Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials

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Summary

Background The melanocortin 4 receptor (MC4R), a component of the leptin–melanocortin pathway, plays a part in bodyweight regulation. Severe early-onset obesity can be caused by biallelic variants in genes that affect the MC4R pathway. We report the results from trials of the MC4R agonist setmelanotide in individuals with severe obesity due to either pro-opiomelanocortin (POMC) deficiency obesity or leptin receptor (LEPR) deficiency obesity.

Methods These single-arm, open-label, multicentre, phase 3 trials were done in ten hospitals across Canada, the USA, Belgium, France, Germany, the Netherlands, and the UK. Participants aged 6 years or older with POMC or LEPR deficiency obesity received open-label setmelanotide for 12 weeks. Participants with at least 5 kg weight loss (or ≥5% if weighing <100 kg at baseline) entered an 8-week placebo-controlled withdrawal sequence (including 4 weeks each of blinded setmelanotide and placebo treatment) followed by 32 additional weeks of open-label treatment. The primary endpoint, which was assessed in participants who received at least one dose of study medication and had a baseline assessment (full analysis set), was the proportion of participants with at least 10% weight loss compared with baseline at approximately 1 year. A key secondary endpoint was mean percentage change in the most hunger score of the 11-point Likert-type scale at approximately 1 year on the therapeutic dose, which was assessed in a subset of participants aged 12 years or older in the full analysis set who demonstrated at least 5 kg weight loss (or ≥5% in paediatric participants if baseline bodyweight was <100 kg) over the 12-week open-label treatment phase and subsequently proceeded into the placebo-controlled withdrawal sequence, regardless of later disposition. These studies are registered with ClinicalTrials.gov, NCT02896192 and NCT03287960.

Findings Between Feb 14, 2017, and Sept 7, 2018, ten participants were enrolled in the POMC trial and 11 participants were enrolled in the LEPR trial, and included in the full analysis and safety sets. Eight (80%) participants in the POMC trial and five (45%) participants in the LEPR trial achieved at least 10% weight loss at approximately 1 year. The mean percentage change in the most hunger score was −27·1% (n=7; 90% CI −40·6 to −15·0; p=0·0005) in the POMC trial and −43·7% (n=7; −54·8 to −29·1; p<0·0001) in the LEPR trial. The most common adverse events were injection site reaction and hyperpigmentation, which were reported in all ten participants in the POMC trial; nausea was reported in five participants and vomiting in three participants. In the LEPR trial, the most commonly reported treatment-related adverse events were injection site reaction in all 11 participants, skin disorders in five participants, and nausea in four participants. No serious treatment-related adverse events occurred in both trials.

Interpretation Our results support setmelanotide for the treatment of obesity and hyperphagia caused by POMC or LEPR deficiency.

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Introduction

Obesity is a complex, multifactorial disease that results in considerable morbidity and mortality worldwide.[1,2] Some forms of early-onset severe obesity are due to genetic variants that disrupt the melanocortin pathway, which plays a pivotal part in bodyweight regulation and has been a major focus of drug discovery efforts.[2] The melanocortin pathway consists of neurons in the hypothalamus that activate the melanocortin 4 receptor (MC4R).[3–5] Leptin, which is produced in adipose tissue, binds to the leptin receptor (LEPR) on pro-opiomelanocortin (POMC)-expressing neurons in the hypothalamus. In the fed state, leptin stimulates POMC production, which is processed by proprotein convertase subtilisin and kexin type 1 (PCSK1) into melanocortin peptides (α-melanocyte-stimulating hormone [α-MSH] and β-MSH) that bind to and activate MC4R, thereby reducing food intake.[4,5]

POMC deficiency and LEPR deficiency are rare genetic disorders of obesity resulting from biallelic variants in *POMC* or *PCSK1* and *LEPR*, respectively.[6,7] Genetic

Research in context

Evidence before this study

We searched PubMed for English-language articles published before June 17, 2020, describing clinical trials investigating the use of melanocortin 4 receptor (MC4R) agonists in individuals with severe obesity due to pro-opiomelanocortin (POMC) or leptin receptor (LEPR) deficiencies, using the search string "(proopiomelanocortin[Title/Abstract] OR "leptin receptor"[Title/Abstract]) AND ("Melanocortin-4 Receptor"[Title/Abstract]) AND agonist[Title/Abstract]" with the "Clinical Trials" filter on. Two relevant articles were found: one describing a phase 2 trial investigating setmelanotide in three participants with LEPR deficiency and the other describing a phase 2 trial investigating setmelanotide in two participants with POMC deficiency. In both of these trials, setmelanotide treatment was associated with reductions in hunger and substantial weight loss.

Added value of this study

In the two international, multicentre, phase 3 trials described here, setmelanotide was associated with significant weight loss and reductions in hunger scores after approximately 1 year in individuals with POMC or LEPR deficiency obesity. To our knowledge, these trials represent the largest trials of participants with POMC or LEPR deficiency obesity treated with an MC4R agonist, and results are consistent with the previous phase 2 trials.

Implications of all the available evidence

Taken with previous evidence, these results support the long-term use of setmelanotide for the treatment of obesity and hyperphagia caused by POMC or LEPR deficiency. Further evaluation of setmelanotide is warranted in other disorders resulting from variants in the central melanocortin pathway that cause impaired MC4R activation.

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disorders of obesity including POMC, PCSK1, and LEPR deficiency are ultrarare diseases that might be underdiagnosed because of a lack of awareness of the disorders among health-care professionals, multiple clinical features that might overlap with other forms of obesity, and genetic testing rarely being considered for determining the cause of obesity.[2,8,9] Individuals with these disorders have severe hunger (hyperphagia) and early-onset severe obesity resulting from impaired MC4R pathway signalling.[2] Variants in *POMC* can also result in adrenocorticotropic hormone deficiency, hypothyroidism, hypogonadism, and hypopigmentation due to loss of POMC-derived melanocortin peptides.[7,10–13] Variants in *PCSK1* can result in increased proinsulin and postprandial hypoglycaemia, hypogonadism, hypocortisolism, and malabsorption due to impaired prohormone processing.[14–16] Variants in *LEPR* can also result in hypogonadism, hypothyroidism, growth hormone deficiency, high infection risks, and sepsis-related mortality, possibly from impaired immune function.[6,17–21]

Setmelanotide is an MC4R agonist that has been shown to reduce bodyweight and hunger in individuals with obesity caused by POMC or LEPR deficiency.[22,23] In a previous phase 2 trial,[22,23] reductions in hunger and substantial weight loss were observed in three participants with LEPR deficiency and two participants with POMC deficiency after follow-up ranging from 42 to 61 weeks. We report the results of two phase 3 trials, in which we aimed to evaluate the efficacy of setmelanotide for reducing bodyweight and hunger in individuals with POMC deficiency obesity or LEPR deficiency obesity.

Methods

Study design and participants

These two single-arm, open-label, multicentre, phase 3 trials were done in ten hospitals in North America (Canada and the USA) and Europe (Belgium, France, Germany, the Netherlands, and the UK). Individuals were recruited by study investigators from site databases and any genetic obesity registries to which investigators had access. The POMC trial (NCT02896192) included individuals aged 6 years or older with obesity caused by POMC deficiency, defined as homozygous or compound heterozygous variants in *POMC* or *PCSK1*, and a BMI of at least 30 kg/m² (for individuals aged 18 years or older) or a bodyweight of more than the 95th percentile for age on growth chart assessment (in those aged 6 years or older to younger than 18 years). The LEPR trial (NCT03287960) included individuals aged 6 years or older with obesity caused by LEPR deficiency, defined as homozygous or compound heterozygous variants in *LEPR*, and the same BMI and bodyweight criteria as described for the POMC trial. Key exclusion criteria for both trials included a recent diet or exercise regimen, or both, resulting in weight loss or stabilisation and previous gastric bypass surgery resulting in more than 10% weight loss with no evidence of weight regain. A full list of inclusion and exclusion criteria is shown in the appendix (p 6). Locations of *POMC* and *LEPR* variants are shown in the appendix (p 7).

These trials were done in accordance with the International Council on Harmonisation Good Clinical Practice guidelines and the ethical principles founded in the Declaration of Helsinki. Each study protocol was approved by the institutional review board or independent ethics committee at each study site. Written informed consent was provided by each participant, or their guardian or legal representative.

Procedures

The trials were similarly designed, with participants receiving study treatment for 52 weeks (including 4 weeks on placebo) after the establishment of their individualised therapeutic dose (appendix p 13).

Participants entered an open-label dose titration phase following enrolment. Setmelanotide was injected subcutaneously once daily at a starting dose of 1·0 mg for adults (aged 18 years or older) and 0·5 mg for paediatric participants (aged younger than 18 years). Doses were up-titrated every 2 weeks by 0·5 mg until reaching an individualised therapeutic dose, defined as weight loss of approximately 2–3 kg per week for adults or approximately 1–2 kg per week for paediatric participants, up to a maximum dose of 3·0 mg, based on observed weight loss in the phase 2 study.[22] The duration of the dose titration phase varied from 2 weeks to 12 weeks, with the final 2 weeks being at the therapeutic dose. After establishment of the individualised therapeutic dose, participants entered a 10-week open-label treatment phase. Following the open-label treatment phase (a total of 12 weeks of treatment at the individualised therapeutic dose), participants who reached a weight loss threshold of at least 5 kg reduction in weight (or ≥5% weight loss for participants weighing <100 kg at baseline) entered the 8-week double-blind, placebo-controlled withdrawal sequence. Participants received 4 weeks of setmelanotide and 4 weeks of placebo during this phase. Participants then resumed open-label active treatment at the previously established therapeutic dose for 32 additional weeks for a total time on therapeutic dose of 48 weeks. Participants, investigators, study site staff, clinical research organisation staff providing site management, and medical monitors did not have access to the treatment sequence being administered during the withdrawal sequence. The treatment sequence was not randomised. Rhythm Pharmaceuticals (Boston, MA, USA) manually determined the treatment sequence and supplied all study drugs. Rhythm Pharmaceuticals intended that, for the withdrawal phase, all participants would start with setmelanotide treatment and then switch to placebo. This approach would allow participants to maximise weight loss before starting placebo and consistency when comparing results across participants.

Outcomes

In both trials, the primary endpoint was the proportion of participants who achieved at least 10% weight loss compared with baseline at approximately 1 year. Safety and tolerability were assessed by vital signs (including heart rate and blood pressure), as well as the frequency and severity of adverse events using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) grading system. Key secondary endpoints included mean percentage change in bodyweight at approximately 1 year on therapeutic dose, mean percentage change in the most hunger score of the 11-point Likert-type scale in participants aged 12 years or older at approximately 1 year on the therapeutic dose, and proportion of participants who achieved at least 25% reduction in the most hunger score at approximately 1 year on therapeutic dose. Other secondary endpoints included change in waist circumference and metabolic parameters, and percentage change in body fat mass at approximately 1 year of treatment; the proportion of participants meeting categorical thresholds of 5%, 15%, 20%, 25%, 30%, 35%, and 40% weight loss from baseline; reversal of weight gain and hunger reduction during the placebo-controlled withdrawal sequence (during withdrawal from drug); and safety and tolerability of setmelanotide. All other endpoints are listed in the appendix (p 4).

The weight loss thresholds of 5%, 15%, 20%, 25%, 30%, 35%, and 40% were chosen as secondary endpoints so that, in the event that the primary endpoint was met and clinically and statistically meaningful weight loss was demonstrated, these secondary endpoints would be important in more robustly characterising the effects of setmelanotide in individuals with obesity due to POMC and LEPR deficiency. Hunger scores were determined in participants aged 12 years or older using an 11-point Likert-type scale, where 0 indicates not hungry at all and 10 indicates hungriest possible, recorded in a daily diary and averaged to calculate weekly scores for analysis. The most hunger score was captured using the question: "In the last 24 hours, how hungry did you feel when you were the most hungry?" The Likert-type hunger scale has not been validated.

Weight was measured at every visit, with measurements being taken in triplicate at each timepoint with participants wearing light clothing or underwear, with no shoes and an empty bladder. Body fat was determined at screening and at 12 weeks and 52 weeks following the start of the therapeutic dose using an appropriate method that was available at the site (eg, dual-energy X-ray absorptiometry or bioelectrical impedance analysis). Depression was assessed by the Patient Health Questionnaire-9, and suicidality was assessed by the Columbia Suicidality Severity Rating Scale. Further details on additional endpoints and assessments are included in the appendix (p 4).

Statistical analysis

Because of the rarity of POMC deficiency obesity and LEPR deficiency obesity, the power estimation is limited. A small sample size (about ten participants) was planned for each trial because these diseases are very rare; the primary justification for the planned sample size was logistical. The pivotal group of patients used for this primary analysis were the first approximately ten participants enrolled and were clearly documented. However, enrolment was kept open after enrolment of pivotal participants for the purpose of collecting additional supporting data. Data from any additional participants are not reported in this analysis. The primary endpoint for both trials was the proportion of participants in the full analysis set (defined as all participants who received at least one dose of study medication and had a baseline assessment) who demonstrated at least 10% weight reduction at approximately 1 year. With approximately ten

participants planned for each trial, assuming the target proportion of at least 50% after approximately 1 year of treatment, the study provides approximately 94·5% power to detect a difference from the historical reference rate of 5% at a one-sided α level of 0·05. Given the low prevalence of this disease, and the planned small number of participants to be enrolled in this trial, a one-sided α level of 0·05 was chosen as the scientific approach for primary statistical testing, with corresponding 90% CIs, where appropriate. Details describing the selection of a 5% historical reference rate are included in the appendix (p 4).

The primary hypothesis was tested using an exact binomial test at a one-sided α level of 0·05. Results were compared with the proportion of responses from historical data in the target population, where it is expected that at least 5% of participants in the population of interest will achieve 10% weight loss. The primary endpoint was analysed in the full analysis set, and some of the key secondary endpoints were analysed in both the full analysis set and designated use set (defined as the subset of participants in the full analysis set who demonstrated ≥5 kg weight loss [or ≥5% in paediatric participants if baseline bodyweight was <100 kg] over the 12-week open-label treatment phase and subsequently proceeded into the placebo-controlled withdrawal sequence, regardless of later disposition).

All key secondary endpoints (mean percentage change from baseline in bodyweight and mean percentage change and ≥25% reduction in the most hunger score at approximately 1 year on therapeutic dose) were analysed using a linear mixed-effects model in the designated use set. Some key secondary endpoints were also analysed in the full analysis set. The analysis of the proportion of participants aged 12 years or older who achieved a 25% or greater reduction in the most hunger score at approximately 1 year at the therapeutic dose in the full analysis set was done identically to the primary analysis. Formal statistical hypothesis testing was done on the secondary efficacy endpoints with all tests carried out at the one-sided, 0·05 level of significance, for a comparison of change from baseline, with no comparator population.

For all endpoints, the last value obtained before the first dose of active treatment with setmelanotide was considered the baseline value for statistical analyses. All endpoints assessed at approximately 1 year on therapeutic dose were determined from the week-52 visit, which followed 48 weeks of setmelanotide treatment at the individualised therapeutic dose and 4 weeks of placebo. Statistical analyses were done with SAS statistical software (version 9.2 or higher). Additional statistical methods are summarised in the appendix (p 4).

These studies are registered with ClinicalTrials.gov, NCT02896192 and NCT03287960.

Role of the funding source

The funder of the study designed the trial with assistance from academic investigators. The funder aided in data collection, data analysis, data interpretation, and writing of the report. More than one author had full access to all the data from the study and verified the data reported in the manuscript. The corresponding author had final responsibility for the decision to submit for publication.

	Participants with POMC deficiency obesity (n=10†)	Participants with LEPR deficiency obesity (n=11)
Age, years	18·4 (6·2; 11·0–30·0)	23·7 (8·4; 13·0–37·0)
Sex		
Male	5 (50%)	3 (27%)
Female	5 (50%)	8 (73%)
Genotype		
Compound heterozygous	2 (20%)	6 (55%)
Homozygous	8 (80%)	5 (45%)
Ethnicity		
Hispanic or Latino	1 (10%)	0
Not Hispanic or Latino	8 (80%)	11 (100%)
Unknown	1 (10%)	0
Race		
White	7 (70%)	10 (91%)
Other	3 (30%)	1 (9%)
Bodyweight, kg	118·7 (37·5; 55·9–186·7)	133·3 (26·0; 89·4–170·4)
BMI, kg/m²	40·4 (9·0; 26·6–53·3)	48·2 (10·4; 35·8–64·6)
Most hunger score‡	8·0 (0·8; 7·0–9·0)	7·1 (1·0; 5·0–8·0)

Data are mean (SD; range) and n (%). LEPR=leptin receptor. POMC=pro-opiomelanocortin. *Data shown are for the safety analysis set, except where otherwise indicated. †Includes nine participants with variants in *POMC* and one with a variant in *PCSK1*. ‡The most hunger score assessed in participants aged 12 years or older in the full analysis set is based on an 11-point Likert-type scale, where 0 indicates not hungry at all, and 10 indicates hungriest possible.

Table 1: **Baseline characteristics***

Results

Between Feb 14, 2017, and Sept 7, 2018, ten participants were enrolled in the POMC trial and 11 in the LEPR trial, and these participants were included in the full analysis and safety sets (table 1; figure 1). Nine participants in the POMC trial and seven participants in the LEPR trial were included in the designated use set.

In the POMC trial, nine participants had variants in *POMC* and one in *PCSK1*, and eight participants had homozygous variants and two had compound heterozygous variants (appendix p 7). The mean age of participants was 18·4 years (SD 6·2); two participants were aged younger than 12 years. The mean BMI at baseline was 40·4 kg/m² (SD 9·0; table 1). For the six participants aged younger than 18 years, the mean baseline BMI Z score was 3·4 (SD 0·6). The mean most hunger score at baseline was 8·0 (SD 0·8; table 1). Other conditions at baseline included adrenocorticotropic hormone deficiency in nine participants, hypothyroidism in five participants, type 1

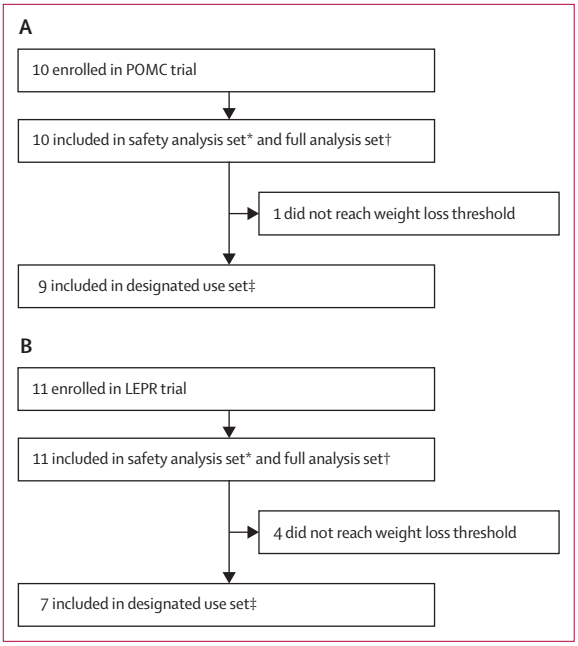

Figure 1: **Participant disposition in the POMC trial (A) and LEPR trial (B)**
LEPR=leptin receptor. POMC=pro-opiomelanocortin. *All participants who received at least one dose of study medication. †All participants who received at least one dose of study medication and had a baseline assessment. ‡Participants in the full analysis set who demonstrated 5 kg or more weight loss (or ≥5% in paediatric participants if baseline bodyweight was <100 kg) over the 12-week open-label treatment phase and subsequently proceeded into the placebo-controlled withdrawal sequence, regardless of later disposition.

diabetes in two participants, and type 2 diabetes in one participant. Concomitant medications in more than one participant included hydrocortisone (n=9), levothyroxine sodium (n=5), ibuprofen (n=4), supradyn (n=4), ferrous sulphate (n=2), insulin glargine (n=2), metformin (n=2), omeprazole (n=2), paracetamol (n=2), ramipril (n=2), and vitamin D (n=2). Other insulin medications received by one participant included human insulin, insulin aspart, and insulin lispro.

In the LEPR trial, five participants had homozygous variants and six had compound heterozygous variants (appendix p 7). The mean age of participants was 23·7 years (SD 8·4). The mean BMI at baseline was 48·2 kg/m² (SD 10·4; table 2). Among the three participants aged younger than 18 years, the mean baseline BMI Z score was 3·5 (SD 0·4). The mean most hunger score at baseline was 7·1 (SD 1·0). Other conditions at baseline included type 2 diabetes in two participants and hypogonadotropic hypogonadism in two participants. Concomitant medications in more than one participant included cholecalciferol (n=5), ibuprofen (n=4), paracetamol (n=4), desloratadine (n=3), ferrous sulphate (n=3), mometasone furoate (n=3), amoxicillin with clavulanate potassium (n=2), folic acid (n=2), metformin (n=2), and oestrogen replacement therapy (n=2).

It was initially intended that all participants would start with setmelanotide treatment for 4 weeks in the double-blind withdrawal phase and then switch to placebo for the remaining 4 weeks. However, one participant in the POMC study received placebo treatment before setmelanotide treatment in the withdrawal phase.

In the POMC trial, the setmelanotide therapeutic dose was 2·5 mg in three, 2·0 mg in one, and 1·5 mg in six participants. Nine (90%) of ten participants in the POMC trial met the weight loss threshold during the initial 12-week open-label treatment phase and completed the full 52 weeks of study treatment (including 4 weeks on placebo); one participant (with *POMC* gene variants, which were not functionally relevant) was withdrawn during the initial open-label treatment phase for not meeting the weight loss threshold. In the LEPR trial, the setmelanotide therapeutic dose was 3·0 mg in two, 2·5 mg in six, and 2·0 mg in two participants, and 1·5 mg in one participant. Four (36%) of 11 participants did not meet the weight loss threshold during the initial 12-week open-label treatment phase. Seven (64%) of 11 participants met the weight loss threshold during the initial 12-week open-label treatment phase, and six participants completed the full 52 weeks of study treatment (including 4 weeks on placebo); two early discontinuations were due to possible treatment-related mild hypereosinophilia (n=1) and death from a road traffic accident as a motor vehicle passenger (n=1).

In the POMC trial, eight (80%) of ten participants achieved at least 10% weight loss compared with baseline at approximately 1 year (p<0·0001 compared with historical data). Of the two participants who did not meet the primary endpoint, one (with a *PCSK1* variant) had confounding comorbidities and received treatment with risperidone for approximately 20 weeks for major depressive disorder. The depressive episode occurred when the participant noticed the return of hyperphagia and weight regain during the placebo phase. In the LEPR trial, five (45%) of 11 participants achieved at least 10% weight loss compared with baseline at approximately 1 year (p=0·0001 compared with historical data).

Of the eight participants who met the 10% weight loss threshold in the POMC trial, all met the 20% threshold, seven met the 25% threshold, three met the 30% threshold, and one met the 35% threshold. Of the five participants who met the 10% weight loss threshold in the LEPR trial, all met the 15% threshold, two met the 20% threshold, and none met the 25% threshold.

The percentage change in bodyweight for the full analysis set is shown in figure 2. In the POMC trial, the mean percentage change in bodyweight compared with baseline at approximately 1 year for the designated use set was −25·6% (SD 9·9; 90% CI −28·8 to −22·0; p<0·0001; table 2). During the double-blind, placebo-controlled withdrawal sequence, the mean absolute change in bodyweight was −3·0 kg (SD 2·5) with active treatment and 5·5 kg (3·0) with placebo, for a mean absolute change between periods of 8·5 kg (5·4; 90% CI 4·9 to 12·1; p=0·0029) in the designated use set (n=8; appendix p 8).

	Participants with POMC deficiency obesity			Participants with LEPR deficiency obesity		
	Baseline (n=10)	Approximately 1 year at therapeutic dose (n=10)	Percentage change from baseline (n=10)	Baseline (n=11)	Approximately 1 year at therapeutic dose (n=9)	Percentage change from baseline (n=9)
Bodyweight*, kg	115·0 (37·8)†	83·1 (21·4)†	−25·6% (9·9); 90% CI −28·8 to −22·0; p<0·0001	131·7 (32·6)‡	115·0 (29·6)‡	−12·5% (8·9); 90% CI −16·1 to −8·8; p<0·0001
Waist circumference*, cm	118·9 (17·6)†	100·5 (12·4)†	−14·9% (7·6); 90% CI −18·4 to −11·4; p<0·0001	127·3 (22·5)‡	114·4 (20·0)§	−7·2% (5·0); 90% CI −9·9 to −4·0; p=0·0002
Body composition*, kg						
Non-bone lean mass	57·8 (19·3)†	46·6 (10·3)¶	−10·7% (8·2); 90% CI −14·4 to −4·7; p=0·0028	58·5 (9·5)§	52·2 (8·5)§	−7·4% (5·1); 90% CI −9·2 to −4·6; p=0·0004
Total fat mass	55·3 (21·1)†	30·3 (11·3)¶	−38·6% (15·4); 90% CI −50·2 to −31·9; p<0·0001	69·3 (24·6)§	53·6 (25·1)§	−15·0% (14·6); 90% CI −24·8 to −6·3; p=0·0086
Cardiovascular parameters						
Heart rate, beats per min	81·0 (12·1)	75·4 (7·2)	−5·8% (11·4); 90% CI −12·5 to 0·8; p=0·14	79·5 (12·6)	77·9 (16·5)	−1·3% (15·5); 90% CI −10·9 to 8·3; p=0·80
Diastolic blood pressure, mm Hg	73·1 (10·8)	71·5 (9·2)	−1·8% (6·3); 90% CI −5·4 to 1·8; p=0·38	67·7 (5·8)	66·5 (8·6)	−1·6% (13·0); 90% CI −9·7 to 6·5; p=0·73
Systolic blood pressure, mm Hg	111·6 (7·8)	109·8 (6·1)	−1·4% (5·1); 90% CI −4·3 to 1·6; p=0·42	121·7 (8·8)	115·1 (14·6)	−3·8% (9·9); 90% CI −9·9 to 2·4; p=0·29
Glucose metabolism						
Fasting glucose, mg/dL	135·8 (107·7)	107·0 (85·5)	−17·2% (18·8); 90% CI −28·1 to −6·3; p=0·018	106·1 (49·2)	108·9 (55·4)	−0·7% (7·0); 90% CI −5·0 to 3·7; p=0·78
HbA_{1c}, %	6·1% (1·8)	5·8% (1·9)	−4·0% (10·5); 90% CI −10·1 to 2·1; p=0·26	5·7% (0·8)‡	5·5% (0·7)‖	−4·9% (7·8); 90% CI −12·3 to 2·6; p=0·24
HbA_{1c}, mmol/mol	43·5 (20·5)‡	39·1 (23·6)‡	..	54·8 (40·9)**	53·8 (38·8)**	..
Insulin during oral glucose load††, nmol/L	136·0 (104·6)¶	78·8 (104·1)‡	..	134·9 (104·3)†	129·5 (40·9)‡‡	..
Lipids, mg/dL						
HDL cholesterol	40·4 (17·7)	52·9 (14·1)	45·0% (43·8); 90% CI 19·6 to 70·3; p=0·010	41·9 (14·4)	49·2 (16·2)	19·6% (24·0); 90% CI 4·8 to 34·5; p=0·040
LDL cholesterol	88·7 (25·9)	80·6 (28·2)	−7·6% (23·1); 90% CI −21·1 to 5·8; p=0·32	105·8 (24·8)	93·3 (22·1)	−10·0% (12·1); 90% CI −17·5 to −2·5; p=0·038
Triglycerides	178·4 (158·3)	78·9 (24·8)	−36·6% (30·4); 90% CI −54·2 to −19·0; p=0·0041	112·3 (46·0)	96·5 (30·2)	−7·0% (26·6); 90% CI −23·4 to 9·5; p=0·46
Alanine aminotransferase, IU/L	35·6 (22·3)	17·2 (6·5)	..	22·2 (8·8)	16·8 (7·6)**	..
Aspartate aminotransferase, IU/L	33·1 (16·1)	22·2 (5·4)	..	23·4 (5·4)	19·5 (4·04)**	..
Bilirubin, µmol/L	7·6 (2·6)	8·2 (3·9)	..	6·8 (3·7)	8·0 (7·4)	..
Creatinine, µmol/L	49·7 (12·5)	55·2 (16·2)	..	58·1 (14·8)	56·6 (17·5)	..

Data are mean (SD) unless otherwise indicated. All measures were taken in the fasting state. LEPR=leptin receptor. POMC=pro-opiomelanocortin. *In the designated use set. †n=9. ‡n=7. §n=6. ¶n=8. ‖n=5. **n=4. ††Following collection of pre-meal blood samples, participants were given a standard oral glucose tolerance test meal, and additional blood samples were obtained at approximately 30, 60, 90, and 120 min after meal start; data are area under the receiver operating characteristic curve. ‡‡n=3.

Table 2: **Changes in anthropometric, cardiovascular, and metabolic parameters compared with baseline at approximately 1 year while receiving therapeutic dose of setmelanotide (safety analysis set)**

The mean waist circumference decreased from 118·9 cm (SD 17·6) at baseline to 100·5 cm (12·4) at approximately 1 year on therapeutic dose, with a mean percentage change of −14·9% (7·6; 90% CI −18·4 to −11·4; p<0·0001; table 2). At approximately 1 year, participants aged 18 years or older had a mean change in BMI of −9·3 kg/m² (SD 6·9; 90% CI −17·4 to −1·2; p=0·073; n=4), and participants aged younger than 18 years had a mean change in BMI Z score of −1·6 (0·9; −2·3 to −0·91; p=0·0059; n=6; appendix p 9) compared with baseline. The mean percentage change in BMI in participants in the designated use set irrespective of age was −27·8% (SD 9·9; 90% CI −31·7 to −23·7; p<0·0001; appendix p 9). A representative BMI chart from a participant showing historical BMI from the age of 3 years until study enrolment and for 1 year on study is provided in the appendix (p 14).

In the LEPR trial, the mean percentage change in bodyweight compared with baseline at approximately 1 year for the designated use set was −12·5% (SD 8·9; 90% CI −16·1 to −8·8; p<0·0001; table 2). During the double-blind, placebo-controlled withdrawal sequence,

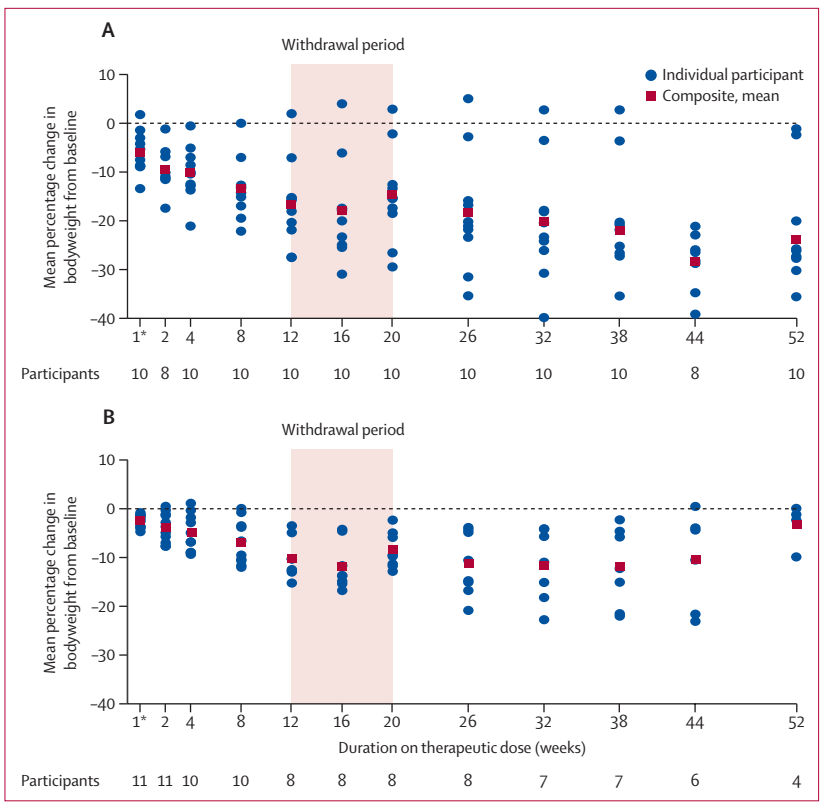

Figure 2: **Effect of setmelanotide on weight loss in participants with POMC (A) or LEPR (B) deficiency obesity in the full analysis set**

Values from baseline to before the final 2 weeks of the dose titration phase are not shown. LEPR=leptin receptor. POMC=pro-opiomelanocortin. *Start of therapeutic dose.

the mean absolute change in bodyweight was –2·1 kg (SD 1·7) with active treatment and 5·0 kg (2·3) with placebo, for a mean absolute change between periods of 7·0 kg (3·4; 90% CI 4·6 to 9·5; p=0·0014) in the designated use set (appendix p 8). Of four participants with weight recorded at both 44 and 52 weeks, one participant lost weight between week 44 and 52. The mean waist circumference decreased from 127·3 cm (SD 22·5) at baseline (n=7) to 114·4 cm (20·0) at approximately 1 year on therapeutic dose (n=6), with a mean percentage change of –7·2% (5·0; 90% CI –9·9 to –4·0; p=0·0002; table 2) compared with baseline at approximately 1 year (n=6). At approximately 1 year, participants aged 18 years or older had a mean change in BMI of –5·2 kg/m² (SD 3·9; 90% CI –8·1 to –2·3; p=0·013; n=7), and participants younger than 18 years had a mean change in BMI Z score of –0·5 (0·4; –1·1 to 0·1; p=0·14; n=3) compared with baseline (appendix p 9). The mean percentage change in BMI in all participants irrespective of age was –13·1% (SD 9·4; 90% CI –16·9 to –9·6; p<0·0001; appendix p 9).

In the POMC trial, the mean most hunger score decreased from 8·1 (SD 0·8) at baseline to 5·8 (2·0) at approximately 1 year on therapeutic dose in seven participants aged 12 years or older, with a mean percentage change of –27·1% (28·1; 90% CI –40·6 to –15·0; p=0·0005) in the designated use set (figure 3A). Four (50%) of eight participants in the full analysis set and three (43%) of seven participants in the designated use set had at least 25% reduction in the most hunger score compared with baseline at approximately 1 year (appendix p 10). During the double-blind, placebo-controlled withdrawal sequence, the mean most hunger score was 4·9 (SD 2·6) following active treatment and 7·1 (2·1) following placebo, for a mean absolute change between periods of 2·2 (3·6; 90% CI –0·8 to 5·2; p=0·19) in the designated use set (n=6; appendix p 8).

In the LEPR trial, the mean most hunger score decreased from 7·0 (SD 0·8) at baseline to 4·1 (2·1) at approximately 1 year on therapeutic dose in seven participants aged 12 years or older, with a mean percentage change of –43·7% (23·7; 90% CI –54·8 to –29·1; p<0·0001) in the designated use set (figure 3B). Eight (73%) of 11 participants in the full analysis set and six (86%) of seven participants in the designated use set had at least 25% reduction in the most hunger score compared with baseline at approximately 1 year (appendix p 10). During the double-blind, placebo-controlled withdrawal sequence, the mean most hunger score was 3·1 (SD 1·6) following active treatment (n=7) and 6·4 (2·3) following placebo (n=6), for a mean absolute change between periods of 3·1 (2·7; 90% CI 0·9 to 5·3; p=0·038) in the designated use set (appendix p 8).

In both trials, setmelanotide was associated with significant improvement in HDL cholesterol concentration but was not associated with significant changes in HbA_{1c} (table 2). In three participants with diabetes and HbA_{1c} above the upper limit of normal (ULN) at baseline, HbA_{1c} remained above the ULN throughout the study. In the POMC trial, but not the LEPR trial, setmelanotide was associated with a significant improvement in fasting glucose and triglycerides. In participants with POMC deficiency, mean fasting glucose changed from 135·8 mg/dL (SD 107·7) at baseline to 107·0 mg/dL (85·5) at approximately 1 year, with a mean percentage decrease of –17·2% (18·8; 90% CI –28·1 to –6·3; p=0·018; table 2). In participants with LEPR deficiency, mean fasting glucose changed from 106·1 mg/dL (SD 49·2) at baseline to 108·9 mg/dL (55·4) at approximately 1 year, with a mean percentage decrease of –0·7% (7·0; 90% CI –5·0 to 3·7; p=0·78; table 2). Body fat decreased at approximately 1 year (appendix p 15). In the POMC trial, mean percentage change in non-bone lean mass was –10·7% (SD 8·2; 90% CI –14·4 to –4·7; p=0·0028) and the change in total fat mass was –38·6% (15·4; –50·2 to –31·9); p<0·0001; table 2). In the LEPR trial, mean percentage change in non-bone lean mass was –7·4% (SD 5·1; 90% CI –9·2 to –4·6; p=0·0004) and the change in total fat mass was –15·0% (14·6; –24·8 to –6·3; p=0·0086; table 2). In the POMC trial, the mean change in resting energy expenditure (REE) compared with baseline at approximately 1 year was

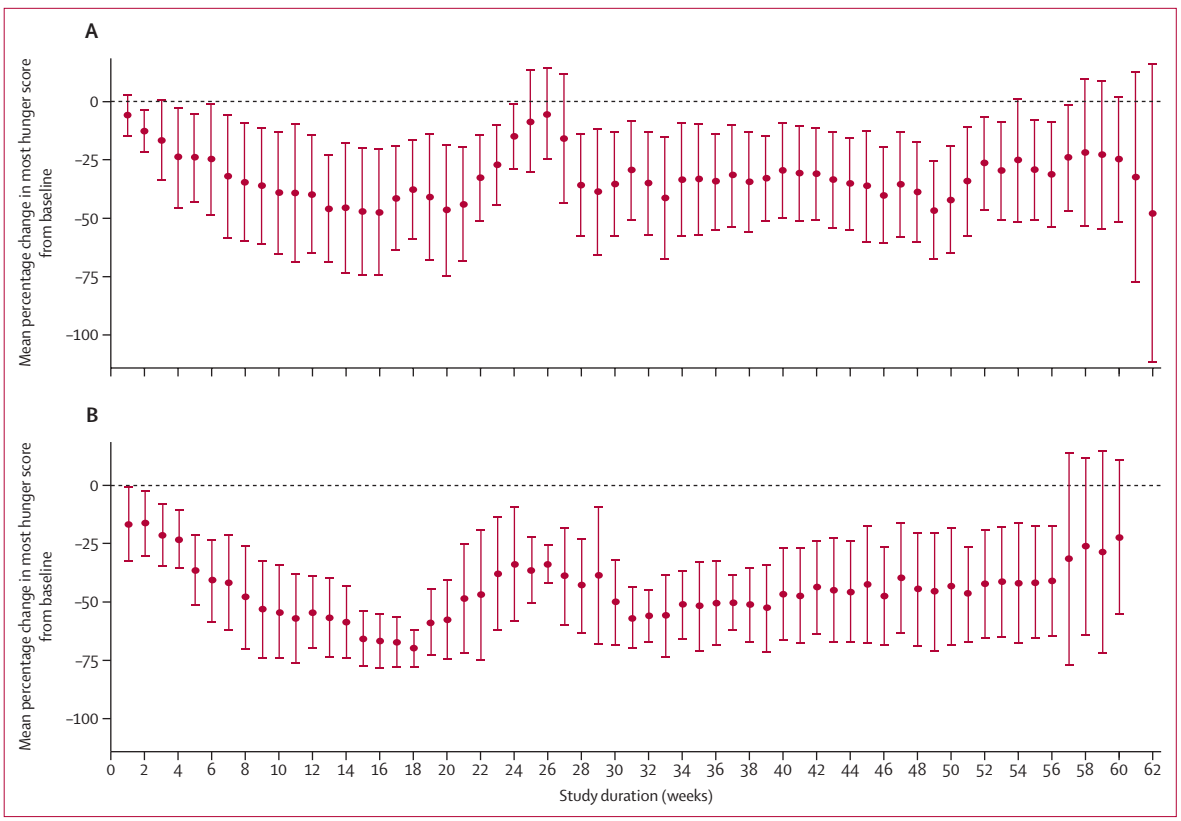

Figure 3: **Mean percentage change in most hunger score from baseline in individuals aged 12 years or older with POMC (A) or LEPR (B) deficiency obesity in the designated use set**

Study week is reported relative to baseline and includes time during the dose titration phase. Error bars are the 90% CI. Seven participants were included in the analysis for all study weeks in both trials. LEPR=leptin receptor. POMC=pro-opiomelanocortin.

–706·3 kcal (SD 351·7) per day (n=7). In the LEPR trial, the mean change in REE compared with baseline at approximately 1 year was –74·6 kcal (SD 309·0) per day (n=4; appendix p 16).

In the POMC trial, the most commonly reported treatment-related adverse events included injection site reaction and hyperpigmentation, which were recorded for all ten participants; nausea was reported in five participants and vomiting in three participants (table 3). Five serious adverse events (depression, major depression, acute adrenocortical insufficiency, pneumonia, and pleurisy) were reported in four participants; none was considered to be related to setmelanotide treatment. No treatment-emergent adverse events led to study drug withdrawal or death. In the LEPR trial, the most commonly reported treatment-related adverse events were injection site reaction in all 11 participants, skin disorders in five participants (eg, pigmentation disorder, skin hyperpigmentation, and discolouration), and nausea in four participants (table 3). All adverse events of nausea resolved without sequelae. Treatment-related grade 1 intermittent spontaneous penile erections were reported in one participant, which resolved without sequelae, and the participant completed the trial. Four serious adverse events (cholecystitis, suicidal ideation, gastric banding reversal, and road traffic accident leading to death) were reported in three participants; none was considered to be related to setmelanotide treatment. One participant discontinued the trial because of grade 1 hypereosinophilia, which was considered to be possibly related to setmelanotide treatment and resolved following discontinuation. A representative image of skin hyperpigmentation and change in melanin content over time based on mexameter (or similar) readings is shown in the appendix (pp 17–18).

No treatment-related cardiovascular adverse events were reported, and there was no evidence that setmelanotide was associated with changes in blood pressure or heart rate (appendix p 19). In the POMC trial, the mean percentage change in heart rate was –5·8% (SD 11·4; 90% CI –12·5 to 0·8; p=0·14), the mean percentage change in diastolic blood pressure was –1·8% (6·3; –5·4 to 1·8; p=0·38), and the mean percentage change in systolic blood pressure was –1·4% (5·1; –4·3 to 1·6; p=0·42; table 2). In the LEPR trial, the mean percentage change in heart rate was –1·3% (SD 15·5; 90% CI –10·9 to 8·3; p=0·80), the mean percentage change in diastolic blood pressure was –1·6% (13·0; –9·7 to 6·5; p=0·73), and the mean percentage change in systolic blood pressure was –3·8% (9·9; –9·9 to 2·4; p=0·29; table 2).

	Participants with POMC deficiency obesity (n=10)	Participants with LEPR deficiency obesity (n=11)
Treatment-related adverse events	10 (100%)	11 (100%)
Injection site reaction	10 (100%)	11 (100%)
Skin and subcutaneous disorders related to hyperpigmentation	10 (100%)	5 (45%)
Skin hyperpigmentation	10 (100%)	4 (36%)
Pigmentation disorder	0	4 (36%)
Skin discolouration	0	2 (18%)
Nausea	5 (50%)	4 (36%)
Vomiting	3 (30%)	..
Serious adverse events	4* (40%)	3† (27%)
Serious treatment-related adverse events	0	0
Treatment-emergent adverse events leading to discontinuation	0	1 (9%)
Treatment-emergent adverse events leading to death	0	1 (9%)‡

Data are n (%). LEPR=leptin receptor. POMC=pro-opiomelanocortin.
*Serious adverse events were depression, major depression, acute adrenocortical insufficiency, pneumonia, and pleurisy. †Serious adverse events were cholecystitis, suicidal ideation, gastric banding reversal, and road traffic accident leading to death. ‡One participant died from injuries sustained during a car accident (not related to setmelanotide treatment).

Table 3: **Treatment-emergent adverse events in the safety analysis set**

In the POMC trial, using the Columbia Suicidality Severity Rating Scale, one participant reported suicidal ideation at baseline but did not report suicidal ideation at approximately 1 year. An additional participant who did not report suicidal ideation at baseline reported suicidal ideation at approximately 1 year. In the LEPR trial, no cases of suicidal ideation and behaviour were reported at either baseline or at approximately 1 year. The mean percentage change in Patient Health Questionnaire-9 scores compared with baseline at approximately 1 year was –13·0% (SD 53·4; p=0·29) in the POMC trial (n=7) and 3·7% (9·1; p=0·49) in the LEPR trial (n=6; data not shown), suggesting no treatment-related worsening of depression.

Discussion

In these two multicentre, phase 3 trials, the MC4R agonist setmelanotide was associated with significant weight loss and reduction in hunger scores in individuals with POMC or LEPR deficiency obesity after approximately 1 year of treatment. To our knowledge, these trials represent the largest trials of participants with POMC or LEPR deficiency obesity treated with a pharmacological agent and confirm the efficacy and safety of setmelanotide. The results were consistent with early reports in two phase 2 trials in five participants.[22,23]

There appeared to be numerical differences in weight loss and hunger reduction with POMC and LEPR deficiency obesity; however, the differences between responses in these two groups have not been statistically compared because data were from separate studies. Weight loss of at least 10% was observed in 80% of participants in the POMC trial and 45% in the LEPR trial, and the mean percentage change in bodyweight at approximately 1 year was greater in participants in the POMC trial than in the LEPR trial (–25·6% *vs* –12·5%). In individuals with POMC deficiency obesity, production of the POMC-derived peptides α-MSH and β-MSH, the endogenous MC4R ligands, is impaired. Setmelanotide (an MC4R agonist) is therefore potentially able to completely restore signalling at MC4R.[22] By comparison, LEPR is upstream of POMC, and expression is observed on agouti-related peptide-positive neurons as well as POMC-positive neurons;[24] therefore, setmelanotide might only partially restore signalling.

The mean age in both trials was relatively young, with the POMC trial enrolling slightly younger participants (mean age 18·4 years) than the LEPR trial (23·7 years). However, the difference in mean age between participants in each trial might not be significant because of the small populations. Additionally, the lifespan of patients with POMC and LEPR deficiency has so far not been systematically analysed.

The effect of setmelanotide on REE is unclear. Consistent with the lowering of weight and fat mass, REE decreased over time in participants with POMC and LEPR deficiency.[25] Indeed, previous research has shown that activation of MC4R increases REE in humans and rodents.[26,27] It is possible that, in the current study, the decreases in REE were not as low as would be observed in individuals with a similar degree of weight loss without setmelanotide treatment. These decreases in REE would need to be assessed using gold-standard measures (ie, calorimetric chambers), which were not used in this study.

Setmelanotide was well tolerated in all individuals, and no new safety concerns were observed. Similar to the phase 2 results,[22,23] the most common treatment-related adverse events were injection site reactions and hyperpigmentation. One participant had a possible treatment-related adverse event of mild hypereosinophilia; although the mechanism for this is unclear. In contrast to first-generation MC4R agonists, which have been shown to activate the sympathetic nervous system, setmelanotide did not lead to increases in heart rate or blood pressure.[22,23,28,29] Setmelanotide is a more potent activator of MC4R than the first-generation MC4R agonist LY2112688, resulting in activation of downstream G protein-based signalling.[23] This might result in some apparent differences in setmelanotide efficacy compared with first-generation MC4R agonists.

Although multiarm, randomised controlled trial designs are the gold standard for evaluating efficacy, the large participant number needed is often not feasible for rare diseases.[30] Because of the rarity of POMC and LEPR deficiency obesity, limitations of these trials

include lack of randomisation, small sample sizes, and limited statistical power, which could confound the results. Because of the small sample sizes, there could have been a possibility for type I error inflation and the potential for bias. These trials were open label and non-comparative; however, all participants entered a placebo-controlled withdrawal sequence. Parental genotypes to assess cis–trans relationships of compound heterozygous variants were not required for study inclusion, given the rarity of the disease and the clinical characteristics and phenotypes of the patients. Another limitation was that there are no validated hunger assessments for hyperphagia associated with rare genetic disorders of obesity. As such, we used a Likert-type tool to estimate hunger that drastically changed with setmelanotide administration. Overall, the efficacy and safety profile of setmelanotide supports its potential long-term use as a treatment for early-onset severe obesity and hyperphagia caused by POMC or LEPR deficiency. Further evaluation of setmelanotide is warranted in other disorders resulting from variants in the central melanocortin pathway that cause impaired MC4R activation.

Contributors

KC, EvdA, JA, AB, WKC, HC, KDW, ISF, JG-L, GG, KK, CP, LP, JS, MS, GY, MW, and PK contributed to data collection, data analysis, data interpretation, writing and revision of the content, and review and approval.

Declaration of interests

KC is a consultant for LNC Therapeutics, Danone Research, and Confo Therapeutics. GG, HC, MS, and GY are employees of Rhythm Pharmaceuticals. All other authors declare no competing interests.

Data sharing

Anonymised individual participant data and study documents can be requested from Rhythm Pharmaceuticals for further research.

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