Investigating the Efficacy of Nimacimab Alone or in Combination with Tirzepatide, and as a Maintenance Therapy Post Tirzepatide Discontinuation in a Diet-Induced Obesity (DIO) Mouse Model

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Background

While incretin agonists represent a breakthrough in weight loss treatment, real-world data highlight heterogeneous responses, with 10-20% of patients classified as non-responders (1,2) and up to 70% of patients discontinuing treatment within the first year (3). In addition, follow-on therapy is often required to maintain weight loss, since patients who discontinue incretin therapy tend to rapidly regain the majority of the weight lost. Thus, there is an urgent need for new metabolic targets to treat patients with suboptimal incretin responses as well as to provide improved maintenance therapy options. The G-protein-coupled receptor cannabinoid receptor 1 (CB1R) is a clinically validated target that plays a key role in energy homeostasis. Here, we report preclinical studies investigating the efficacy of nimacimab, a peripherally restricted CB1R antibody with potent inverse agonist activity, both alone or in combination with incretin therapies for sustainable weight loss.

Key Questions

- Can nimacimab enhance optimal and suboptimal doses of incretin agonists?
- How durable is nimacimab's effect on weight loss after treatment discontinuation?
- Can nimacimab be used as a maintenance therapy after tirzepatide discontinuation?
- Is caloric-restriction the primary mechanism of nimacimab-driven weight loss?

Methods

6-8 week-old C57BL/6 human CB1R transgenic (hCB1) male mice, in which the mouse Cnr1 gene has been replaced with the human CNR1 gene, were fed a 60% high-fat diet for 16 weeks to yield an average weight of ~45 g. The mice were randomized based on body weight and body composition into groups of n=8 animals and placed in individual housing for daily food intake measurements before dosing. Here we report the findings from 3 independent studies. Body weight and food consumption were monitored daily. Body composition was analyzed by EchoMRI. To investigate the driving mechanisms of nimacimab's weight loss, mice in a pair-fed group had their calories restricted to match the daily calories consumed by the nimacimab group.

Results

Nimacimab Enhances Tirzepatide Weight Loss

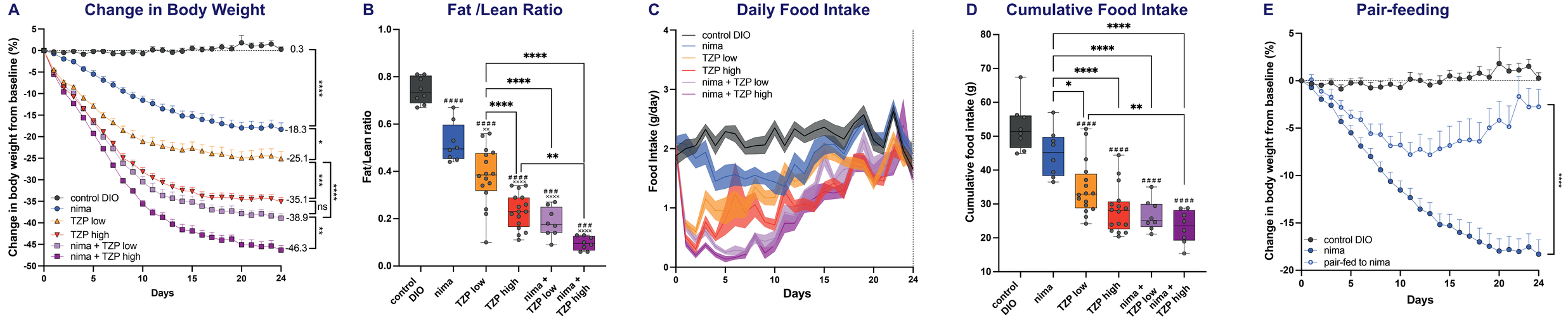

Figure 1. Nimacimab enhances efficacy of a low and a high dose of tirzepatide. Mice with DIO fed a HFD were treated with saline (control DIO), nimacimab 240 mg/kg Q3D (nima), tirzepatide 3 nmol/kg QD (TZP low), tirzepatide 10 nmol/kg QD (TZP high), or the combination of nimacimab 240 mg/kg Q3D with tirzepatide 3 nmol/kg QD (TZP low + nima) for 24 days. (A) % change in body weight from baseline. (B) Fat/Lean mass ratio at end of treatment, day 23. Fat mass and lean mass were measured by EchoMRI. (C) Daily food intake. (D) Cumulative food intake shows significant reduction in food intake induced by tirzepatide but not by nimacimab treatment. (E) Food intake was controlled by pair-feeding the control DIO mice to the nima HFD fed mice. Data are presented as mean ± SEM, n=8-16 per group. For (A) and (E) two-way ANOVA analysis followed by Tukey's multiple comparison tests. Significance reported at day 24. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 vs control DIO. Nimacimab is significantly different to all treated groups. For (B) and (D), one-way ANOVA followed by Tukey's multiple comparison tests. # # # # p<0.0001 vs control DIO, xx p<0.01, xxxx p<0.0001 vs nima. *p<0.05, **p<0.01, ****p<0.0001, ns=not significant.

Nimacimab Results in Sustainable Weight Loss After Treatment Discontinuation and is an Effective Maintenance Therapy After Tirzepatide Discontinuation

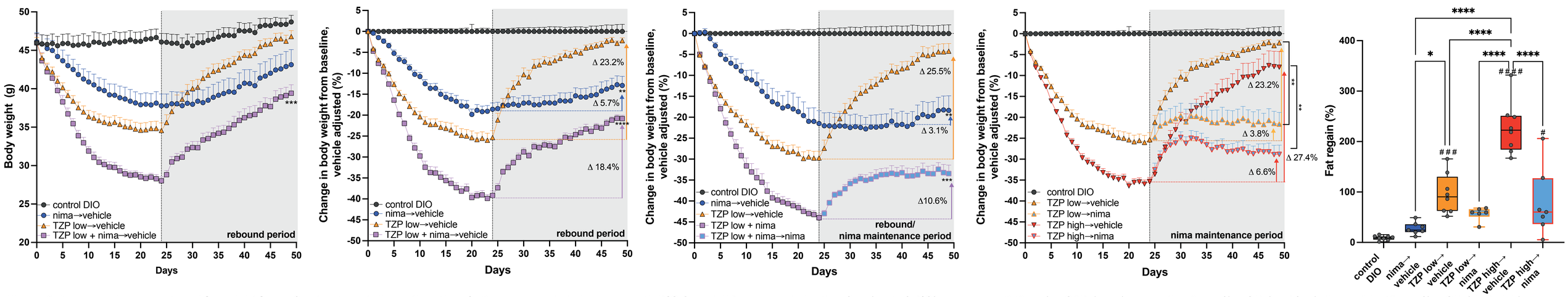

Figure 2. Nimacimab has sustainable weight loss after treatment discontinuation. In 2 independent studies, mice with DIO fed a HFD were treated with saline (control DIO), nimacimab 240 mg/kg Q3D (nima), tirzepatide 3 nmol/kg QD (TZP low), tirzepatide 10 nmol/kg QD (TZP high), or the combination of nimacimab 240 mg/kg Q3D with tirzepatide 3 nmol/kg QD (TZP low + nima) for 24 days. After discontinuation of TZP and nimacimab, some groups were treated with nimacimab 240 mg/kg Q3D for an additional 21 days (TZP low →nima, TZP high →nima, TZP low + nima→nima, blue symbols). The gray region indicates the rebound or maintenance phase. (A) Body weight. (B-D) % change in body weight from baseline, adjusted to the daily change in body weight from baseline for the control DIO group. Data are presented as mean ± SEM, n=7-8 per group. TZP low and TZP high groups had n=16 until end of treatment when they were randomized into vehicle or nima (n=8). Statistical significance was determined using two-way ANOVA or Mixed-effects analysis followed by Tukey's multiple comparison tests for the rebound/maintenance phase. Significance reported at day 49 vs control DIO, or otherwise noted. **p<0.01, *** p<0.001, ****p<0.0001. (E) Fat regain during the rebound period was calculated as the % change in fat mass from day 23 to day 46. Statistical significance was determined using One-way ANOVA analysis followed by Tukey's multiple comparison tests. *p<0.05, ****p<0.0001, # # # p<0.001, # # # # p<0.0001 vs control DIO.

Nimacimab Enhances Semaglutide Weight Loss

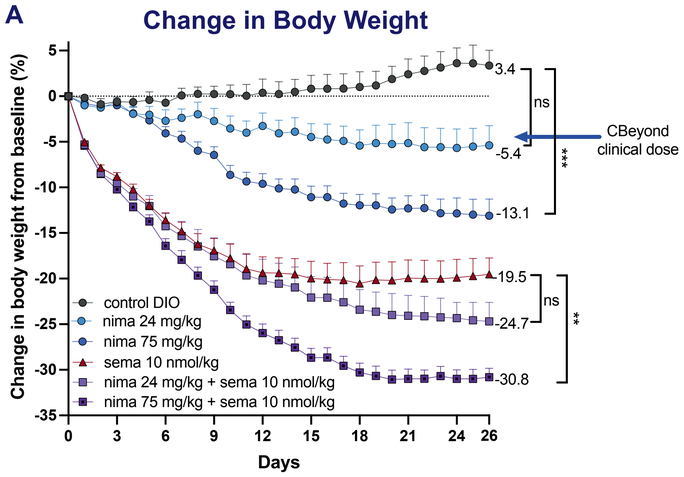

Figure 3. Nimacimab significantly enhances weight loss in combination with semaglutide. Mice with DIO fed a HFD were treated with saline (control DIO), nimacimab 24 mg/kg or 75 mg/kg Q3D, semaglutide 10 nmol/kg QD, or the combination of nimacimab 24 mg/kg Q3D with semaglutide 10 nmol/kg QD, or nimacimab 75 mg/kg Q3D with semaglutide 10 nmol/kg QD for 26 days. (A) % Change in body weight from baseline. Data are presented as mean ± SEM, n=7-8 per group. Statistical significance was determined using Mixed-effect analysis followed by Tukey's multiple comparison tests. **p<0.01, *** p<0.001, ****p<0.0001. 24 mg/kg nimacimab is significantly different to semaglutide and both combos (**p<0.01, ***p<0.001, and p<0.0001 respectively). CBeyond™ Phase-2 clinical trial (NCT06577090) are comparable to a suboptimal dose of 24 mg/kg Q3D in mice. Increasing the dose 3x times has the potential to unlock significant efficacy as a monotherapy and in combination with semaglutide. ns=not significant.

Takeaway

- Nimacimab significantly enhanced weight loss when combined with suboptimal or clinically active dose levels of TZP.
- Nimacimab resulted in durable weight loss after treatment discontinuation.
- Nimacimab significantly improved rebound profile after TZP discontinuation.
- Caloric restriction is not the primary driver of nimacimab-driven weight loss.
- An active vs a suboptimal dose of nimacimab significantly enhanced weight loss induced by semaglutide.

Collectively, these findings support multiple clinical strategies for obesity management with nimacimab. Clinically significant weight loss can be achieved with fully active doses of each therapeutic agent, while combination with lower, more tolerable doses of incretin agonists may offer a better-tolerated and more durable option for long-term maintenance in chronic weight management.

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References

1. Jethani et al, 2025 Dandelion Research: Measuring GLP-1 Efficacy in the Real World.
2. Real-World Trends in GLP-1 Treatment Persistence and Prescribing for Weight Management. Issue Brief: May 2024
3. Rodriguez et al., 2025 JAMA Netw Open Discontinuation and Reinitiation of GLP-1 Receptor Agonists Among US Adults with Overweight and Obesity.