Characterisation of CagriSema dose reductions in the REDEFINE 1 trial

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Aim

- To characterise CagriSema dose reductions in the REDEFINE 1 study to improve understanding of their timing and associated clinical factors.

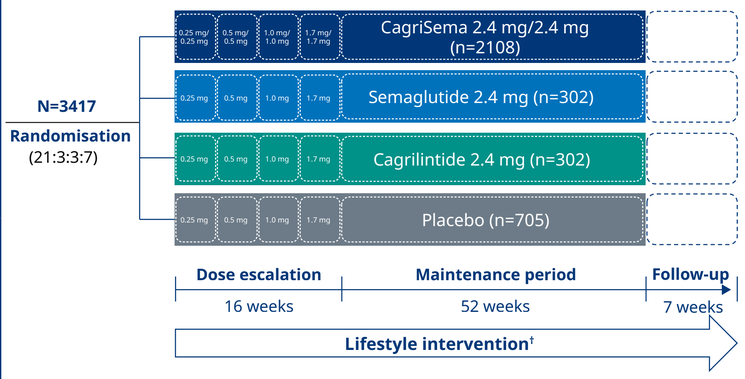
Introduction

- In the REDEFINE 1 trial, treatment with once-weekly subcutaneous (s.c.) cagrilintide 2.4 mg and semaglutide 2.4 mg (CagriSema 2.4 mg/2.4 mg) for 68 weeks resulted in 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 design of the REDEFINE 1 trial permitted the dose of CagriSema to be reduced at investigator discretion. For this reason, not all participants randomised to CagriSema completed the trial on the maximum dose.

Methods

- In the phase 3a REDEFINE 1 trial (NCT05567796), 3417 adults with a body mass index (BMI) ≥30 kg/m^2 or ≥27 kg/m^2 with ≥1 obesity-related complication were randomised to once-weekly s.c. CagriSema (n=2108), semaglutide (n=302), cagrilintide (n=302) or placebo (n=705), plus lifestyle intervention, for 68 weeks.
- CagriSema was initiated at a dose of 0.25 mg/0.25 mg and planned to increase 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 events 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 on the maximum tolerated dose.
- This analysis characterised CagriSema dose reductions in relation to treatment duration, weight loss, BMI, and gastrointestinal adverse events (GI AEs).

Figure 1. REDEFINE 1 trial design[1]

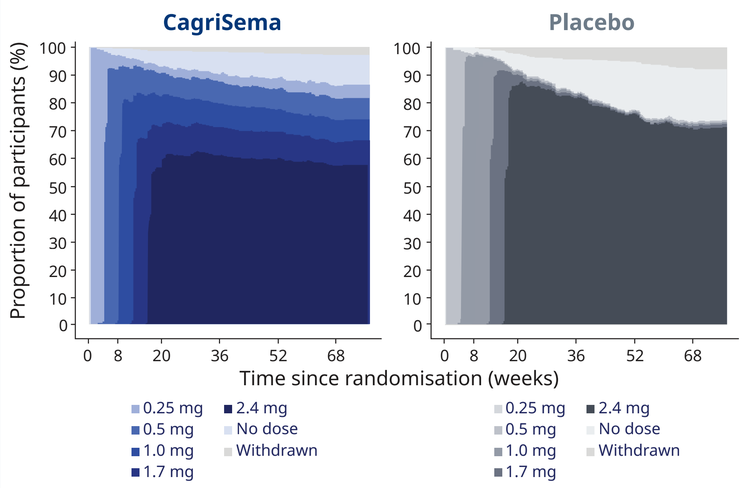


†As an adjunct to lifestyle intervention (~500 kcal/day diet plus 150 min/week of physical activity).

Results

- At week 68, 1209 participants (57.4%) in the CagriSema group were receiving 2.4 mg/2.4 mg. A total of 1575 (74.7%) participants treated with CagriSema reached the highest dose at any time point. Cumulative dose levels over time are shown in **Figure 2**.

Figure 2. Cumulative CagriSema dose levels over time[1]



Dose level distribution vs. time since randomisation. Percentages are based on the number of participants in the full analysis set.

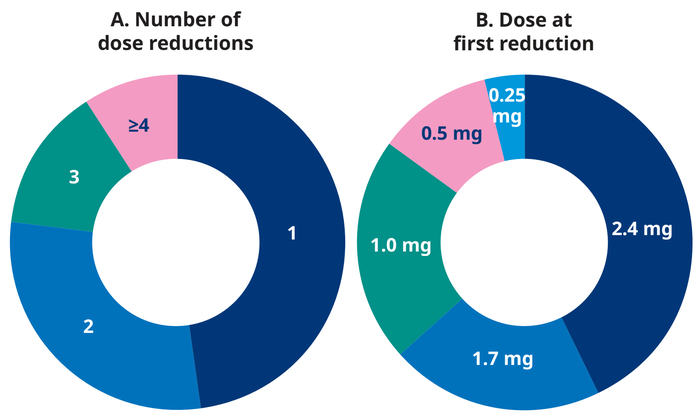
No dose: proportion of participants that had no dose within the last 14 days;

Withdrawn: proportion of participants that withdrew (consent) from study.

Placebo group data shown to indicate adherence to trial protocol; most discontinuations in the placebo group were due to a lack of efficacy.

- In total, 2063 dose reductions occurred in 1101 participants receiving CagriSema, reflecting the protocol permitting individualisation of therapy.
  - Of those 1101 participants, 48% had one reduction, 29% had two reductions, 14% had three reductions, and 9% had ≥4 reductions (**Figure 3A**)
  - 42% of first reductions were from 2.4 mg, 20% from 1.7 mg, 21% from 1 mg and 11% from 0.5 mg, and 6.3% from 0.25 mg (**Figure 3B**)

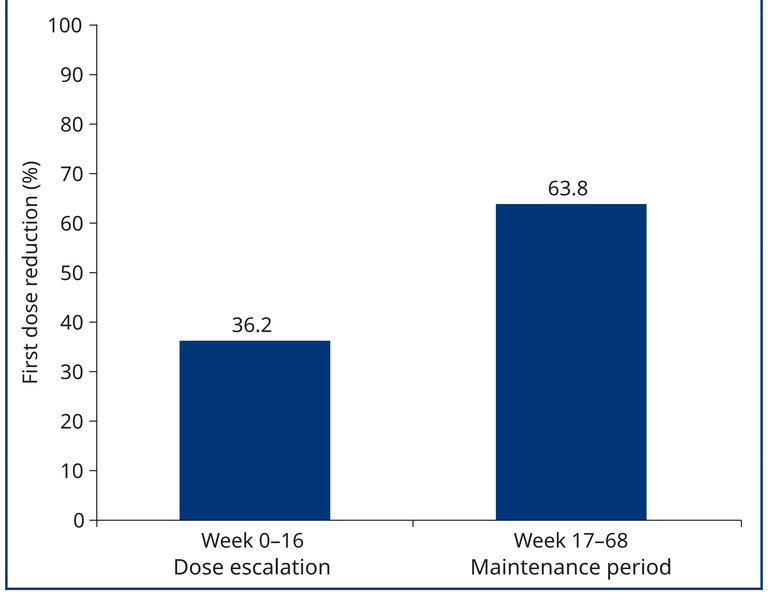
Figure 3. (**A**) Number of CagriSema dose reductions and (**B**) CagriSema dose at time of first reduction



Reductions from CagriSema 0.25 mg represent participants with interruption of treatment (i.e., temporarily off-treatment).

- The mean duration of CagriSema treatment at the time of the first dose reduction was 26 weeks (median = 21 weeks), with 64% of first dose reductions occurring after the 16-week dose escalation period (**Figure 4**).

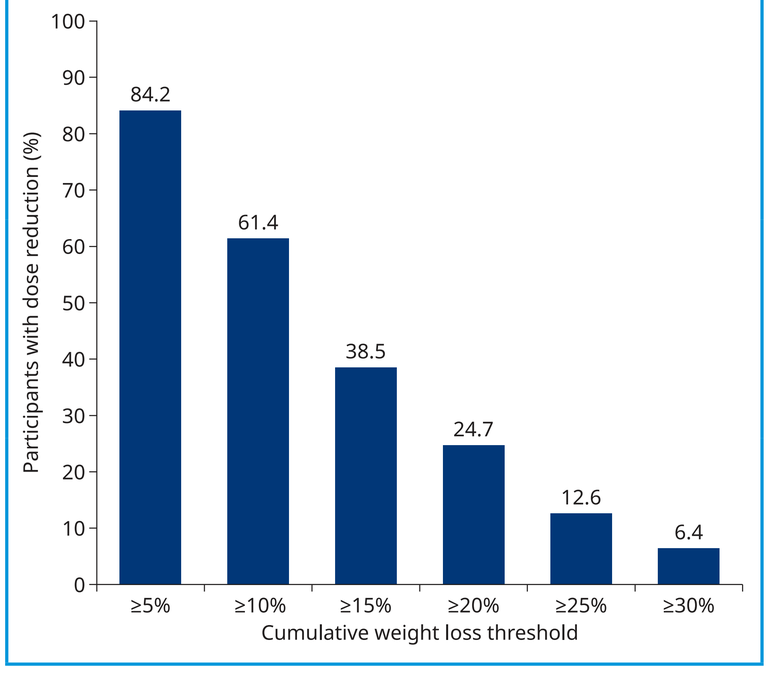
Figure 4. Timing of first CagriSema dose reduction relative to baseline



- CagriSema dose reductions frequently followed clinically meaningful weight loss. Mean weight loss at the time of first dose reduction was 14%, with 24.8% of participants having lost ≥20% of body weight before their first dose reduction (**Figure 5**).

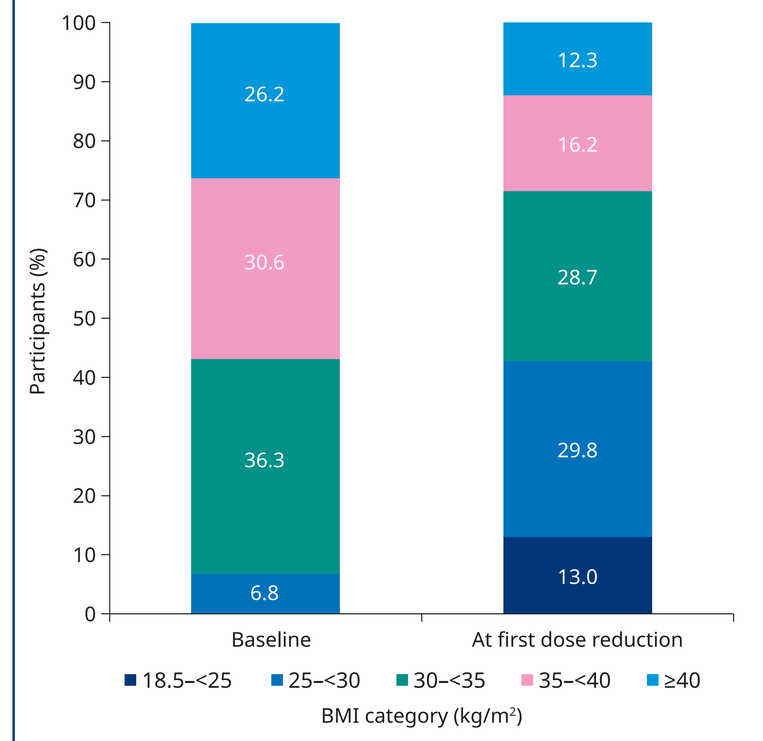
Figure 5. Cumulative weight loss at time of first CagriSema dose reduction

Key result



- Mean BMI in participants receiving CagriSema was 32.1 kg/m^2 at time of first reduction (median = 31.0 kg/m^2), from a mean baseline BMI of 37.3 kg/m^2 (median = 35.9 kg/m^2) (**Figure 6**). A total of 42.8% of participants had a BMI <30 kg/m^2 at the time of their first reduction (vs. 6.8% at baseline).

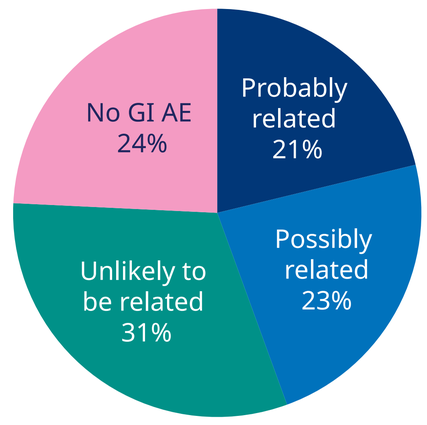
Figure 6. Categorical BMI at baseline and at time of first CagriSema dose reduction



Reductions from CagriSema 0.25 mg represent participants with interruption of treatment (i.e., temporarily off-treatment).

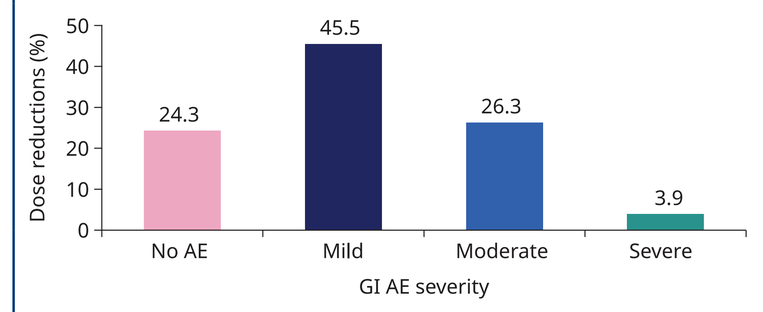
- As judged by the investigator, among participants with dose reductions, 24% reported no GI AEs before their first reduction, and in 31% of participants the most recent GI AE was assessed as unlikely to be treatment-related (**Figure 7**).
- Overall, the majority of GI AEs were mild-to-moderate and 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 8**).

Figure 7. Proportion of participants with a recent GI AE prior to dose reduction, and for those reporting a GI AE, the investigator-rated likelihood that most recent GI AE was CagriSema-related



GI AE, gastrointestinal adverse event

Figure 8. Presence and severity of gastrointestinal adverse events at the time of first dose reduction



AE, adverse event; GI, gastrointestinal.

Conclusion

- CagriSema dose reductions appear to have been influenced by factors beyond tolerability, as dose reductions often followed clinically meaningful weight loss.
- Most dose reductions occurred after clinically meaningful weight loss, supporting flexible, individualised dosing.
- In more than half of cases, dose reductions were not associated with GI AEs, or the GI AEs were unlikely to be related to treatment.
- Overall, these findings highlight the heterogeneity in obesity and treatment responses and support the need for individualised, patient-centred dose management in clinical practice.

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Reference:

(**1**) Garvey WT et al. *N Engl J Med* 2025;393(7):635–647.