

Relationship between mean CagriSema dose and weight loss in the REDEFINE 1 trial

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Aim

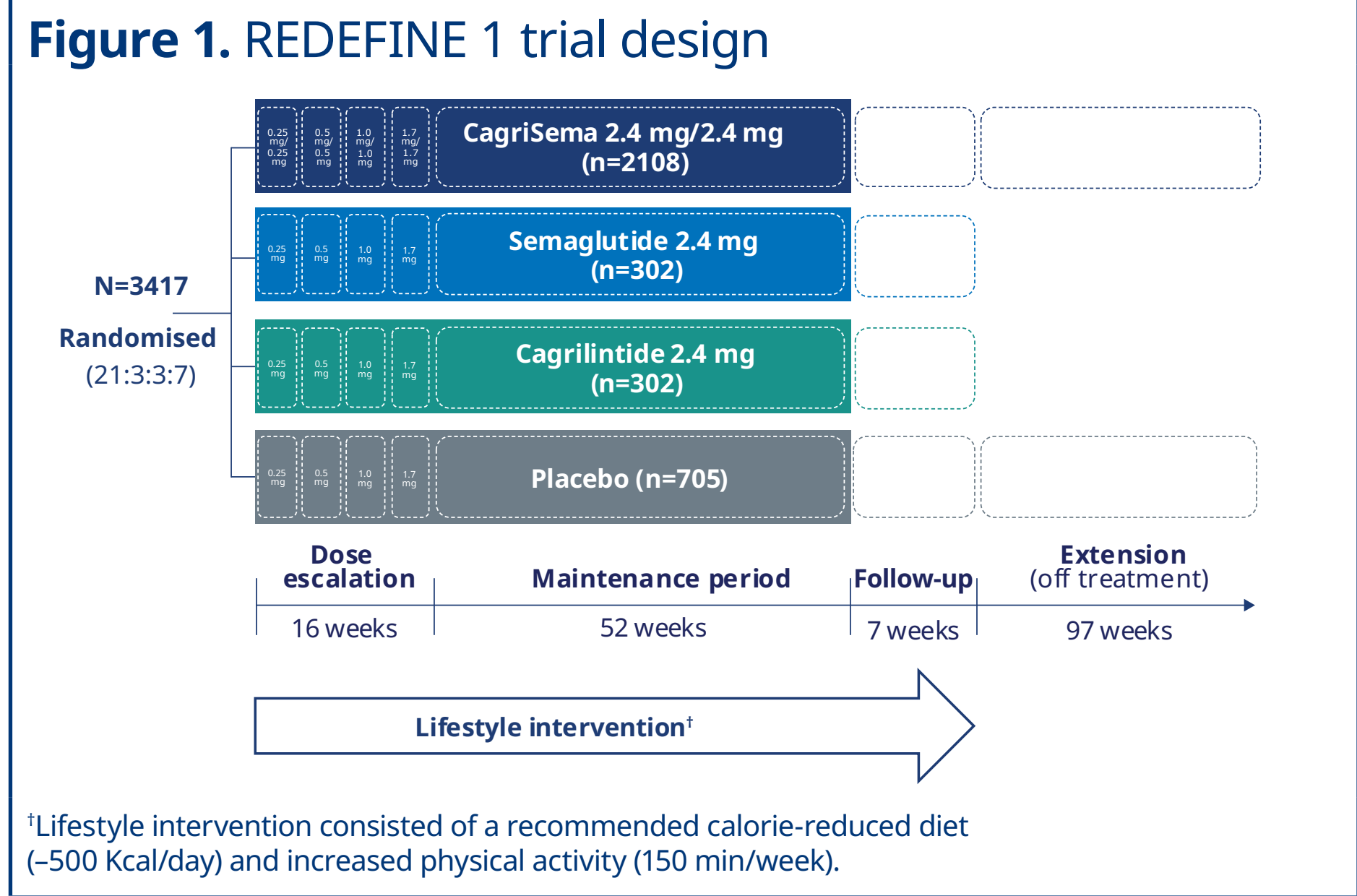
- To characterise the relationship between mean CagriSema dose during the REDEFINE 1 maintenance period and baseline characteristics and relative body weight reduction, as well as to assess safety and tolerability.

Introduction

- In the REDEFINE 1 trial, treatment with once-weekly subcutaneous cagrilintide 2.4 mg and semaglutide 2.4 mg (CagriSema 2.4 mg/2.4 mg) for 68 weeks resulted in a mean weight loss of 22.7% compared with 2.3% with placebo in adults with overweight or obesity and without diabetes (trial product estimand).¹
- The REDEFINE 1 trial design permitted the dose of CagriSema to be reduced at the investigator's discretion, similar to real-world clinical practice.
- For this reason, not all participants randomised to CagriSema completed the trial on the maximum dose.
- At week 68, 1209 participants (57.4%) in the CagriSema group were receiving 2.4 mg/2.4 mg. A total of 1575 participants (74.7%) treated with CagriSema reached the highest dose at any time point.¹

Methods

- In the phase 3 REDEFINE 1 trial (NCT05567796), 3417 adults with a body mass index (BMI) ≥30 kg/m² or ≥27 kg/m² with ≥1 obesity-related complication were randomised to once-weekly subcutaneous CagriSema (n=2108), semaglutide (n=302), cagrilintide (n=302) or placebo (n=705) groups, plus lifestyle intervention, for 68 weeks.
- CagriSema was initiated at a dose of 0.25 mg/0.25 mg and increased every 4 weeks until the maximum dose of 2.4 mg/2.4 mg was reached at week 16, followed by a 52-week maintenance period (Figure 1).
- Investigators were permitted to delay dose escalation or reduce the dose if the current dose was associated with adverse effects or if the participant reached a BMI in the lower normal range and had a health concern.
- Participants who were unable to reach the target maintenance dose were permitted to continue with the maximum tolerated dose.
- Four participant groups based on mean CagriSema dose received during the maintenance period (weeks 17–68) were assessed: >0–0.5 mg, >0.5–1.0 mg, >1.0–1.7 mg and >1.7–2.4 mg.
- Baseline characteristics, mean body weight reduction (%), BMI and gastrointestinal (GI) adverse event (AE) incidence were assessed by mean CagriSema dose.



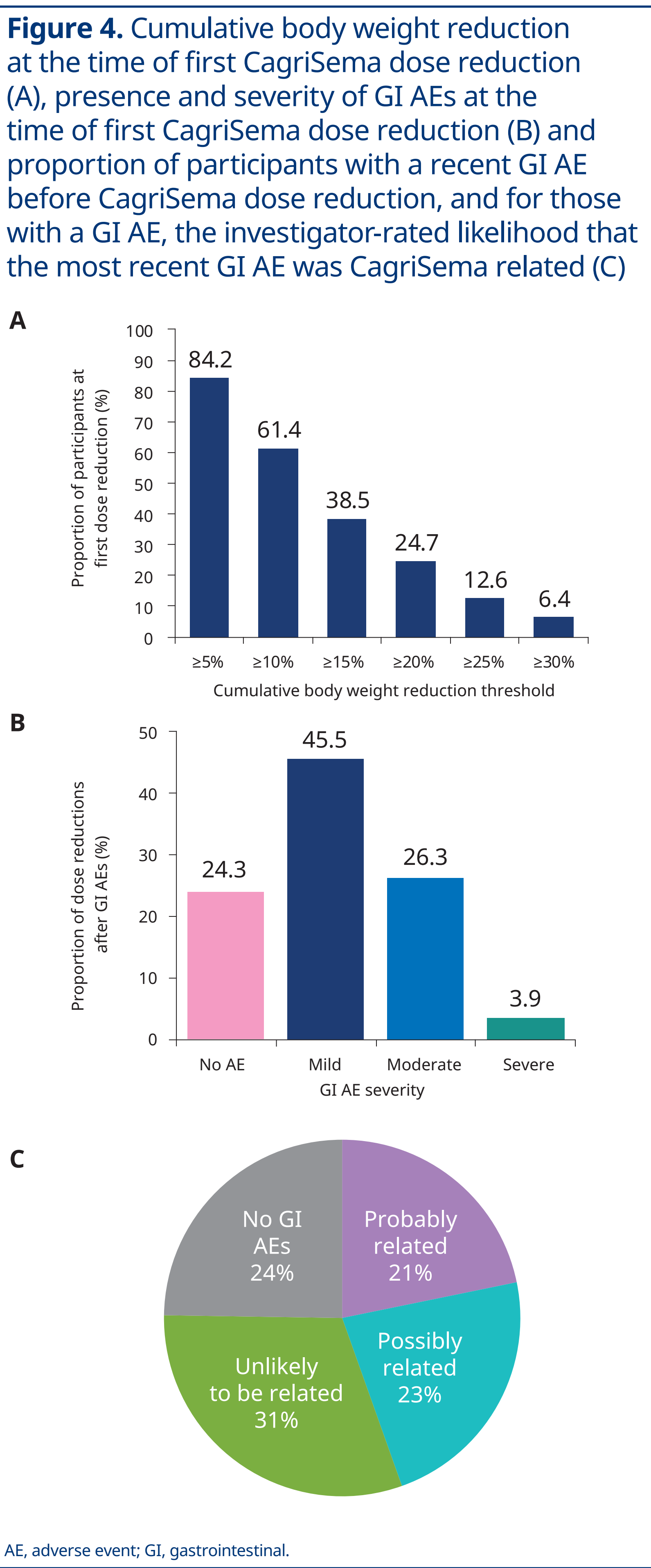
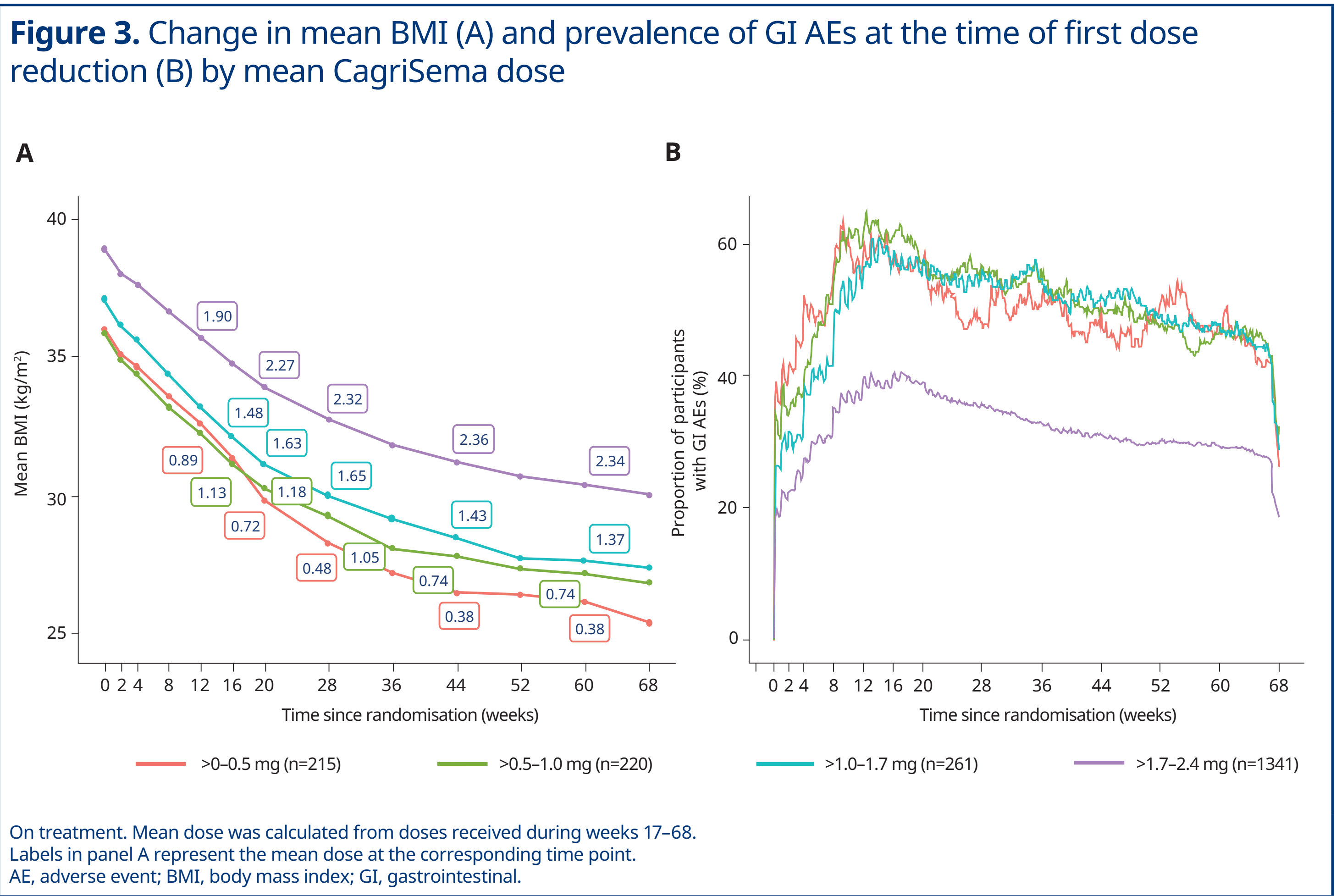
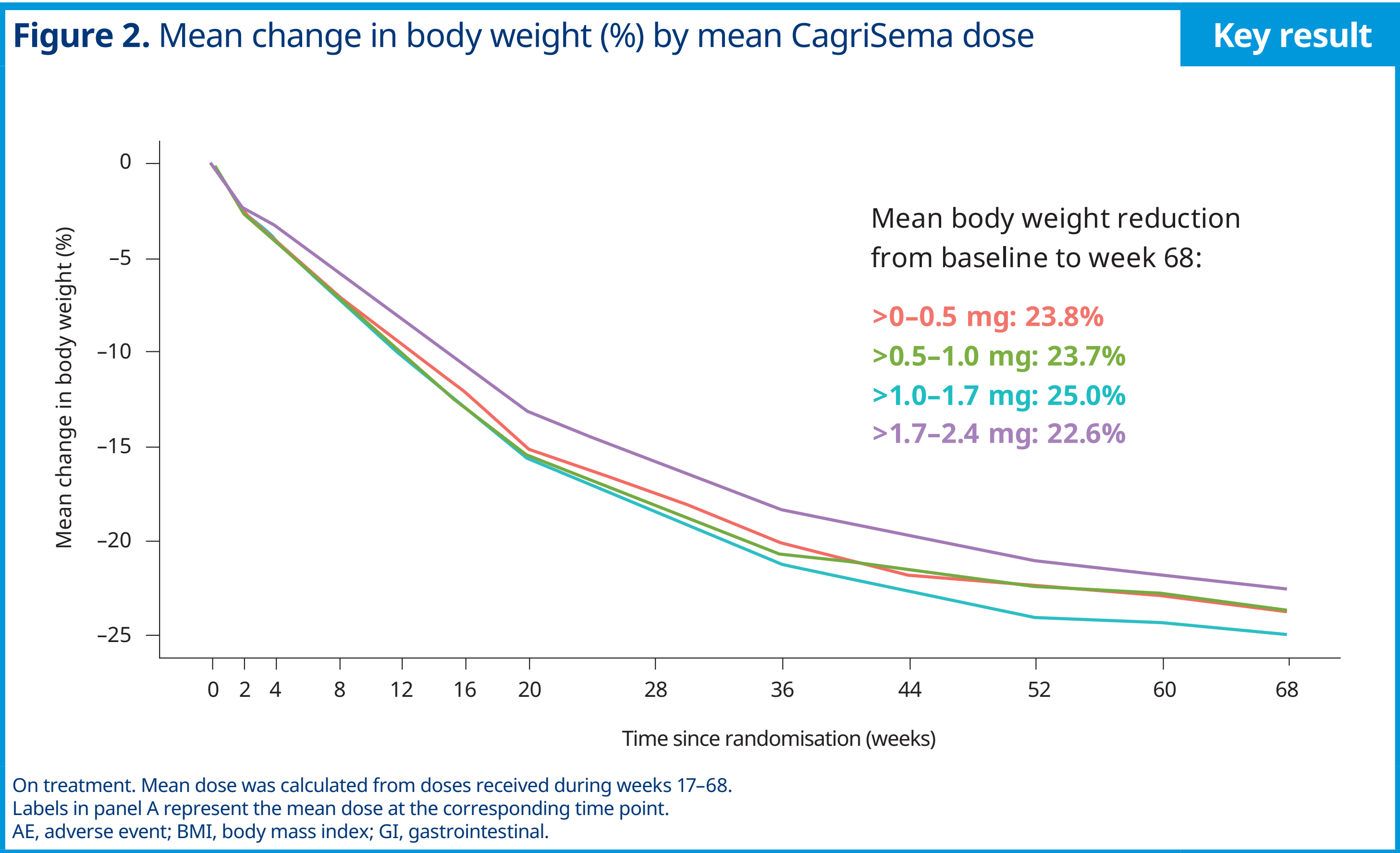
Results

- Baseline characteristics by mean CagriSema dose received during the maintenance period are shown in **Table 1**.
- At the end of the trial, most participants (64%) were in the highest mean dose group (>1.7–2.4 mg), with few in the lower dose groups (>0–0.5 mg, 10%; >0.5–1.0 mg, 10%; and >1.0–1.7 mg, 12%).
- A mean CagriSema dose of >1.7–2.4 mg was associated with greater baseline BMIs compared with the lower CagriSema doses.
- All CagriSema dosing groups presented with a similar percentage weight loss trajectory throughout the trial, with substantial weight loss observed in all groups at the end of the trial (**Figure 2**).
 - Mean body weight reductions from baseline to week 68 by mean dose group were 23.8% for >0–0.5 mg, 23.7% for >0.5–1.0 mg, 25.0% for >1.0–1.7 mg and 22.6% for >1.7–2.4 mg.
 - No clear linear relationship was observed between mean CagriSema dose and mean percentage weight loss up to week 68.
- A similar trajectory of reduction in BMI was also observed across all CagriSema dose groups from baseline to week 68 (**Figure 3A**).
- Figure 3B presents GI AE incidence from baseline to week 68 by mean CagriSema dose during the maintenance period. A mean CagriSema dose of >1.7–2.4 mg was associated with a lower incidence of GI AEs compared with the other CagriSema doses.
- CagriSema dose reductions frequently followed clinically meaningful weight loss. Mean weight loss at the time of first dose reduction was 14.0%, with 24.7% of participants having lost ≥20% of body weight before their first dose reduction (**Figure 4A**).
- The majority of GI AEs were mild to moderate and rarely led to discontinuation of CagriSema (5.9%). At the time of first dose reduction, 45.5% of ongoing GI AEs were mild and 26.3% were moderate (**Figure 4B**).
- In more than half of the participants, CagriSema dose reductions were not associated with GI AEs or GI AEs were unlikely to be related to treatment (**Figure 4C**).

Table 1. Baseline demographics and characteristics

Characteristic	Mean CagriSema dose			
	>0–0.5 mg (n=215)	>0.5–1.0 mg (n=220)	>1.0–1.7 mg (n=261)	>1.7–2.4 mg (n=1341)
Age, years				
18–64	186 (86.5)	200 (90.9)	244 (93.5)	1268 (94.6)
65–74	23 (10.7)	18 (8.2)	16 (6.1)	64 (4.8)
≥75	6 (2.8)	2 (0.9)	1 (0.4)	9 (0.7)
Sex				
Female	158 (73.5)	169 (76.8)	189 (72.4)	866 (64.6)
Race				
White	145 (67.4)	164 (74.5)	201 (77.0)	947 (70.6)
BMI, kg/m ² , mean (SD)	36.0 (6.0)	35.9 (6.0)	37.1 (6.0)	38.9 (6.8)

Data are n (%) unless otherwise stated. Mean dose was calculated from doses received during weeks 17–68. Percentages may not total 100 due to rounding. BMI, body mass index; SD, standard deviation.



Conclusion

- Clinically relevant body weight reductions were observed across all CagriSema maintenance dose groups, indicating substantial inter-individual variability in dose responsiveness.
- No clear relationship was observed between mean CagriSema dose and mean body weight reduction up to week 68, indicating heterogeneity in effect, with some participants highly responsive to submaximal doses.
- CagriSema dose reductions often followed clinically meaningful weight loss and appear to have been influenced by factors beyond tolerability.
- The REDEFINE 1 protocol allowed for dose modifications, thereby providing insights into management of patients in real-world clinical practice.