Efficacy and safety of monlunabant in adults with obesity and metabolic syndrome: a double-blind, randomised, placebo-controlled, phase 2a trial

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Summary

Background Monlunabant, a novel cannabinoid receptor 1 (CB1R) inverse agonist, has shown encouraging weight loss efficacy and tolerability. We aimed to evaluate the efficacy and safety of monlunabant in individuals with obesity and metabolic syndrome.

Methods This 16-week, randomised, double-blind, placebo-controlled, dose-ranging phase 2a trial, conducted at 25 outpatient research centres in Canada, enrolled adults with obesity and metabolic syndrome. Participants were randomly assigned (1:1:1:1) by means of an interactive response system to once-daily oral tablets of monlunabant 10 mg, 20 mg, 50 mg, or placebo. The participants, site staff, sponsor, and contract research organisation were masked to treatment allocation. The primary endpoint was mean bodyweight (kg) change from baseline at week 16 versus placebo, assessed in all eligible randomised participants, whereas the safety analysis was done in all randomised participants who received at least one dose of trial product. The estimator for the primary estimand was analysed using a mixed model for repeated measures, assuming missing data are missing at random. This trial is registered with ClinicalTrials.gov (NCT05891834) and is complete.

Findings From Sept 8, 2023, to Jan 26, 2024, 409 individuals were screened for eligibility. In total, 243 individuals were randomly assigned to monlunabant 10 mg (n=61), monlunabant 20 mg (n=61), monlunabant 50 mg (n=60), and placebo (n=61); 242 participants received treatment, including 167 (69%) females and 75 (31%) males. 183 (76%) of 242 participants completed the trial: 50 (82%) of 61 received monlunabant 10 mg, 42 (70%) of 60 received monlunabant 20 mg, 34 (57%) of 60 received monlunabant 50 mg, and 57 (93%) of 61 received placebo. At week 16, participants receiving monlunabant showed statistically significant weight loss compared with those receiving placebo (least squares mean difference *vs* placebo of –6·4 kg [95% CI –8·0 to –4·9] for monlunabant 10 mg, –6·9 kg [–8·5 to –5·3] for monlunabant 20 mg, and –8·0 kg [–9·7 to –6·4] for monlunabant 50 mg). Adverse events were mostly mild to moderate gastrointestinal and psychiatric disorders and were seen in 42 (69%) of 61 participants in the monlunabant 10 mg group, 47 (78%) of 60 participants in the monlunabant 20 mg group, 55 (92%) of 60 participants in the monlunabant 50 mg group, and 42 (69%) of 61 participants in the placebo group. Withdrawals due to adverse events appeared dose-dependent, occurring in eight (13%) participants who received monlunabant 10 mg, 16 (27%) who received monlunabant 20 mg, 25 (42%) who received monlunabant 50 mg, and none who received placebo, driven by nausea, anxiety, diarrhoea, irritability, and sleep disorder. No deaths were reported.

Interpretation Participants receiving monlunabant showed statistically significant and clinically meaningful weight loss compared with those receiving placebo for all tested doses. Only slightly greater weight loss was observed at higher doses, whereas adverse events appeared dose dependent. Further investigation is needed to assess the safety and efficacy of lower doses of monlunabant, to evaluate its potential as a medication for obesity.

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Introduction

Obesity and metabolic syndrome represent substantial global health challenges, with high prevalence and substantial effects on individual wellbeing, quality of life, morbidity, and mortality.[1] According to WHO, the prevalence of obesity—defined by a BMI of at least 30 kg/m²—has more than doubled among adults since 1990 and, in 2022, 890 million adults were living with obesity.[2] Obesity costs the US health-care system US$173 billion a year.[3] The presence of abdominal obesity, together with dyslipidaemia, hypertension, and insulin resistance, generally defines metabolic syndrome, a complex condition that increases the risk of type 2 diabetes and cardiovascular disease.[4,5] The increasing worldwide burden of obesity and metabolic syndrome emphasises the urgent need for effective treatment

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See Online for appendix

Research in context

Evidence before this study

On Feb 14, 2025, we searched PubMed for studies published from database inception, using the search "monlunabant OR MRI-1891 OR INV-202" and no language restrictions, which yielded six results. Preclinical evidence showed significant weight loss accompanied by improved insulin resistance in a mouse model of high-fat diet-induced obesity, receiving monlunabant 3 mg/kg per day. To date, the only clinical evidence for monlunabant is a phase 1b trial in which 37 adults with features of metabolic syndrome were randomly assigned to receive monlunabant 25 mg per day or placebo as once-daily oral tablets for 28 days. The trial showed that monlunabant was well tolerated and resulted in weight loss and improvements in other markers of metabolic syndrome.

Added value of this study

Our trial provides new insights into the efficacy and safety of monlunabant, a novel cannabinoid receptor 1 (CB1R) inverse agonist, in individuals with obesity and metabolic syndrome. The findings show that monlunabant leads to statistically significant and clinically meaningful weight loss across all tested doses compared with placebo after 16 weeks of treatment. Additionally, the trial highlights the dose-dependent nature of adverse events, primarily gastrointestinal and psychiatric disorders, which were mostly mild to moderate in severity. The high rate of early withdrawals due to adverse events, which appears dose-dependent, challenges the interpretation of the results. The findings of this study suggest that there might be a therapeutic window for monlunabant at lower doses.

Implications of all the available evidence

The implications of this trial, combined with existing evidence, suggest that monlunabant has potential as a novel treatment option for people with obesity and metabolic syndrome, if a safe and effective therapeutic window can be established. However, the dose-dependent adverse events highlight the need for careful dose optimisation and monitoring. Future research should focus on long-term efficacy and safety, particularly at lower doses, to establish whether a safe and effective therapeutic range exists. Additionally, further studies are needed to explore the mechanistic pathways of monlunabant's effects and to provide evidence of its benefits in different populations with obesity.

options. Several medications for obesity with diverse modes of action are currently on the market,[6] but there continues to be a need for new treatment modalities for individuals who are unable to tolerate existing treatment options or require additive metabolic benefits.

Endocannabinoids are lipid mediators that induce effects similar to those of plant-derived cannabinoids, such as increased appetite, euphoria, and promotion of sleep and relaxation, by interacting with the same receptors—cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CB2R). CB1Rs are highly prevalent in the brain, but they are also present at much lower yet functionally pertinent quantities in various peripheral tissues. In contrast, CB2R expression is restricted to cells of the immune and haematopoietic systems. Activation of CB1R boosts appetite, which prompted the development and approval of the first-in-class CB1R inverse agonist, rimonabant, as a medication for obesity. In people with obesity or overweight and metabolic syndrome, rimonabant not only reduced bodyweight and adiposity but also mitigated all aspects of metabolic syndrome, including insulin resistance, dyslipidaemia, liver fat, and hypertension.[7–10] However, rare, but serious neuropsychiatric side-effects related to the mode of action, particularly involving suicidal ideation and behaviour, led to rimonabant's withdrawal from the market[11] and further pharmaceutical development of this class of medications ceased.[12]

Preclinical evidence suggested, however, that activation of peripheral CB1R contributes to obesity and its metabolic complications via increased lipogenesis,[13] so their selective targeting might retain the metabolic benefit of CB1R blockade while minimising neuropsychiatric risks.[14] Monlunabant (also known as MRI-1891 or INV-202) is a second-generation CB1R inverse agonist designed to reduce brain penetrance while retaining high potency and selectivity for CB1R. Monlunabant also displays signalling bias as it preferentially inhibits CB1R-induced β-arrestin 2 recruitment over G protein activation.[15] In a mouse model of high-fat diet-induced obesity, chronic treatment with a maximally effective dose of monlunabant 3 mg/kg per day elicited significant weight loss accompanied by improved insulin resistance, but did not result in acute brain CB1R occupancy or trigger behaviours that could be predictive of serious psychiatric adverse effects in humans.[15] In a recent phase 1b trial in adults with features of metabolic syndrome, treatment for 28 days with monlunabant 25 mg per day resulted in reductions in bodyweight, waist circumference, and BMI, as well as decreases in total cholesterol and LDL cholesterol, with no serious or severe adverse effects.[16] We report the results of a proof-of-concept, phase 2a trial to evaluate the efficacy and safety of three different doses of the novel CB1R inverse agonist monlunabant compared with placebo for 16 weeks in individuals with obesity and metabolic syndrome.

Methods

Study design and participants

This phase 2a, randomised, double-blind, placebo-controlled, proof-of-concept, multicentre trial, with an optional, open-label extension, was conducted at 25 sites (outpatient clinical research centres) in Canada. Study sites were initially identified based on prior experience in

obesity or metabolic syndrome, followed by an assessment of feasibility in terms of each site's patient population, staff qualifications, facilities, and past performance. The protocol (appendix pp 21–105) and amendments were approved by the institutional review board or an independent ethics committee at each site (Advarra [IRB#00000971]; lead site approval number SSU00226284), and the trial complied with the International Conference on Harmonization Good Clinical Practice guidelines[17] and the Declaration of Helsinki.[18] The trial is registered with ClinicalTrials.gov (NCT05891834) and is complete. All participants provided written informed consent. There was no patient or public involvement in the design, conduct, or reporting of this phase 2a proof-of-concept study.

Eligible participants were aged 18–75 years with BMI ≥30 kg/m², and metabolic syndrome defined as the presence of at least three of the five following criteria at screening: (1) increased waist circumference (males ≥102 cm, females ≥89 cm); (2) fasting glucose ≥100 mg/dL or ≥5·6 mmol/L or HbA_{1c} >5·7% or >39 mmol/mol; (3) triglycerides ≥150 mg/dL or ≥1·69 mmol/L; (4) HDL cholesterol <40 mg/dL or <1·03 mmol/L for males or <50 mg/dL or <1·29 mmol/L for females; and (5) hypertension (systolic >130 mm Hg and/or diastolic >85 mm Hg).

Key exclusion criteria included diabetes requiring medication for management, use of a glucagon-like peptide-1 agonist or other weight loss drug, or substantial weight change (>5 kg) in the past 3 months, history of bariatric surgery, use of systemic corticosteroids, active diagnosis or history of a significant (as assessed by investigator) psychiatric disorder, including but not restricted to: (1) major depression within the previous 2 years; (2) any history of a suicide attempt or suicidal ideation; (3) a history of other severe psychiatric disorder (eg, schizophrenia, bipolar disorder); (4) taking antidepressants, atypical antipsychotics, or mood stabilisers, as well as a score on the 9-question Patient Health Questionnaire (PHQ-9) of at least 15 at baseline, active substance abuse in the previous 12 months, use of cannabis or cannabinoid-containing compounds within 90 days, history of epilepsy or intracranial surgery, and use identified through screening (and prohibition during the entire duration of the trial) of a strong inducer or inhibitor of cytochrome P450 3A4, 2D6, or 2C19. Full inclusion and exclusion criteria are provided in the appendix (pp 3–4). Sex was self-reported and the options provided were male or female. Race was self-reported and the options provided were White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, or other.

Randomisation and masking

Participants were randomly assigned (1:1:1:1) to receive monlunabant (10 mg, 20 mg, or 50 mg), or placebo. An unmasked biostatistician generated and implemented the randomisation scheme, and the randomisation occurred through an interactive response system and with a block size of 4. The unmasked biostatistician had no other involvement in the rest of the trial. Monlunabant tablets contained 5, 10, or 25 mg per tablet, and two tablets were needed to reach the daily doses in each group. Placebo tablets were identical in appearance to the monlunabant tablets. The participants, site staff, sponsor, and contract research organisation were masked to treatment allocation.

Procedures

The first dose of the assigned study drug was administered by the investigator or designated personnel at the trial sites. Participants were instructed how to self-administer monlunabant doses once daily as oral tablets with food at approximately the same time each day for 16 weeks. Compliance was assessed by tablet counts, based on drug bottles returned to the site at each visit. Non-compliance was defined as taking less than 80% or more than 120% of the assigned trial drug dose during any outpatient evaluation period (visit to visit). Discontinuation for non-compliance was at the investigator's discretion.

The doses of monlunabant 10 mg, 20 mg, and 50 mg per day were chosen based on data from the phase 1 clinical development programme. The programme indicated good tolerability and no safety concerns in healthy volunteers (investigating up to 50 mg per day for 14 days), as well as in adults with features of metabolic syndrome (25 mg per day for 28 days), in whom a significant decrease in bodyweight was also shown.[16]

Changes in concomitant therapy were discouraged. A list of prohibited medications is provided in the appendix (p 5). No lifestyle intervention or advice was provided.

During the treatment period, participants attended trial site visits at weeks 4, 8, 12, and 16, when clinical assessments, clinical laboratory assessments, pharmacokinetic assessments, and assessments of safety and medication were performed. A structured retention programme was not prospectively implemented. Instead, retention advice on managing gastrointestinal adverse events was provided on request. Dose reduction was not allowed; if participants could not tolerate the dose, the treatment was discontinued and the participant discontinued the trial. Participants who prematurely discontinued the trial were asked to attend an early termination visit and no further follow-up was done.

The safety data were reviewed by an independent and external data and safety monitoring board on an ongoing basis.

Outcomes

The primary endpoint was the mean change from baseline in bodyweight (kg) at week 16. The secondary endpoints were mean change from baseline at each site visit in bodyweight (%), waist circumference, lipids (triglycerides, HDL cholesterol, LDL cholesterol, VLDL cholesterol, total cholesterol, apolipoprotein B), and

markers of glucose control (HbA_{1c}, insulin, C-peptide). The participants were not required to be fasting for the collection of blood samples, but results only from fasting participants were reported for insulin, glucose, C-peptide, triglycerides, and VLDL cholesterol.

Safety endpoints were adverse events, serious adverse events, predefined adverse events of special interest, number of discontinuations due to adverse events, suicidality measured with the Columbia Suicide Severity Rating Scale (C-SSRS), symptoms of depression measured with PHQ-9, symptoms of anxiety measured with the 7-question General Anxiety Disorder scale (GAD-7), clinical laboratory assessments, physical examinations, and vital signs, and were summarised for each visit when collected. Adverse events of special interest included anxiety (including a GAD-7 score ≥10), irritability (including a GAD-7 score ≥10), sleep disturbance, depression (including a PHQ-9 score ≥10), tremors, suicidality (defined as any type 4 or 5 suicidal ideation or any suicidal behaviour as per C-SSRS), and seizure or convulsion.

Exploratory endpoints were biomarkers of injury or inflammation and fibrosis (CRP, leptin, TNF, IL-6, IL-18). In a subpopulation of around 50 participants from selected trial sites, changes in body composition from baseline to week 16 were assessed using dual-energy x-ray absorptiometry (DXA), in terms of fat mass, fat-free mass, fat mass percentage, and fat-free mass percentage. Lung function assessments were also performed and will be reported in a separate publication. We also did post-hoc assessments of fasting plasma glucose and homoeostasis model assessment-estimated insulin resistance.

Statistical analysis

A sample size of 240 participants (60 in each group) was required to provide more than 90% power at an overall significance level of 0·05 in the comparison of at least one dose of monlunabant versus placebo to detect a placebo-adjusted change from baseline in bodyweight of 10%, assuming an SD of 15 kg, a baseline weight of 108 kg,[16] and a dropout rate of 15%. Little previous knowledge of the potential treatment effect was available, hence it was not considered meaningful to incorporate further details from the primary analysis into the sample size calculation.

Efficacy endpoints were assessed in all randomly assigned participants other than those deemed ineligible after randomisation (per the intention-to-treat principle, termed the full analysis set) and safety endpoints were assessed in all randomly assigned participants who received at least one dose of trial product (per the treatment actually received, termed the safety analysis set). The primary estimand applied a hypothetical strategy for handling intercurrent events, including data from the full analysis set and including all observations after randomisation until withdrawal or end of treatment (week 16), but excluding observations after intercurrent events of prohibited medication that affect weight. Intercurrent events of early treatment discontinuation were handled through the study design, in which participants who permanently discontinued the trial drug would be requested to return for an early termination visit and discontinue the trial. This estimand aims to establish what the effect of taking the drug as intended is. It does not distinguish whether treatment discontinuation was due to adverse events or lack of efficacy. The estimator for the primary estimand was analysed using a mixed model for repeated measures, assuming missing data is missing at random, with treatment, visit, sex, and treatment-by-visit interaction as fixed effects, as well as baseline weight as a covariate, and participant as a random-effect factor (intercept), implemented as an unstructured covariance structure. This approach makes the fewest assumptions on the variance at each visit and correlation between visits. The primary endpoint was presented as the least-squares mean difference and 95% CI between each of the monlunabant groups and the placebo group. The secondary endpoints were analysed in a similar manner. Exploratory endpoints were summarised with descriptive statistics. For the primary endpoint, subgroup analyses by sex (male *vs* female) and baseline BMI (30–<35 kg/m² *vs* 35–<40 kg/m² *vs* ≥40 kg/m²), a per-protocol analysis (ie, in all participants in the full analysis set who did not have a major protocol deviation), and a post-hoc jump-to-reference sensitivity analysis were also done. For handling multiplicity, a hierarchical testing method was used. Statistical testing was performed as a one-sided test at a 0·05 overall significance level in the following prespecified order for the primary endpoint: (1) monlunabant 20 mg versus placebo, (2) monlunabant 50 mg versus placebo, (3) monlunabant 10 mg versus placebo. Formal testing would continue only if the treatment difference from previous steps was statistically significant. All secondary endpoints and supportive analyses were considered as descriptive evidence of efficacy and were analysed without any procedures to account for multiple comparisons. Summaries of safety outcomes were presented descriptively. Analyses were done using SAS (version 9.4) and according to a statistical analysis plan (appendix pp 106–154).

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The funder supplied the study drug. This article was drafted under the guidance of the authors, with medical writing and editorial support by a medical writer employed at Novo Nordisk.

Results

From Sept 8, 2023, to Jan 26, 2024, 409 individuals were screened for eligibility, of whom 243 were randomly assigned to monlunabant 10 mg per day (n=61),

monlunabant 20 mg per day (n=61), monlunabant 50 mg per day (n=60), or placebo (n=61; figure 1). One participant in the monlunabant 20 mg group was withdrawn before receiving treatment due to a protocol deviation (blood drawing difficulties), leaving 242 for analysis (full analysis set, safety analysis set, and per-protocol set). In total, 183 (76%) of 242 participants completed the trial. There were more withdrawals at higher doses of monlunabant (11 [18%] of 61 in the monlunabant 10 mg group, 18 [30%] of 60 in the monlunabant 20 mg group, and 26 [43%] of 60 in the monlunabant 50 mg group), primarily due to adverse events. In the placebo group, four (7%) of 61 participants withdrew, including two withdrawals due to protocol deviation and two withdrawals at the participant's request; none in the placebo group withdrew due to adverse events.

Baseline characteristics were well balanced across groups (table 1). Overall, the trial included more female participants than male (167 [69%] participants were female and 75 [31%] were male), mean age was 53·5 years (SD 12·1), 206 (85%) were White, mean BMI was 39·7 kg/m² (SD 6·7), mean bodyweight was 110·1 kg (SD 22·8), and mean waist circumference was 119·9 cm (SD 15·1). Mean HbA_{1c} was 5·9% (SD 0·5) or 41.2 mmol/mol (SD 5·8), with 172 (71%) participants being in the prediabetic or diabetic range. A total of seven (3%) participants had anxiety disorders and 20 (8%) had sleep disorders.

Treatment compliance was high across all groups, with the median proportion of assigned doses taken being 98·2% (IQR 89·5–100) in the monlunabant 10 mg group, 99·4% (96·1–100) in the monlunabant 20 mg group, 98·5% (87·8–100) in the monlunabant 50 mg group, and 99·1% (98·2–100) in the placebo group. A total of 57 (93%) participants in the monlunabant 10 mg group, 50 (83%) in the monlunabant 20 mg group, 49 (82%) in the monlunabant 50 mg group, and 59 (97%) in the placebo group were compliant (ie, taking between 80% and 120% of the assigned trial drug dose). None of the participants were excluded due to non-compliance and no participants took prohibited

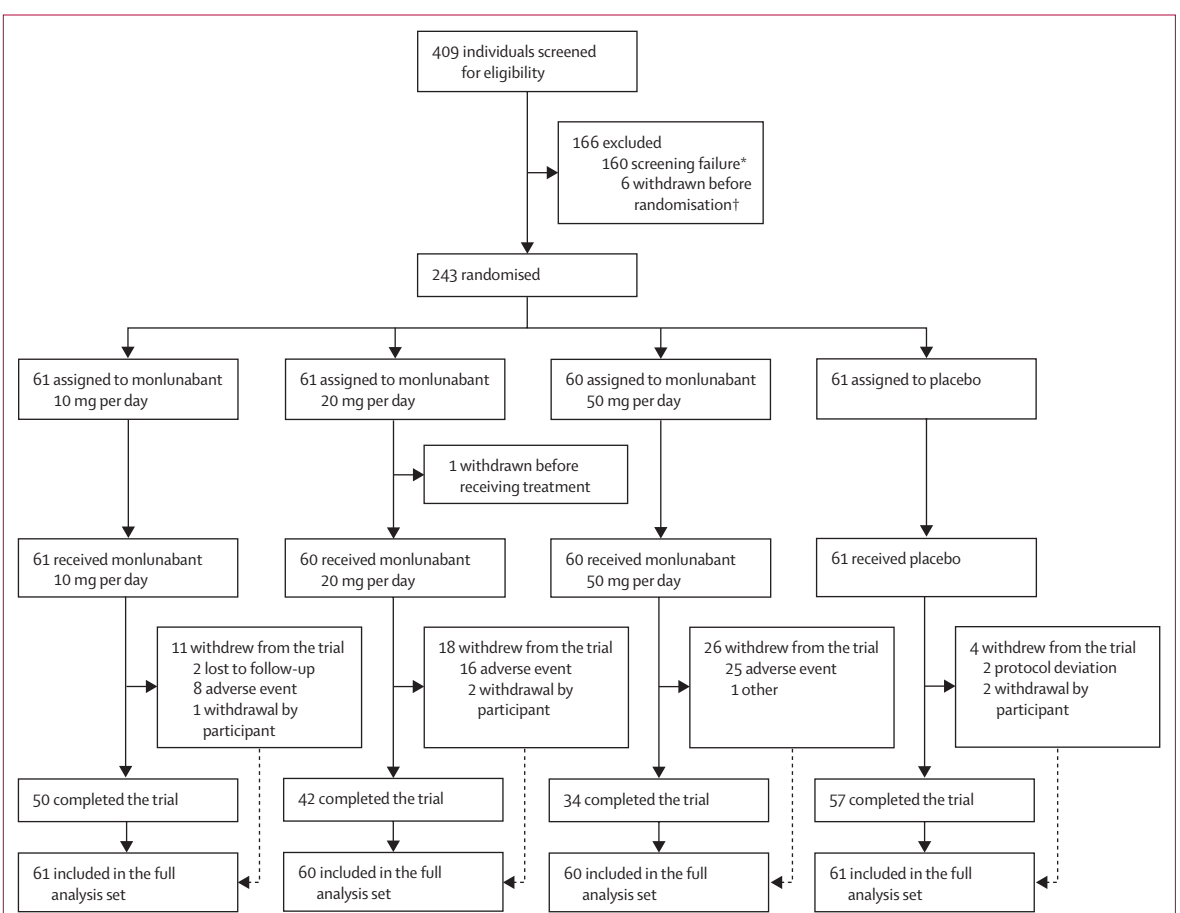

Figure 1: **Trial profile**

*The main reasons for screening failure were not having at least three of five criteria for metabolic syndrome, or having an active diagnosis or history of a significant psychiatric disorder (for specific reasons for screening failures, please see appendix p 6). †For the six participants withdrawn before randomisation, five were withdrawals by participant and one was a decision by the physician. Inclusion and exclusion criteria are listed in the appendix (pp 3–4).

	Monlunabant 10 mg (n=61)	Monlunabant 20 mg (n=60)	Monlunabant 50 mg (n=60)	Placebo (n=61)	Overall (n=242)
Age, years	50·4 (13·4)	52·7 (12·1)	55·1 (10·7)	55·9 (11·7)	53·5 (12·1)
Sex					
Female	42 (69%)	44 (73%)	39 (65%)	42 (69%)	167 (69%)
Male	19 (31%)	16 (27%)	21 (35%)	19 (31%)	75 (31%)
Region					
North America (Canada)	61 (100%)	60 (100%)	60 (100%)	61 (100%)	242 (100%)
Race					
White	48 (79%)	53 (88%)	52 (87%)	53 (87%)	206 (85%)
Black or African American	7 (11%)	3 (5%)	2 (3%)	3 (5%)	15 (6%)
Asian	5 (8%)	4 (7%)	6 (10%)	5 (8%)	20 (8%)
Multiple	1 (2%)	0	0	0	1 (1%)
Weight, kg	112·6 (23·1)	107·9 (17·1)	112·0 (26·9)	108·0 (23·3)	110·1 (22·8)
BMI, kg/m²	40·6 (6·8)	39·6 (5·4)	39·7 (7·4)	39·0 (6·9)	39·7 (6·7)
30–<35	15 (25%)	12 (20%)	19 (32%)	17 (28%)	63 (26%)
35–<40	17 (28%)	25 (42%)	20 (33%)	23 (38%)	85 (35%)
≥40	29 (48%)	23 (38%)	21 (35%)	21 (34%)	94 (39%)
Waist circumference, cm	121·3 (14·5)	118·4 (12·5)	120·2 (17·6)	119·6 (15·4)	119·9 (15·1)
HbA_{1c}, mmol/mol	40·8 (4·7)	40·8 (5·1)	41·4 (7·0)	42·0 (6·3)	41·2 (5·8)
HbA_{1c}, %	5·9 (0·4)	5·9 (0·5)	5·9 (0·6)	6·0 (0·6)	5·9 (0·5)
<5·7	19 (31%)	19 (32%)	17 (28%)	15 (25%)	70 (29%)
≥5·7	42 (69%)	41 (68%)	43 (72%)	46 (75%)	172 (71%)
Systolic blood pressure, mm Hg	136 (14)	133 (13)	133 (12)	133 (13)	134 (13)
Diastolic blood pressure, mm Hg	84 (8)	84 (9)	84 (8)	84 (7)	84 (8)
Fasting triglycerides, mmol/L*	1·7 (0·8)	1·8 (0·9)	1·8 (0·8)	1·7 (0·9)	1·8 (0·9)
HDL cholesterol, mmol/L	1·3 (0·4)	1·3 (0·3)	1·3 (0·3)	1·4 (0·4)	1·3 (0·4)
LDL cholesterol, mmol/L	3·4 (0·9)	3·4 (1·1)	3·3 (1·0)	3·4 (1·0)	3·4 (1·0)
Fasting VLDL cholesterol, mmol/L†	0·8 (0·4)	0·8 (0·4)	0·8 (0·4)	0·8 (0·4)	0·8 (0·4)
Total cholesterol, mmol/L	4·8 (0·9)	4·8 (1·2)	4·8 (1·0)	4·9 (0·9)	4·8 (1·0)
Apolipoprotein B, g/L‡	0·84 (0·19)	0·87 (0·23)	0·82 (0·22)	0·87 (0·21)	0·85 (0·21)
Fasting plasma glucose, mmol/L§	5·4 (0·6)	5·7 (0·9)	5·7 (1·0)	5·8 (1·2)	5·6 (0·9)
Fasting insulin, pmol/L¶	161·6 (153·3)	155·8 (159·7)	147·8 (76·6)	150·6 (101·0)	153·9 (126·6)
Fasting C-peptide, nmol/L¶	1·1 (0·5)	1·1 (0·5)	1·1 (0·4)	1·1 (0·4)	1·1 (0·5)
PHQ-9 total score	1·8 (1·9)	1·6 (2·2)	1·9 (1·9)	1·6 (2·2)	1·7 (2·0)
GAD-7 total score	0·6 (1·6)	0·8 (1·3)	0·7 (1·3)	0·9 (1·6)	0·8 (1·5)
Comorbidities‖					
Hypertension	24 (39%)	32 (53%)	34 (57%)	37 (61%)	127 (52%)
Dyslipidaemia	13 (21%)	17 (28%)	19 (32%)	14 (23%)	63 (26%)
Sleep disorder**	6 (10%)	4 (7%)	5 (8%)	5 (8%)	20 (8%)
Glucose tolerance impaired	3 (5%)	4 (7%)	2 (3%)	2 (3%)	11 (5%)
Attention deficit hyperactivity disorder	1 (2%)	2 (3%)	4 (7%)	1 (2%)	8 (3%)
Anxiety disorders	1 (2%)	4 (7%)	1 (2%)	1 (2%)	7 (3%)

Values are mean (SD) or n (%). Percentages might not add up to 100 due to rounding. Data are shown for all randomised participants, except the participant who was withdrawn before receiving treatment (ie, 242 participants in total). GAD-7=7-item General Anxiety Disorder scale. PHQ-9=9-question Patient Health Questionnaire. *Data were available for 58, 57, 59, and 60 participants for monlunabant 10 mg, 20 mg, 50 mg, and placebo, respectively, ie, 234 participants in total. †Data were available for 59, 57, 59, and 60 participants for monlunabant 10 mg, 20 mg, 50 mg, and placebo, respectively, ie, 235 participants in total. ‡Data were available for 56, 58, 56, and 55 participants for monlunabant 10 mg, 20 mg, 50 mg, and placebo, respectively, ie, 225 participants in total. §Data were available for 57, 57, 59, and 60 participants for monlunabant 10 mg, 20 mg, 50 mg, and placebo, respectively, ie, 233 participants in total. ¶Data were available for 51, 52, 54, and 49 participants for monlunabant 10 mg, 20 mg, 50 mg, and placebo, respectively, ie, 206 participants in total. ‖Dyslipidaemia covers the preferred terms: dyslipidaemia, hypertriglyceridaemia, hyperlipidaemia, hypercholesterolaemia. Sleep disorder covers the preferred terms: sleep disorder, insomnia, poor quality sleep. Anxiety disorders covers the preferred terms: anxiety, anxiety disorder, post-traumatic stress disorder. **Self-reported by the participants.

Table 1: **Demographics and baseline characteristics**

medication that affected their weight (ie, intercurrent event) while on treatment.

At week 16, bodyweight had decreased in all monlunabant groups, reaching an estimated least-squares mean weight loss of 7·1 kg (SEM 0·6) in the monlunabant 10 mg group, 7·7 kg (0·6) in the monlunabant 20 mg group, 8·8 kg (0·6) in the monlunabant 50 mg group, and 0·7 kg (0·5) in the placebo group (table 2). Bodyweight data were available at week 16 for 48 (79%) of 61 participants in the monlunabant 10 mg group, 39 (65%) of 60 in the monlunabant 20 mg group, 34 (57%) of 60 in the monlunabant 50 mg group and 54 (89%) of 61 in the placebo group. The full analysis set contributed to the primary analysis with missing data handled by the mixed model of repeated measurements. Participants in the monlunabant groups had statistically and clinically significant weight loss at week 16 across all tested doses compared with placebo (estimated treatment difference of –6·4 kg [95% CI –8·0 to –4·9] for monlunabant 10 mg, –6·9 kg [–8·5 to –5·3] for monlunabant 20 mg, and –8·0 kg [–9·7 to –6·4] for monlunabant 50 mg, *vs* placebo; figure 2A, table 2). Observed mean bodyweight decreased over the course of the trial in all monlunabant groups; weight loss increased marginally with higher doses and did not appear to stabilise at week 16 (figure 2B). The subgroup analyses showed a higher estimated weight loss in females versus males and in participants with higher baseline BMI versus lower baseline BMI; however, the statistical significance of the interaction between treatment and subgroup was not tested (appendix p 7). The per-protocol analysis results matched the primary analysis, as no participants were excluded for major protocol deviations. A post-hoc jump-to-reference sensitivity analysis also showed statistically significant treatment effects compared with placebo and suggested the results were clinically meaningful, although the treatment effects were smaller and showed closer similarity between doses than the primary analysis (appendix p 7).

Overall, the estimated mean percentage decrease in bodyweight was 5·9–7·4% in the monlunabant groups compared with placebo, and, notably, estimated mean waist circumference was reduced by 3·8–5·4 cm compared with placebo (table 2; appendix p 8). Statistically significant estimated improvements of –0·16 to –0·17 percentage points were noted for HbA_{1c} across the monlunabant groups compared with placebo, with no clear dose–response trend (table 2; appendix p 9). For triglycerides, small but statistically significant estimated improvements were seen for the monlunabant 10 mg and 50 mg groups compared with placebo (table 2). For most other lipids, no estimated improvements were noted, and no clear estimated improvements were seen for insulin and C-peptide compared with placebo.

Adverse events were reported in 42 (69%) of 61 participants in the monlunabant 10 mg group, 47 (78%) of 60 participants in the monlunabant 20 mg group, and 55 (92%) of 60 participants in the monlunabant 50 mg group (table 3). The number of participants who reported adverse events in the placebo group (42 [69%] of 61) was similar to the monlunabant

	N	Change from baseline (SEM)	Compared with placebo, ETD (95% CI)	p value
Primary endpoint				
Bodyweight, kg				
Monlunabant 10 mg	61	–7·1 (0·6)	–6·4 (–8·0 to –4·9)	<0·0001
Monlunabant 20 mg	60	–7·7 (0·6)	–6·9 (–8·5 to –5·3)	<0·0001
Monlunabant 50 mg	60	–8·8 (0·6)	–8·0 (–9·7 to –6·4)	<0·0001
Placebo	61	–0·7 (0·5)	0 (ref)	..
Secondary endpoints				
Bodyweight, %				
Monlunabant 10 mg	61	–6·5 (0·5)	–5·9 (–7·2 to –4·5)	<0·0001
Monlunabant 20 mg	60	–6·9 (0·5)	–6·3 (–7·7 to –4·9)	<0·0001
Monlunabant 50 mg	60	–8·0 (0·6)	–7·4 (–8·9 to –6·0)	<0·0001
Placebo	61	–0·6 (0·5)	0 (ref)	..
Waist circumference, cm				
Monlunabant 10 mg	61	–6·0 (0·8)	–4·3 (–6·4 to –2·2)	0·0001
Monlunabant 20 mg	60	–5·5 (0·8)	–3·8 (–6·0 to –1·6)	0·0008
Monlunabant 50 mg	60	–7·1 (0·9)	–5·4 (–7·7 to –3·1)	<0·0001
Placebo	61	–1·7 (0·7)	0 (ref)	..
Triglycerides, mmol/L*				
Monlunabant 10 mg	58	–0·2 (0·1)	–0·3 (–0·5 to –0·1)	0·0021
Monlunabant 20 mg	57	0·1 (0·1)	–0·1 (–0·3 to 0·1)	0·45
Monlunabant 50 mg	59	–0·1 (0·1)	–0·3 (–0·5 to 0·0)	0·031
Placebo	60	0·1 (0·1)	0 (ref)	..
HDL cholesterol, mmol/L				
Monlunabant 10 mg	61	0·0 (0·0)	0·0 (–0·1 to 0·1)	0·93
Monlunabant 20 mg	60	0·0 (0·0)	0·0 (–0·1 to 0·1)	0·90
Monlunabant 50 mg	60	0·1 (0·0)	0·1 (0·0 to 0·2)	0·032
Placebo	61	0·0 (0·0)	0 (ref)	..
LDL cholesterol, mmol/L				
Monlunabant 10 mg	61	–0·2 (0·1)	–0·1 (–0·3 to 0·2)	0·67
Monlunabant 20 mg	60	–0·4 (0·1)	–0·3 (–0·5 to 0·0)	0·022
Monlunabant 50 mg	60	–0·2 (0·1)	–0·1 (–0·3 to 0·1)	0·48
Placebo	61	–0·1 (0·1)	0 (ref)	..
VLDL cholesterol, mmol/L*				
Monlunabant 10 mg	59	–0·1 (0·0)	–0·2 (–0·3 to –0·1)	0·0009
Monlunabant 20 mg	57	0·0 (0·0)	0·0 (–0·1 to 0·1)	0·54
Monlunabant 50 mg	59	–0·1 (0·0)	–0·1 (–0·2 to 0·0)	0·049
Placebo	60	0·1 (0·0)	0 (ref)	..
Total cholesterol, mmol/L				
Monlunabant 10 mg	61	–0·2 (0·1)	–0·1 (–0·4 to 0·1)	0·21
Monlunabant 20 mg	60	–0·3 (0·1)	–0·2 (–0·4 to 0·0)	0·049
Monlunabant 50 mg	60	–0·1 (0·1)	0·0 (–0·3 to 0·2)	0·76
Placebo	61	–0·1 (0·1)	0 (ref)	..
Apolipoprotein B, g/L				
Monlunabant 10 mg	56	–0·033 (0·019)	–0·021 (–0·07 to 0·03)	0·41
Monlunabant 20 mg	58	–0·058 (0·020)	–0·046 (–0·10 to 0·00)	0·077
Monlunabant 50 mg	56	–0·039 (0·021)	–0·027 (–0·08 to 0·03)	0·32
Placebo	55	–0·012 (0·018)	0 (ref)	..

(Table 2 continues on next page)

	N	Change from baseline (SEM)	Compared with placebo, ETD (95% CI)	p value
(Continued from previous page)				
HbA_{1c}, %				
Monlunabant 10 mg	61	−0·15 (0·04)	−0·16 (−0·26 to −0·05)	0·0028
Monlunabant 20 mg	60	−0·15 (0·04)	−0·16 (−0·26 to −0·05)	0·0036
Monlunabant 50 mg	60	−0·16 (0·04)	−0·17 (−0·28 to −0·06)	0·0029
Placebo	61	0·01 (0·04)	0 (ref)	..
Insulin, pmol/L*				
Monlunabant 10 mg	51	−27·5 (10·3)	−15·8 (−43·1 to 11·5)	0·25
Monlunabant 20 mg	52	−22·0 (10·5)	−10·3 (−38·0 to 17·3)	0·46
Monlunabant 50 mg	54	1·7 (11·3)	13·3 (−15·7 to 42·3)	0·37
Placebo	49	−11·7 (9·6)	0 (ref)	..
C-peptide, nmol/L*				
Monlunabant 10 mg	51	−0·07 (0·05)	−0·07 (−0·20 to 0·06)	0·27
Monlunabant 20 mg	52	−0·03 (0·05)	−0·04 (−0·17 to 0·09)	0·55
Monlunabant 50 mg	54	0·09 (0·05)	0·08 (−0·05 to 0·22)	0·23
Placebo	49	0·01 (0·04)	0 (ref)	..

Change from baseline means estimated for the hypothetical estimand based on a mixed model for repeated measures including treatment, visit, sex, and the interaction between treatment and visit, as fixed factors, baseline bodyweight as a covariate, and participant as a random effect factor. ETD=estimated treatment differences. *Only results from fasting participants were reported for insulin, C-peptide, triglycerides, and VLDL cholesterol.

Table 2: **Efficacy endpoints, change from baseline at week 16**

10 mg group. The number of participants with adverse events leading to early withdrawal from the trial increased with higher doses of monlunabant. Most of the adverse events were mild to moderate in severity and non-serious. Two serious adverse events (malaria in the monlunabant 10 mg group and stroke in the monlunabant 20 mg group) were reported in the trial, and both were considered not related to the trial product by the investigators. Of 27 severe adverse events, 20 (seven in the monlunabant 10 mg group, five in the monlunabant 20 mg group, and eight in the monlunabant 50 mg group) were considered related to the trial product (mainly nausea, diarrhoea, and vomiting, but also adjustment disorder with mixed mood, weakness, dizziness, hot flushes, tearful and cries easily, increased anxiety, insomnia, abdominal pain, panic attack, irritability). No deaths were reported.

The adverse events leading to early withdrawal from the trial mainly occurred in the first half of the trial (appendix p 15). The onset of most gastrointestinal adverse events was immediately after initiating treatment (appendix p 15), whereas psychiatric adverse events were distributed over the first half of the trial (appendix p 15).

The most frequent adverse events in the monlunabant groups by system organ class were gastrointestinal disorders, followed by psychiatric disorders (figure 3). The most frequent adverse events by preferred term were nausea, followed by hot flush, anxiety, decreased appetite, diarrhoea, vomiting, and irritability (appendix p 16). The most common adverse events leading to early withdrawal from the trial were within the gastrointestinal and psychiatric disorders system organ classes (table 3; appendix pp 17–18), driven by events of nausea, anxiety, diarrhoea, irritability, and sleep disorder.

Psychiatric adverse events were reported in 17 (28%) participants in the monlunabant 10 mg group, 20 (33%) participants in the monlunabant 20 mg group, 25 (42%) participants in the monlunabant 50 mg group, and one (2%) in the placebo group, with events of mainly mild to moderate severity, none were serious, and most (45 [71%] of 63) participants recovered (appendix p 19). The reported outcome of adverse events with a start date in the main phase includes observation until study discontinuation or database lock, whichever comes first.

Although anxiety was among the most frequent of adverse events, mean scores for symptoms of depression, measured with PHQ-9, and anxiety, measured with the GAD-7 scale, stayed within the normal range, as the majority of participants had minimal depression (ie, scores of 0 to 4) and minimal anxiety (ie, scores of 0 to 4) both at baseline and at week 16 (appendix p 20). Six participants were referred to a mental health specialist (four events in three participants in the monlunabant 10 mg group and six events in three participants in the monlunabant 50 mg group).

Suicidality was measured with the C-SSRS, and no type 4 or 5 suicidal ideation or suicidal behaviour were reported (table 3). Two participants (one in the monlunabant 10 mg group and one in the monlunabant 50 mg group) reported suicidal ideation type 1, corresponding to low-risk suicidal ideation, and no type 2 to 5 suicidal ideation or any suicidal behaviour was reported.

There were no clinically relevant findings for safety-related clinical laboratory assessments, physical examinations, and vital signs.

Reductions in the monlunabant groups were observed for leptin (observed mean ratio to baseline of 0·73–0·83 at week 16, with observed geometric means of 42·7–51·9 pg/mL at baseline) and CRP (observed mean ratio to baseline of 0·62–0·90 at week 16, with observed geometric means of 4·26 to 4·73 mg/L at baseline; appendix p 13). No meaningful changes were seen for the other biomarkers.

In the subpopulation that had DXA scans performed (52 participants at baseline and 36 participants at week 16), the observed mean fat mass percentages at baseline were 45·3% (SD 6·6) for monlunabant 10 mg, 47·4% (5·4) for monlunabant 20 mg, 44·5% (7·9) for monlunabant 50 mg, and 44·0% (6·4) for placebo (appendix p 14). After 16 weeks, fat mass percentages had decreased, with an observed mean change of −0·9 percentage points (SD 2·2) in ten participants in the monlunabant 10 mg group, −1·1 percentage point (1·7) in four participants in the monlunabant 20 mg group, −2·8 percentage points (2·9) in eight participants in the monlunabant 50 mg group, and 0·0 percentage points (1·1) in 14 participants in the placebo group. On

average, the weight loss consisted of 34% fat mass and 67% fat-free mass in the monlunabant 10 mg group, 65% fat mass and 35% fat-free mass in the monlunabant 20 mg group, and 63% fat mass and 37% fat-free mass in the monlunabant 50 mg groups.

The proportion of observed participants losing at least 5% of their bodyweight by week 16 compared with baseline increased with dose, whereas the proportion of participants achieving at least 10% weight loss was similar across doses (appendix p 10; post hoc). In the monlunabant groups, HbA_{1c} improvements were mainly observed among participants with HbA_{1c} of at least 5·7% at baseline (observed mean change in HbA_{1c} of –0·21 to –0·23 percentage points) in contrast to participants with HbA_{1c} less than 5·7% (observed mean change in HbA_{1c} of 0·02 to –0·08 percentage points; appendix p 11; post hoc).

Post-hoc results for homoeostasis model assessment-estimated insulin resistance indicated reductions in all groups, which appeared numerically larger at lower doses (observed mean change from baseline to week 16: –1·9 [SD 6·7] for monlunabant 10 mg, –1·5 [7·0] for monlunabant 20 mg, –0·1 [3·0] for monlunabant 50 mg; –0·4 [3·4] for placebo), whereas no clear pattern was observed for fasting plasma glucose or blood pressure (appendix p 12).

Discussion

This proof-of-concept, phase 2a trial investigated the efficacy and safety of treatment with monlunabant for 16 weeks in adults with obesity and metabolic syndrome. The trial showed statistically significant and clinically meaningful weight loss across all tested doses with estimated treatment differences ranging from –6·4 kg to –8·0 kg (–5·9% to –7·4%) after 16 weeks compared with placebo. The weight loss increased only slightly with higher doses but did not appear to reach a plateau at week 16 and was accompanied by dose-dependent psychiatric and gastrointestinal adverse events, resulting in high rates of withdrawal. No severe suicidal ideation was reported.

Whether the weight loss effects from monlunabant will continue beyond 16 weeks remains uncertain. The optional open-label extension phase of this study (36 weeks of treatment with monlunabant 20 mg for participants who completed 16 weeks of double-blind treatment) will provide further information on whether the weight loss might continue. This study also indicated small reductions in waist circumference (estimated treatment differences of –3·8 cm to –5·4 cm compared with placebo), possibly reflecting reduced visceral adiposity, and the DXA findings from 36 participants suggested improvement in body composition with increased fat-free mass percentage in all monlunabant groups. Some improvements in HbA_{1c} were also noted, although these were small and unlikely to be clinically meaningful in a population with obesity but mostly without diabetes, and there was no clear dose–response trend. Whether these small improvements in HbA_{1c} are a result of weight loss or represent a direct effect of monlunabant cannot be deduced from our study. No clear improvements were seen in lipid profile, except for small numerical improvements in triglycerides with no clear dose–response tendency, although the moderate degree of dyslipidaemia at baseline might have reduced the effects of monlunabant. Finally, some reductions were observed for leptin and CRP in the monlunabant groups. Similar endpoints were previously investigated for first-generation CB1R inverse agonists, such as taranabant,[19,20] otenabant,[21] and rimonabant,[22] in individuals with overweight or obesity.

Dose-dependent adverse events and early withdrawals due to adverse events were observed, which were mainly due to gastrointestinal and psychiatric disorders, driven by events of nausea, anxiety, diarrhoea, irritability, and sleep disorder. The majority of adverse events were non-serious and not severe. The types of most frequent adverse events observed and types of most frequent adverse events

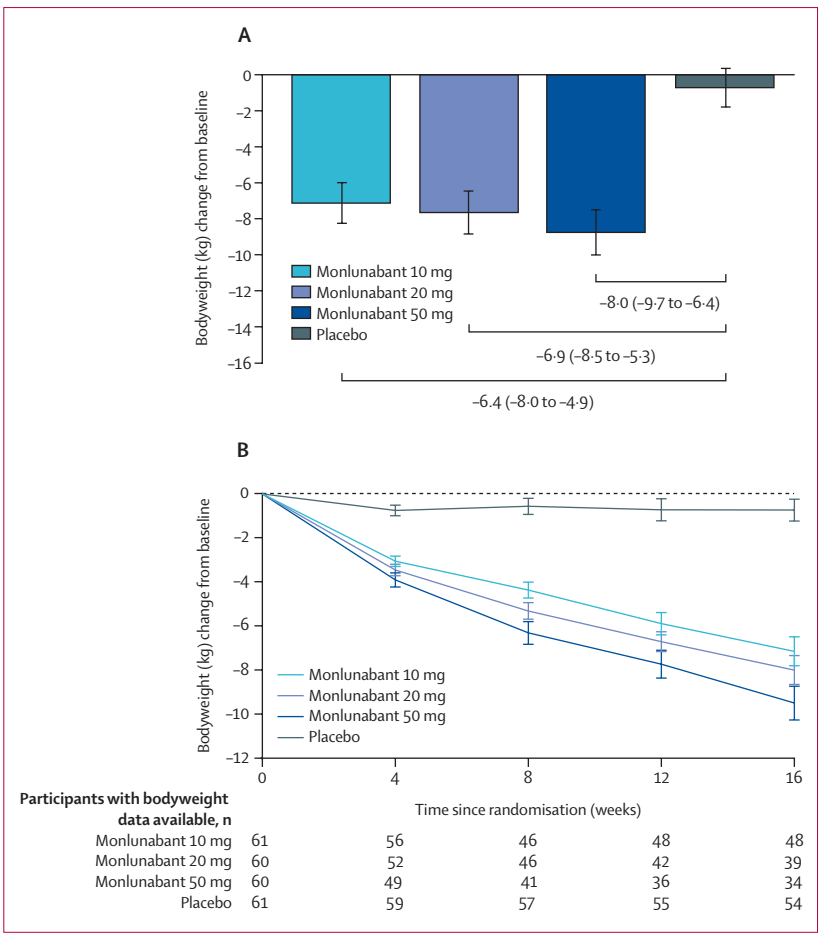

Figure 2: **Bodyweight change from baseline**
(A) Estimated change in bodyweight from baseline to week 16 (95% CI). Overall mean baseline bodyweight was 110·1 kg. The estimated treatment differences with 95% CIs are noted for each monlunabant group compared with the placebo group. (B) Observed mean change (SEM) in bodyweight (kg) for each group over time. Numbers shown in the lower panel are number of participants contributing to the mean.

	Monlunabant 10 mg (n=61)		Monlunabant 20 mg (n=60)		Monlunabant 50 mg (n=60)		Placebo (n=61)	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
All adverse events	42 (69%)	218	47 (78%)	242	55 (92%)	262	42 (69%)	131
Serious adverse events	1 (2%)	1	1 (2%)	1	0	0	0	0
Fatal adverse events	0	0	0	0	0	0	0	0
Maximum severity								
Mild	19 (31%)	74	18 (30%)	82	23 (38%)	69	29 (48%)	93
Moderate	19 (31%)	36	22 (37%)	55	26 (43%)	66	12 (20%)	17
Severe	4 (7%)	8	7 (12%)	7	6 (10%)	10	1 (2%)	2
Adverse events of special interest*	16 (26%)	25	16 (27%)	21	23 (38%)	47	1 (2%)	1
Anxiety	8 (13%)	8	6 (10%)	6	16 (27%)	18	0	0
Irritability	6 (10%)	6	6 (10%)	7	10 (17%)	10	1 (2%)	1
Sleep disturbance†	7 (11%)	8	4 (7%)	4	10 (17%)	10	0	0
Depression	2 (3%)	2	3 (5%)	3	5 (8%)	5	0	0
Tremors‡	1 (2%)	1	1 (2%)	1	4 (7%)	4	0	0
Suicidality	0	0	0	0	0	0	0	0
Seizure or convulsions	0	0	0	0	0	0	0	0
Adverse events leading to early withdrawal from the trial	8 (13%)	28	16 (27%)	31	25 (42%)	50	0	0
Psychiatric disorders	6 (10%)	9	6 (10%)	8	13 (22%)	22	0	0
Gastrointestinal disorders	4 (7%)	5	8 (13%)	8	12 (20%)	18	0	0
Nervous system disorders	3 (5%)	4	4 (7%)	5	1 (2%)	1	0	0
Vascular disorders	3 (5%)	3	2 (3%)	2	4 (7%)	4	0	0
General disorders and administration-site conditions	3 (5%)	3	2 (3%)	4	0	0	0	0
Investigations	1 (2%)	1	1 (2%)	1	1 (2%)	2	0	0
Metabolism and nutrition disorders	1 (2%)	1	1 (2%)	1	1 (2%)	1	0	0
Renal and urinary disorders	1 (2%)	1	0	0	1 (2%)	1	0	0
Skin and subcutaneous tissue disorders	1 (2%)	1	1 (2%)	1	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	0	1 (2%)	1	0	0
Reproductive system and breast disorders	0	0	1 (2%)	1	0	0	0	0

C-SSRS=Columbia Suicide Severity Rating Scale. GAD-7=General Anxiety Disorder-7. PHQ-9=Patient Health Questionnaire-9. *Protocol-defined adverse events of special interest, ie, anxiety (including a GAD-7 score ≥10), irritability (including a GAD-7 score ≥10), sleep disturbance, depression (including a PHQ-9 score ≥10), tremors, suicidality (defined as any type 4 or 5 suicidal ideation or any suicidal behaviour as per C-SSRS), and seizure or convulsion. †Of the 22 events of sleep disturbances, 20 were considered related to the trial product (seven in the monlunabant 10 mg group, four in the monlunabant 20 mg group, and 9 in the monlunabant 50 mg group). Of these, 12 were mild (six in the monlunabant 10 mg group, two in the monlunabant 20 mg group, and four in the monlunabant 50 mg group), seven were of moderate severity (one in the monlunabant 10 mg group, two in the monlunabant 20 mg group, and four in the monlunabant 50 mg group), and one was severe (in the monlunabant 50 mg group). All but three events (in the monlunabant 50 mg group) were resolved. ‡Of the six events of tremors, five (one in the monlunabant 10 mg group, one in the monlunabant 20 mg group, and three in the monlunabant 50 mg group) were considered related to the trial product. Of these, three (one in each monlunabant group) were mild and two (both in the monlunabant 50 mg group) were of moderate severity. All events were resolved.

Table 3: **Adverse events**

leading to drug withdrawals were, overall, similar to those observed for taranabant and otenabant.[19–21] Nausea was the most frequent adverse event and hot flush was the second most frequent adverse event in our study. Hot flushes were reported for taranabant as well, but with lower frequency.[19] The optional open-label extension phase of this study will provide further information on safety, including the nature of the adverse events beyond 16 weeks.

Until now, there has been no mechanistic evidence from well designed clinical studies to support activity of monlunabant in the brain. However, the progressive increase in psychiatric adverse events in the dose range tested in this study suggests brain penetrance of monlunabant. The precise mode of action behind monlunabant-mediated gastrointestinal adverse events remains unclear. Preclinical evidence has shown that chronic, but not acute, treatment of mice with a monlunabant dose of 10 mg/kg resulted in substantial brain CB1R occupancy, as documented by CB1R PET, whereas treatment with the submaximal weight-reducing dose of 1 mg/kg did not result in brain CB1R occupancy following either acute or chronic administration.[15] Previously, the withdrawal of rimonabant from the market due to serious safety concerns about neuropsychiatric harms, especially in the clinical setting after approval, led to the cessation of research into this

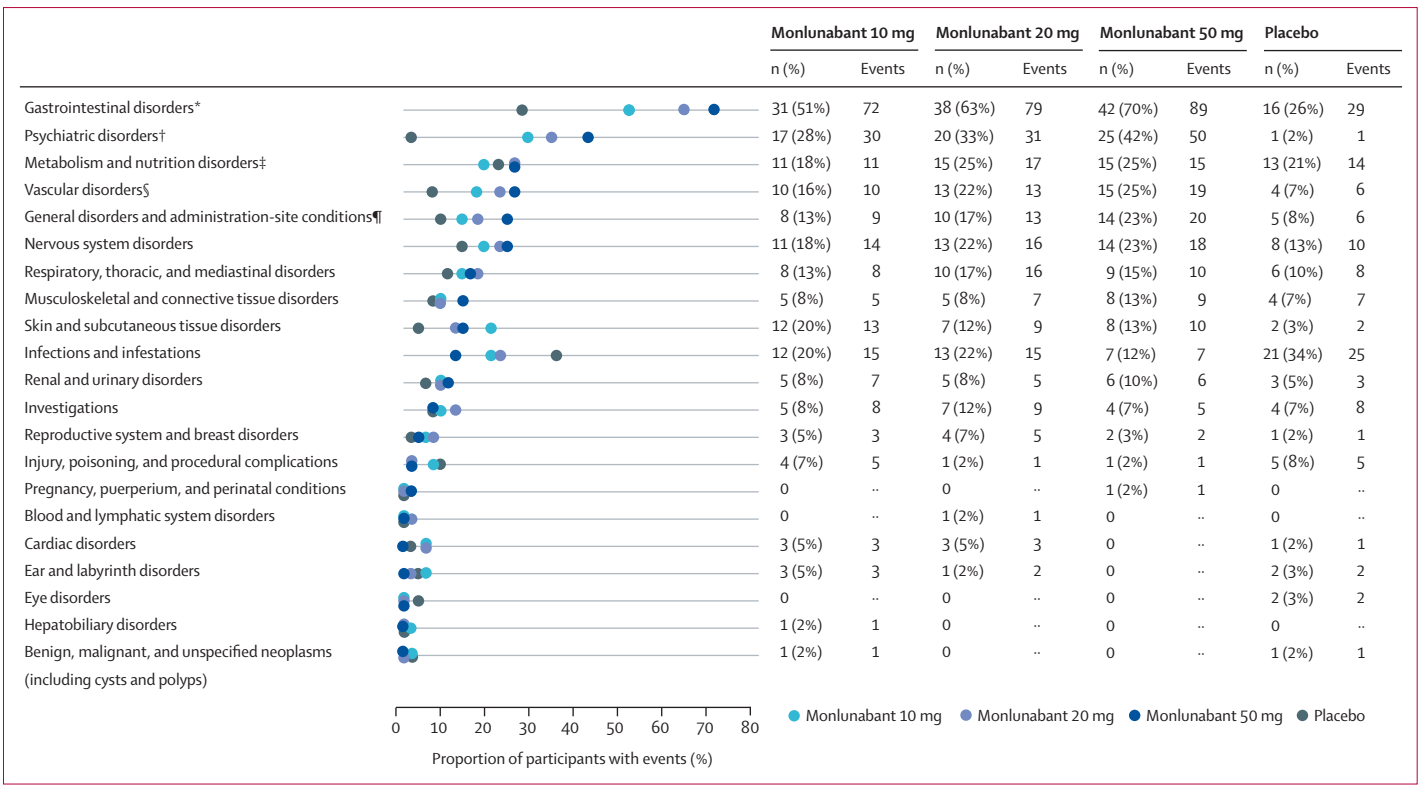

Figure 3: **Adverse events by system organ class**

Adverse events by system organ class in descending order of percentage of participants reporting at least one event in the monlunabant 50 mg group. Note that the y axis runs from 0% to 80%, rather than to 100%, for space reasons. *Gastrointestinal disorders were mainly nausea, diarrhoea, vomiting, soft faeces, abdominal pain, eructation, gastro-oesophageal reflux disease, and constipation. †Psychiatric disorders were mainly anxiety, irritability, insomnia, depression, and affect lability. ‡Metabolism and nutrition disorders were mainly decreased appetite and increased appetite. §Vascular disorders were mainly hot flush. ¶General disorders and administration-site conditions were mainly fatigue, asthenia, influenza-like illness, and chills.

therapeutic class. Other effective therapeutic classes of medications for obesity exist, but there remains a need for new modes of action for people who cannot tolerate existing options or do not achieve sufficient weight loss on existing medications for obesity, and for treatments that offer more convenient administration, such as oral medications. Our findings suggest that a therapeutic window might exist for monlunabant, as the lower doses of monlunabant in our study provided similar weight loss as the highest dose but with fewer side-effects. Weight reduction in the participants in our study appeared to be near maximal at the 10 mg dose. This finding suggests that the dose dependence of weight loss effects might be below 10 mg. Further research is needed to find out if a specific dose range exists in which monlunabant is effective and with a better safety profile. A phase 2b trial is planned to investigate a lower dose range.

The strengths of our study include the randomised, double-blinded and placebo-controlled design as well as the high treatment compliance (no individuals were excluded due to non-compliance). The study also has limitations. There was no follow-up of participants after treatment discontinuation. Overall, there was more withdrawals in the monlunabant groups compared with placebo, in a dose-dependent manner, mostly due to adverse events. We have little information about the participants who withdrew, both in terms of the primary adverse event leading to each withdrawal, and the outcome of the adverse events after withdrawal. Consequently, data on the primary endpoint are available for only about half of the participants in the 50 mg group at week 16, which introduces uncertainty, and could potentially introduce substantial bias when interpreting the efficacy and safety endpoints. We used a hypothetical strategy to handle treatment discontinuations, whereby the treatment effect was estimated as if the intercurrent event did not occur or was mitigated. However, with high discontinuation rates due to adverse events, this assumption is not reliable and is a limitation of the trial results. This limitation is mostly explained by the study design and its purpose. Given that this study was a proof-of-concept, phase 2a trial with a short duration and expected rapid enrolment, it was decided that participants would permanently discontinue the study following treatment discontinuation. Per the protocol, the required follow-up period after treatment discontinuation was 2 weeks, which limited the ability to confirm the duration and resolution of adverse events that were still ongoing at the time of discontinuation. There was no structured retention programme created for this

study. Dose reduction was not allowed and, if a participant could not tolerate the dose, they discontinued the study. Furthermore, endpoints of fasting blood glucose, the proportion of patients who achieved higher than 5% or 10% weight loss, and changes in systolic and diastolic blood pressure, which are commonly included in obesity studies, were not predefined in the protocol. Another limitation is that baseline values of dyslipidaemia and insulin resistance were borderline pathological, which makes it difficult to detect a statistically significant normalisation by treatment. Finally, the study was conducted in a single country, had strict inclusion and exclusion criteria for comorbidities and medication, and a comprehensive list of prohibited medication, which limit the generalisability of its findings.

In conclusion, this proof-of-concept, phase 2a trial showed statistically and clinically significant weight loss compared with placebo for all doses of monlunabant tested (10 mg, 20 mg, and 50 mg) in individuals with obesity and metabolic syndrome. Adverse events were mainly dose-dependent gastrointestinal and psychiatric disorders of mild to moderate severity. The rate of withdrawals was high, mainly due to adverse events, more frequent at higher doses, and indicated that the 50 mg monlunabant dose was not tolerable. The high rate of dose-dependent withdrawals due to adverse events challenges the interpretation of the results. Because the effects on weight loss appear to increase only marginally with higher doses and the adverse events were dose-dependent, there might be a therapeutic window for monlunabant. Further investigation of monlunabant at lower doses and with a close monitoring of adverse events is needed to establish if a safe, effective, and clinically relevant dose range of monlunabant exists.

Contributors

GC and KL contributed to the study design. J-SP was involved in the conduct of the trial and contributed to data collection. TH-H did the statistical analyses. All authors interpreted the data. GK, DD, and LA contributed from their clinical and investigational expertise in the obesity field and added significant contributions to the interpretation of the data. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication. All authors contributed to the data interpretation and manuscript writing (assisted by a medical writer employed at Novo Nordisk), approved the final version of the manuscript, and vouch for data accuracy and fidelity to the protocol. TH-H, JL, J-SP, and GC have accessed and verified the underlying data reported in the manuscript.

Declaration of interests

FKK, OF, and TH-H are shareholders and employees of Novo Nordisk. JL is an employee of Novo Nordisk. GC and KL were employees of Inversago Pharma (a Novo Nordisk company) and owned Inversago Pharma stock options. GK is listed as the inventor on a US patent (issued) covering monlunabant. J-SP is a site principal investigator for the study and is a Research Director of family medicine at Laval University. LA received research funding from Eli Lilly, Novo Nordisk, Altimunne, and Skye Bioscience; consulting fees as a consultant or advisory board attendee from Boehringer Ingelheim, Currax Pharmaceuticals, Eli Lilly, Altimmune, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Novo Nordisk, Pfizer, Veru Pharmaceuticals, Zealand Pharmaceuticals, and Amgen; honoraria for lectures or presentations from Boehringer Ingelheim, Skye Bioscience, Zealand Pharmaceuticals, Jamieson Wellness, and Pfizer; support for attending meetings and/or travel from Jamieson Wellness; patent pending for Flytehealth; is a member of the Board of Directors for Flytehealth, Jamieson Wellness, and ERX Pharmaceuticals; and has equity interests from Jamieson Wellness, Flytehealth, Kallyope, Mediflix, MBX Bioscience, Syntis, Veru Pharmaceuticals, and Skye Bioscience. DD has received speaker and advisory board fees from Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and AstraZeneca; research grants from Eli Lilly, Novo Nordisk, and Boehringer Ingelheim; support for attending meetings and/or travel from Novo Nordisk and Boehringer Ingelheim; and participation in an executive committee for the European Federation of Internal Medicine and the European Association for the Study of Obesity.

Data sharing

Individual participant data will be shared in datasets in a de-identified, anonymised format. Data will be made available after research completion, and approval of the product and product use in the EU and the USA. Data will be shared with bona fide researchers submitting a research proposal requesting access to data. An access request proposal form and the access criteria can be found at https://www.novonordisk-trials.com/.

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