Demonstrating the sufficiency of peripheral CB1 inhibition to promote weight loss using clinical pharmacokinetic and pharmacodynamic models

Luciano G. Braga[1], Lynle Go[1], Sadhana N. Rajeev[2], Tu Diep[2], Puneet Arora[2], Chris Twitty[2], Shawn Morales[2]

[1]Everest Clinical Research Corp., Ontario, Canada. [2]Skye Bioscience Inc., San Diego, United States.

Background

CB1 inhibitors and weight loss:

- Cannabinoid receptor 1 (CB1) inhibitors promote weight loss via metabolic effects
- Central (brain) CB1 inhibition is linked to neuropsychiatric adverse events (AEs)

First-generation CB1 inhibitor:

- Rimonabant: High brain penetrance → peripheral inhibition at higher doses, but significant central inhibition
- Effective weight loss is associated with neuropsychiatric AEs

Second-generation inhibitor:

- Monlunabant: Improved peripheral restriction relative to first-generation inhibitors
- Ph2 data: similar weight loss at all doses, dose-dependent increases in neuropsychiatric AEs

Novel antibody-based CB1 inhibitor:

- Nimacimab: Antibody-based inhibitor with nearly complete peripheral restriction
- Excellent Ph1 safety profile with promising preclinical efficacy

Key question:

- Is peripheral CB1 inhibition alone sufficient for weight loss, or is central inhibition required to enable efficacy?

Objectives

Primary goals:

- Evaluate the efficacy of systemic (peripheral) vs. central (brain) CB1 inhibition for weight loss
- Assess safety (neuropsychiatric AEs) related to central inhibition

Approach:

- Use PK (clinical data) and PD (*in vitro* potency) to model central (brain) or systemic (peripheral – plasma/serum) drug exposure relative to the magnitude of receptor inhibition

Methods

Comparative analysis:

- Modeled clinical PK/PD profiles of rimonabant, monlunabant, and nimacimab

Data sources:

- Published clinical trial data (Ph1 and Ph3)
- Skye Ph1 clinical trial data

Simulation tools:

- Monolix® (V2021R1) for PK/PD simulations
- Phoenix WinNonlin™ (V8.3) for scenario analysis
- R

Modeling approach:

- Extracted dose-response profiles for CB1 pathway inhibition
- Fitted data into 4-parameter logistic models to estimate target engagement

Collected Published Information

PK/PD analysis:

Simulated brain and systemic distribution of:

- Rimonabant (5 mg and 20 mg QD, Ph3 doses)
- Monlunabant (10 mg, 20 mg, and 50 mg QD, Ph2 doses)
- Nimacimab (200 mg QW, Ph2 dose)

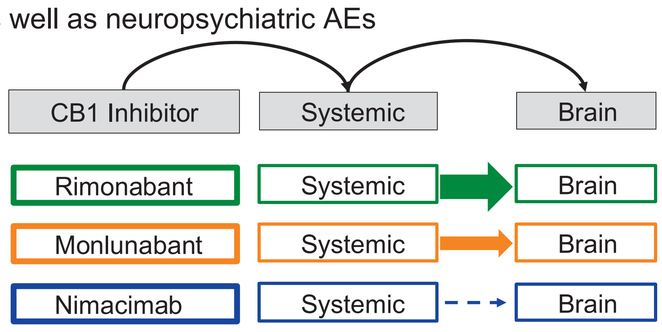
Models utilized conservative values of brain exposure

CB1 Inhibitor	% Brain Exposure (ratio brain:periphery)
Rimonabant	440% – 1400%
Monlunabant	7% – 19%
Nimacimab	0.1%

Key metrics:

- IC_{90} as an inhibitory threshold: 90% of target engagement (brain vs. systemic)
- Correlation with weight loss as well as neuropsychiatric AEs

From systemic circulation, the drug can distribute to the brain with varying efficiencies.

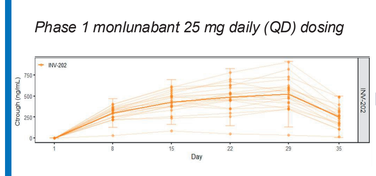


Data Extraction:

- Data extracted from published figures/tables[1-5] or Ph1 data (nimacimab)
- Model fitted to extracted data for monlunabant PK and rimonabant and rimonabant/monlunabant/nimacimab target engagement (receptor occupancy vs. drug concentration) [1-5]

1. Data extracted

Phase 1 monlunabant 25 mg daily (QD) dosing

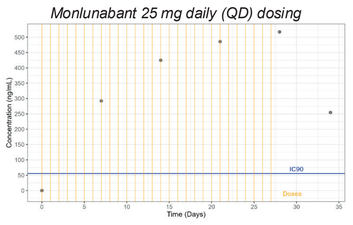


Adapted from Crater *et al*, 2023

Monlunabant plasma concentrations from the phase 1 trial were extracted from a published figure

2. Data fit

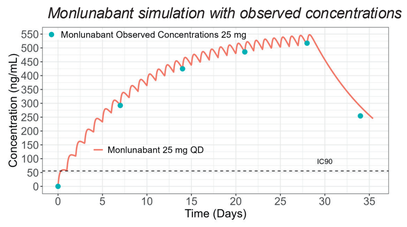
Monlunabant 25 mg daily (QD) dosing



A model was developed and fitted to the extracted data

3. Study simulated

Monlunabant simulation with observed concentrations



An example of a PK simulation with monlunabant dosed at 25 mg QD overlayed with the extracted data

Conflicts of interest: The author is a consultant for Skye Bioscience, a biopharmaceutical company developing therapies for obesity and metabolic diseases.

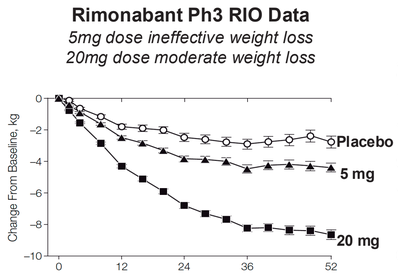
Contact: smorales@skyebioscience.com

Results

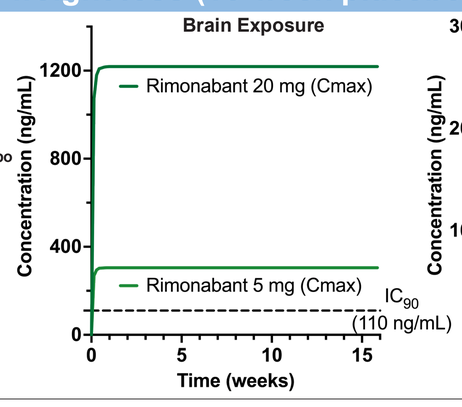
Rimonabant Data: ~3% weight loss (16-week placebo-adjusted)

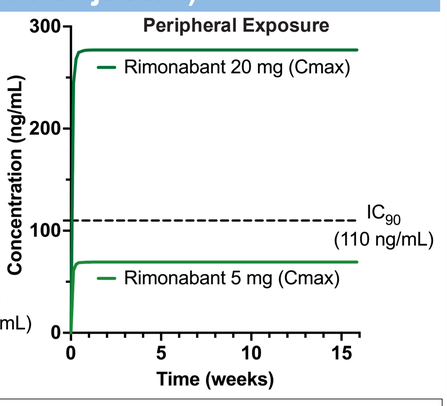
Rimonabant Ph3 RIO Data

5mg dose ineffective weight loss
20mg dose moderate weight loss



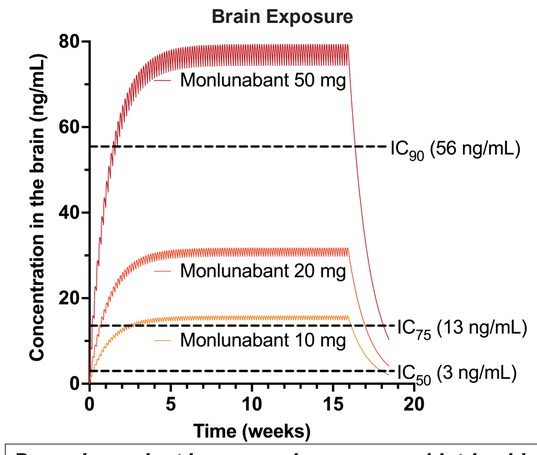
Després JP. et. .al. 2005 N Engl J Med 2005;353:2121-2134
DOI: 10.1056/NEJMoa044537



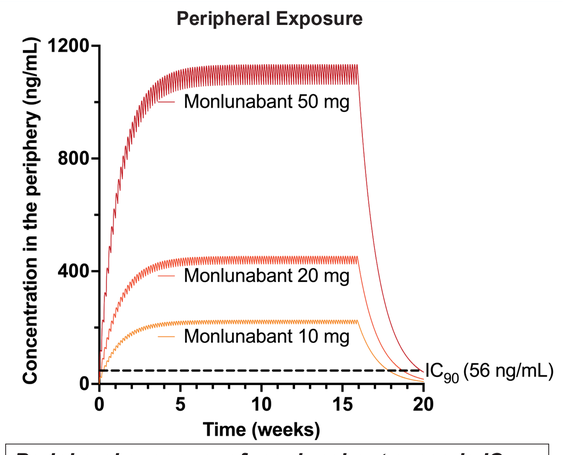


Rimonabant (Ph3 data):
5 mg dose: effective inhibition in the brain (>IC_{90}) but below threshold of inhibition (<IC_{90}) in the periphery → ineffective weight loss with neuropsychiatric AEs present[6].
20 mg dose: effective inhibition (>IC_{90}) in the brain and periphery → significant weight loss with neuropsychiatric AEs[6].

Monlunabant Data: ~6% weight loss (16-week placebo-adjusted)



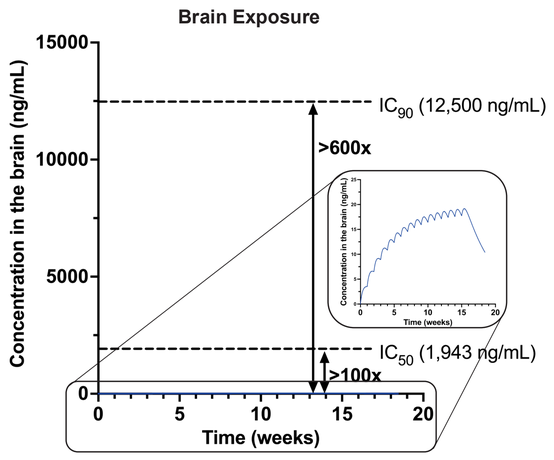
Dose-dependent increases in neuropsychiatric side effects may result from increased exposure in the brain
"Reporting of mild to moderate neuropsychiatric side effects, primarily anxiety, irritability, and sleep disturbances, was more frequent and dose dependent with monlunabant compared to placebo."
Source: Novo Nordisk A/S September 20, 2024



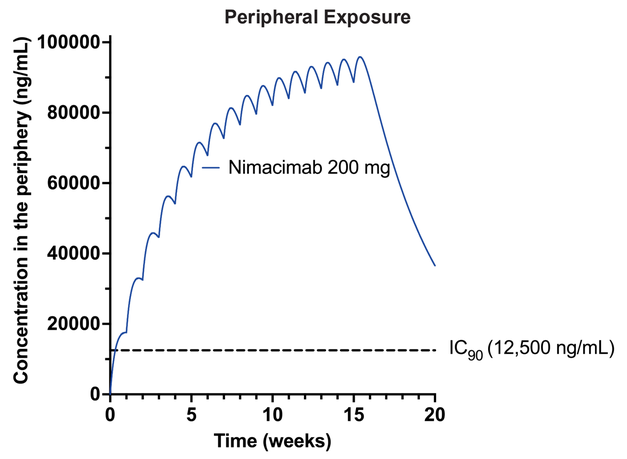
Peripheral exposure of monlunabant exceeds IC_{90} at all doses
"All doses of monlunabant achieved a statistically significant weight loss compared to placebo. Limited additional weight loss was seen at higher doses of monlunabant."
Source: Novo Nordisk A/S September 20, 2024

Nimacimab Data

Nimacimab 200 mg QW exceeded the IC_{90} threshold in the plasma but not in the brain



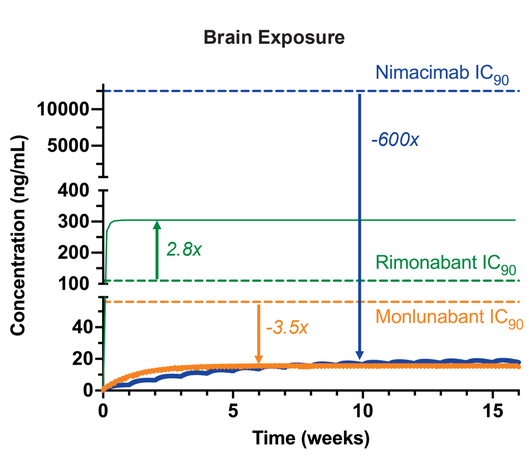
Nimacimab 200 mg QW brain exposure is 600-fold below the IC_{90}



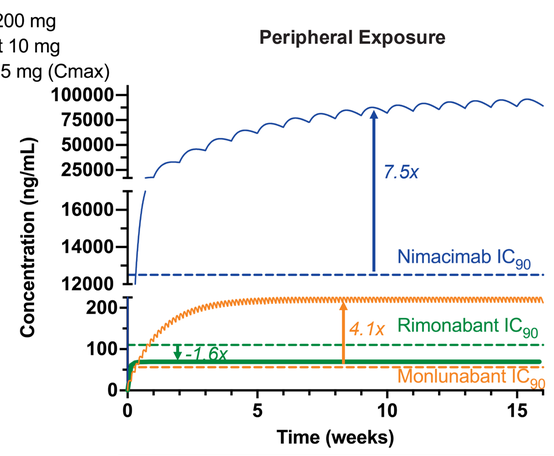
Nimacimab 200 mg QW peripheral exposure is more than 700% above the IC_{90}

Data Summary

Collective modeling shows that peripheral inhibition alone can drive weight loss, irrespective of brain exposure



Drug exposure approaching the IC_{90} in the brain is associated with neuropsychiatric side effects



Peripheral exposure surpassing the IC_{90} is required for effective weight loss

Conclusions

Rimonabant and monlunabant modeling show effective weight loss when IC_{90} is attained in the periphery, but not when IC_{90} is only achieved in the brain. Therefore:

- Systemic (peripheral) CB1 inhibition alone is sufficient for weight loss
- Central inhibition is not required and is linked to neuropsychiatric adverse events

Implications:

- Supports further development of nimacimab, a peripherally restricted CB1 inhibitor antibody
- Nimacimab, has a superior therapeutic window with excellent Ph1 safety profile and similar efficacy (weight loss) in preclinical DIO models compared to small molecules

Future directions:

- Validate findings with ongoing Ph2 obesity clinical trial of nimacimab (NCT06577090)

References

1. Shivshankar et al, 2024; Pharmacological Evaluation of Cannabinoid Receptor Modulators Using GRABeCB2.0 Sensor
2. Liu et al, 2021; Functional Selectivity of a Biased Cannabinoid-1 Receptor (CB1R) Antagonist
3. Crater et al, 2023; Effects of CB1R inverse agonist, INV-202, in patients with features of metabolic syndrome. A randomized, placebo-controlled, double-blind phase 1b study
4. Muller, et al, 2022; Chemical Synthesis, Pharmacokinetic Properties and Biological Effects of JM-00266, a Putative Non-Brain Penetrant Cannabinoid Receptor 1 Inverse Agonist
5. Gao et al, 2011; Asymmetric synthesis and biological evaluation of N-cyclohexyl-4-[1-(2,4-dichlorophenyl)-1-(p-tolyl)methyl]piperazine-1-carboxamide as hCB1 receptor antagonists
6. Després JP. et. .al. 2005; Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia

SCAN ME