An Adaptive Study Design for the Assessment of the Safety, Tolerability, and Pharmacokinetics of Nimacimab after Repeat Dosing in Subjects with Metabolic Associated Steatotic Liver Disease (MASLD)

EASD Annual Meeting, Vienna 2025

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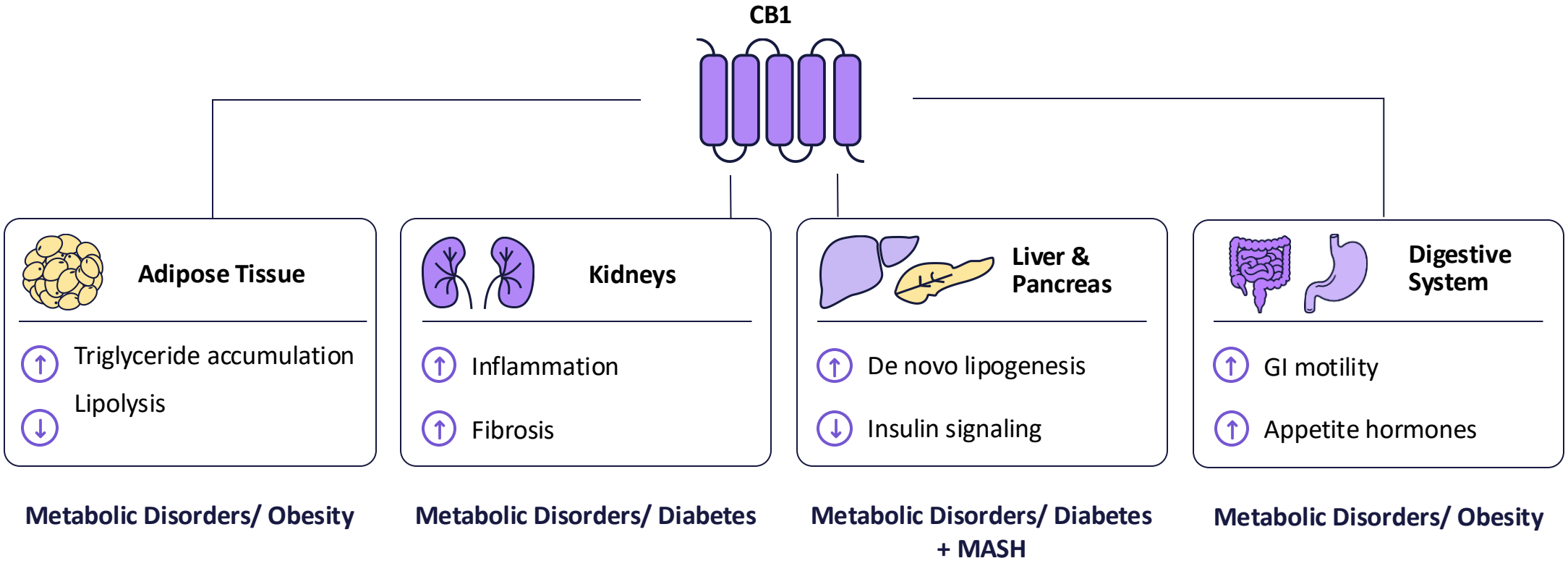
Overview and Study Design

CB1 Receptors Play a Significant Role in Metabolism and Energy Modulation

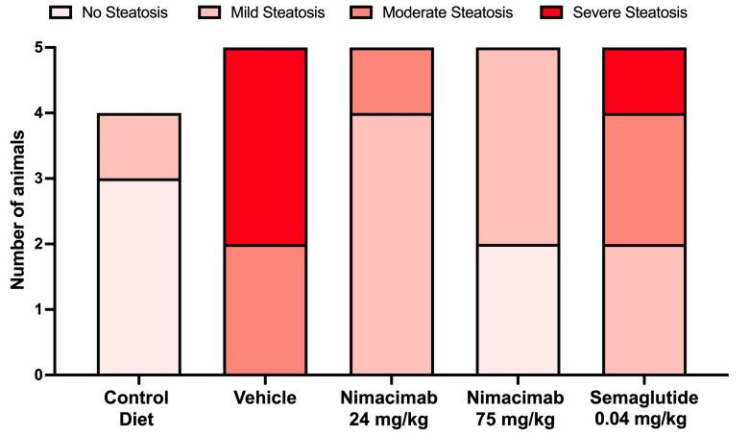
- Active CB1 engagement promotes inflammation, fibrosis, and metabolic dysfunction; blocking peripheral CB1 can reverse negatively-trending pathologies



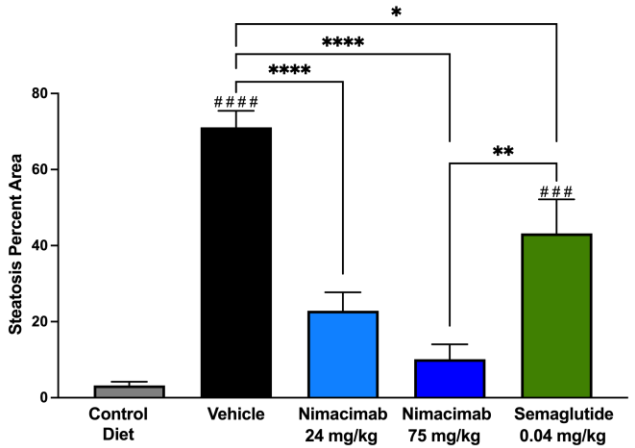
Nimacimab Treatment Reduces Steatosis and Improves Obesity-Related Inflammation in a Murine Diet Induced Obesity Model

Liver Steatosis Analysis

Hepatic Steatosis Score

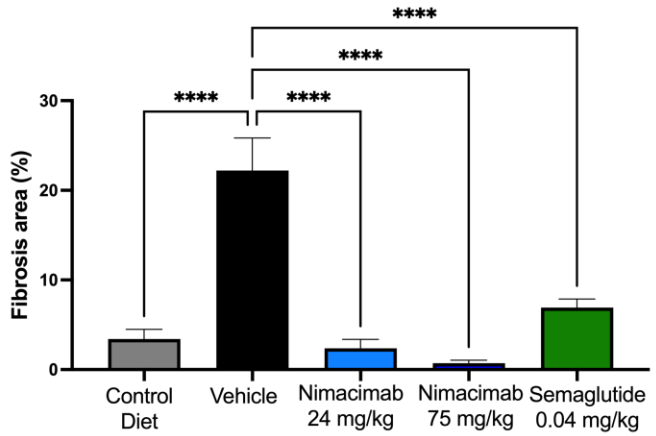


% Steatosis Area in Liver

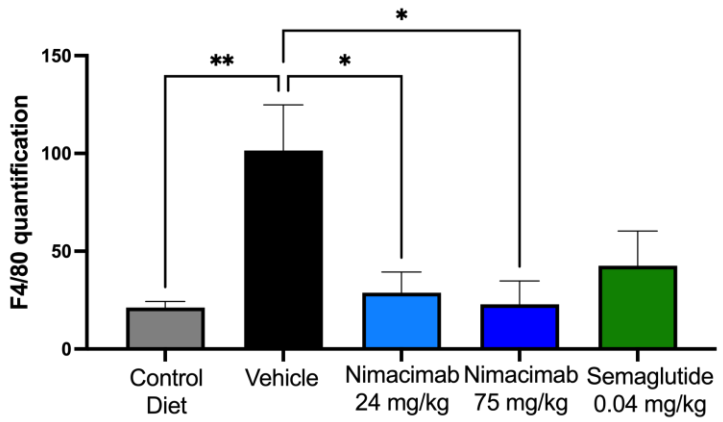


Reduced Liver Fibrosis and Inflammation

Hepatic Fibrosis Area

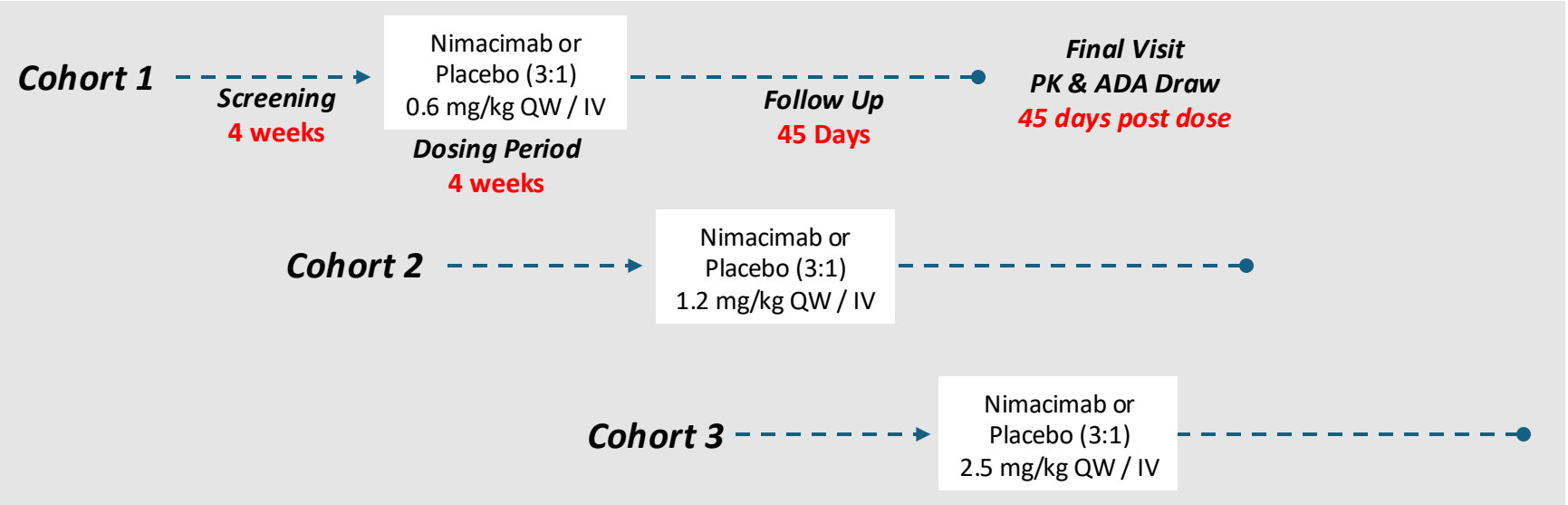


Hepatic Macrophage (F4/80) Density



Phase 1b MAD Study for the Assessment of the Safety, Tolerability, and Pharmacokinetics of Nimacimab – Study Design and Objectives

- **Primary Objective**: Evaluate the safety and tolerability of multiple doses of nimacimab in MASLD subjects
- **Secondary Objective**: Determine the PK of nimacimab and anti-drug antibody (ADA) after multiple doses
- 3 sequential cohorts of up to 28 subjects received 4 weekly IV infusions of nimacimab or placebo (3:1) and were monitored for 45 days after the final dose
- Randomization was stratified by percent liver fat (≤15% and >15%) as determined by MRI-PDFF



Study Eligibility, Disposition and Demographics

- **Eligibility and Disposition**
  - Adult men and women, ages 18 to 65 years of age (inclusive) who had **pre-diabetes or diabetes** and **MASLD** with liver fat percentage by MRI-PDFF of at least 10% and a BMI ≥25 and ≤40 kg/m2 were eligible for inclusion
  - 64 subjects randomized to active treatment and 20 subjects were randomized to placebo
  - The majority of subjects completed 4 weeks of treatment (82/84; 97.6%)
- **Demographics**
  - The overall mean age of the subjects was 53 years (range 20 to 65) and ~50% were male
  - The mean weight was 92.7kg and BMI was 33 kg/m2
  - 68 Subjects (82%) identified as White and 49 (59%) identified as Hispanic or Latino
  - 27 subjects (32%) had previously documented MASLD history; liver ultrasound and/or transient elastography was performed in 56 subjects who had no previous documentation of MASLD
  - 69 subjects (83%) had a diagnosis of Type 2 diabetes and 14 (17%) a diagnosis of prediabetes

Safety and PK Data

Treatment Emergent Adverse Events (TEAEs)

Treatment	Placebo n=20	0.6 mg/kg n=21	1.2 mg/kg n=21	2.5 mg/kg n=21	Active Overall N=63
Any TEAE					
Number of subjects (%)	16 (80.0)	13 (61.9)	17 (81.0)	11 (52.4)	41 (65.1)
Number of events	41	45	46	25	116
Any Serious TEAE					
Number of subjects (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Number of events	0	0	0	0	0
Any TEAE Leading to Study Discontinuation					
Number of subjects (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

- 41 subjects (65%) assigned to receive nimacimab reported 116 TEAEs
- 16 subjects (80%) assigned to receive placebo reported 41 TEAEs
- No Serious TEAEs were reported in the study
- No TEAE led to study discontinuation

Treatment Emergent Adverse Events

Treatment	Placebo n=20	0.6 mg/kg n=21	1.2 mg/kg n=21	2.5 mg/kg n=21	Active Overall N=63
Any TEAE Related to Study Medication					
Number of subjects (%)	4 (20.0)	5 (23.8)	3 (14.3)	2 (9.5)	10 (15.9)
Number of events	4	11	3	3	17
AE Preferred Term in Descending Order of Frequency (Occurring in 3 or More Patients), n (%)					
Diarrhea	8 (40.0)	7 (33.3)	13 (61.9)	6 (28.6)	26 (41.3)
Headache	3 (15.0)	5 (23.8)	3 (14.3)	0 (0.0)	8 (21.7)
Upper Respiratory Tract Infection	2 (10.0)	1 (4.8)	2 (9.5)	3 (14.3)	6 (9.5)
Dizziness	1 (5.0)	2 (9.5)	3 (14.3)	1 (4.8)	6 (9.5)
Nausea	2 (10.0)	2 (9.5)	0 (0.0)	2 (9.5)	4 (6.3)
Vomiting	2 (10.0)	1 (4.8)	2 (9.5)	1 (4.8)	4 (6.3)
Abdominal Pain	0 (0.0)	0 (0.0)	3 (14.3)	0 (0.0)	3 (4.8)

- 10 Subjects (15.9%) reported 17 TEAEs considered possibly related to nimacimab
- 1 subject reported diarrhea and none reported nausea or vomiting that were considered related to nimacimab

GI Tolerability of CB1 Inhibitors

	Nimacimab[1]
Gastrointestinal disorders	**4.8%**
Nausea	0.0%
Diarrhea	1.6%
Vomiting	0.0%
Rate of discontinuation due to GI disorders	0.0%

- CB-1 inhibition appears to be better tolerated than GLP-1RAs, especially when comparing GI disorders, which are the most frequent adverse events related to GLP-1RAs
- The GI tolerability of nimacimab may further improve on that seen with the small molecule inhibitors rimonabant and monlunabant
- Less that 5% of patients receiving nimacimab reported GI related adverse events that were considered possibly attributable to the drug

Source: 1. Skye Internal Data

Related Neurological and Neuropsychiatric AEs

- No neuropsychiatric adverse events of concern, attributable to study drug, were reported in the study

Treatment	Placebo n=20	0.6 mg/kg n=22	1.2 mg/kg n=21	2.5 mg/kg n=21	Active Overall N=63
Dizziness	0 (0.0)	0 (0.0)	1 (4.8)	1 (4.8)	2 (3.2)
Headache	0 (0.0)	2 (9.5)	0 (0.0)	0 (0.0)	2 (3.2)
Lethargy	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	1 (1.6)
Initial insomnia	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	1 (1.6)
Insomnia	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	1 (1.6)
Panic attack	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	1 (1.6)

- There were no significant changes in the Cogstate Computerized Brief Battery Test Scores
- Columbia-Suicide Severity Rating Scale (C-SSRS) was Zero at baseline and Day 29 for all subjects

PK and ADA Assessments

- **Pharmacokinetics**
  - Nimacimab exposure as measured by mean AUC and C_{max} increased with increasing doses
  - At all dose levels, mean $t_{1/2}$ ranged from approximately 18 to 22 days
  - Clearance and volume of distribution were typical for an antibody therapeutic
  - T_{max}, $t_{1/2}$, clearance, and volume of distribution appeared to be independent of dose

- **ADA Response**
  - Immunogenicity was assessed in all subjects throughout the study
  - Only 2 subjects in the 1.2 mg/kg dose group had consistently elevated titers over multiple time points and no detectable ADA pre-dose
  - No subjects with elevated ADA titers over multiple time points were identified in the 0.6 mg/kg or 2.5 mg/kg groups indicating overall a low immunogenicity of the drug over the course of this study

Summary and Next Steps

Nimacimab Phase 1: Summary and Conclusions

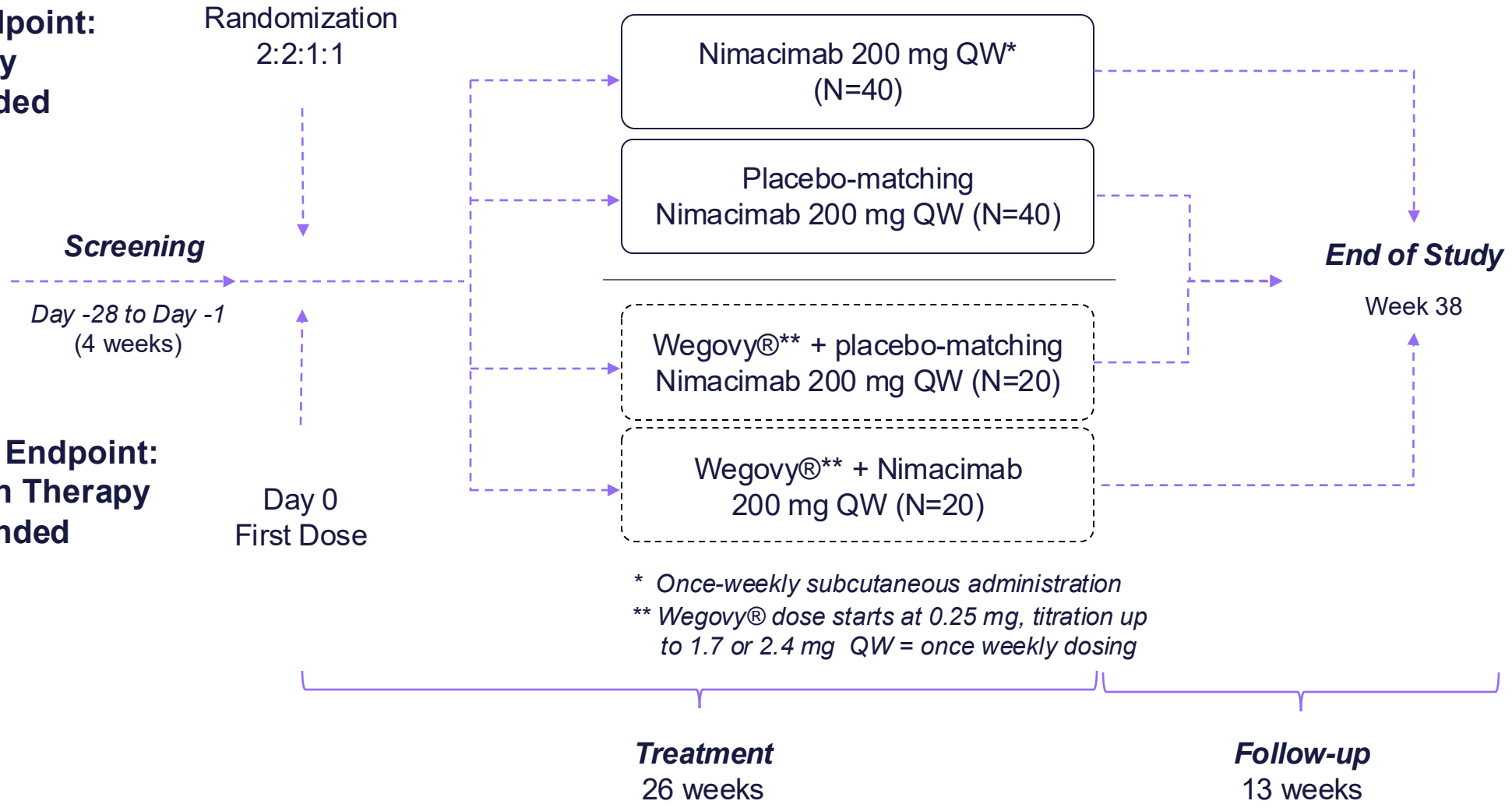
- **Favorable Safety & Tolerability**
  - No serious or severe adverse events reported
  - No neuropsychiatric adverse events, including on C-SSRS and cognitive assessments
  - GI-related AEs (e.g., nausea, vomiting), possibly attributable to nimacimab were rare (4.8%)
- **Consistent Pharmacokinetics**
  - Dose-proportional exposure observed
  - Half-life ~18–22 days, supporting up to monthly dosing
  - Low immunogenicity rates across all doses of nimacimab

Phase 2a CBeyond™ Trial: Patients with Overweight or Obesity

Enrollment completed for initial 26-week treatment period

Primary Endpoint:
Monotherapy
Double-blinded

Exploratory Endpoint:
Combination Therapy
Partially Blinded



Upcoming Clinical and Regulatory Milestones

Phase 1 MAD in Subjects with MASLD

Phase 2a trial in progress
Primary endpoint: weight loss
Topline data expected late Q3/Q4 2025
Topline extension data expected Q2 2026

Phase 2b dose ranging study
Expected to initiate Q2 2026
Topline data Q2 2027

Thank You!

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