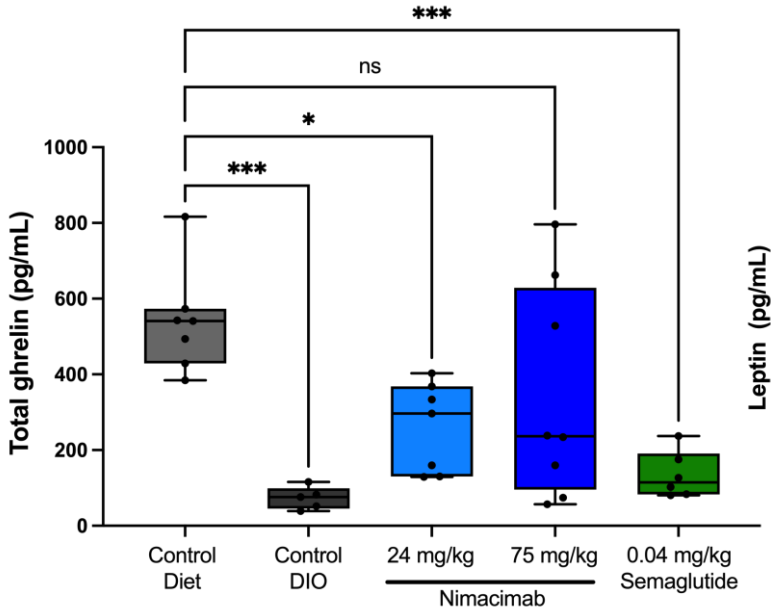
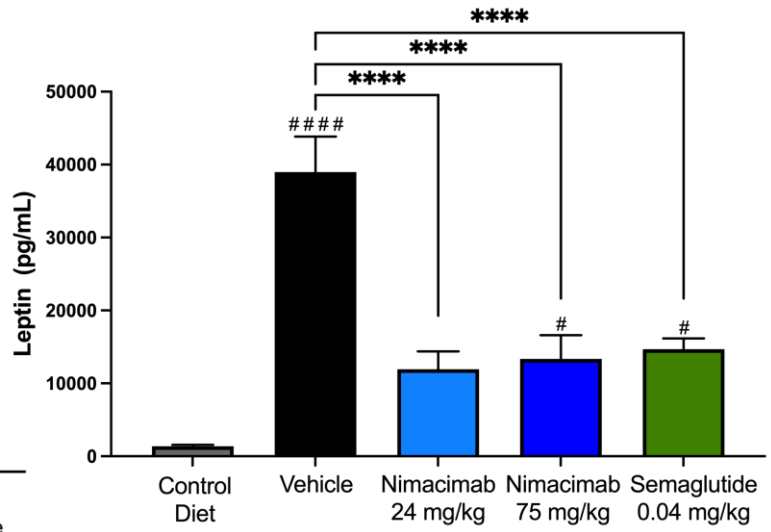
Nimacimab Modulates Appetite-regulating Hormones and Reduces Cumulative Food Intake

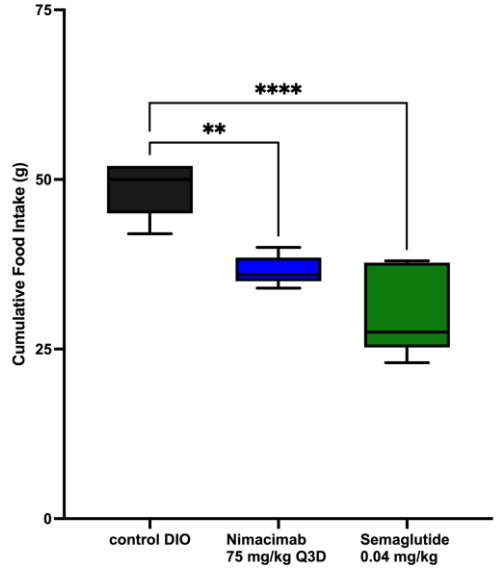
Ghrelin



Leptin

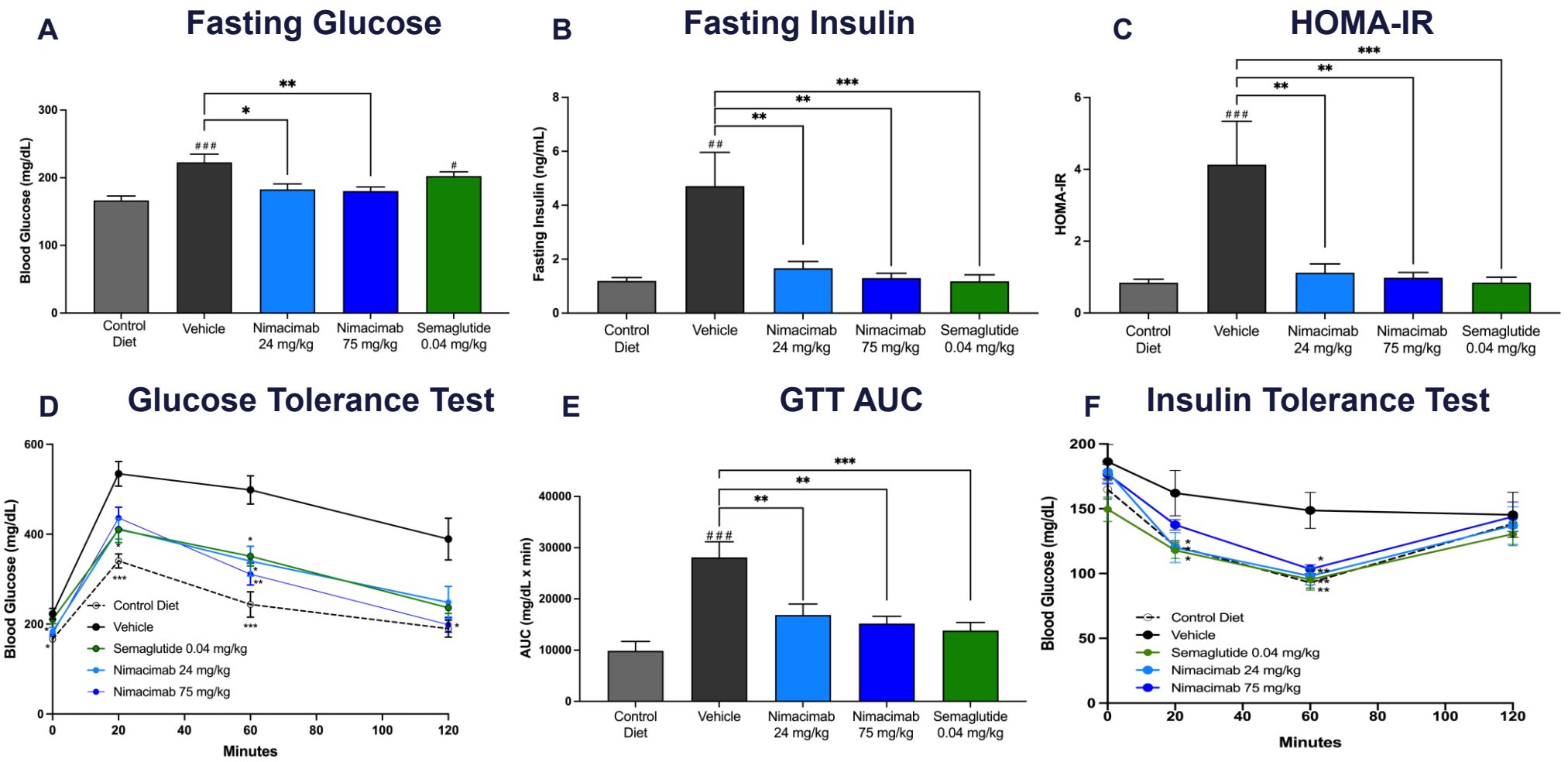


Cumulative Food Intake



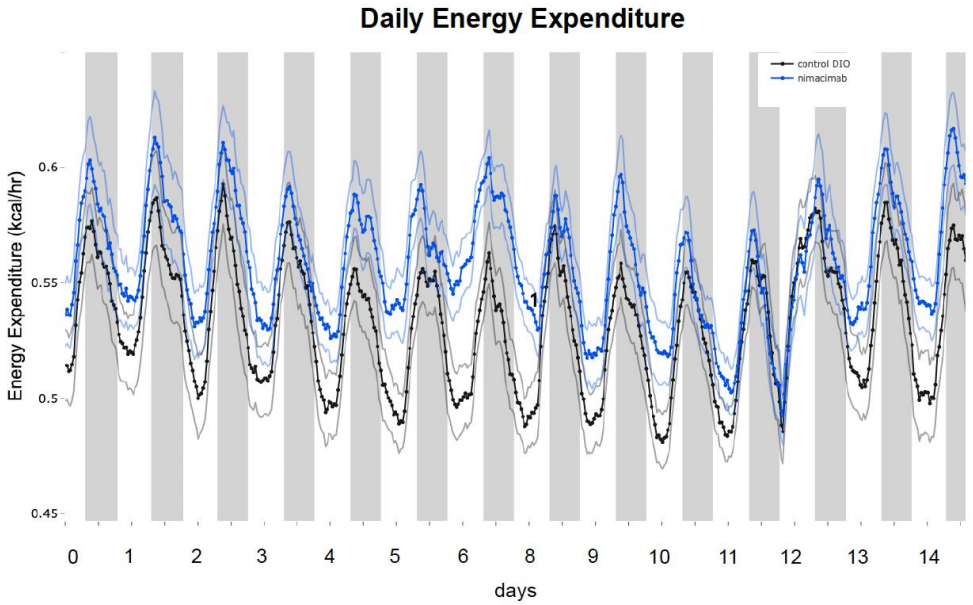
Serum was collected on day 35, and Ghrelin, and Leptin levels were determined with Bio Plex Multi-Plex immunoassay. n=8 per group. One-way ANOVA followed by Tukey's multiple comparisons test. *p<0.05, **p<0.01 ***p<0.001, ****p<0.0001, # p< 0.05, , # # # # p< 0.001 vs control diet. Cumulative food intake, mixed-effect analysis with time and treatment as main factors, followed by Tukey's multiple comparisons test. Data are expressed as mean ± SEM. n=8-9 per group. **p<0.01 vs control DIO.

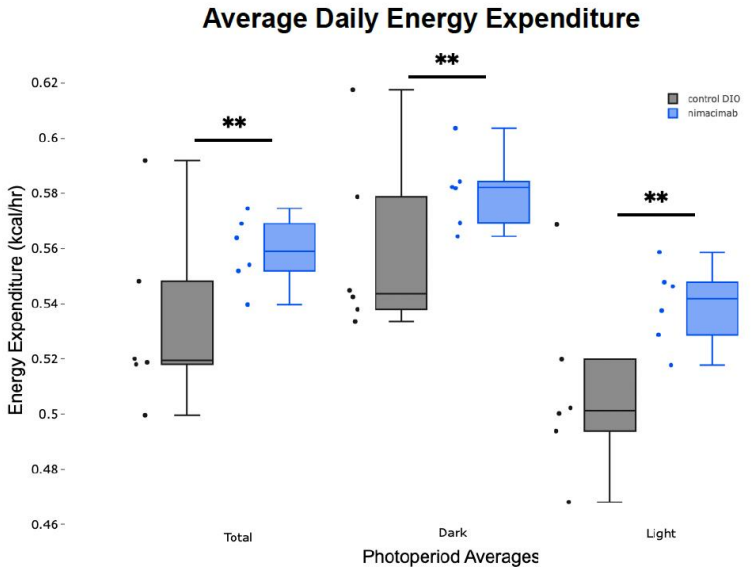
Nimacimab Improves Glycemic Control

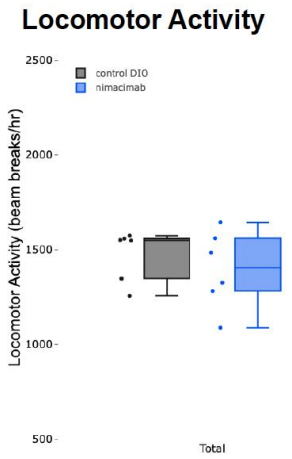


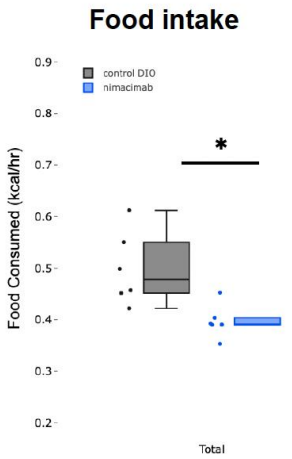
On day 25 of treatment, animals were fasted for 4 h and glucose levels were measured before they were injected 2g/kg glucose. Effect of nimacimab and semaglutide treatments on fasting blood glucose (A), fasting insulin levels (B), HOMA-IR (C), and iPGTT (D). Individual baseline levels of glucose were subtracted to calculate the area under the curve (AUC) (E). On day 28, animals were fasted for 4 h before receiving an intraperitoneal insulin injection (dose 0.75 U/kg at 5 mL/kg) and blood glucose was checked via tail prick to run an ITT (F). For (A), (B), (C), and (E) One-way ANOVA followed by Tukey's multiple comparisons test. For (D) and (F), two-way repeated measurements ANOVA analysis with time and treatment as main factors, followed by Tukey's multiple comparisons test. Data are expressed as mean ± SEM. *n*=8 per group. * *p*<0.05, **p<0.01, *p*<0.001, ****p<0.0001 vs vehicle and # *p*< 0.05, # # *p*<0.01, # # # p<0.001, # # # *p*<0.0001 vs control diet.

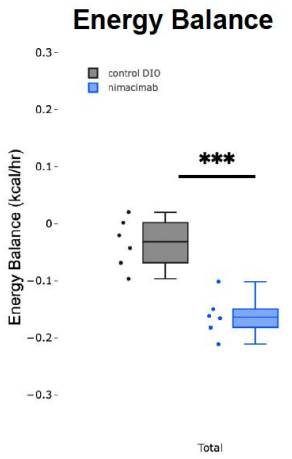
Nimacimab Increases Energy Expenditure

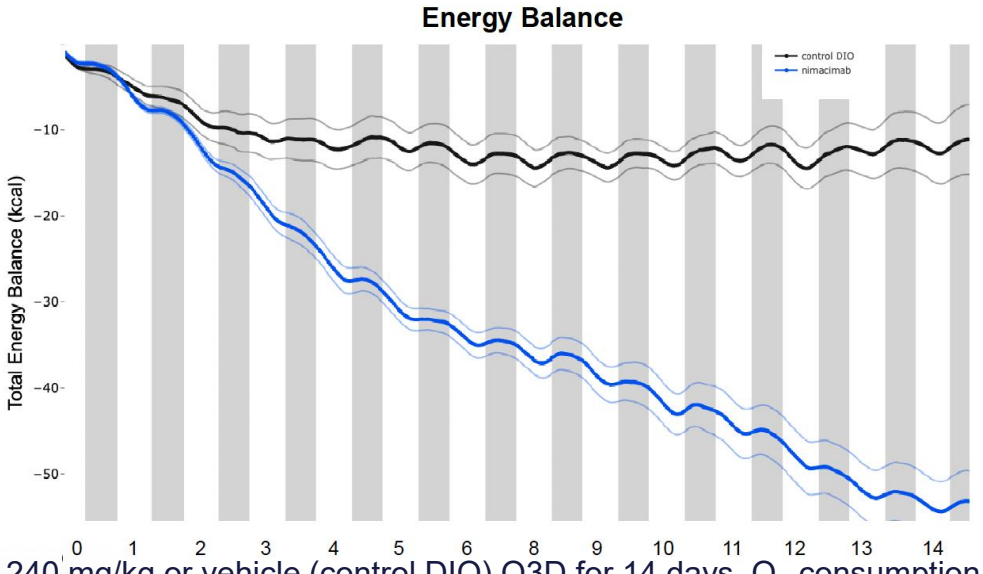






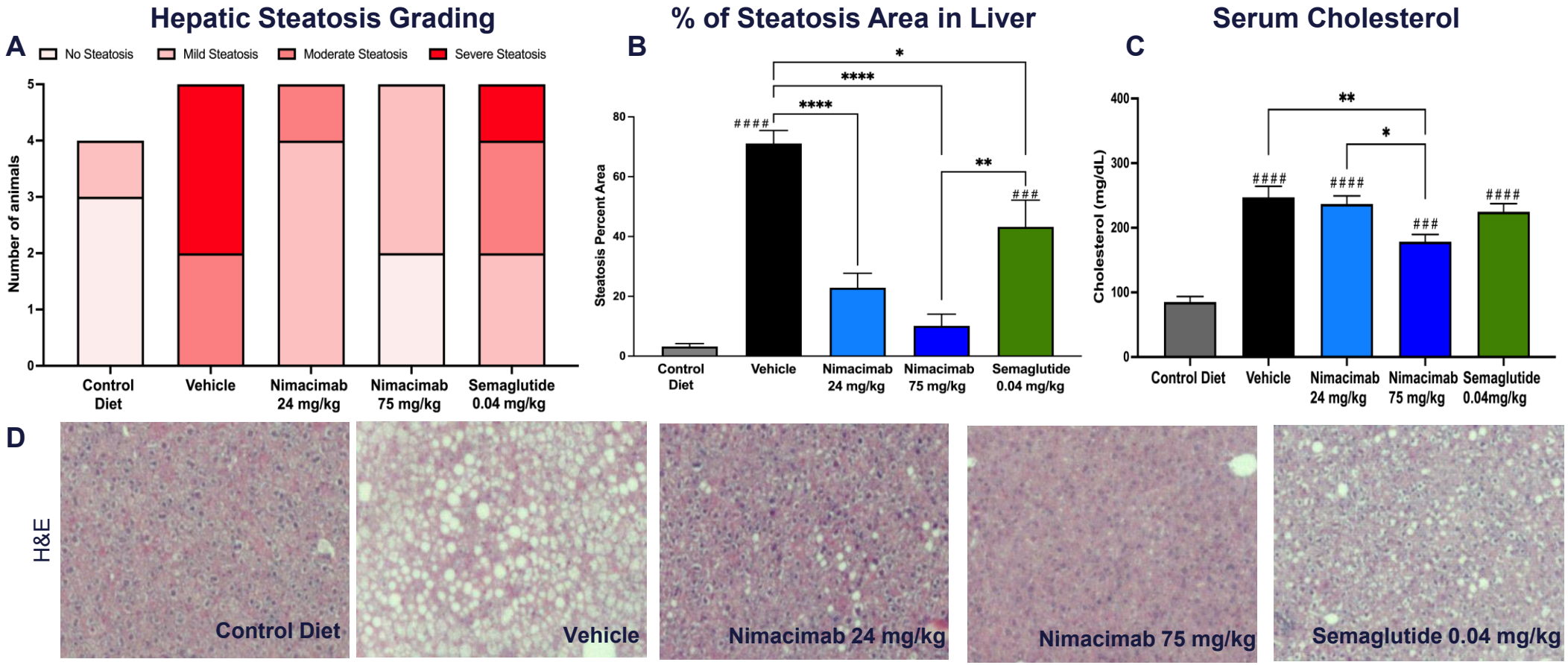






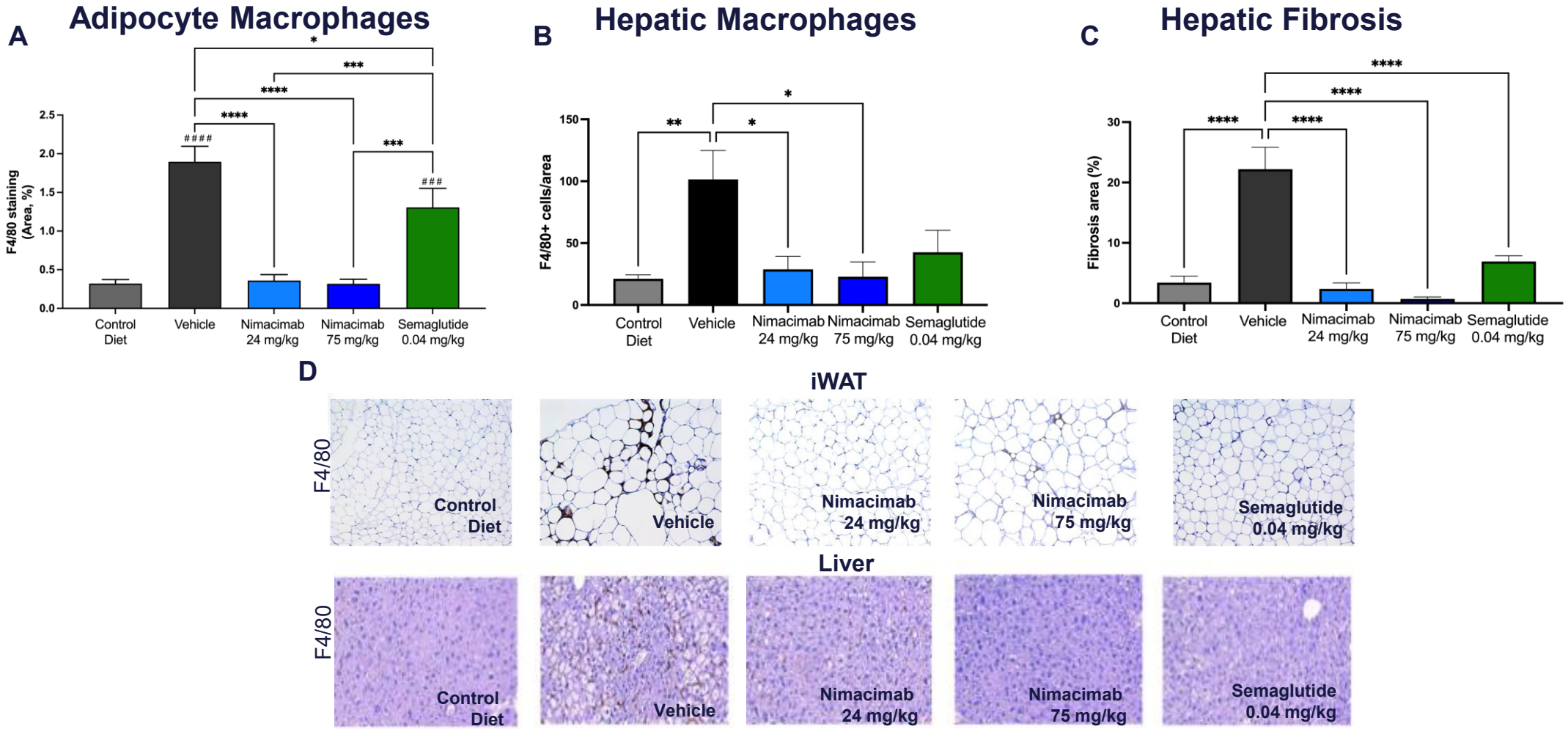
DIO mice (n=6) placed in PhenoMaster metabolic cages were dosed nimacimab 240 mg/kg or vehicle (control DIO) Q3D for 14 days. O_2 consumption, CO_2 production, food/water intake, and activity were recorded. Nimacimab treatment resulted in a significant increase in energy expenditure and a reduction in food intake, leading to a significant reduction in energy balance, in line with significant body weight loss. Locomotion was not changed by nimacimab treatment.

Nimacimab Modulates Lipid Metabolism



(A) H&E-stained liver sections were scored by a pathologist, who was blinded to the treatment groups, 0-3 based on the % of hepatocytes with fat. 0 = no steatosis (<5%), 1 = mild (5-33%), 2 = moderate (>33-66%), and 3 = severe steatosis (>66%). (B) Quantification of steatosis percent area using a computer-aided analysis with Cellprofiler. (C) Cholesterol levels were measured in serum using a commercial kit (Quimica Clinica Aplicada). (D) Representative images of H&E-stained hepatic tissue showing differences in fat deposition among treatment groups. Data are expressed as mean ± SEM. n=4-5 For (B) and (C) One-way ANOVA followed by Tukey's multiple comparisons test. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. # # # # p< 0.0001, # # # p< 0.001 vs control diet.

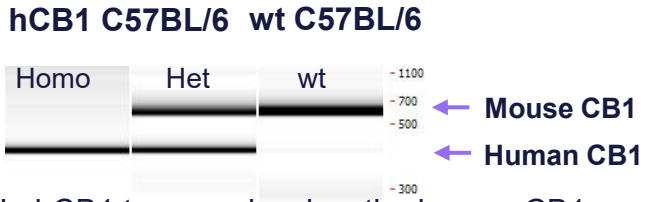
Nimacimab Reduces Obesity-induced Inflammation



Quantification of F4/80 positive cells (macrophages) in adipose tissue (A) and liver (B) was performed with ImageJ. (C) Quantification of collagen deposition from Sirius red staining (% area) to assess fibrosis. (D) Representative images of F4/80 staining in iWAT and liver. For (A), (B) , and (F) One-way ANOVA followed by Tukey's multiple comparisons test. *p<0.05, **p<0.01 ***p<0.001, ****p<0.0001, # # # # p< 0.0001, # # # p< 0.001 vs control diet. Data are expressed as mean ± SEM. n=3-7.

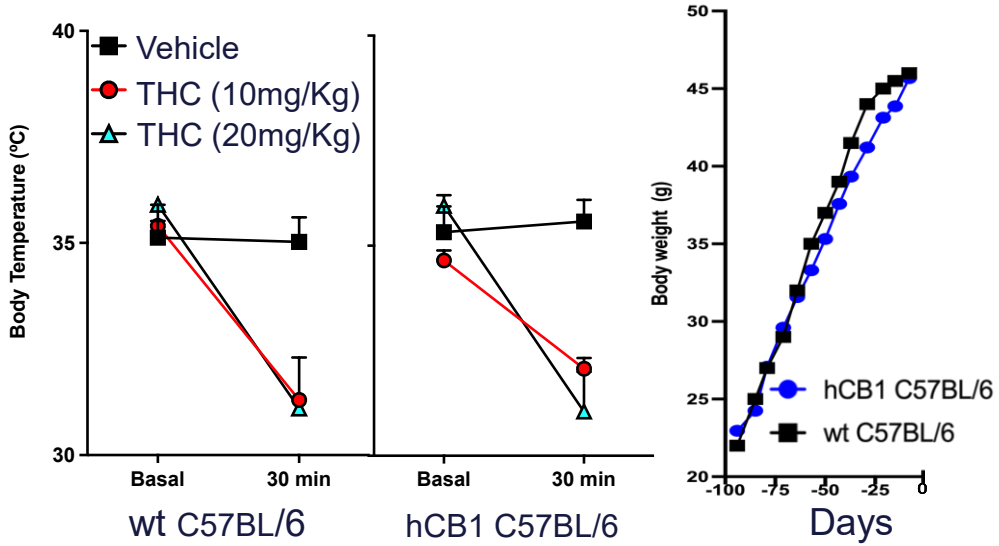
Development and Implementation of a Human CB1 DIO Mice Model to Demonstrate a Dose-response with Nimacimab

A hCB1 Genotyping

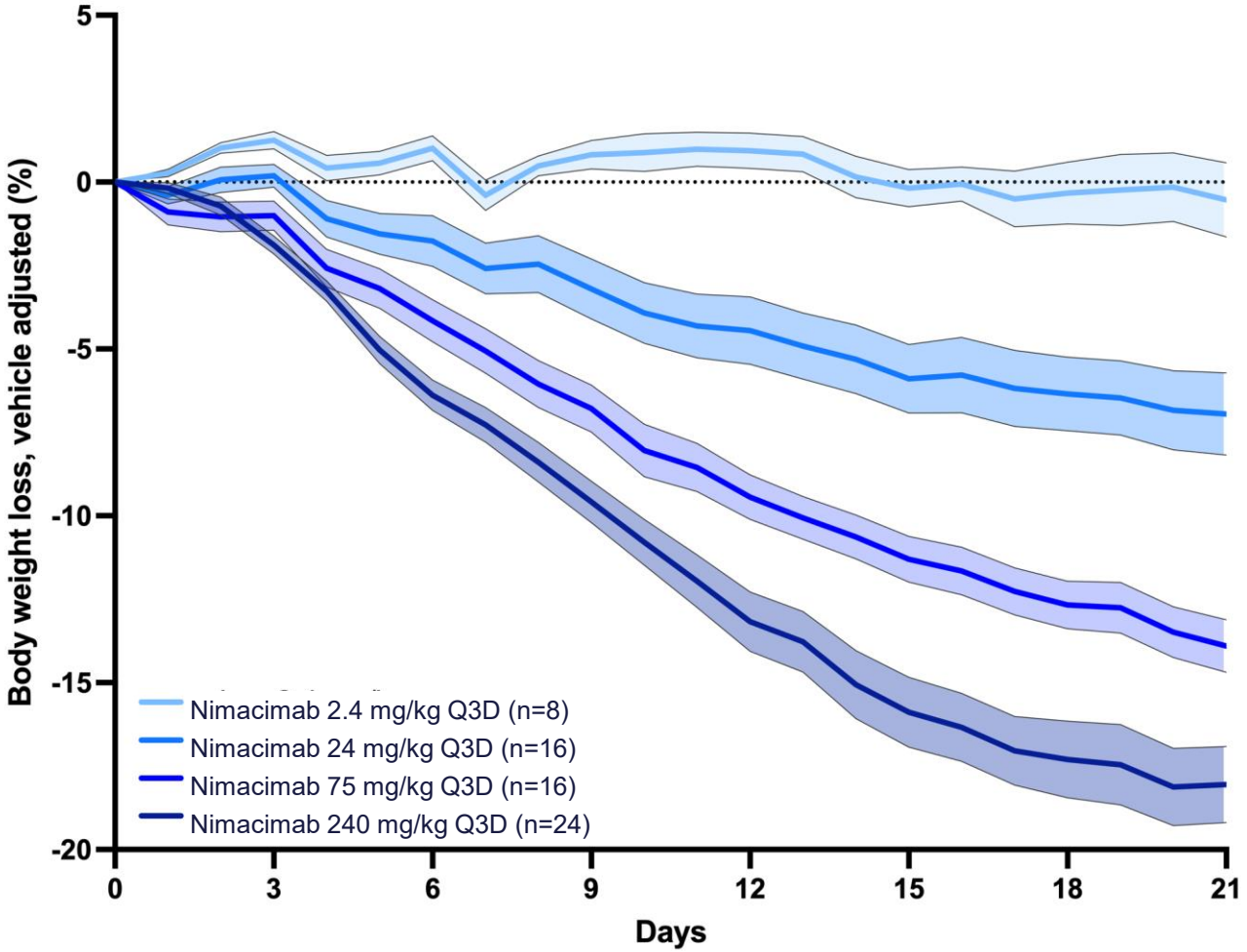


In hCB1 transgenic mice, the human CB1 gene was knocked in, disrupting the mouse CB1 gene.

B Validation of functional CB1 receptors (THC-induced hypothermia) and weight gain with HFD

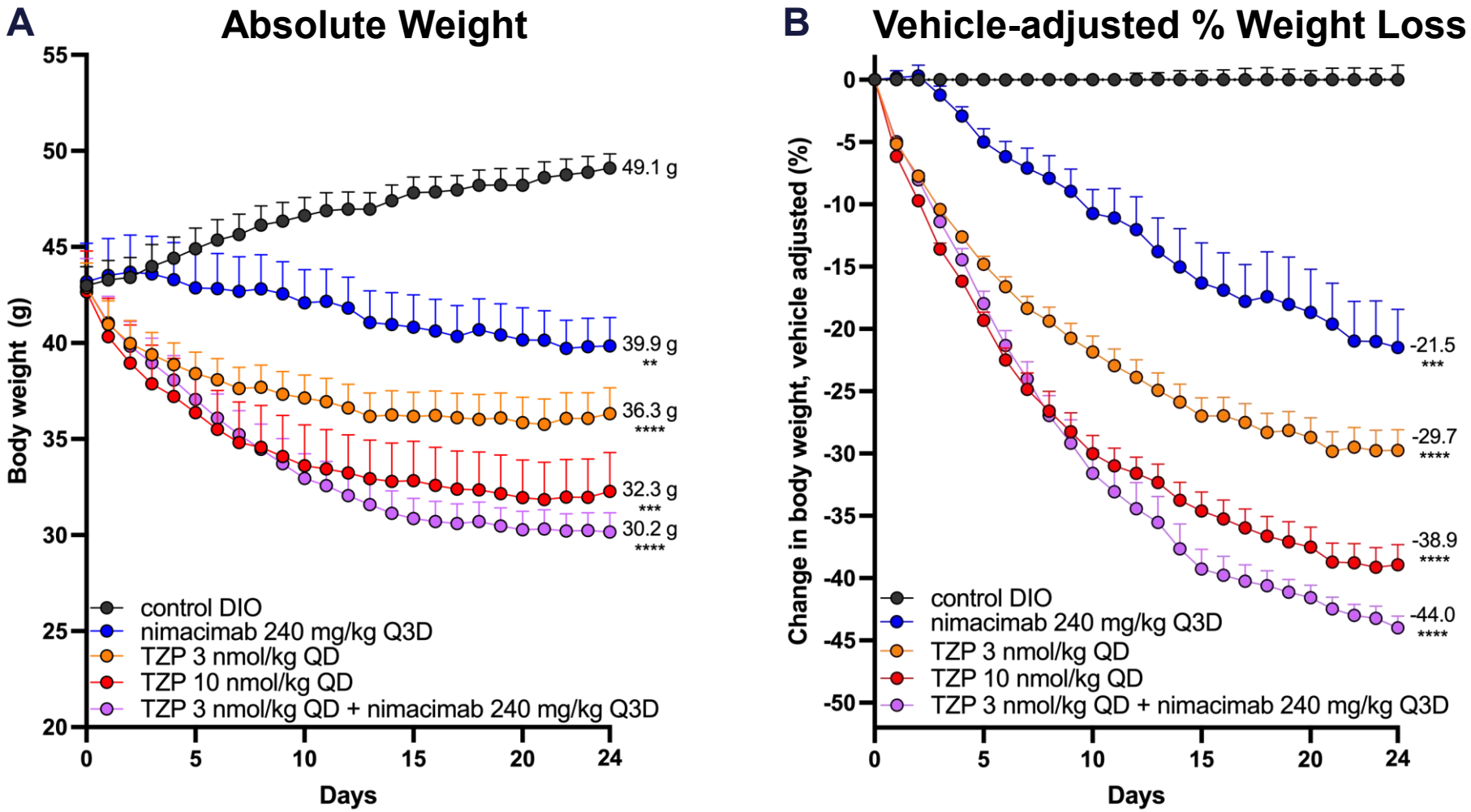


C Dose Curves from Multiple Diet-Induced Obese Studies



(A) Representative qPCR genotyping result of *hCB1* transgenic mice. (B) Wild-type mice (wt) and homozygous hCB1 C57BL/6 were used to induce THC-mediated hypothermia (n=3 per group) and fed a high-fat diet (HFD) to measure weight gain. (C) Mice with DIO fed a high-fat diet were dosed with nimacimab (2.4 mg/kg, 24 mg/kg, 75 mg/kg, or 240 mg/kg IP, Q3D). The control DIO's daily average change in body weight was subtracted from each animal's individual change in body weight to calculate % change in body weight from baseline, vehicle adjusted.

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

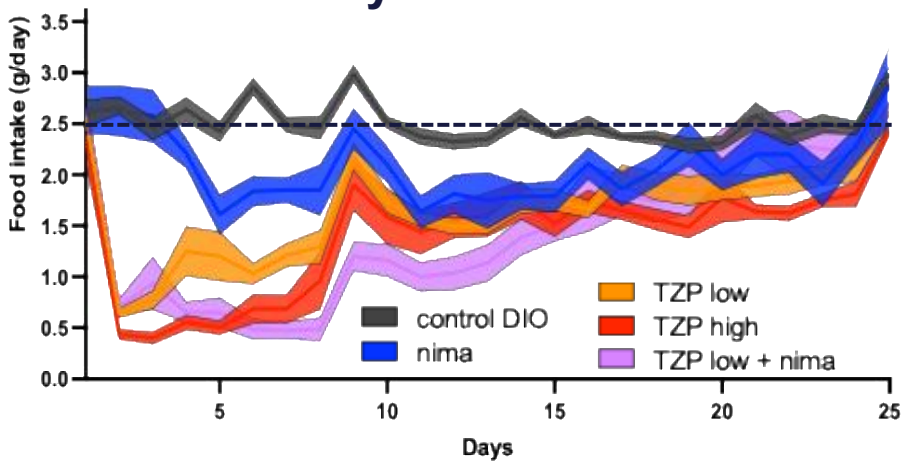


The daily average change in body weight from day 1 of treatment from the vehicle group was subtracted from the individual change in body weight per animal to calculate % change in body weight from baseline, vehicle adjusted. The combination of nimacimab with tirzepatide significantly outperformed either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

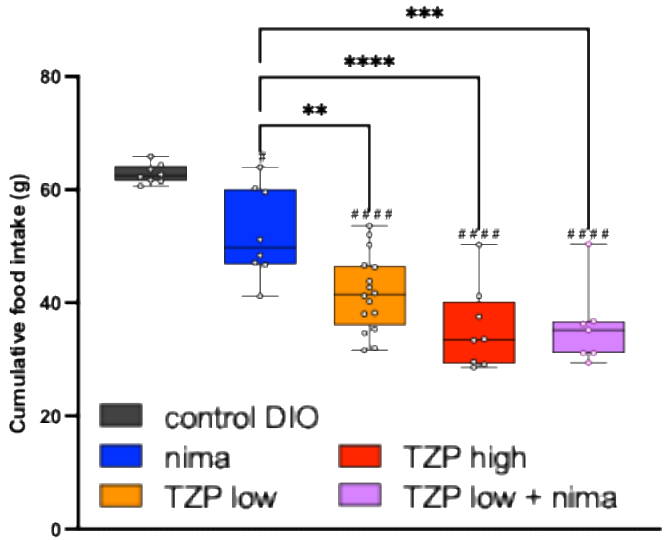
Intermediate Reduction in Food Intake with Nimacimab

Combo improves WL but does not reduce calories, suggesting alternative MOAs

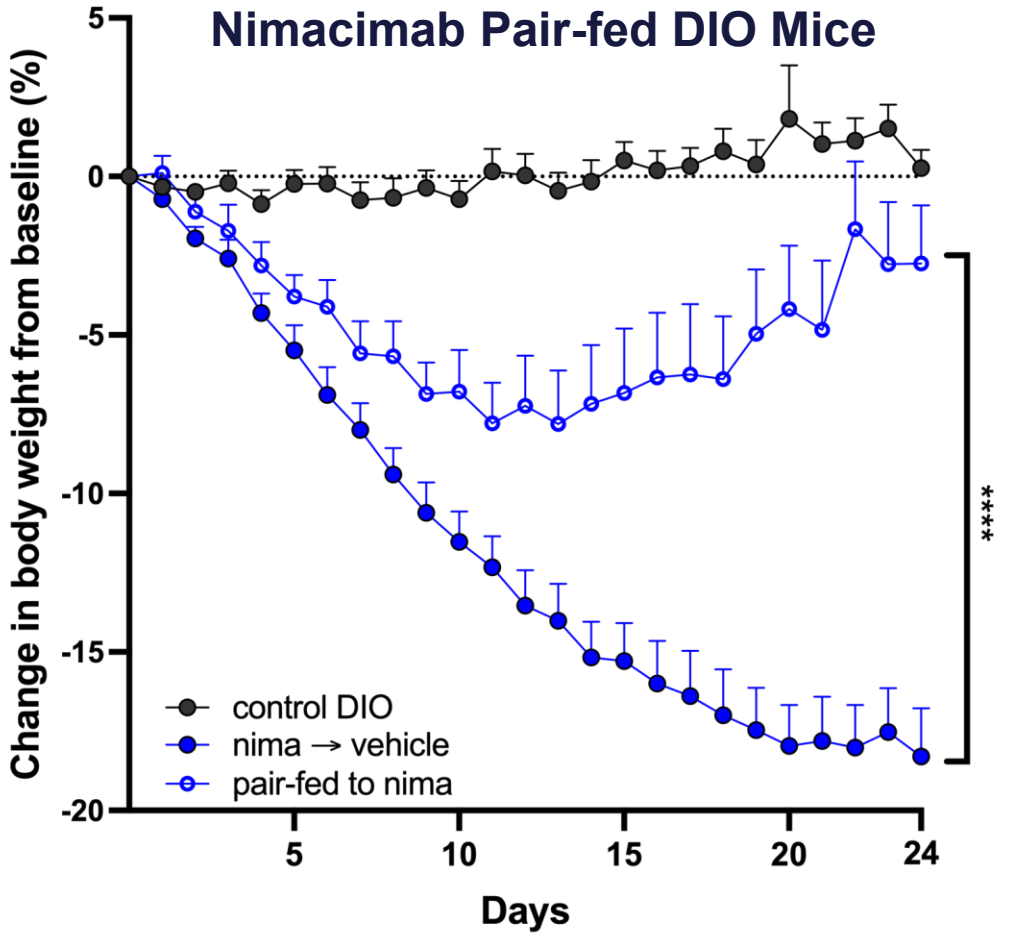
Daily Food Intake



Cumulative Food Intake

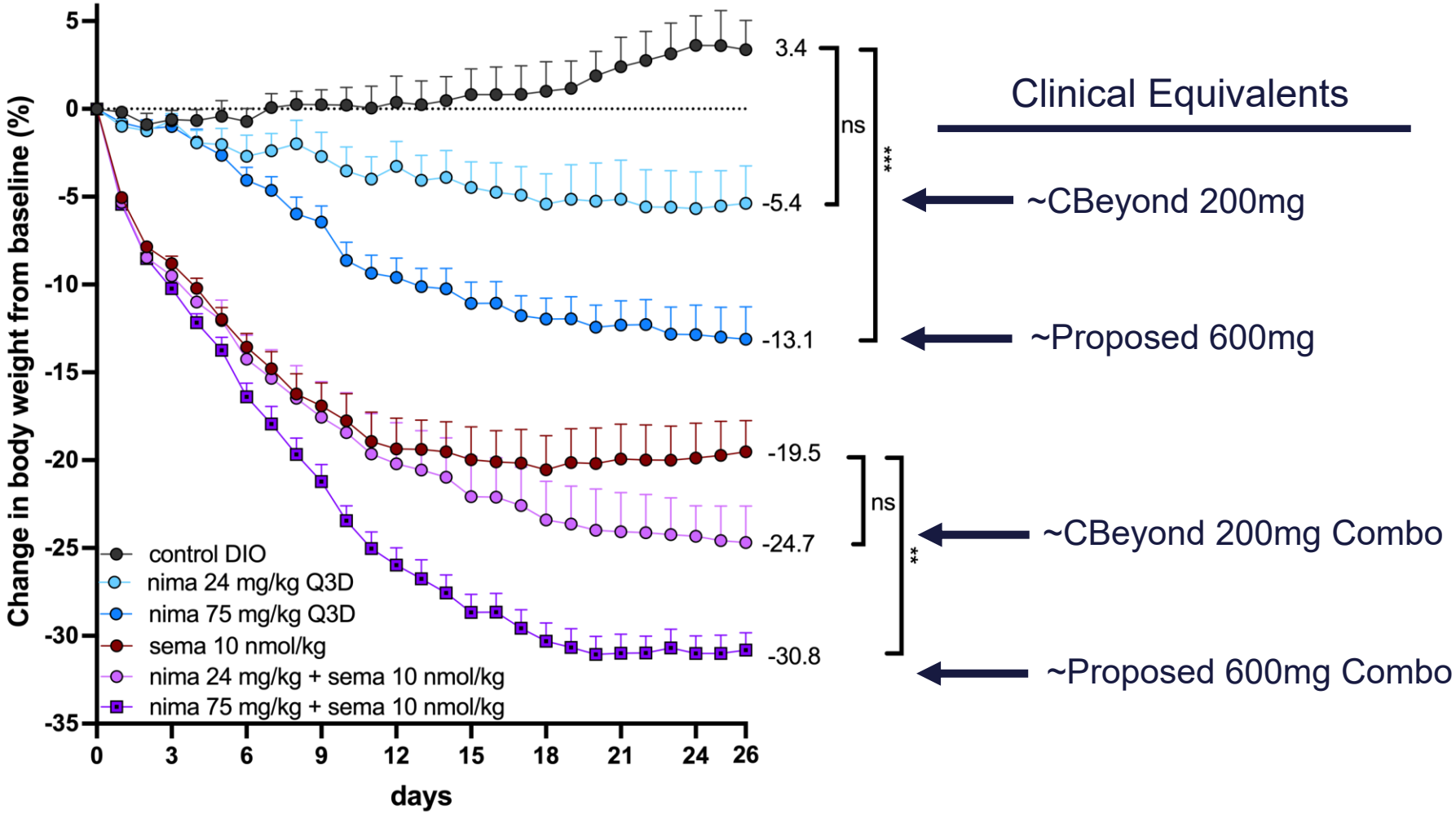


Nimacimab Pair-fed DIO Mice



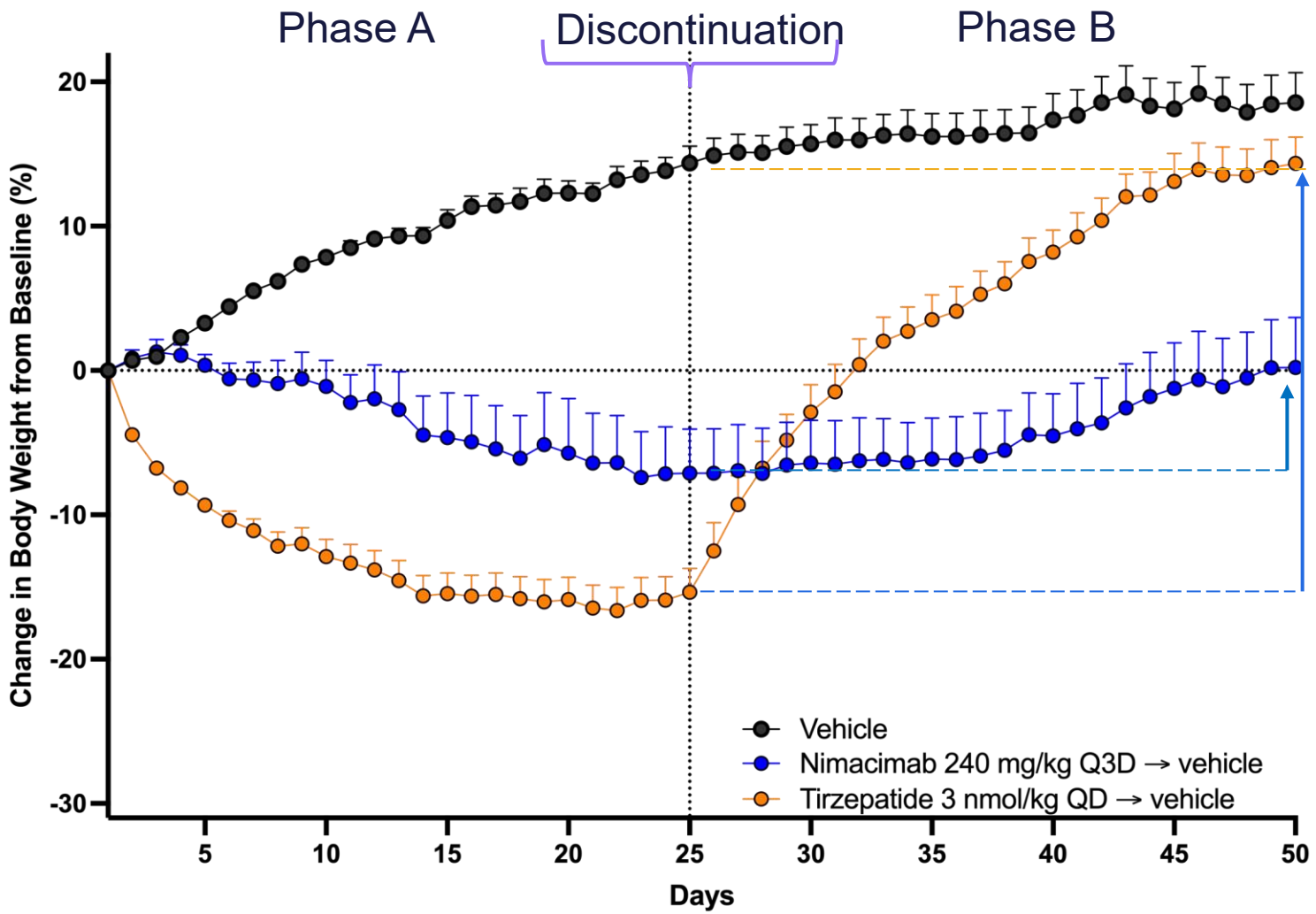
For cumulative food intake, One-way ANOVA followed by Tukey's multiple comparisons test. **p<0.01 ***p<0.001, ****p<0.0001. # p< 0.05, # # # # p< 0.001 vs control DIO. Data is plotted as mean ± SEM. n= 8 per group. Mice with comparable body weight in the pair-fed group had their calories restricted to match the daily calories consumed by the nimacimab group the day before. Pair-fed, *two-way ANOVA analysis followed by Tukey's multiple comparison tests. Significance reported at day 24. ****p<0.0001*

Active Dose of Nimacimab Significantly Enhances Combination with Semaglutide



The control DIO's daily average change in body weight was subtracted from each animal's individual change in body weight 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 26. Data are expressed as mean ± SEM. n=7-8 per group.

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

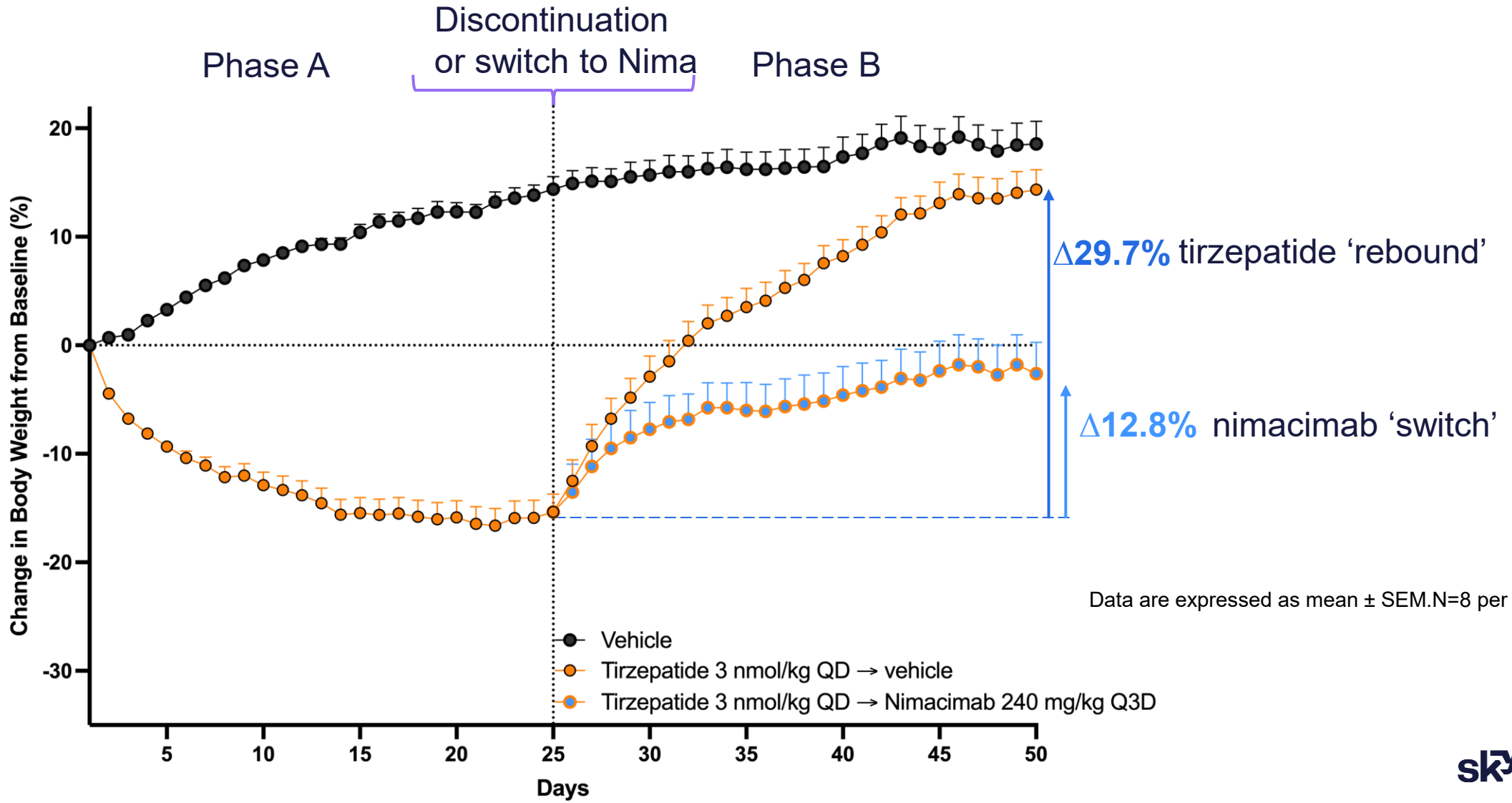


Δ29.7% tirzepatide 'rebound'

Δ7.4% nimacimab 'rebound'

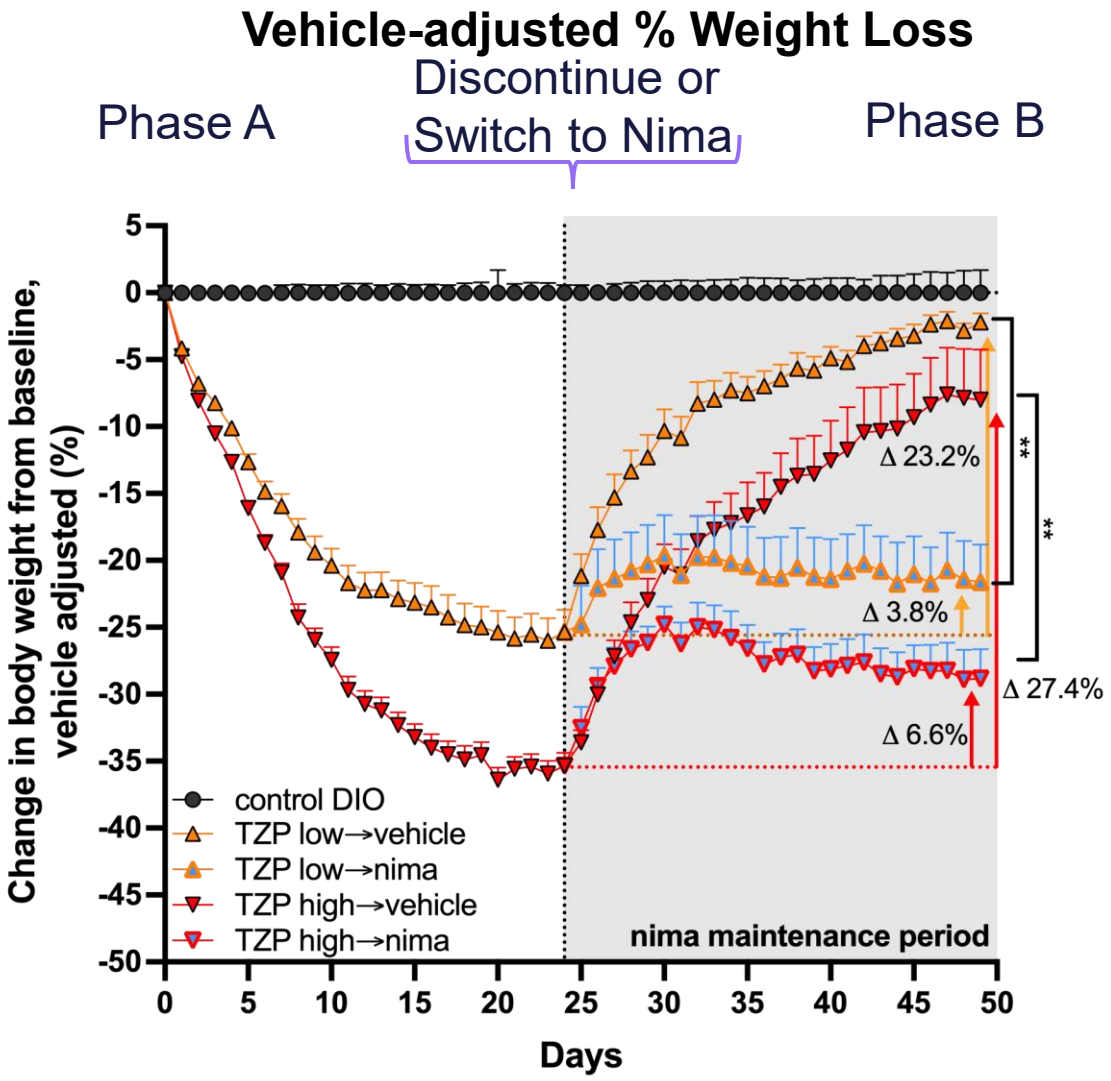
Data are expressed as mean ± SEM. n=8 per group

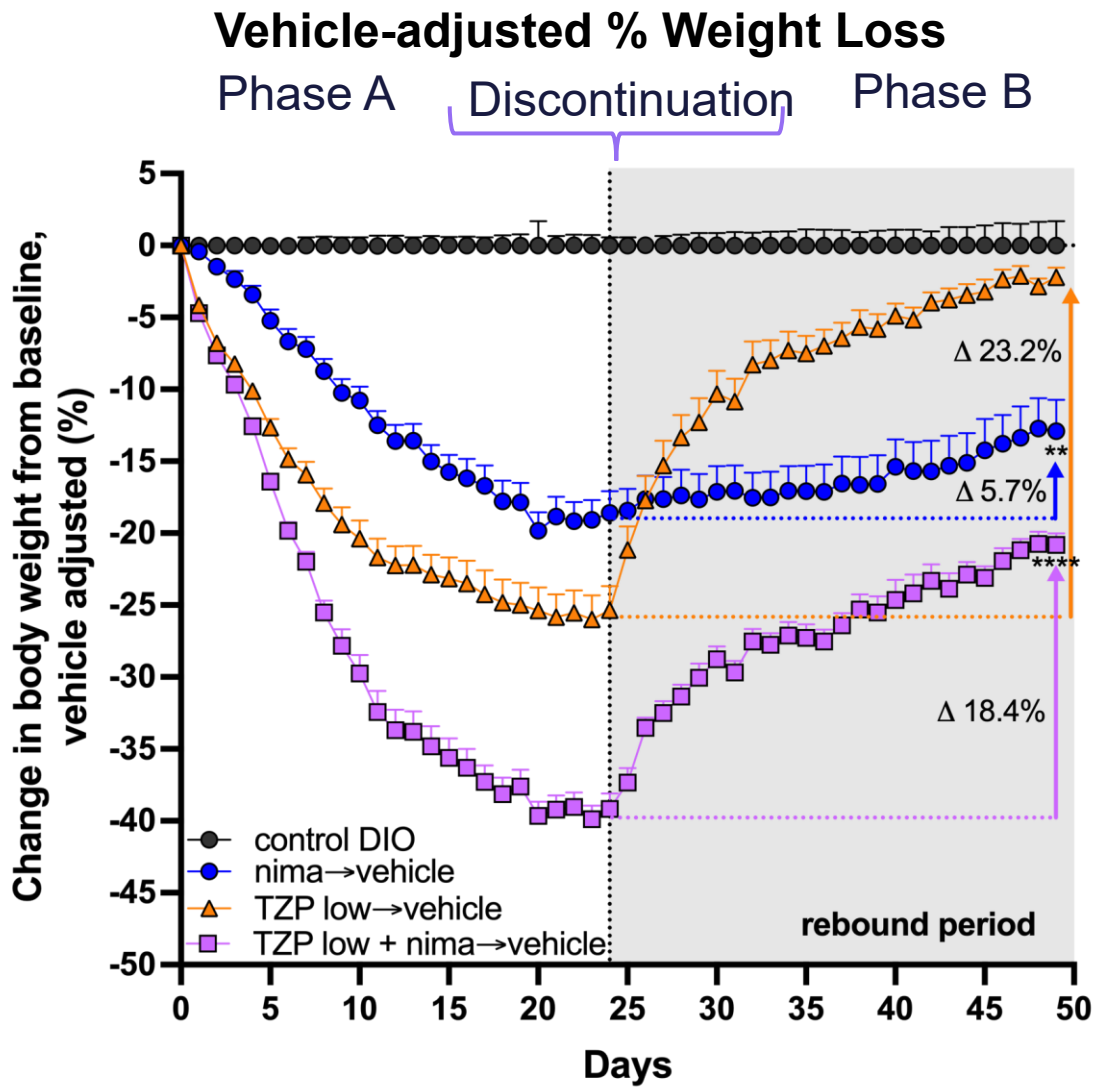
Switching to Nimacimab Treatment Limits Rebound and Shows Significant Potential as Maintenance Therapy



Data are expressed as mean ± SEM.N=8 per group.

Switching to Nimacimab Limits Rebound and Continues to Highlight Potential as Maintenance Therapy



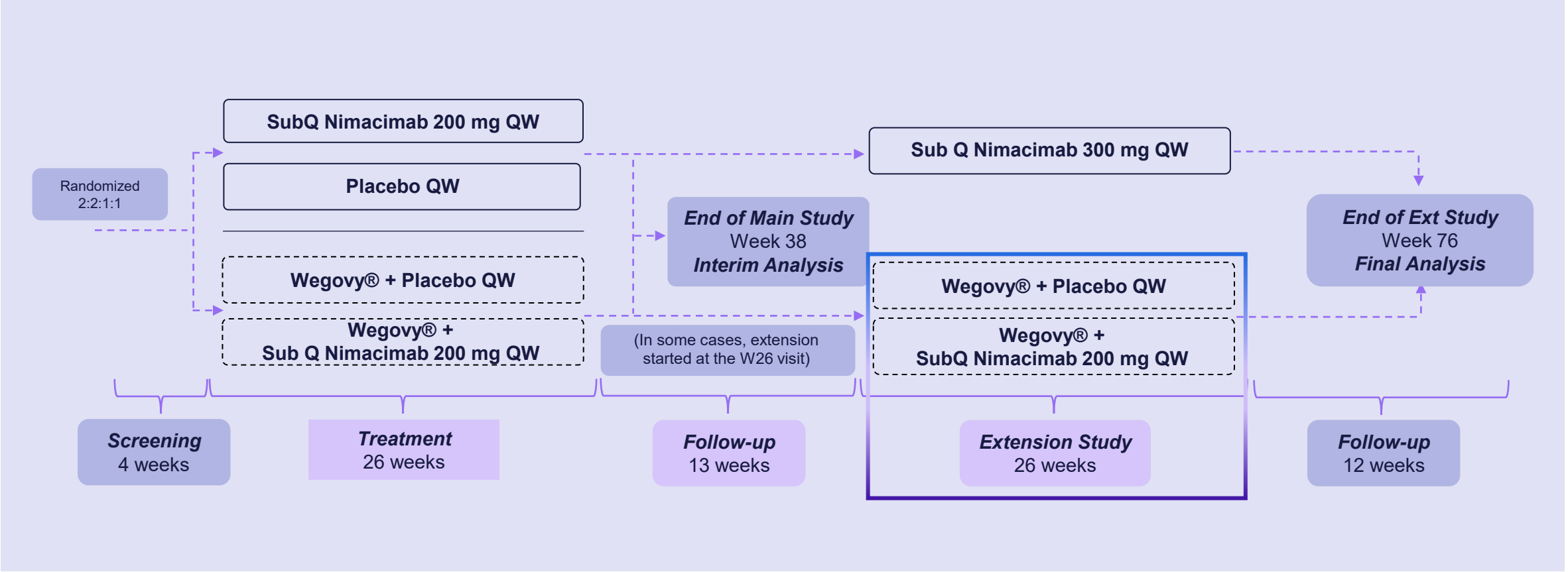


Data are expressed as mean ± SEM. n=7-8 per group.

Review of Interim Extension Study: 52-Week Combination Data

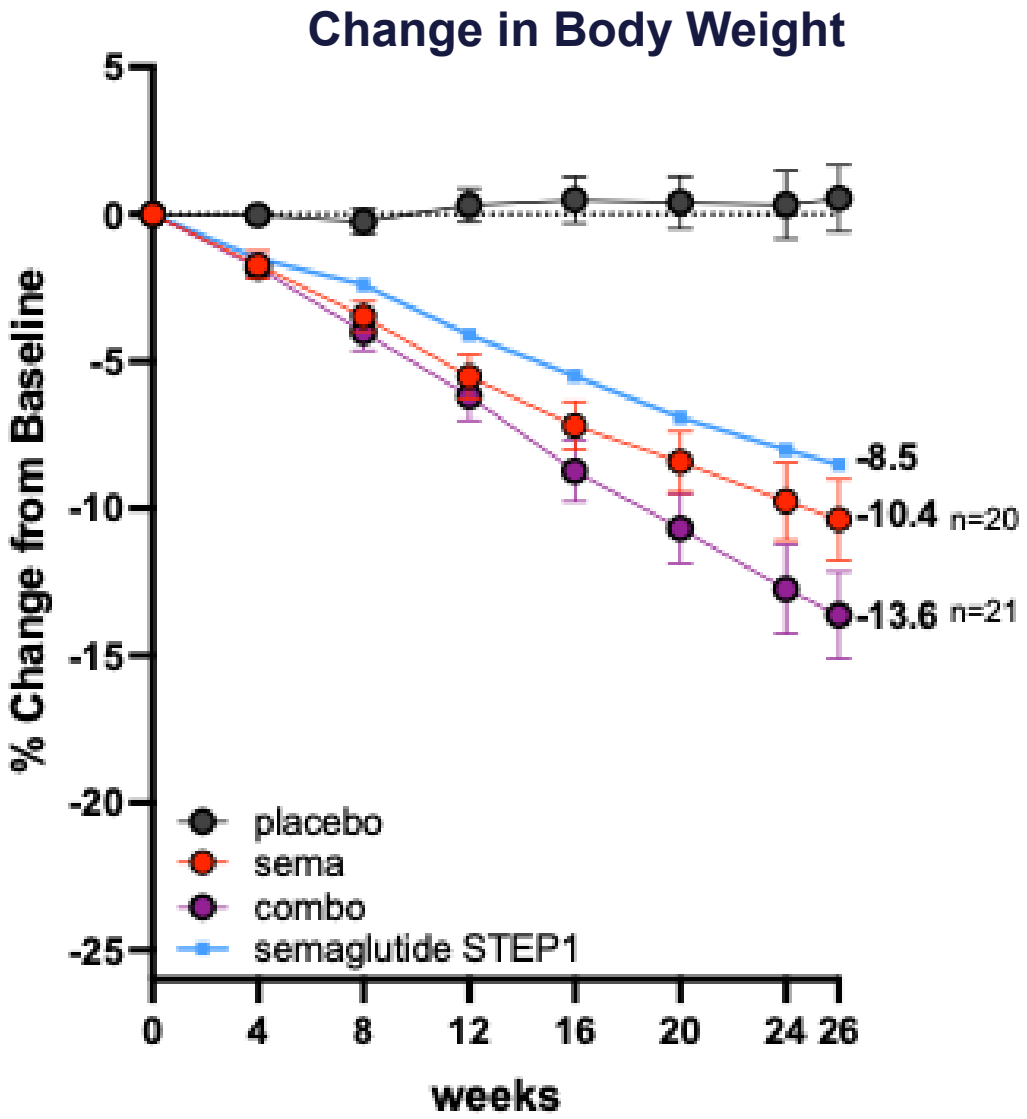
CBeyond Phase 2a Clinical Trial Design for Proof of Concept

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



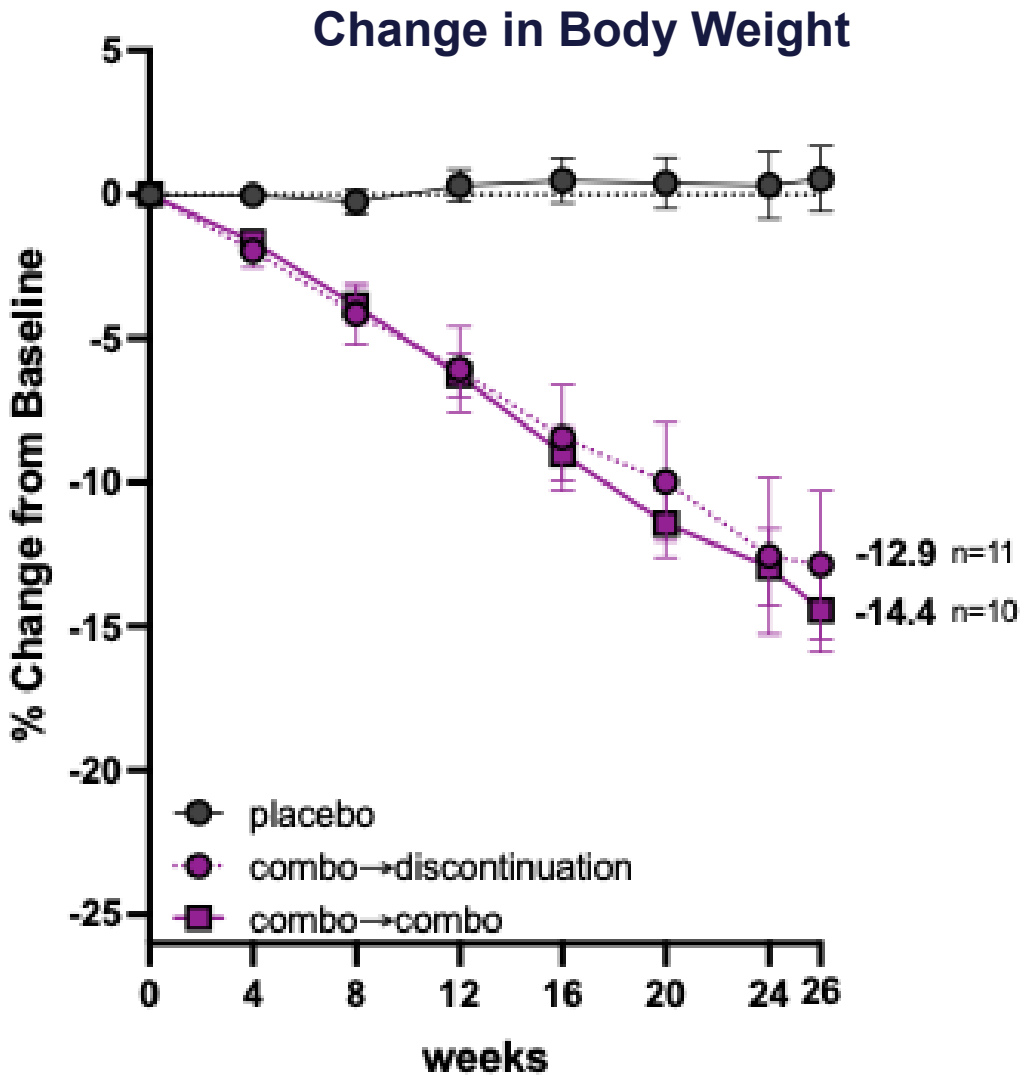
Initial 26-week treatment period completed; 26-week extension study ongoing

Nimacimab + Semaglutide Performed Better Than Semaglutide Alone



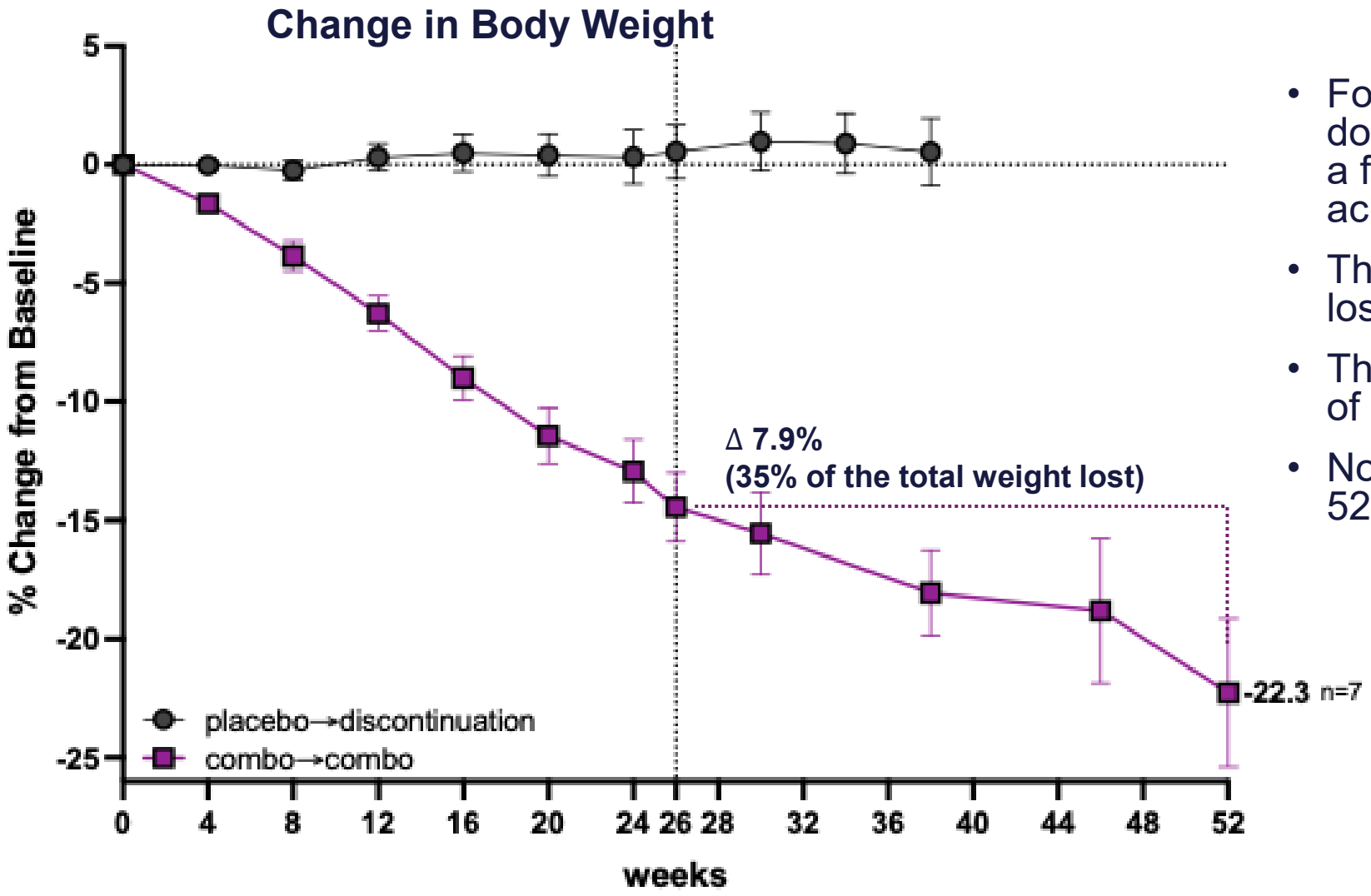
- Combination of nimacimab + semaglutide resulted in a 30% increase compared to semaglutide alone in CBeyond at 26 weeks.
- Semaglutide alone and combination groups in CBeyond outperformed historical semaglutide data (STEP-1).

Combination Subjects Similar between Extension and Follow-up Groups



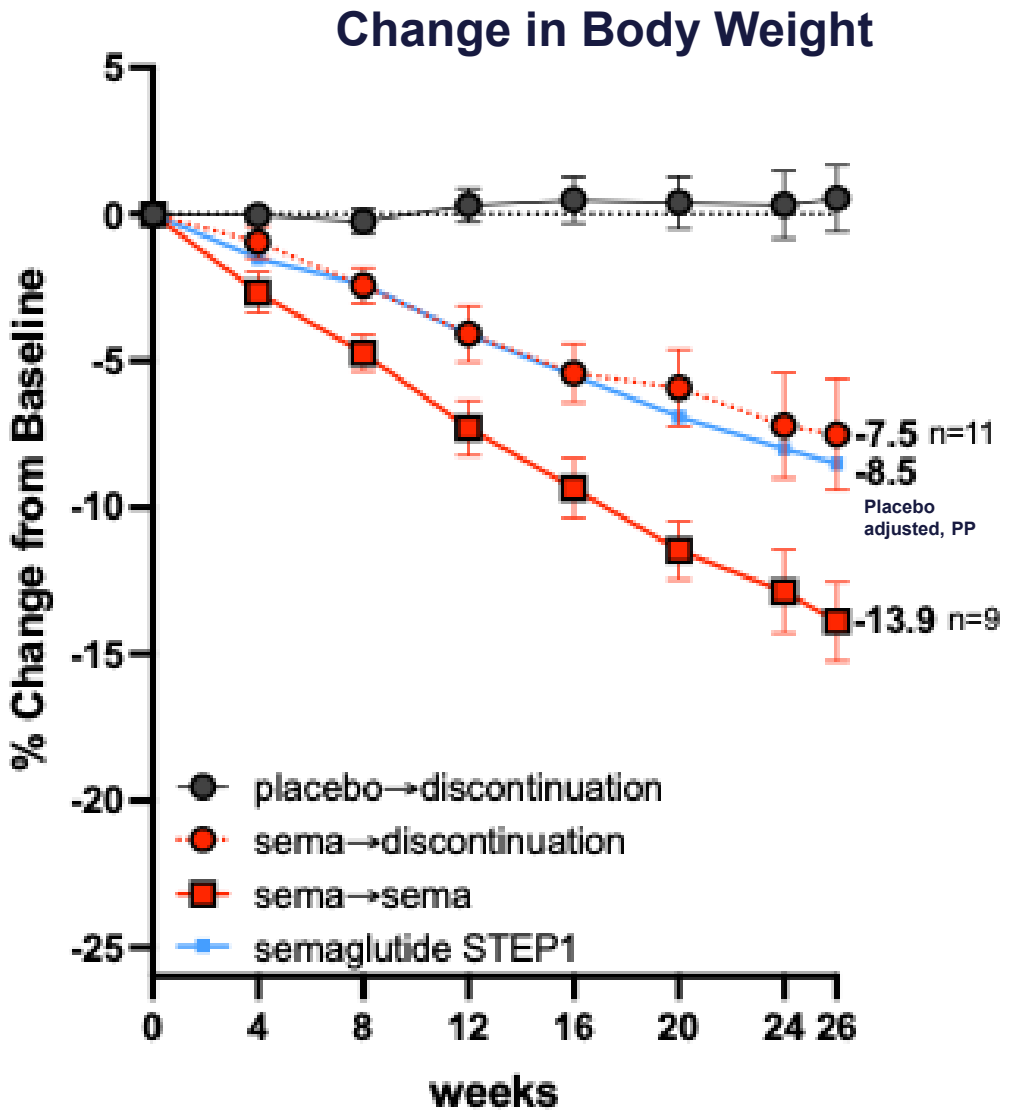
- 10 subjects on active combination (nimacimab + semaglutide) rolled over to extension
- 11 subjects on the nimacimab + semaglutide combination therapy went into off therapy follow up
- There was minimal difference between the two groups in weight loss achieved at 26-weeks.
- We believe this suggests that the extension therapy subset is representative of the larger cohort of subjects on the combination treatment

Combination Group Demonstrated 22.3% Weight Loss at 52-Weeks



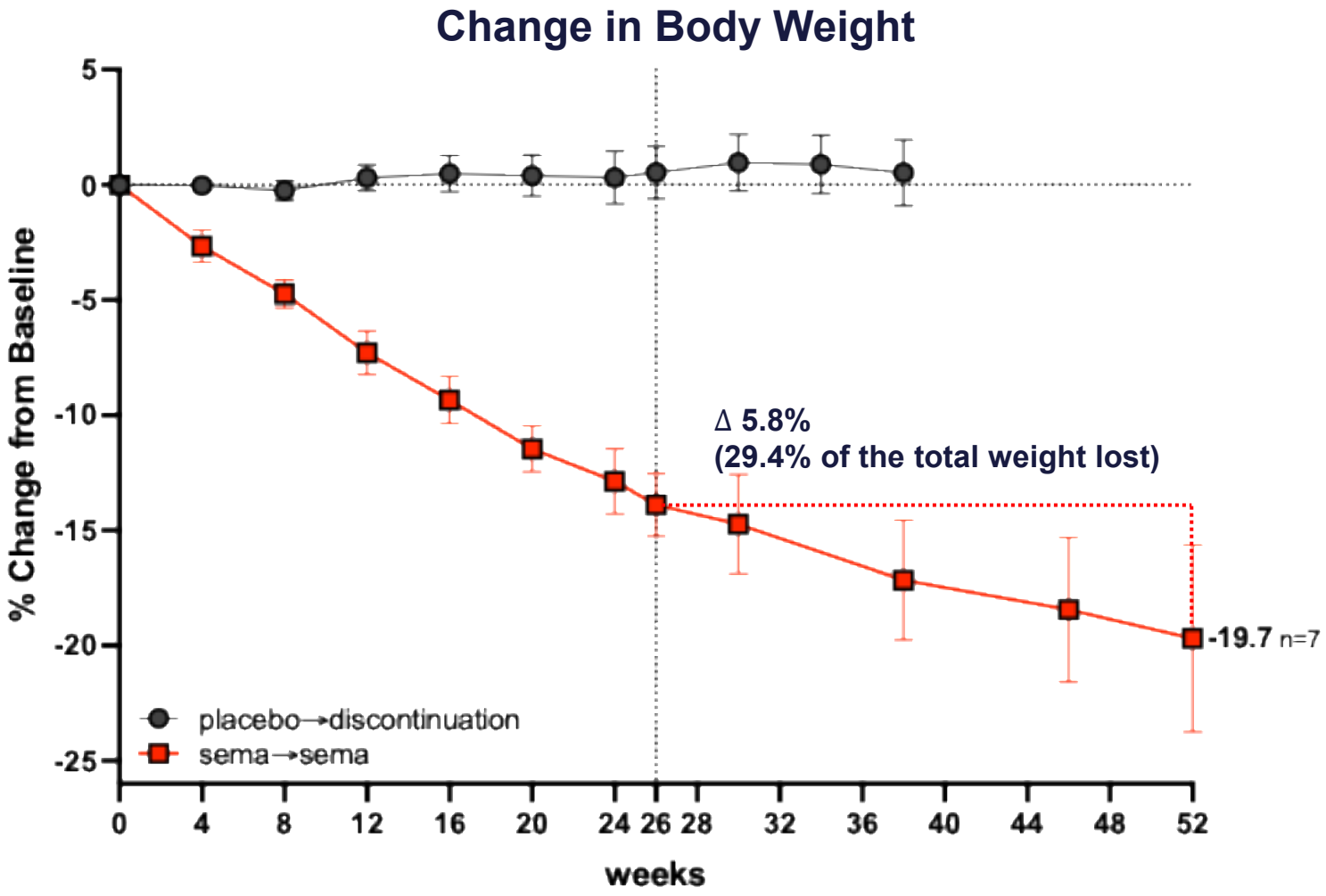
- Following an additional 26-weeks of dosing of nimacimab + semaglutide, a further 7.9% weight loss was achieved
- This represents 35% of total weight loss over 52-weeks.
- The total weight loss after 52 weeks of treatment was 22.3%
- No plateau in weight loss seen at 52 weeks

Semaglutide Subjects Were Different Between Extension and Follow-Up



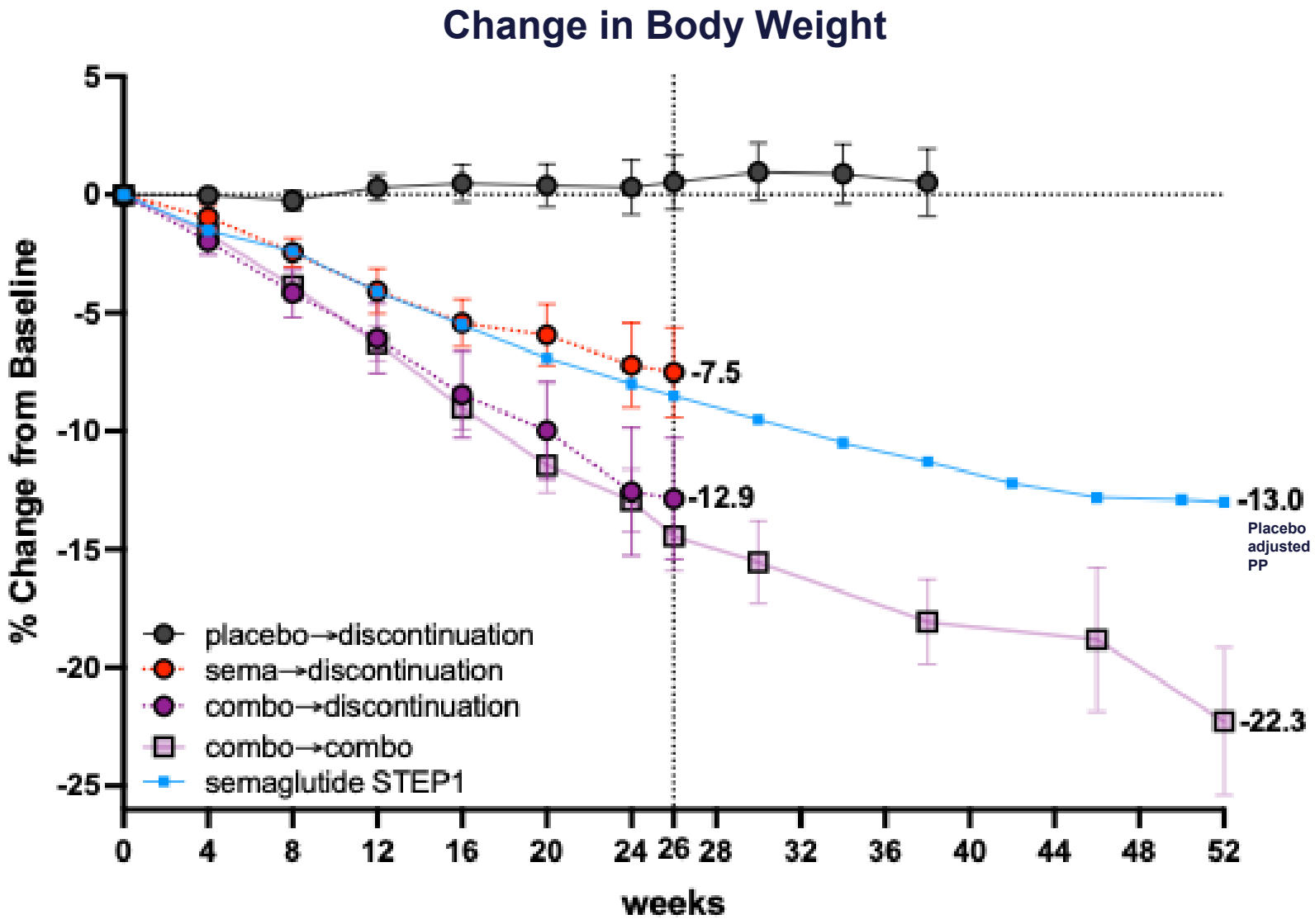
- 9 subjects in the semaglutide alone (with placebo) arm enrolled in the extension study.
- 11 subjects in the semaglutide arm went into off therapy follow
- There was a marked difference in weight loss between these two groups at week 26 (85% greater weight loss in the extension subset)
- This suggest that subset in extension treatment was not representative of the larger cohort and also differs from the historical response to semaglutide
- Subjects who were doing well on semaglutide chose to participate in the extension study
- This subset is a self-selected high-responder population (i.e. Super Responders).

Semaglutide Group Demonstrated a 19.7% Weight Loss at 52-Weeks



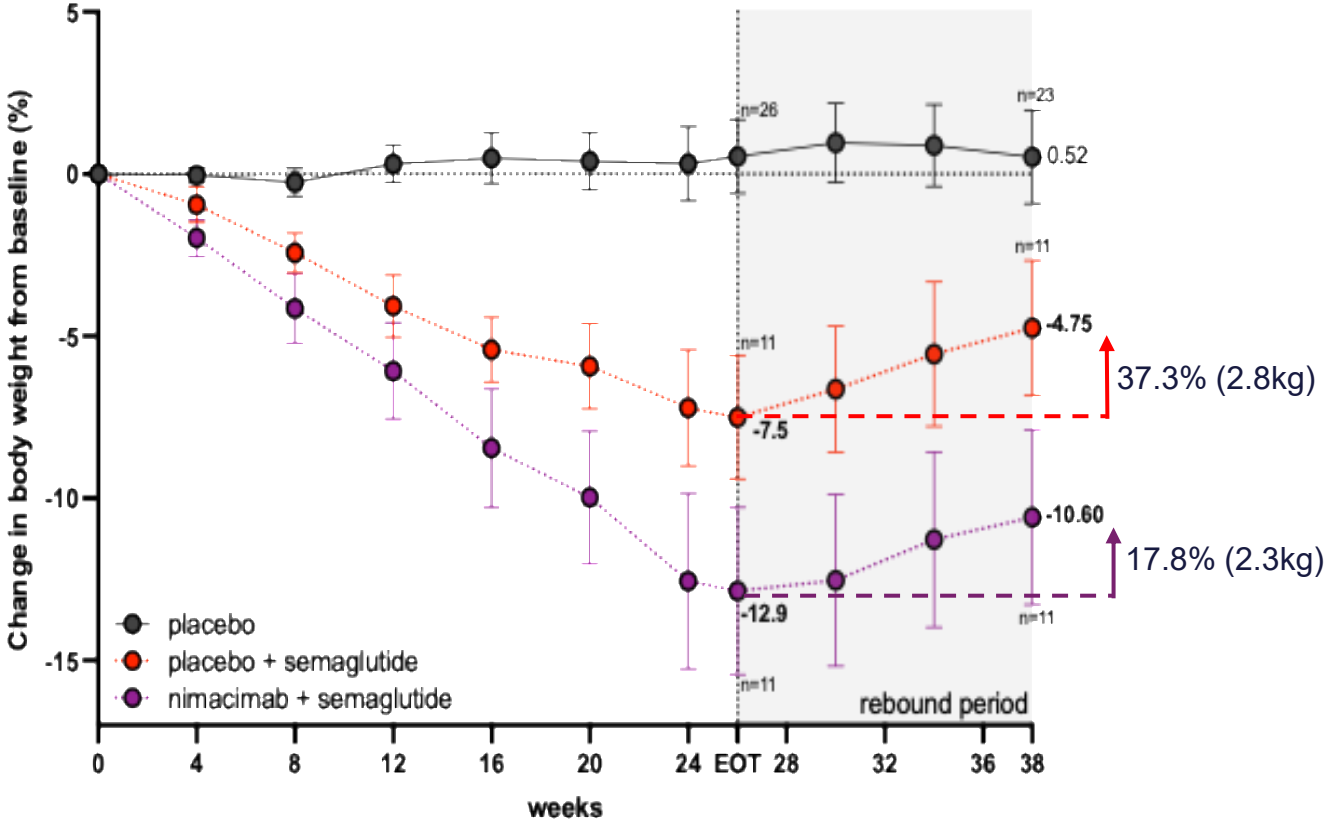
- Following an additional 26-weeks of dosing of semaglutide + placebo, a further 5.8% weight loss was achieved.
- The additional 5.8% represents 29.4% of total weight loss over 52-weeks.
- The total weight loss after 52 weeks of treatment was 19.7%.
- This “Super Responder” population performed better than historical semaglutide.

Nimacimab Converts Patients to “Super Responders”

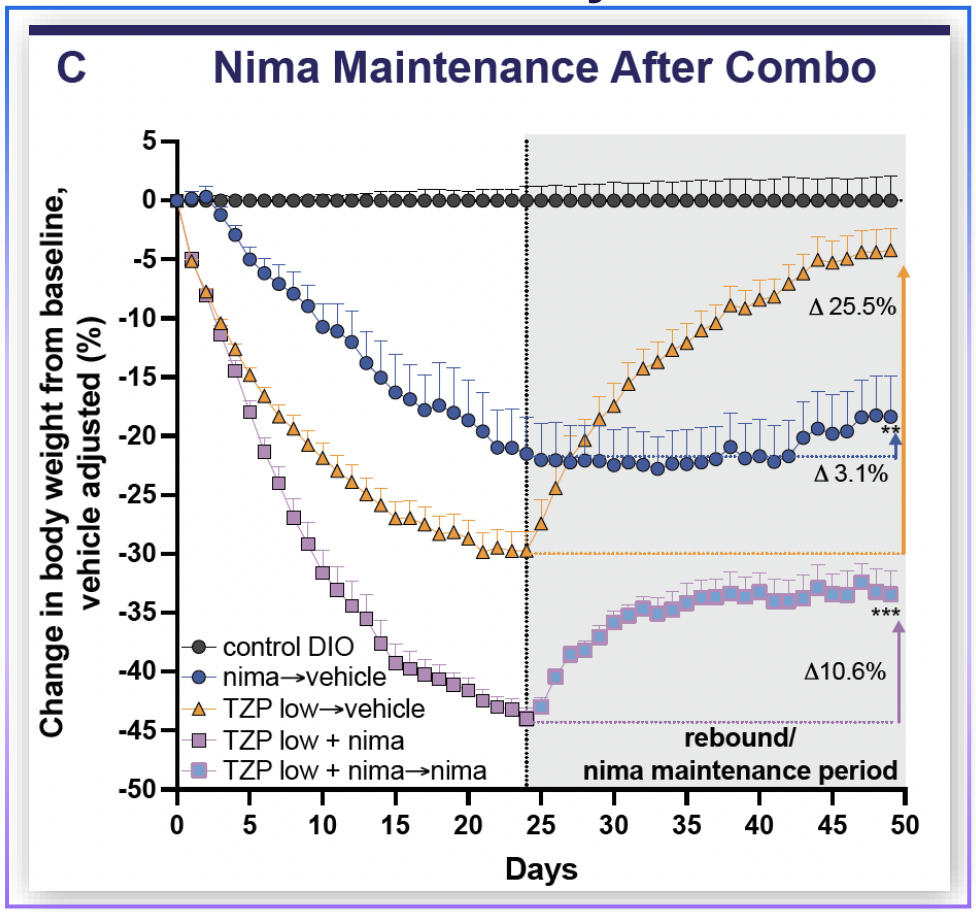


- Unusually high frequency of sema ‘super-responders’ makes it challenging to differentiate the combo effect
- Sema discontinuation group closely mirrors the STEP-1 trajectory
- Both combination cohorts closely track with the more active efficacy curves
- Thus in a larger trial, we would expect the sema cohort to closely follow the STEP-1 curve while the combination cohort **would be expected to sustain ~20–23% weight loss**

Nimacimab Reduces Weight Regain Off-Therapy Follow-Up for 13 Weeks after the Last Dose

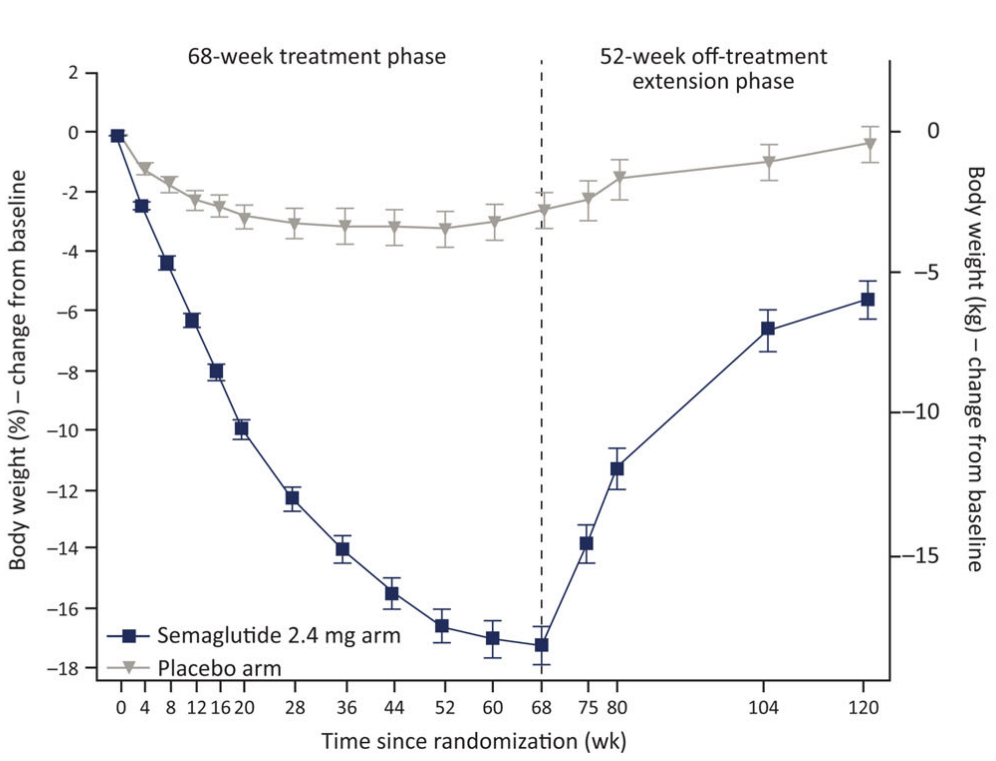


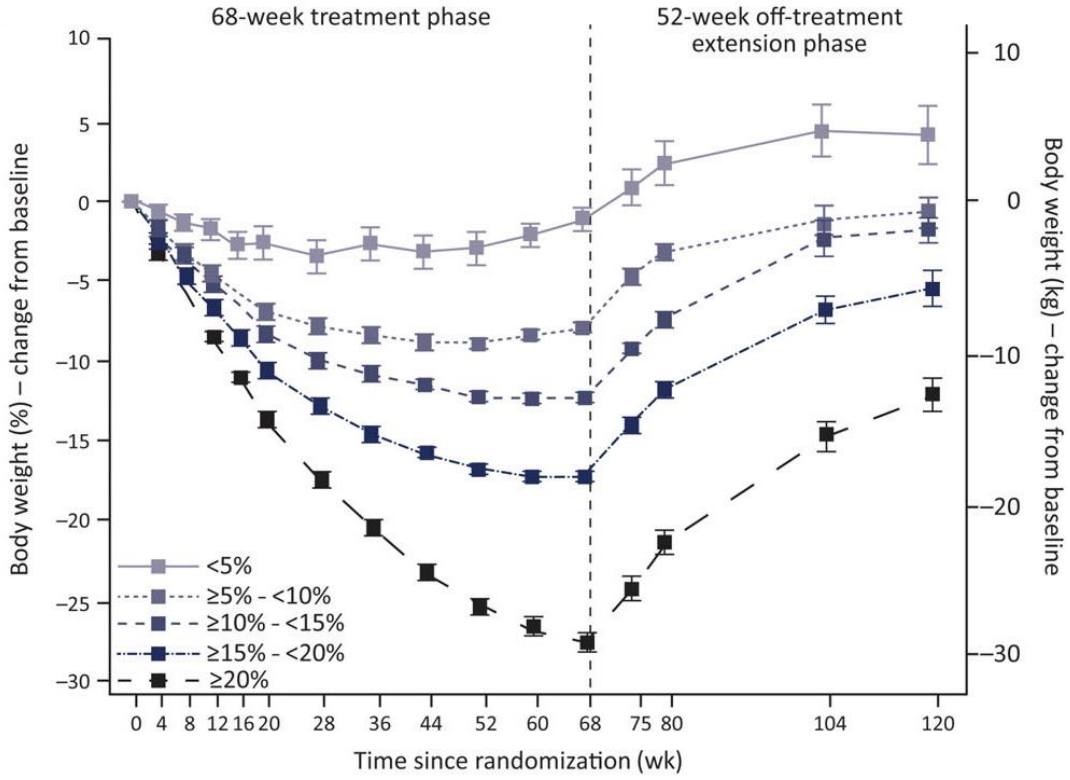
DIO Study



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.

Typical Semaglutide Rebound Profile

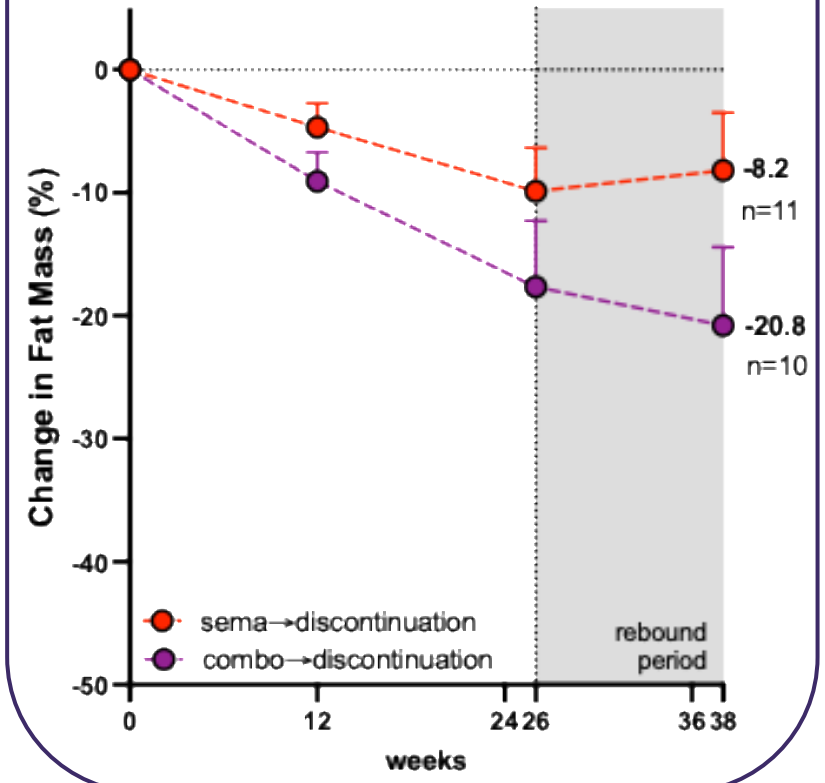




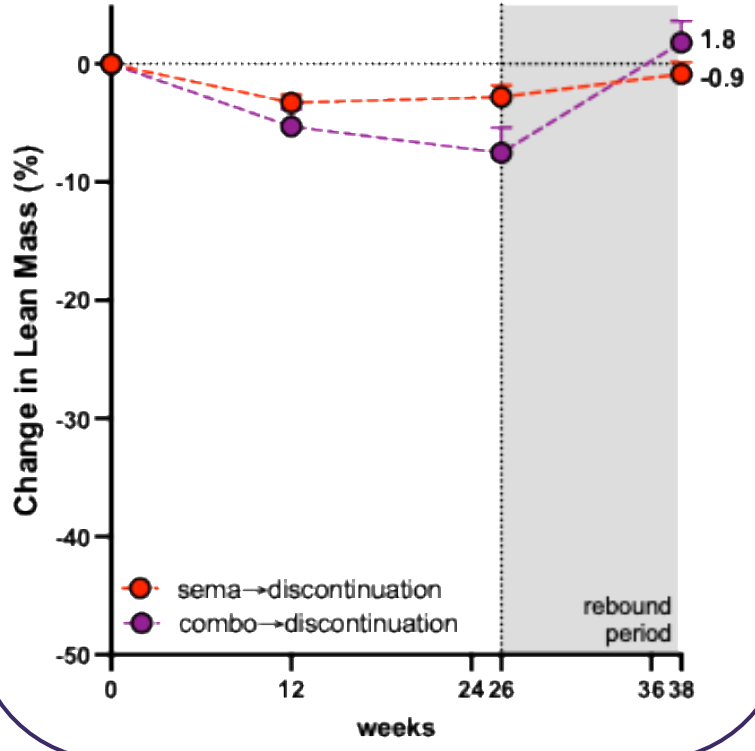
Wilding *et al.*, 2022. *Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension*

Differentiated Body Composition Through 13-Week Follow-Up

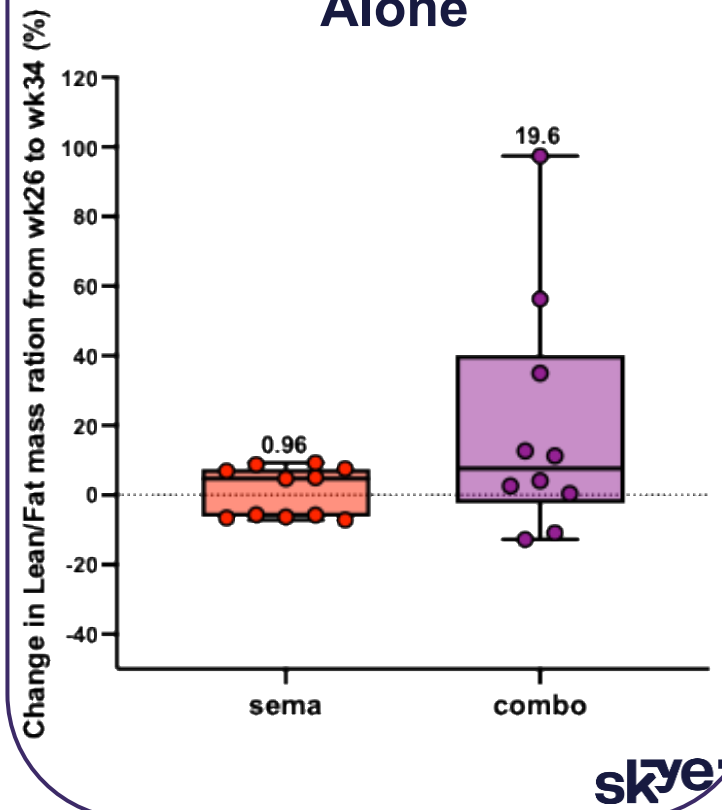
Combo Group Maintains Fat Mass During Follow-Up Period



Combo Group Gains Lean Mass During Follow-Up Period



Lean to Fat Mass Ratio Improves Compared to Sema Alone



Summary and Conclusions

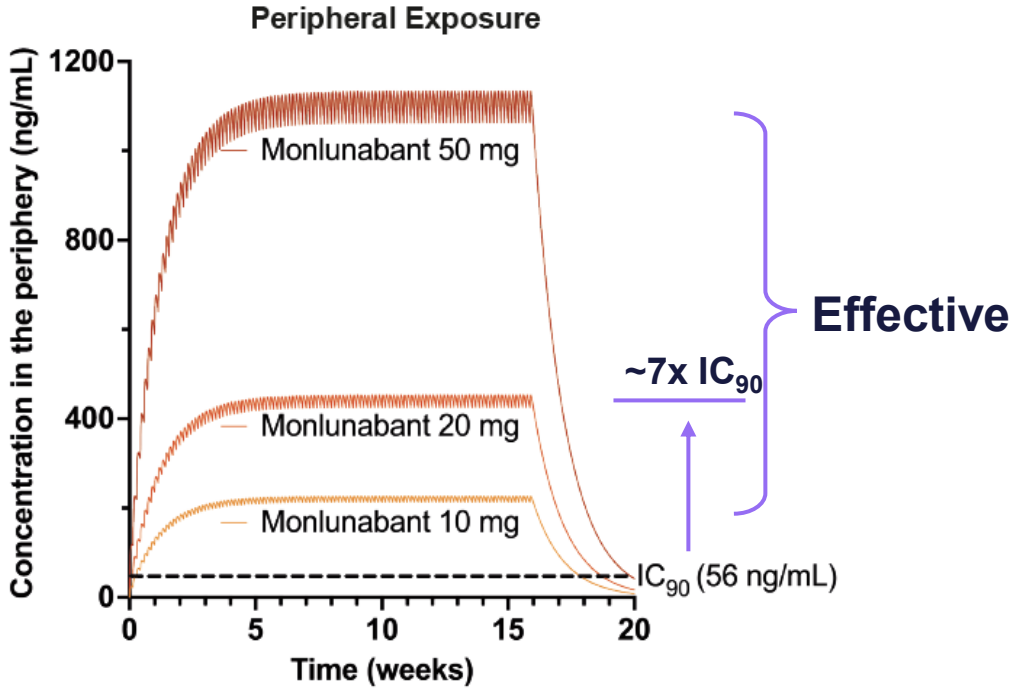
- Weight loss of 22.3% with no evidence of plateau is comparable to other combination therapies at 52 weeks.
- Combination of nimacimab + semaglutide continued to demonstrate safe and tolerable profile at tested doses, similar to semaglutide-alone.
- Durable weight-loss in combination cohort demonstrates improved body composition and maintenance of fat loss during 13-weeks off-treatment period.

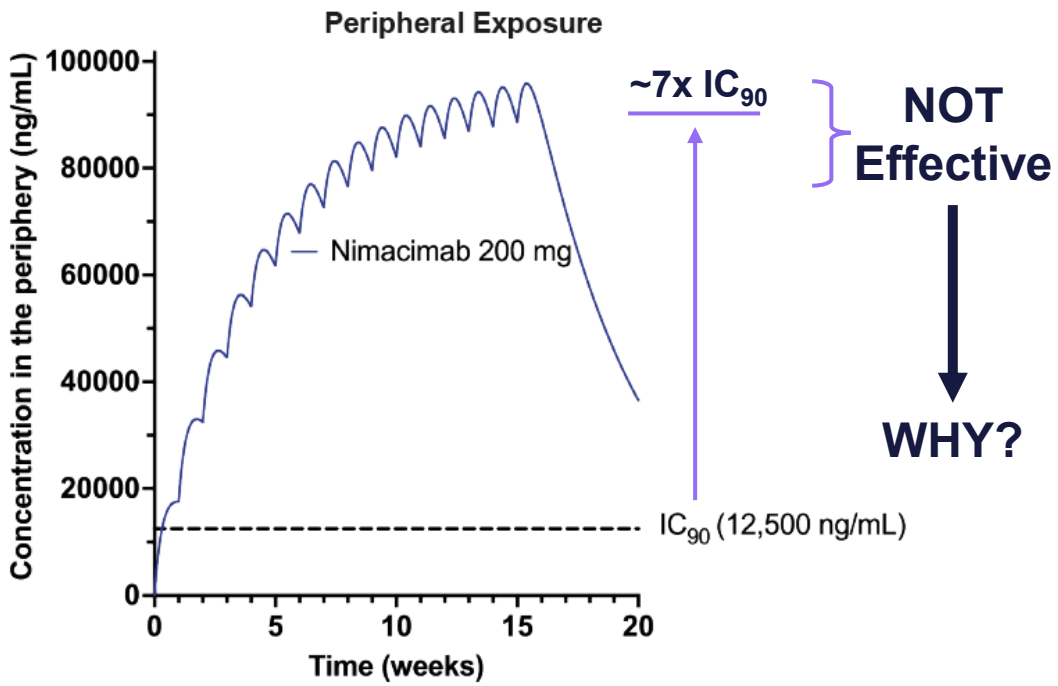
What We Learned From

Dosing Strategy and Rationale

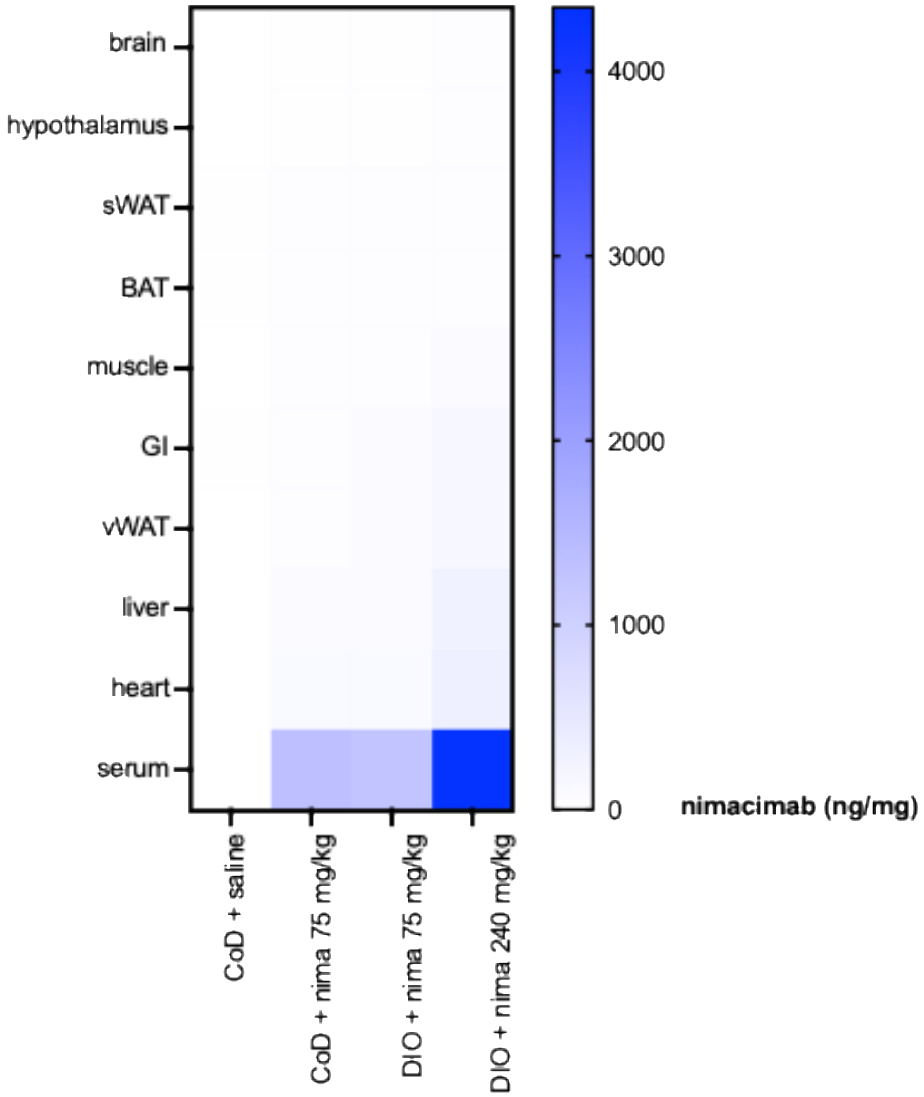
Initial Rationale for CBeyond Dosing

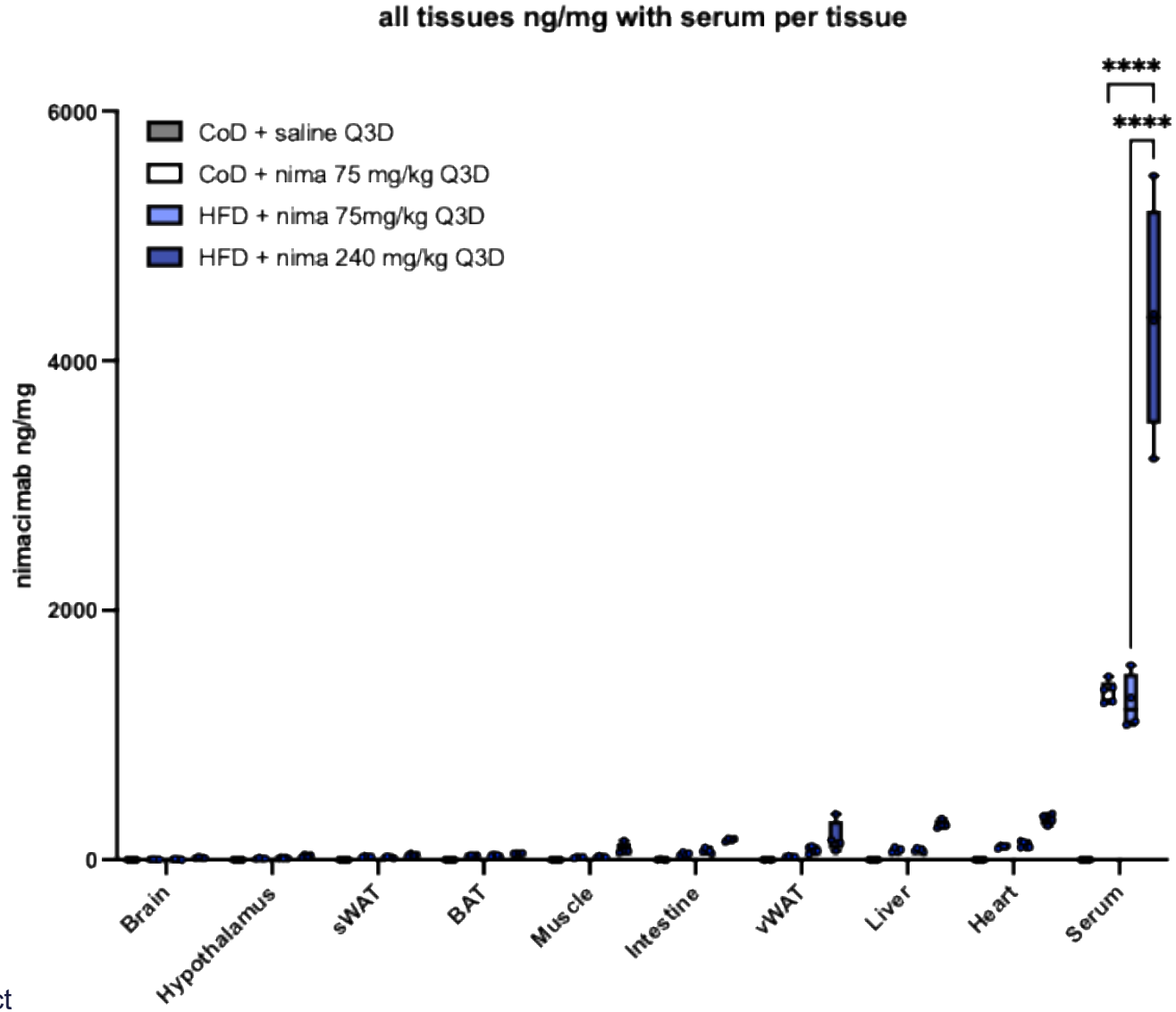
- Before pharmacodynamic data (clinical weight loss or DIO model), Skye developed clinical PK models (Ph1 data) to understand dosing options
- IC_{90} (serum) was used as a surrogate for target engagement
- Similar IC_{90} at $C_{max, ss}$ with 20mg monlunabant and 200mg nimacimab





Nimacimab Biodistribution in Lean and Obese Mice

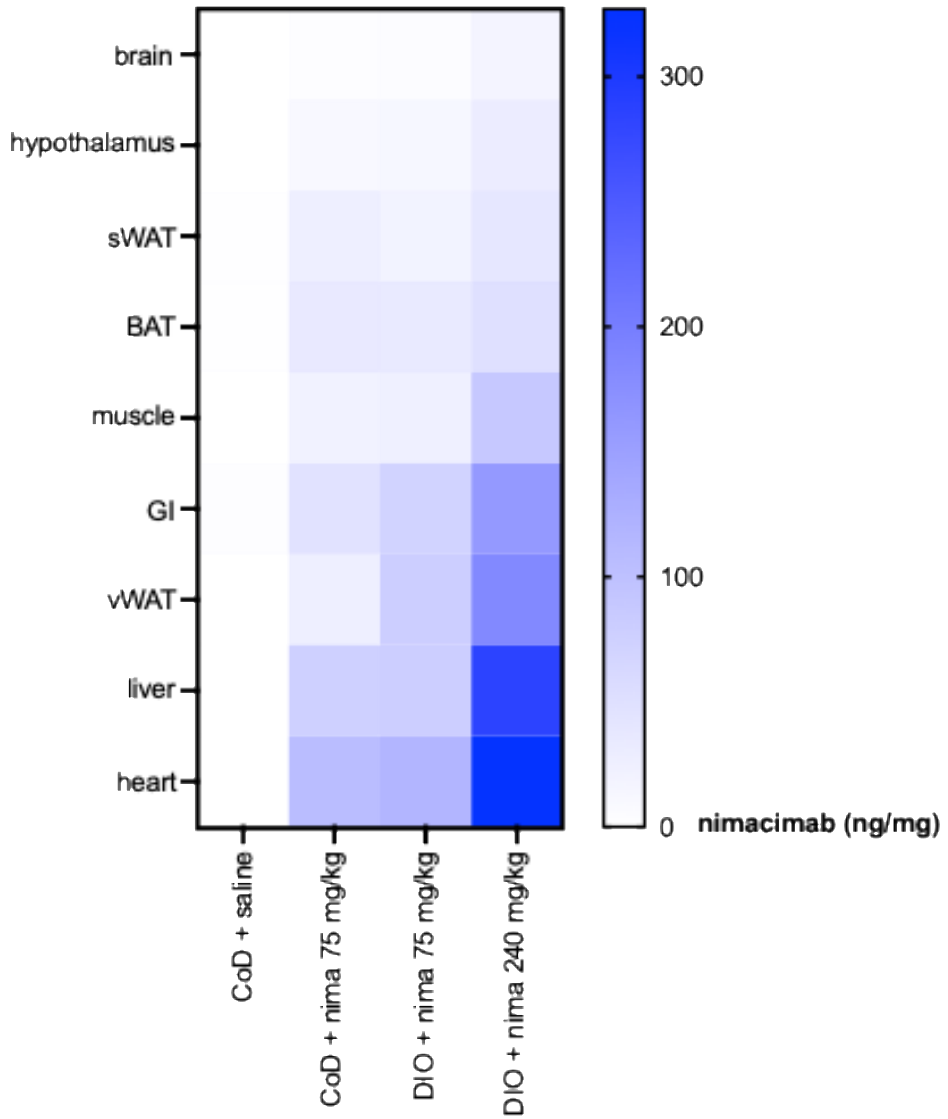


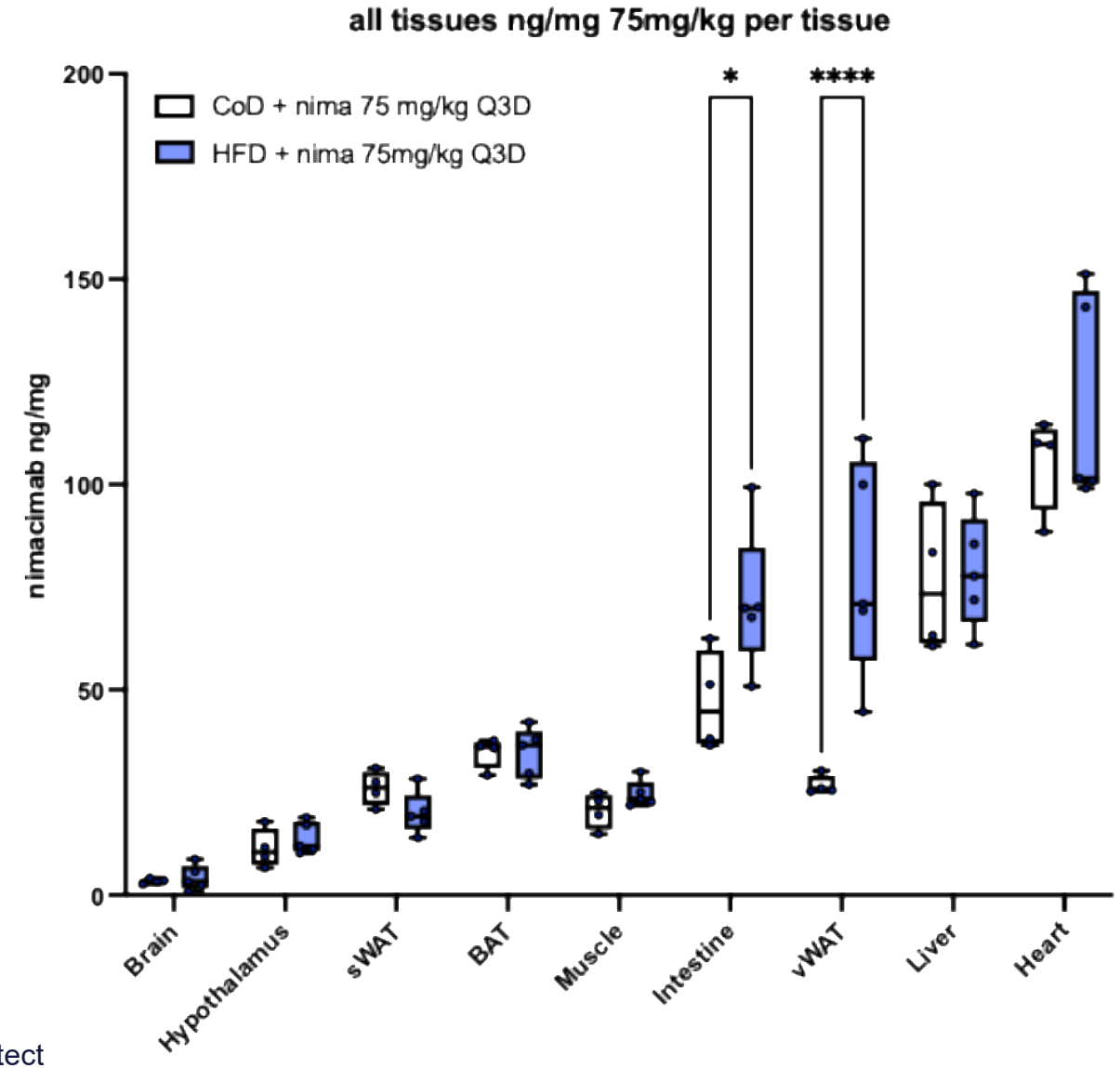


Human IgG ELISA kit (Ray Biotech, catalog# ELH-IGG) was used to detect nimacimab in tissue homogenates. Results are reported as ng of nimacimab/mg of tissue. N=4-5 per group.

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

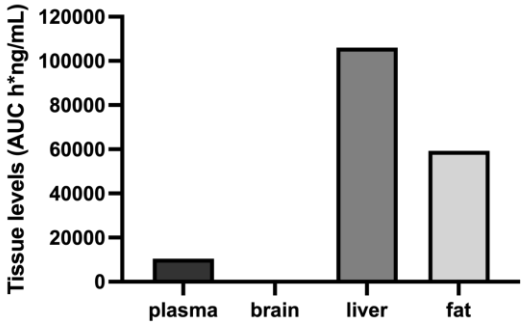
Small molecule

"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

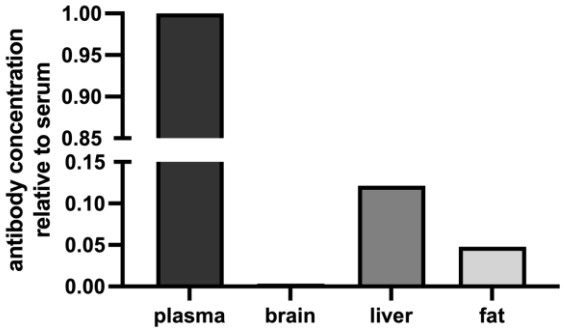


Parameter	Plasma	Brain	Liver	Fat
Tissue/Plasma AUC_{0-last} Ratio	-	0.05	10	6

Antibody

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

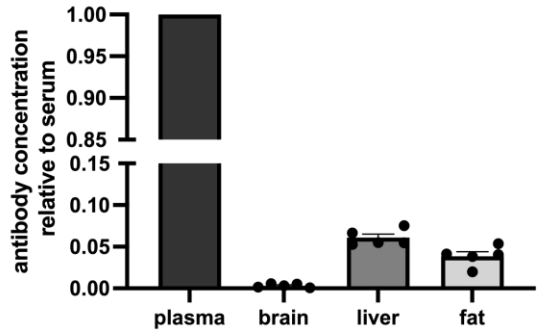
Shah, D. K., & Betts, A. M. *mAbs*, 2013 *5*(2), 297–305



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

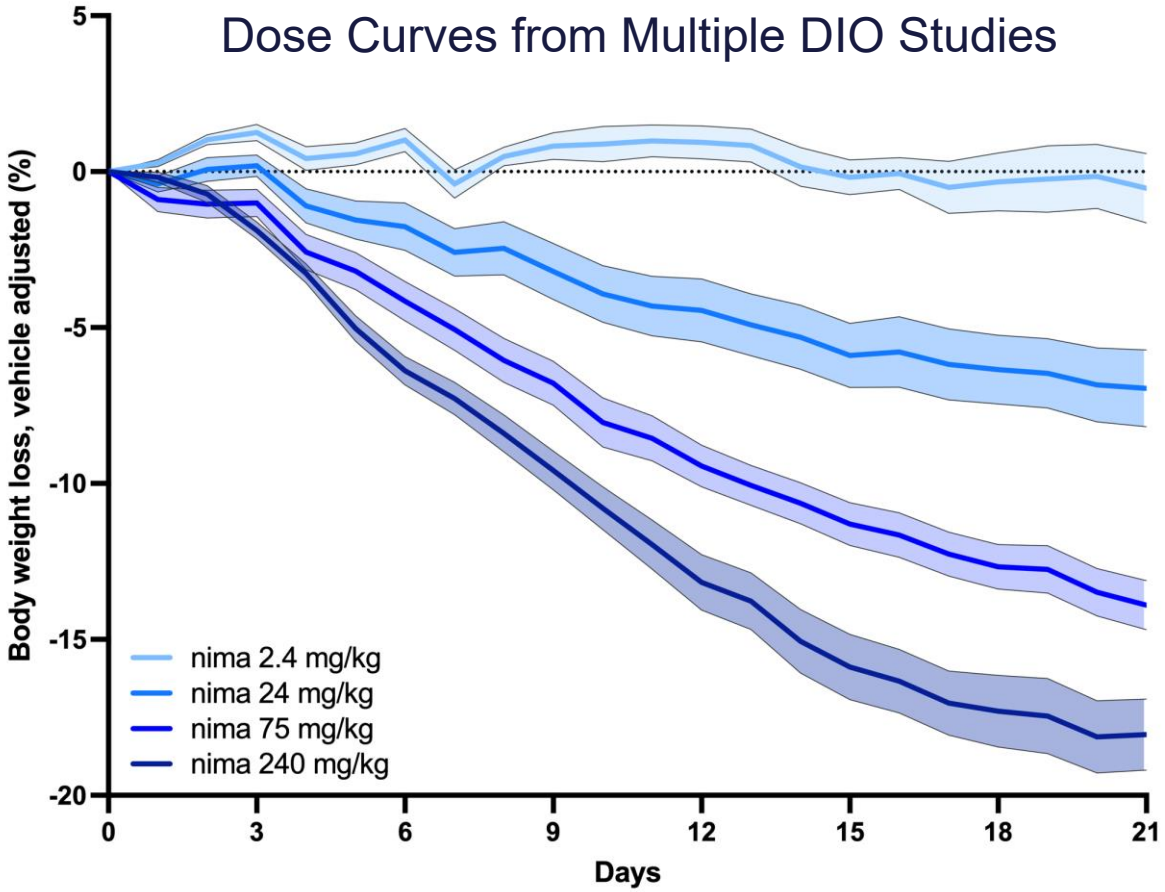
Skye BioD mouse data*

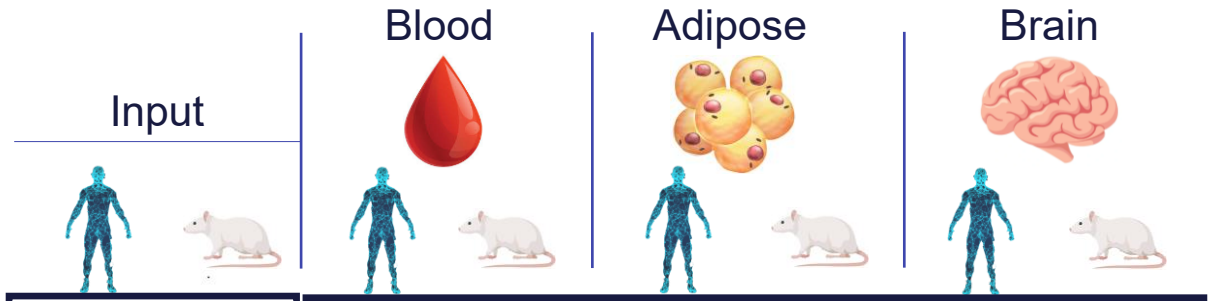
*this is data from the previous slide – ratios are derived tissue vs serum



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

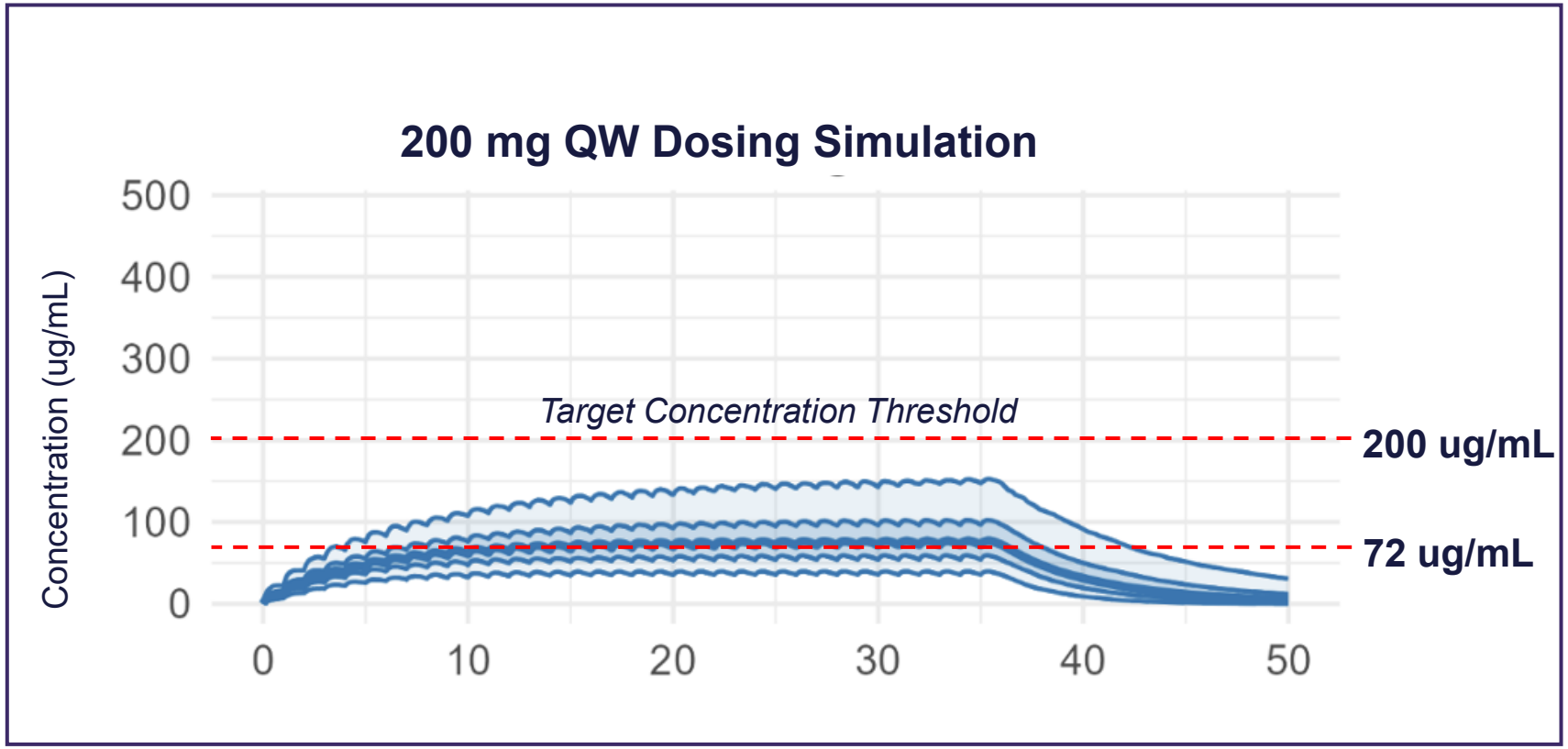




dose		nimacimab concentration (relative to IC_{90})					
200 mg dose	24 mg/kg	7.3x	6.4x	0.4x	0.3x	0.03x	0.02x
600 mg dose	75 mg/kg	22x	20x	1.1x	0.9x	0.1x	0.1x

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).

200 mg QW CBeyond Dosing did not Achieve Significant Concentrations in the Serum



- While 200 mg QW achieved median serum exposures of at least 7x over IC90; however, this dose proved to be sub-optimal.
- Higher dosing strategies need to be evaluated to achieve median serum concentrations of at least 200 ug/mL
- Based on our toxicity data, we believe we can evaluate multiple higher concentrations without safety concern.

How Much Higher Can Nimacimab Be Safely Dosed?

Nimacimab NOAEL based on 26-week NHP study is 75mg/kg

Phase 2b Simulations: Limiting toxicity assessment

Considering the human equivalent dose (HED) from the FDA guidance:

$$HED = 75\,\frac{mg}{kg} \cdot \frac{5.5\ kg}{100\ kg}^{0.33}$$

28.8 $\frac{mg}{kg}$ in humans

In a 100 kg human the equivalent NOAEL dose is 2880mg

Table 1: Conversion of Animal Doses to Human Equivalent Doses Based on Body Surface Area

Species	To Convert Animal Dose in mg/kg to Dose in mg/m², Multiply by k_m	To Convert Animal Dose in mg/kg to HED[a] in mg/kg, Either:	
		Divide Animal Dose By	Multiply Animal Dose By
Human	37	---	---
Child (20 kg)[b]	25	---	---
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates:			
Monkeys[c]	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

[a] Assumes 60 kg human. For species not listed or for weights outside the standard ranges, HED can be calculated from the following formula:
HED = animal dose in mg/kg x (animal weight in kg/human weight in kg)$^{0.33}$.

[b] This k_m value is provided for reference only since healthy children will rarely be volunteers for phase 1 trials.

[c] For example, cynomolgus, rhesus, and stumptail.

Modeling NHP Toxicity Study Provides Guidance for Potential Nimacimab Dosing Regimens

- Skye has conducted two non-human primate toxicology studies both establishing 75mg/kg as NOAEL dose.
    1. **26-Week Subcutaneous Dosing (N=9)**
    2. **4-Week IV Dosing (N=10)**

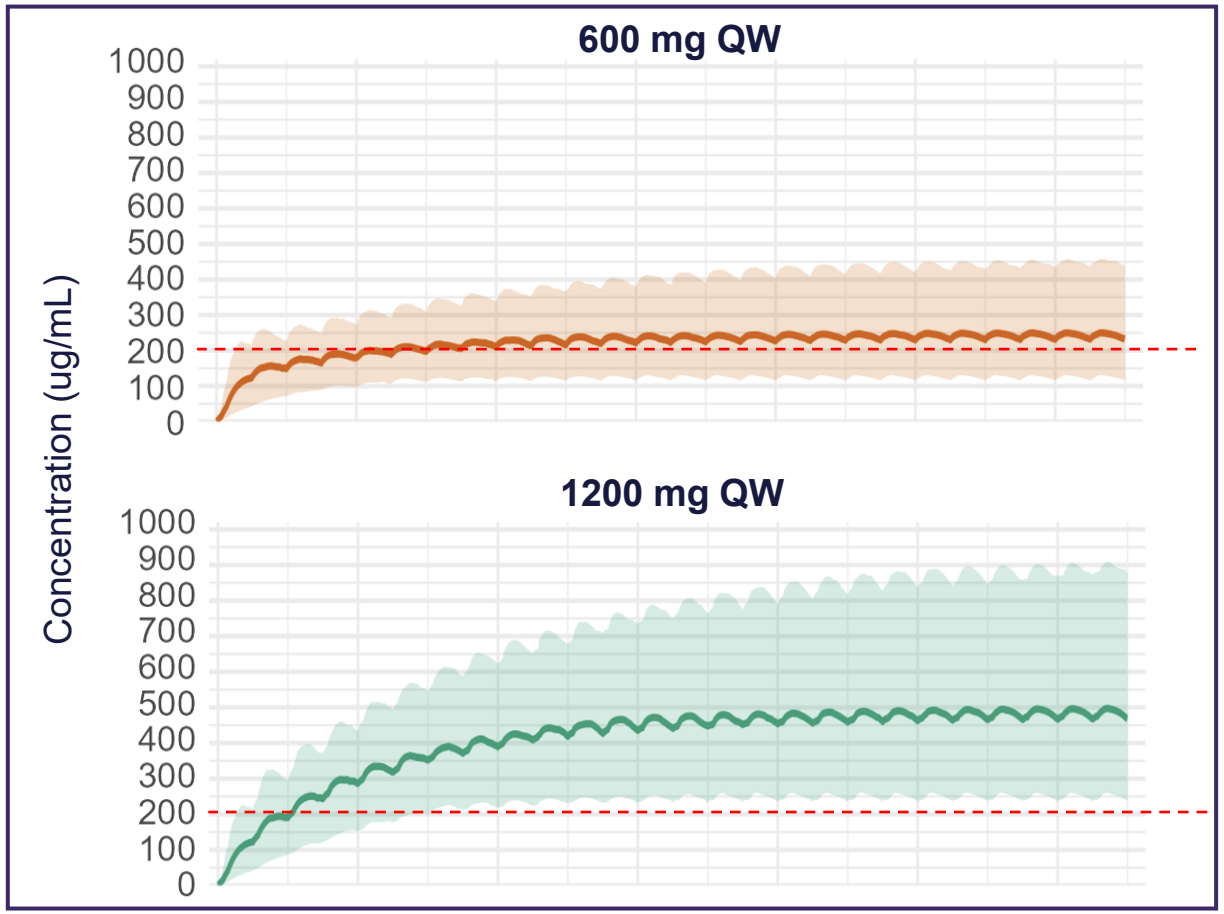
	Cmax	Weekly AUC
26-Week SubQ Study	2150 ug/mL	~305,000 ug*h/mL
4-Week IV Study	2500 ug/mL	~375,000 ug*h/mL

- Direct concentration comparisons (e.g. Cmax and AUC) in non-human primate PK is highly predictive of human PK due to species similarities (S6 ICH Guidance).

- Using these data, we evaluated multiple doses determine safety of potential clinical doses.

Higher Dosing Well Below NOAEL Dose

- In order to achieve at least 200 ug/mL in the serum, we simulated 600 mg QW and 1200 mg QW

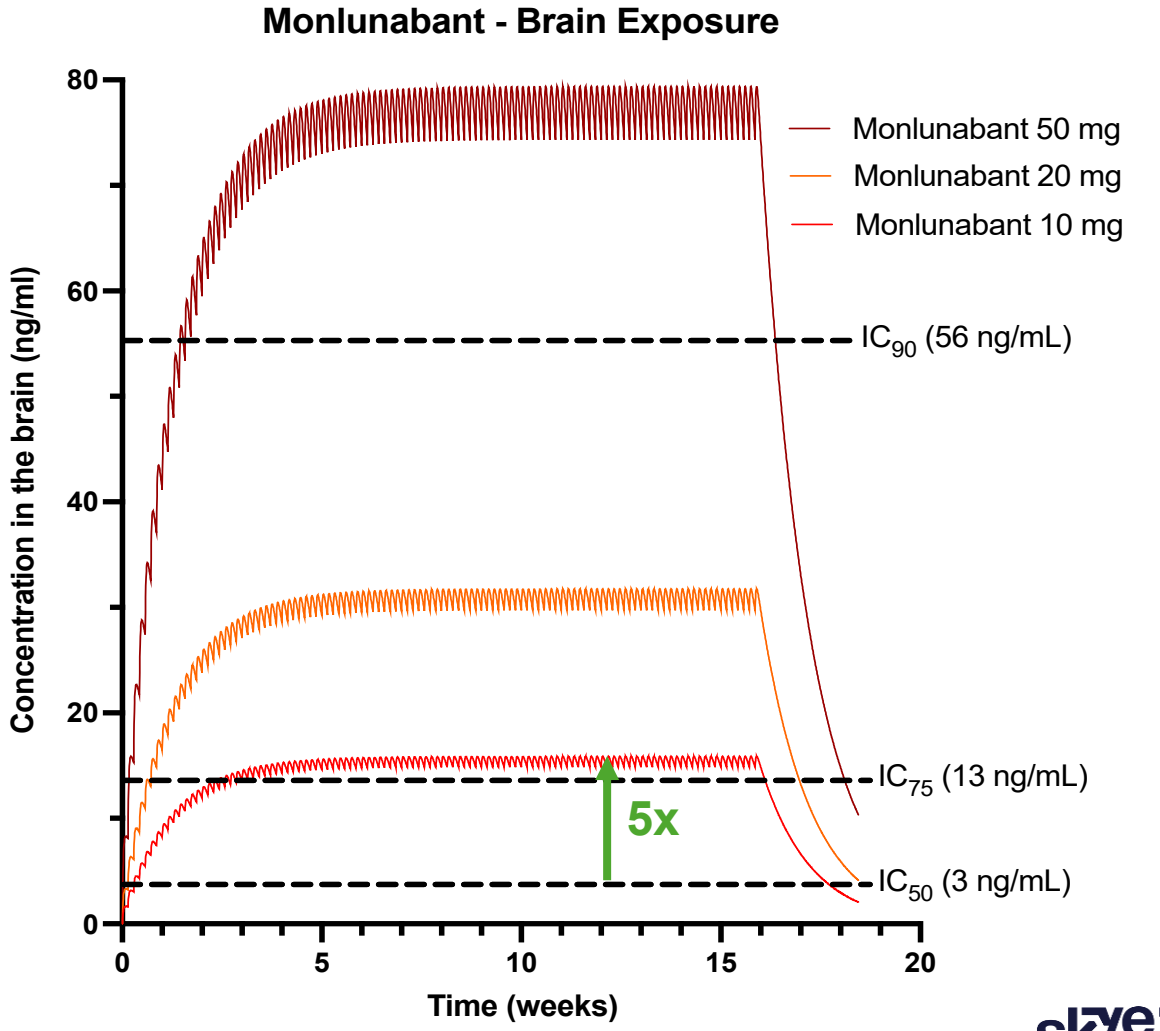


1200 mg QW Exposure vs. NOAEL

Dose	1200 mg Dose	NOAEL Dose (75 mg/kg)	Fold Difference
Mean C_{max} (ug/mL)	499	2150	4.3X
Weekly AUC (ug*h/mL)	81,648	305,000	3.7X

Monlunabant's Dose Dependent Increase in Brain Leads to Dose Dependent Increase in Neuropsychiatric Adverse Events

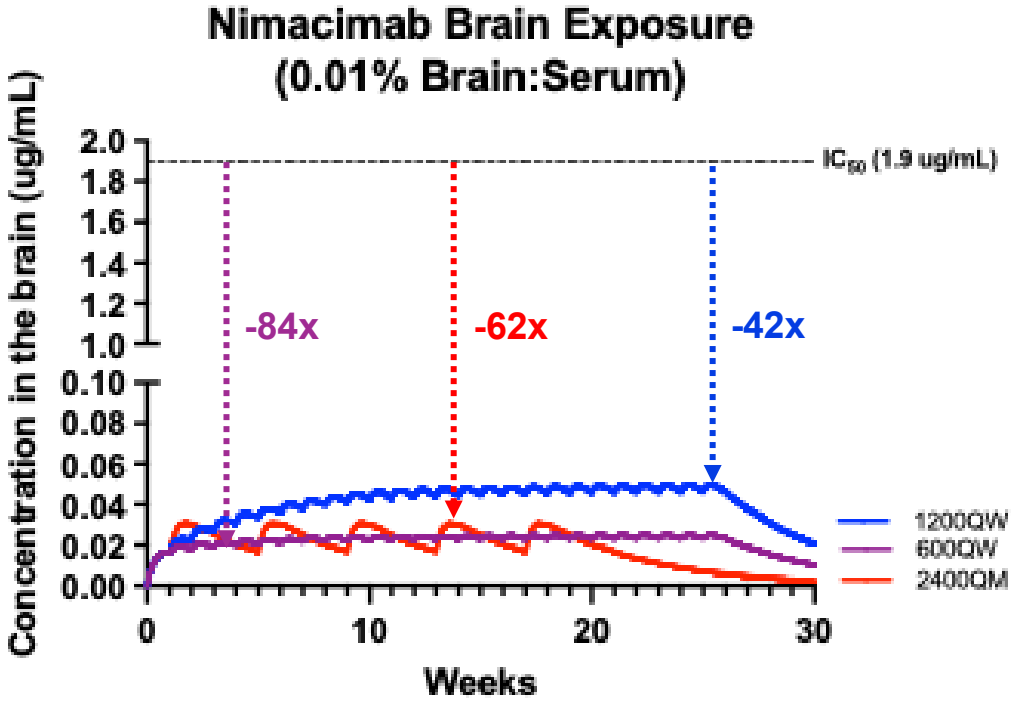
- Monlunbant's Phase 2a 16-week data demonstrated a dose dependent increase in neuropsychiatric side effects (Knop et al.).
- Neuropsychiatric adverse events were identified even at the lowest dose (10mg QD)
- Our modeling demonstrates that with each increasing dose, the concentration gets closer to IC_{90}, with the highest dose exceeding IC_{90}.
- **At the lowest dose of 10mg, monlunbant is already 5x above the IC_{50}**

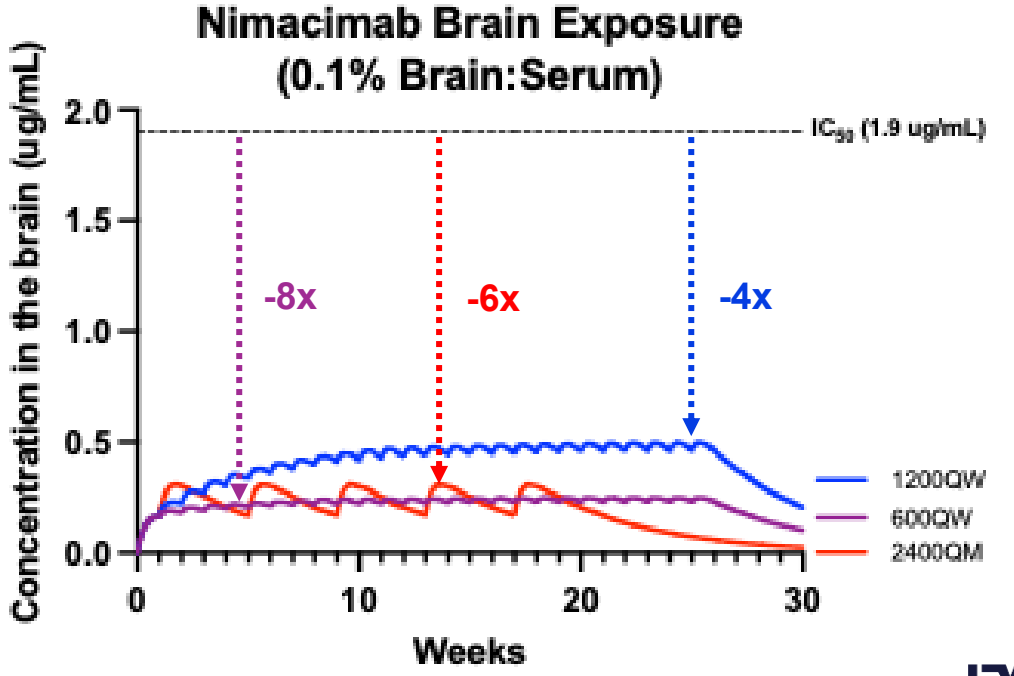


References: Crater *et al*, 2023; Liu *et al*, 2021; Knop *et al*, 2025; Braga *et al.*, 2025

Nimacimab has Wide Safety Margin in the Brain

- Modeling of brain exposure for **nimacimab (antibody)** shows a significantly better safety margin than **monlunabant (small molecule)**.
- Wang et al., demonstrates brain (CSF) to serum concentration ratios are between 0.1%-0.2% for antibodies.
- NHP studies of nimacimab demonstrate brain to serum ratio as low as 0.01%.
- Modeling for best case (0.01% brain:serum) and worst case (0.1% brain:serum), scenarios demonstrates that nimacimab is still significantly below the IC_{50} in the brain.





References: Phase 1 biodistribution study – internal data; NHP biodistribution study – internal data; NHP toxicology study – internal data; Fjord-Larsen *et al.*, 2021; Wang *et al.*, 2018

Clinical Strategy
CBeyond Expansion Study

CBeyond Expansion Study / Part C / IV Dosing

CBeyond

Cohort 2
Randomized 3:1 to either
- Nimacimab 600 mg, QW, IV (n=6), equivalent to ~1000 mg SC
- Matched placebo, QW, IV (n=2)

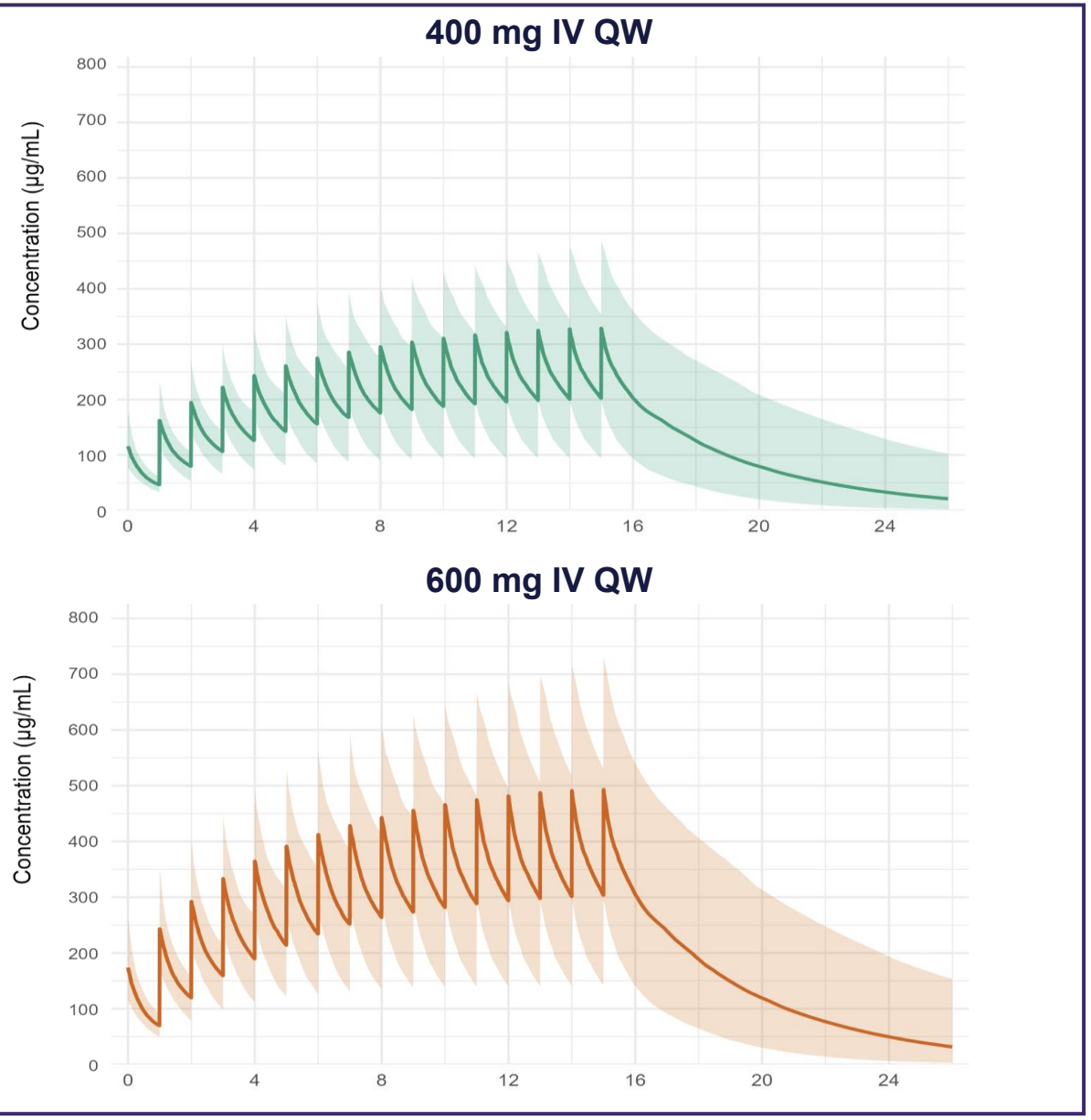
Safe to Proceed to Cohort 2 following Cohort Review Committee safety review of the first 4 participants in Cohort 1 completed 4 weeks of treatment

Cohort 1
Randomized 3:1 to either
- Nimacimab 400 mg, QW, IV (n=6), equivalent to ~600 mg SC
- Matched placebo, QW, IV (n=2)

Within each cohort

Screening Period (4 weeks) → **Treatment Period (15 weeks: 16 doses)** → **Follow-up Period (12 weeks)**

IV Dosing for CBeyond Part C



Time to Target Concentration and Steady State

Weekly Dose	Ctrough >200ug/mL	Time to Steady State
400 mg IV	Week 12	Week 9
600 mg IV	Week 5	Week 9

600 mg QW IV Exposure vs. NOAEL

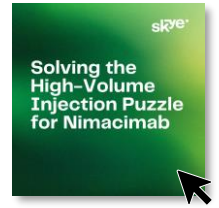
Dose	600 mg IV Dose	NOAEL Dose (75 mg/kg)	Fold Difference
Mean C_{max} (ug/mL)	497	2150	4.3X
Weekly AUC (ug*h/mL)	164,407	305,000	1.9X

Confirming Safety and High Dose Strategy

- The Expansion (Part C) Study will provide key data to confirm that nimacimab will not significantly penetrate the blood-brain barrier and result in neuropsychiatric side effects.

- 16-weeks of dosing will be sufficient exposure to evaluate safety and provide additional PK data to support next dose for Phase 2b.

Achieving Large Volume Dose Administration with ENHANZE®



- Skye has established a global collaboration and licensing agreement with Halozyme Therapeutics to evaluate the co-formulation of nimacimab with ENHANZE® (rHuPH20).

- ENHANZE® is an enzyme that degrades hyaluronan by cleaving B-1,4 linkage between N-acetyl glucosamine and glucuronic acid.

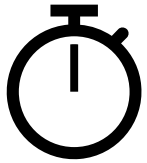
What it does:

ENHANZE® creates temporary space for SC fluid dispersion; reduces tissue backpressure.

How it works:

ENHANZE® works rapidly, locally and transiently in SC space; HA is naturally restored in 1-2 days


Large volume injection up to 10-12 mL


Reduced administration time

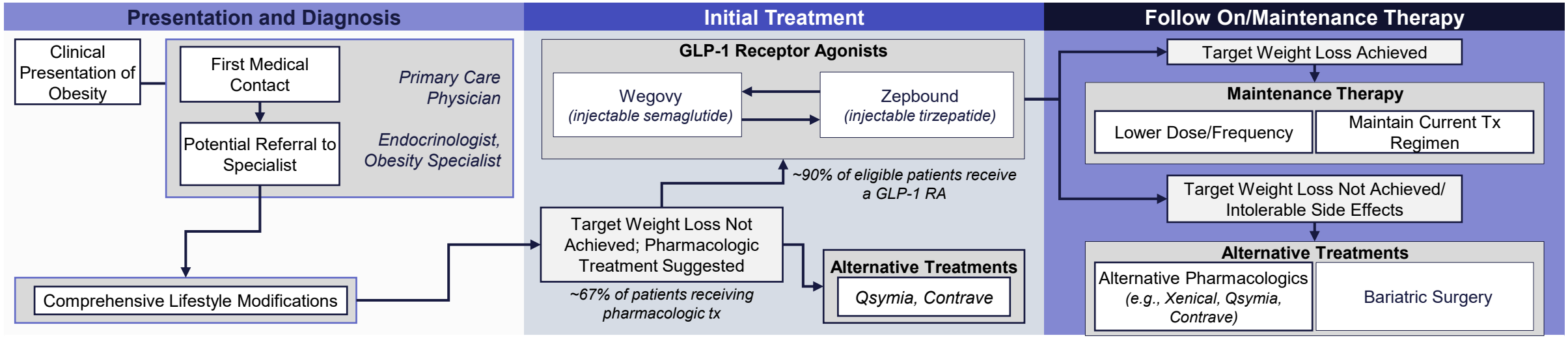

Increased patient preference


Improved absorption

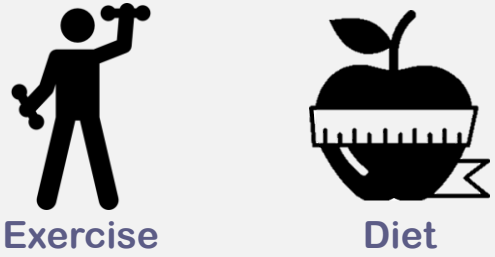

Increased bioavailability

Target Product Profile

Current AOM Pipeline and Treatment Paradigm



Lifestyle Management



GLP-1 RA Preference

zepbound wegovy Saxenda Qsymia Contrave Xenical

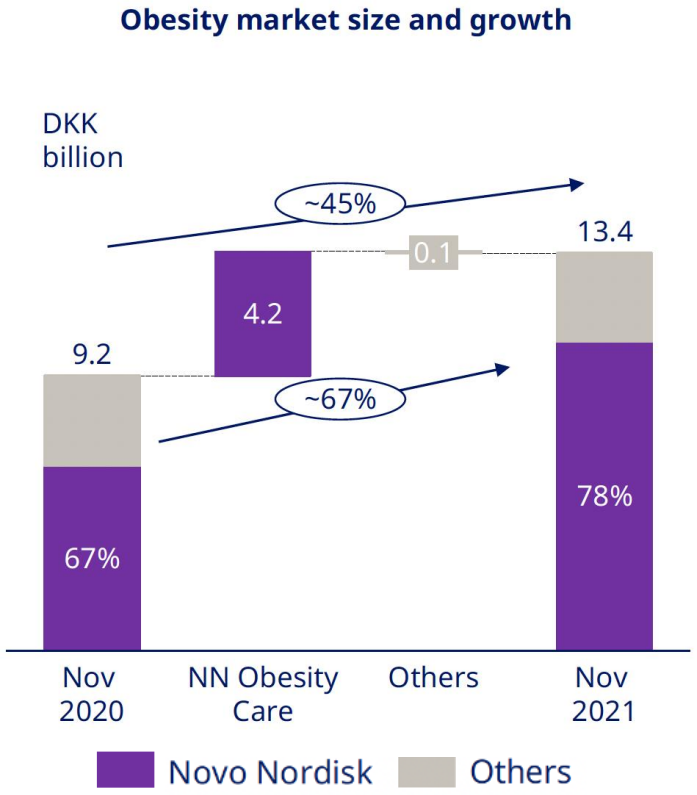
Maintenance Therapy

Qsymia Contrave Xenical

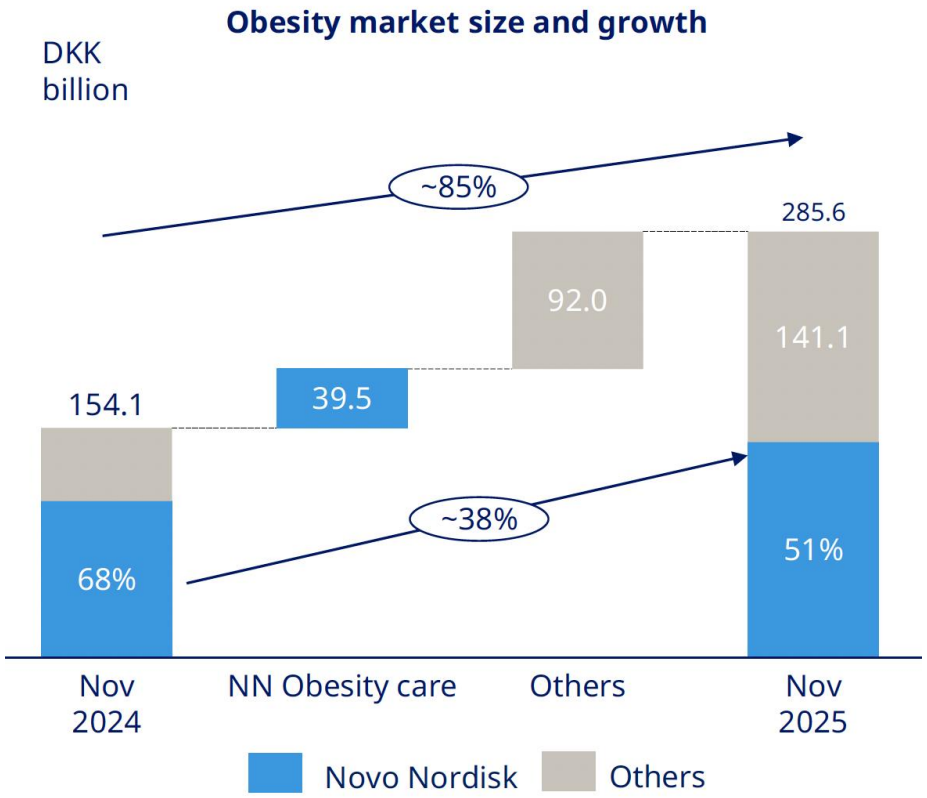
Bariatric Surgery

Novo 2020-2025 Demonstrates the Remarkable Growth of the Obesity Market Driven by Semaglutide (Wegovy®)

Pre-Wegovy® Approval

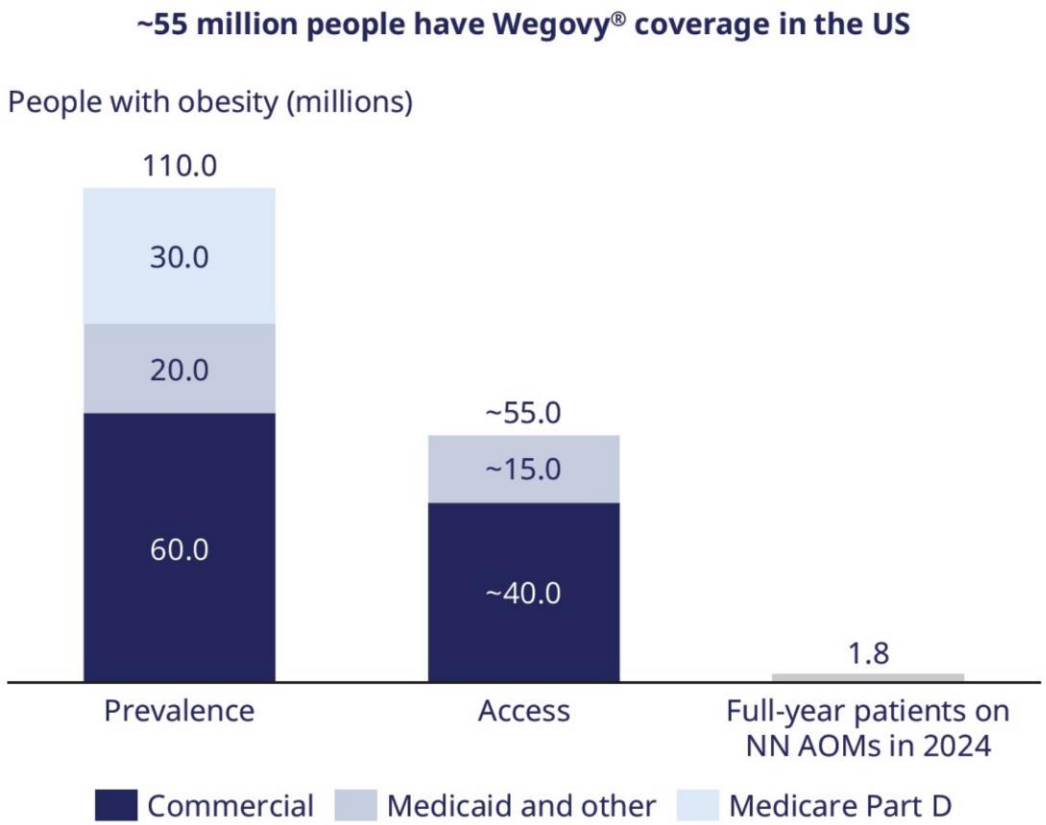


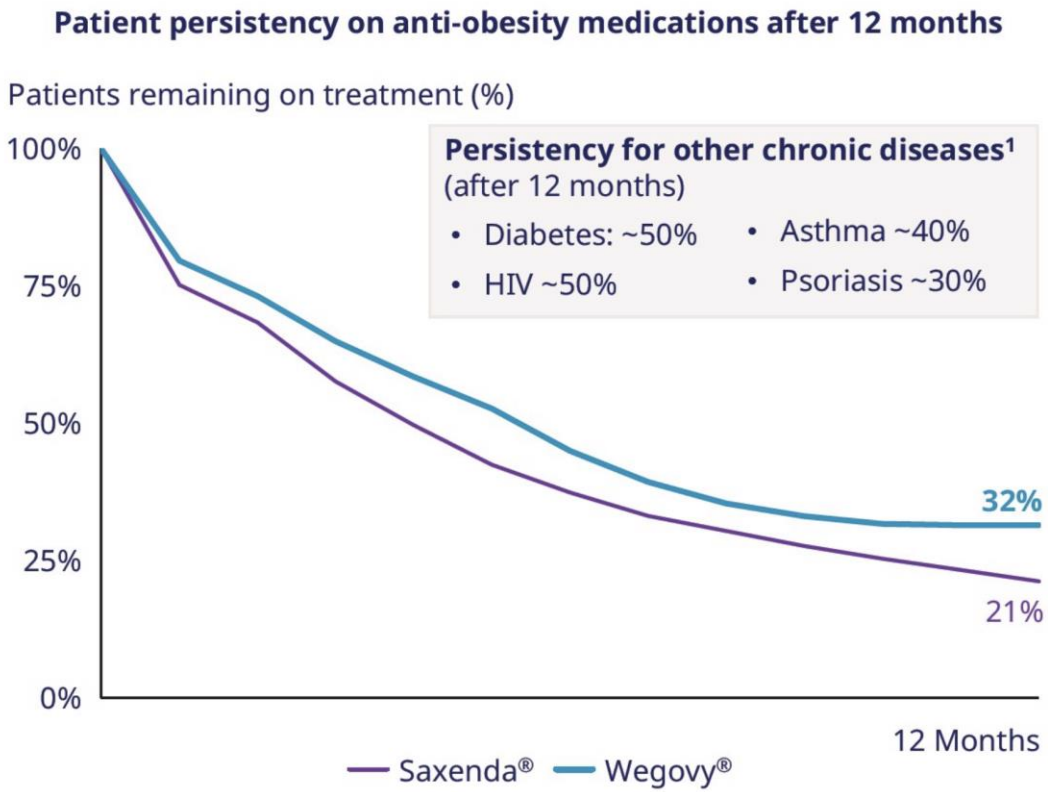
3 Years Post-Wegovy® Approval



Source: Novo Nordisk 2021 and 2025 Full Year Review Presentations

While More Patients Are Receiving Therapy, Few Are Staying On Treatment And Require Additional Options





HOWEVER - This Has Created a True Need For Alternative Options to GLP-1s

Source: Novo Nordisk 2024 Full Year Review Presentations

Significant Growth of Contrave and Qysmia Demonstrates Unmet Need For GLP-1 Experienced Patients

Naltrexone/bupropion

Qsymia®

Phentermine/topiramate

2017

Both drugs commercially failed as 1L therapies

$13M annual sales

Company goes bankrupt and Contrave to Currax Pharmaceuticals

$17M annual sale

Since its launch in 2012, there was ongoing sales decline which continued into 2018

2024

Growth of obesity market with approval of next-gen GLP-1s positively impacted sales

2.2M prescriptions in 2024

"50% year-over-year revenue growth"

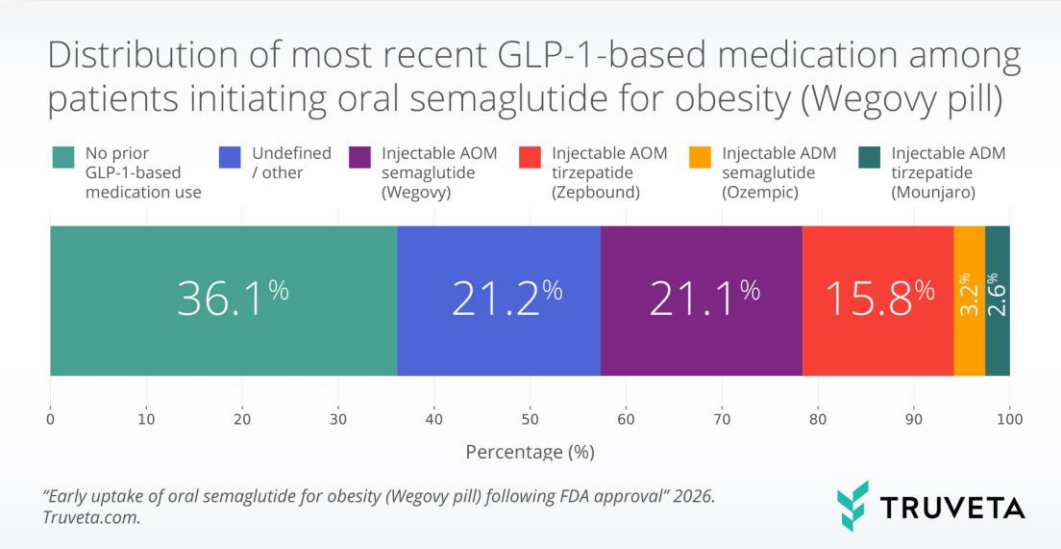
+$500M annual sales since 2020

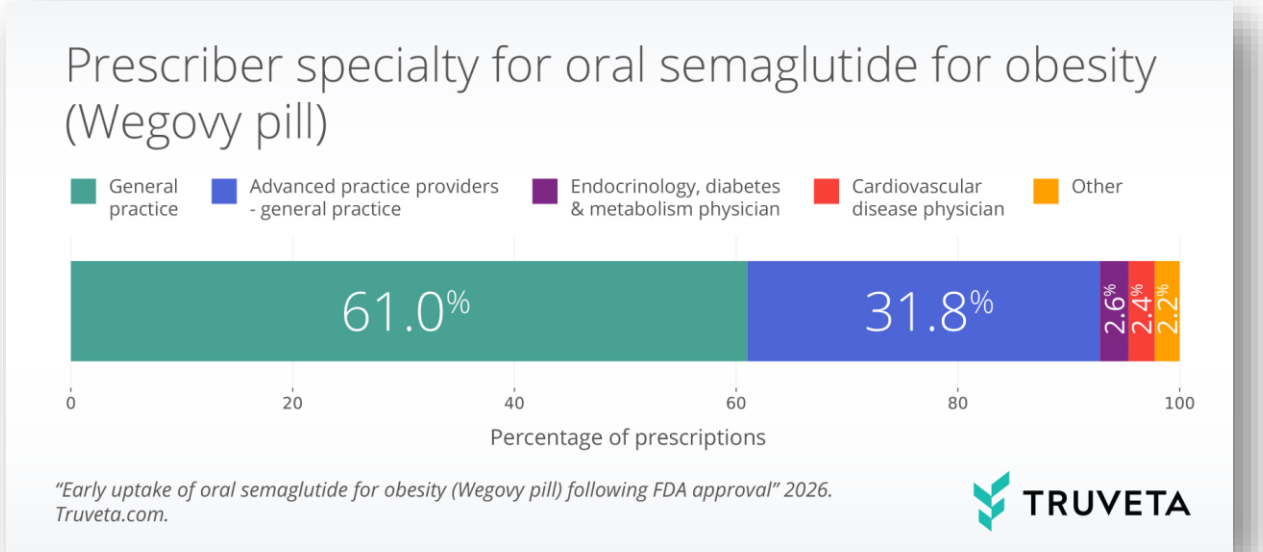
Percentage of Patients Who Do Not Respond to GLP-1s or May Require Additional Weight Loss

		"Non-Responders"	"Needs More WL"
Drug	**Study**	**<5% WL**	**<10% WL**
Semaglutide (SC)	STEP-1	13.6%	30.9%
Semaglutide (Oral)	OASIS-4	20.8%	37.0%
Tirzepatide (5mg - 15mg)	SURMOUNT-1	9.1 – 14.9%	15.5 – 32.5%
Orforglipron	ATTAIN-1	29.2%	55.4%

- While GLP-1s will dominate the 1L setting, it is clear that there remains a significant number of patients that do not respond to therapy, or require additional weight loss.
- Orthogonal mechanisms are necessary to fill this unmet need.
- Oral and next-generation GLP-1s will compete for the same 1L patients.

New Treatments, Including Orals, Will Serve to Expand the Number of GLP-1 Experienced Patients





"...a large proportion initiating oral semaglutide (36.1%) had no prior evidence of GLP-1-therapy use, suggesting that early adoption included a substantial proportion of patients new to using GLP-1 medications."

- Recent approval of Oral Wegovy, demonstrates how new GLP-1 options will increase access and number of patients with obesity on medication.
- This will ultimately increase the number of patients requiring further treatment post-GLP-1 (i.e. GLP-1 experienced patients).
- Until new orthogonal mechanisms are approved, there is a significant white space to support these ***GLP-1 Experienced Patients***

Crowded 1L Space with Significant Price Compression

- NuSH drugs will dominate the 1L setting, but it will become increasingly competitive with less room for profit margin.
- The 2L setting has significant opportunity with few non-NuSH drugs available or being developed.

First Line Therapy

	Incretins	Amylins	Non-NuSH
2026	zepbound, wegovy 2.4mg, wegovy Pill, wegovy 7.2mg, Orfoglipron, CagriSema		Qsymia, Contrave, Xenical
2027	zepbound, wegovy 2.4mg, wegovy Pill, wegovy 7.2mg, Orfoglipron, CagriSema, Retatrutide, Eloralinitide, MET-097i		Qsymia, Contrave, Xenical
2028	zepbound, wegovy 2.4mg, wegovy Pill, wegovy 7.2mg, Orfoglipron, CagriSema, Retatrutide, Eloralinitide, MET-097i	MariTide, Aleniglipron, Ribupatide	
2029	zepbound, wegovy 2.4mg, wegovy Pill, wegovy 7.2mg, Orfoglipron, CagriSema, Retatrutide, Eloralinitide, MET-097i	MariTide, Amycretin, Survodutide, Ribupatide, VK-2375	
2030	zepbound, wegovy 2.4mg, wegovy Pill, wegovy 7.2mg, Orfoglipron, CagriSema, Retatrutide, Eloralinitide, MET-097i	MariTide, Amycretin, Survodutide, CT-388, Petrelinitide	Ribupatide, VK-2375
2031	zepbound, wegovy 2.4mg, wegovy Pill, wegovy 7.2mg, Orfoglipron, CagriSema, Retatrutide, Eloralinitide, MET-097i	MariTide, Amycretin, Survodutide, CT-388, Petrelinitide	Ribupatide, VK-2375, Nimacimab

WAC PRICE
+$1000/month

+60% discount

GTN PRICE
<$400/month

GLP-1 Experienced Patient (Maintenance)	GLP-1 Experienced Patient (Add-On Combination)
Qsymia, Contrave, Xenical	CagriSema
Qsymia, Contrave, Xenical	CagriSema
Qsymia, Contrave, Xenical, MET-097i, Eloralinitide, Aleniglipron	CagriSema
Qsymia, Contrave, Xenical, MET-097i, VK-2375, Eloralinitide, Aleniglipron	CagriSema
Qsymia, Contrave, Xenical, MET-097i, VK-2375, Eloralinitide, Petrelinitide, Aleniglipron	CagriSema, Bimagrumab + tirzepatide
Qsymia, Contrave, Xenical, MET-097i, VK-2375, Bimagrumab, Eloralinitide, Petrelinitide, Aleniglipron, Nimacimab	CagriSema, Bimagrumab + tirzepatide, Nimacimab+GLP1

Nimacimab Complementary, Not Competitive to GLP-1s

Maintenance rationale for late comer GLP1s is to protect the patient base; nimacimab improves persistence and durability of 1L GLP1s

WHY THEY DO IT

Maintenance is a rational same-class play

Lower-risk

regulatory + commercial defense

- Chronic-use precedent is already established
- Studies start in responders already on backbone
- Oral, monthly, COGS, or flex-dose convenience can still create value

WHY IT IS HARD FOR INCRETINS

Hard to win the true add-on slot

≥5%

pivotal semaglutide-adjusted delta

- Dose step-down is retention, not superiority
- Same-class agents will struggle to obtain add-on therapy to label
- Price compression with GLP1s is an advantage for nimacimab

WHY NIMACIMAB WINS

Orthogonal add-on, not another incretin

2L white space

for GLP-1 experienced patients

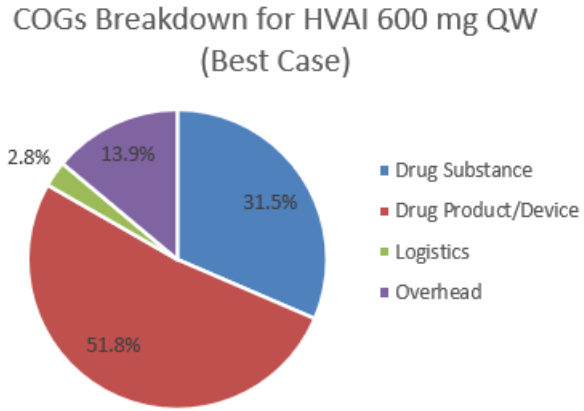
- Augments tirzepatide / semaglutide instead of trying to replace them
- Targets plateaued, titration-limited, or intolerant patients
- More differentiated than same-class maintenance plays

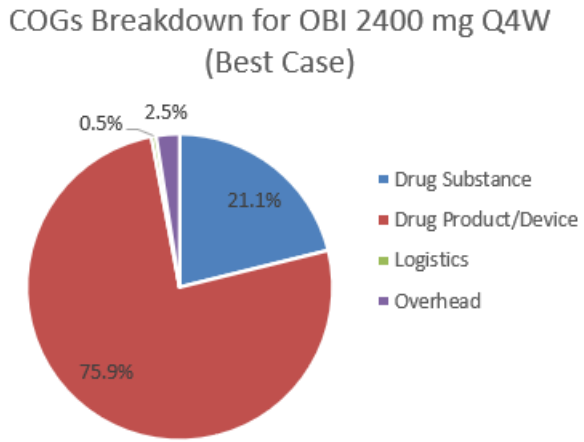
COGS and Commercial Strategy

Nimacimab COGS – Line of Site to Competitive Pricing

- Drug Substance current productivity: 2.5 g/L titer & 40% downstream recovery
  - Process productivity improvement development activities underway; scale-up to 12-15K L planned

Dose	600 mg QW	2400 mg Q4W	600 mg QW	2400 mg Q4W
Case	Base		Best	
Harvest Titer	7.5 g/L		10 g/L	
Purification Yield	75 %		85 %	
DS MFG Scale	12K L		15K L	
COGs/Gram	$32		$17	
COGs/Dose	$46	$240	$36	$202
COGs/Year	$2388	$3125	$1866	$2631
DP Presentation	Autoinjector	On-Body Injector	Autoinjector	On-Body Injector





- Target Annual COGs ≤ $2500-3000/year to achieve 30% margin

Note: COGs modeling uses current industry-standard costing for RMs, MFG & testing costs (direct labor & overhead); not inflation-adjusted.

Competitive Pricing Strategy

- Current pricing of obesity drugs have a 54-67% discount to the wholesale list price (i.e. WAC Price).
- Average patient out-of-pocket costs range from $98 to $500 per month.
- Pricing of nimacimab at an annual WAC price of $8,220 with a 60% discount provides for a competitive out-of-pocket costs of $274/month while maintaining a strong 47% to 33% margin.

Pricing Analysis						
	Monthly List Price	Annual Price	Projected Discount	Monthly Net Price	COGS	Margin
Semaglutide	$1,349	$16,188	63%	~$500	N/A	N/A
Tirzepatide	$1,086	$13,032	54%	~$500	N/A	N/A
Naltrexone/ Bupoprion	$365	$4,380	55%	~$199	N/A	N/A
Phentermine/ Topiramate	$300	$3,600	67%	~$98	N/A	N/A
Nimacimab	**$685**	**$8,220**	**60%**	**$274**	**$144 - $184**	**47% - 33%**

Global Patent Expiration of Semaglutide is a Commercial Opportunity for Nimacimab

- Patents for semaglutide are due to expire in several countries from April 2026 – examples include India, China, Canada, Brazil and Turkey - enabling the development and distribution of generic formulations.
- These countries represent 44% of the global population and 48% of the global obesity burden.
- Researchers predict generic semaglutide could be produced at $28-140 per year per patient
- Nimacimab combined with generic semaglutide could be as affordable or cheaper than any novel GLP-1 (i.e. VK-2357 or CT-388), and better positioned as an alternative treatment to GLP-1 experienced patients.

Financial Overview and Team

Selected Financial Figures & Metrics

- $107M in equity capital raised since August 2023 (no new equity financing issuances since March 2024 PIPE)
- Supported by top-tier specialist life science investors
- Cash runway into Q4 2026, excludes: the clinical cost of any potential Phase 2b study and the CMC cost to resupply such Phase 2b study
- Ongoing strategic investments in scaling manufacturing, operations, R&D, and advancing the clinical pipeline

Stock Information

Listed: Nasdaq	**SKYE**
Stock Price[1]	**$0.88**
Shares Outstanding[2]	**35.1M**
Shares Fully Diluted[2]	**48.7M**
Cash, Cash Equivalents & Short-term Investments [3]	**$17.1M**
Avg. 3-Mo. Daily Trading Volume[1]	**524K**

[1] May 11, 2026 [2] May 8, 2026 [3] Mar 31, 2026

Leadership

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

Executive Management

Punit Dhillon
President & CEO

Tu Diep, MSc
Chief Operating Officer

Chris Twitty, PhD
Chief Scientific Officer

Puneet Arora, MD
Chief Medical Officer

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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Spotlight

CBeyond

The ANATOMY of PROGRESS
EXAMINING PERIPHERAL CB1 INHIBITION IN METABOLIC HEALTH

skye Obesity