# Dulaglutide as Add-on Therapy to SGLT-2 Inhibitors in Patients With Inadequately Controlled Type 2 Diabetes (AWARD-10): A 24-Week, Randomised, Double-Blind, Placebo-Controlled Trial

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## OBJECTIVE

The AWARD-10 study was designed to assess the effects of once weekly dulaglutide (1.5 mg and 0.75 mg) on HbA1c, weight, FSG, and safety, when added on to stable doses of an SGLT-2i ± metformin in patients with inadequately controlled type 2 diabetes

### Background

- Combination of GLP-1 RAs and SGLT-2is is of interest because of mostly complementary mechanisms of action
  - GLP-1 RAs enhance insulin secretion[1-2], slow gastric emptying[3] and reduce body weight[3]
  - SGLT-2is promote urinary glucose excretion[4-6] and reduce body weight[4-6]
  - They have opposing effect on glucagon
    - GLP-1 RAs inhibit glucagon secretion
    - SGLT-2is increase glucagon secretion
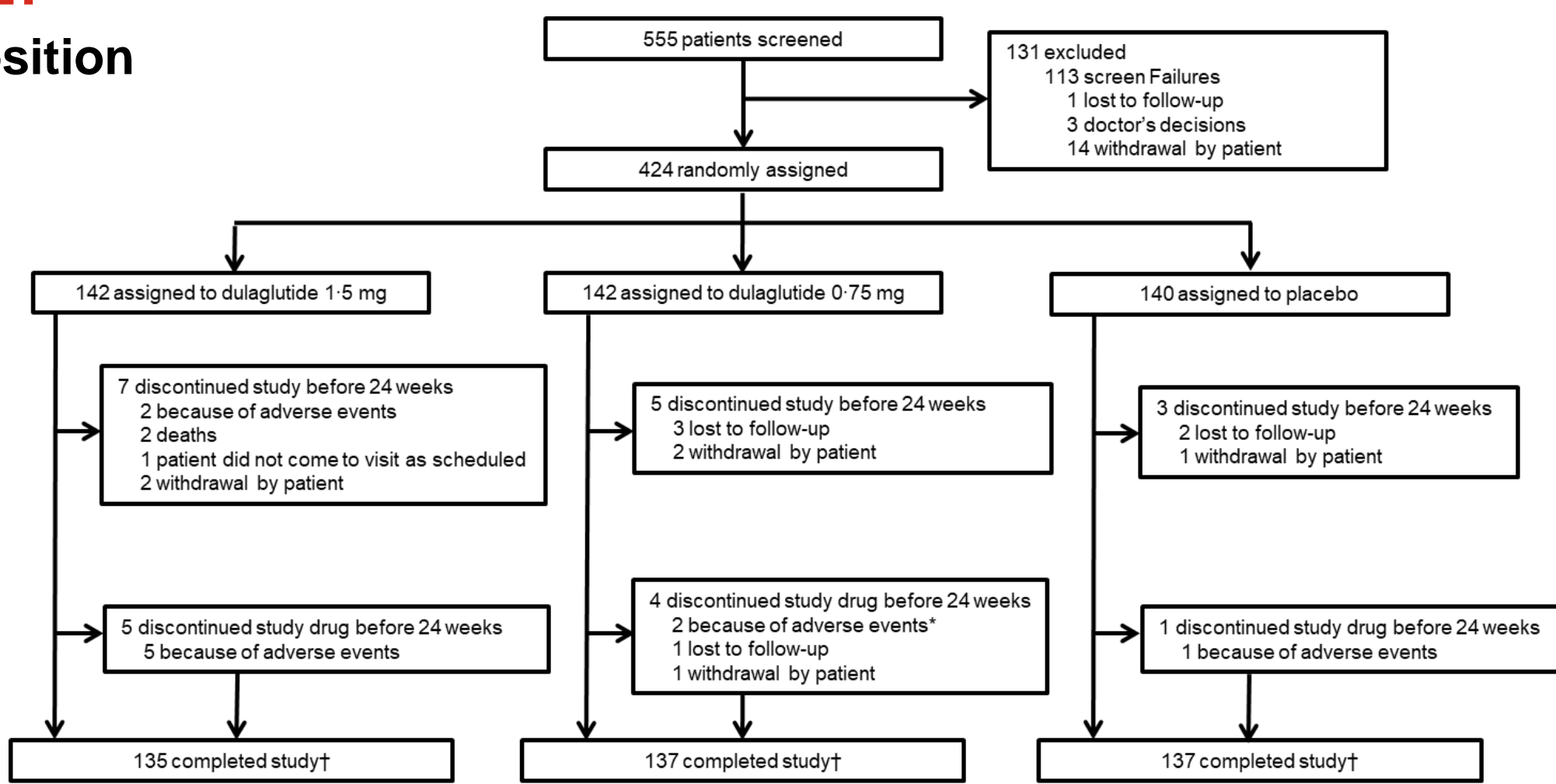- Agents from both classes have been shown to reduce CV risk[7-8]

## STUDY DESIGN
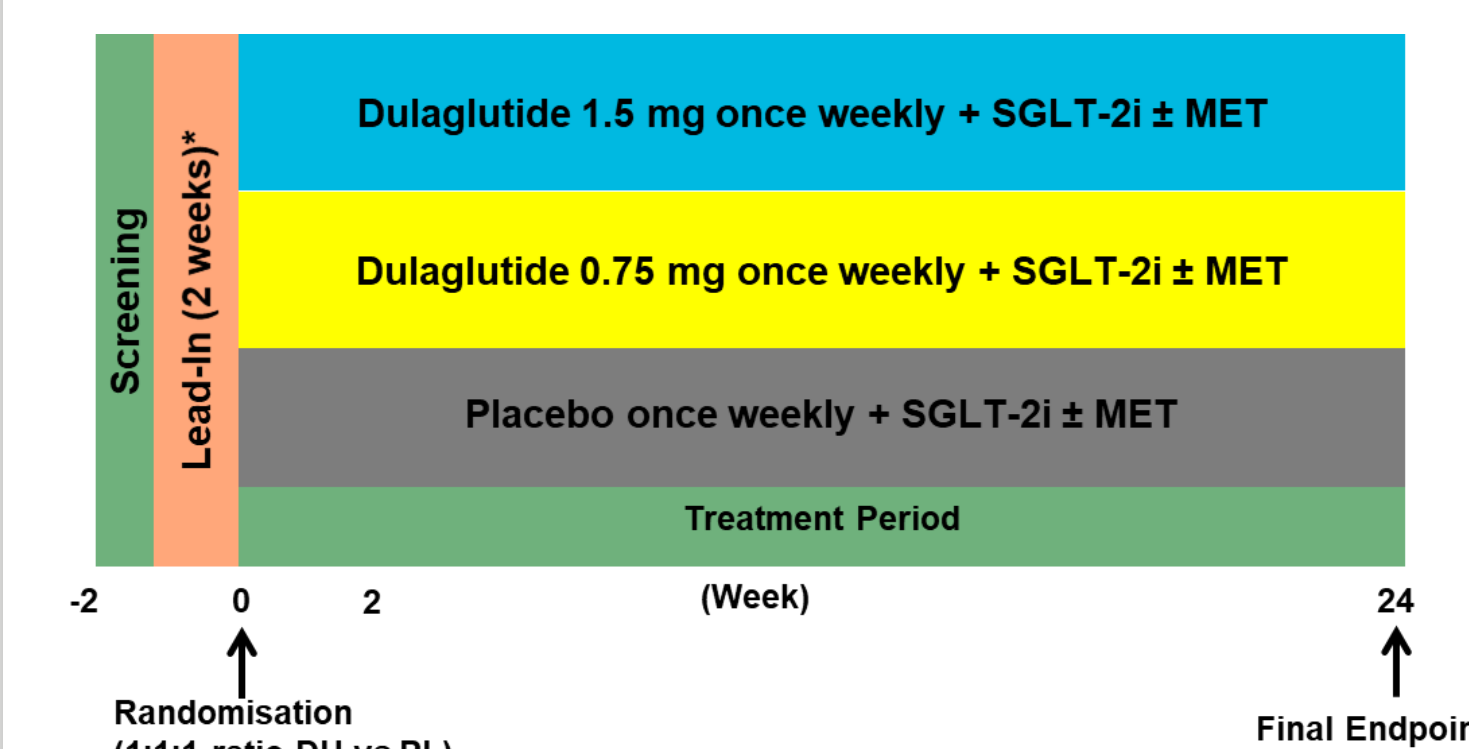


### Key inclusion criteria
- T2D
- HbA1c ≥7.0% and ≤9.5%
- BMI ≤45 kg/m$^2$
- SGLT-2i at locally approved doses ± metformin ≥1500 mg/day

### Key exclusion criteria
- T1D
- History of pancreatitis
- Ketoacidosis or hyperosmolar state/coma
- Recent CV event or active cancer

*Patients requiring adjustment (metformin <1500 mg/day; eGFR 45-59 ml/min/1.73 m$^2$) completed 12-week lead-in

## KEY RESULT

### Patient Disposition



*One patient did not receive any doses of study drug, but completed the study
†Irrespective of duration of exposure to study drug

## Methods

### Primary objective

- Primary objective was to demonstrate superiority of addition of dulaglutide versus the addition of placebo to the ongoing treatment with SGLT-2is for change from baseline in HbA1c after 24 weeks of treatment

### Other objectives at 24 weeks

- Secondary efficacy objectives
  - Percentage of patients achieving HbA1c target of <7.0% and ≤6.5%
  - Change in body weight
  - Change in FSG
  - Change in SMPG profile
  - Change in fasting glucagon
- Secondary safety objectives
  - Adverse events, vitals, ECGs, hypoglycemia
  - Adjudicated pancreatitis, CV events
- Exploratory objectives
  - Percentage of patients achieving HbA1c target <7.0% with no weight gain and no documented symptomatic hypoglycaemia
  - Percentage of patients achieving HbA1c target <7.0% with body weight loss >5%, and no documented symptomatic hypoglycaemia

### Statistical analysis

- Graphical testing approach to control for Type 1 error[9]
  - Primary objective
  - Key secondary objectives
- Mixed model for repeated measures (primary analysis model)
  - Body weight
  - SMPG
  - Vital sign data
- Analysis of covariance model
  - FSG
  - Glucagon
- Chi-square test
  - Categorical measures
- Logistic regression model
  - Percentage of patients achieving HbA1c targets
- Generalized linear model with negative binomial distribution
  - Hypoglycaemia rate

### Baseline characteristics

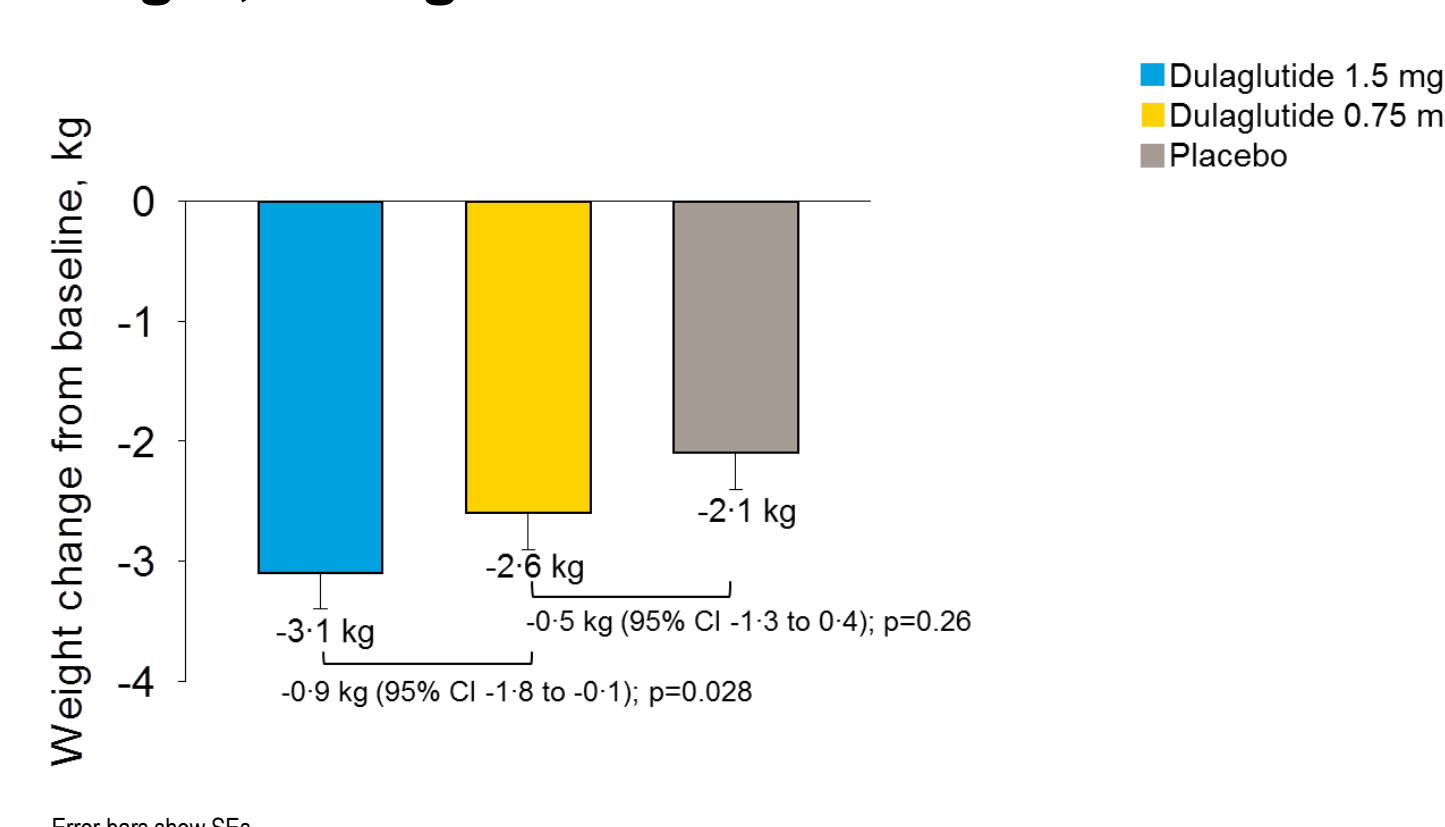| Variable | Dulaglutide 1·5 mg (N=142) | Dulaglutide 0·75 mg (N=141) | Placebo (N=140) |
|---|---|---|---|
| **Sex** | | | |
| Men | 77 (54%) | 69 (49%) | 66 (47%) |
| Women | 65 (46%) | 72 (51%) | 74 (53%) |
| Age (years) | 56.17 (9.26) | 58.55 (9.14) | 57.10 (9.59) |
| Aged ≥65 years | 23 (16%) | 44 (31%) | 31 (22%) |
| Body weight (kg) | 92.87 (19.73) | 91.07 (20.99) | 90.50 (19.47) |
| BMI (kg/m$^2$) | 32.87 (5.56) | 32.77 (6.27) | 32.39 (4.98) |
| Diabetes duration (years) | 9.21 (5.74) | 10.05 (6.56) | 8.87 (6.13) |
| HbA1c concentration (%) | 8.04 (0.65) | 8.04 (0.61) | 8.05 (0.66) |
| HbA1c concentration (mmol/mol) | 64.36 (7.1) | 64.36 (6.67) | 64.47 (7.21) |
| FSG (mg/dL) | 160.65 (33.32) | 162.00 (35.75) | 153.29 (30.47) |
| FSG (mmol/L) | 8.91 (1.85) | 8.99 (1.98) | 8.50 (1.69) |
| SBP (mm Hg) | 129.70 (14.48) | 130.35 (15.66) | 130.57 (13.74) |
| DBP (mm Hg) | 77.10 (8.96) | 76.55 (9.98) | 78.36 (9.46) |
| Treated with metformin, n (%) | 133 (94%) | 135 (96%) | 135 (96%) |

Data are n (%) or mean (SD)

### HbA1c, change from baseline to 24 weeks



Error bars show SEs.
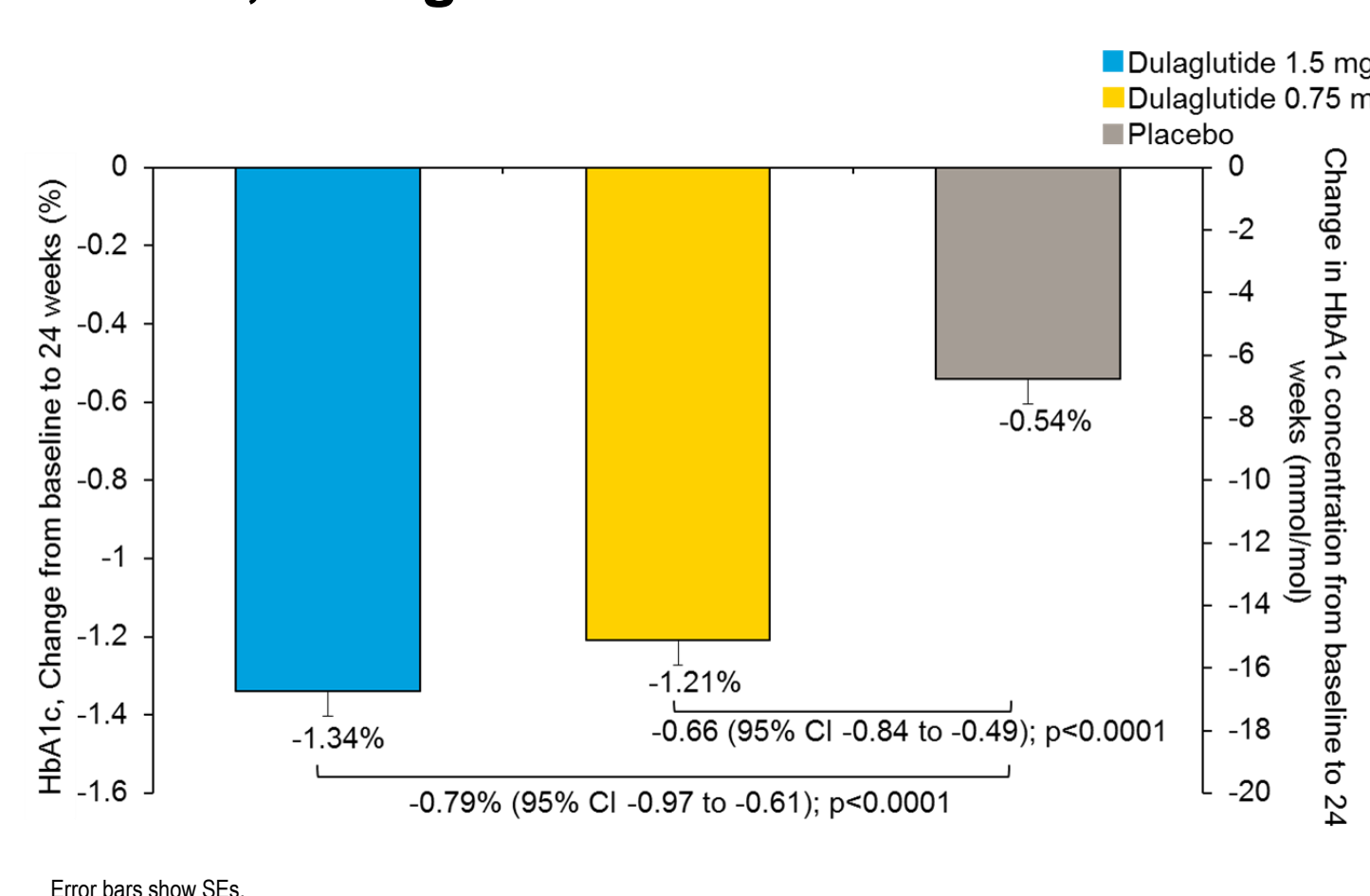
### Percentage of patients achieving HbA1c targets at 24 weeks



Error bars show SEs.

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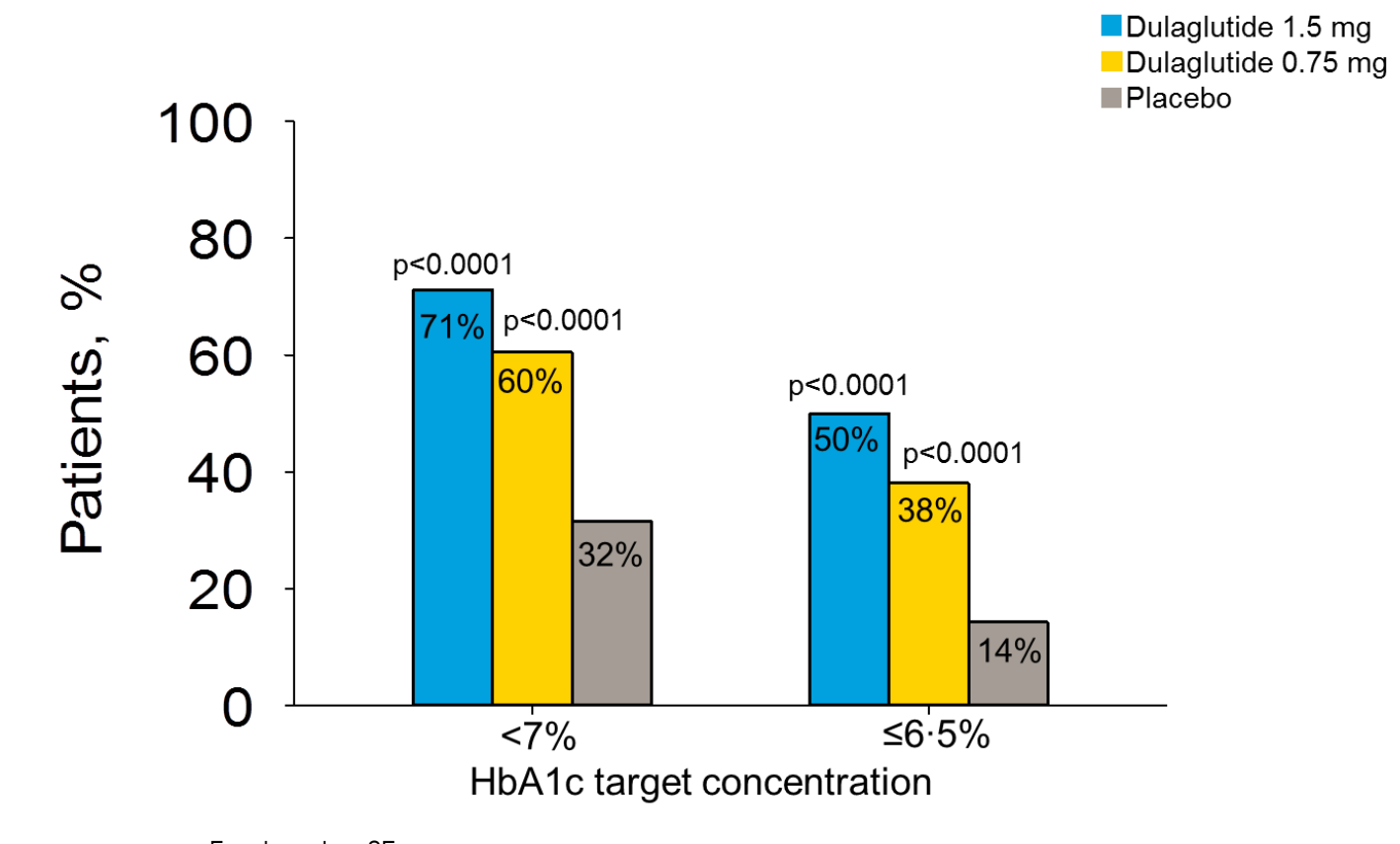
### Weight, change to 24 weeks



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### FSG, change from baseline to 24 weeks
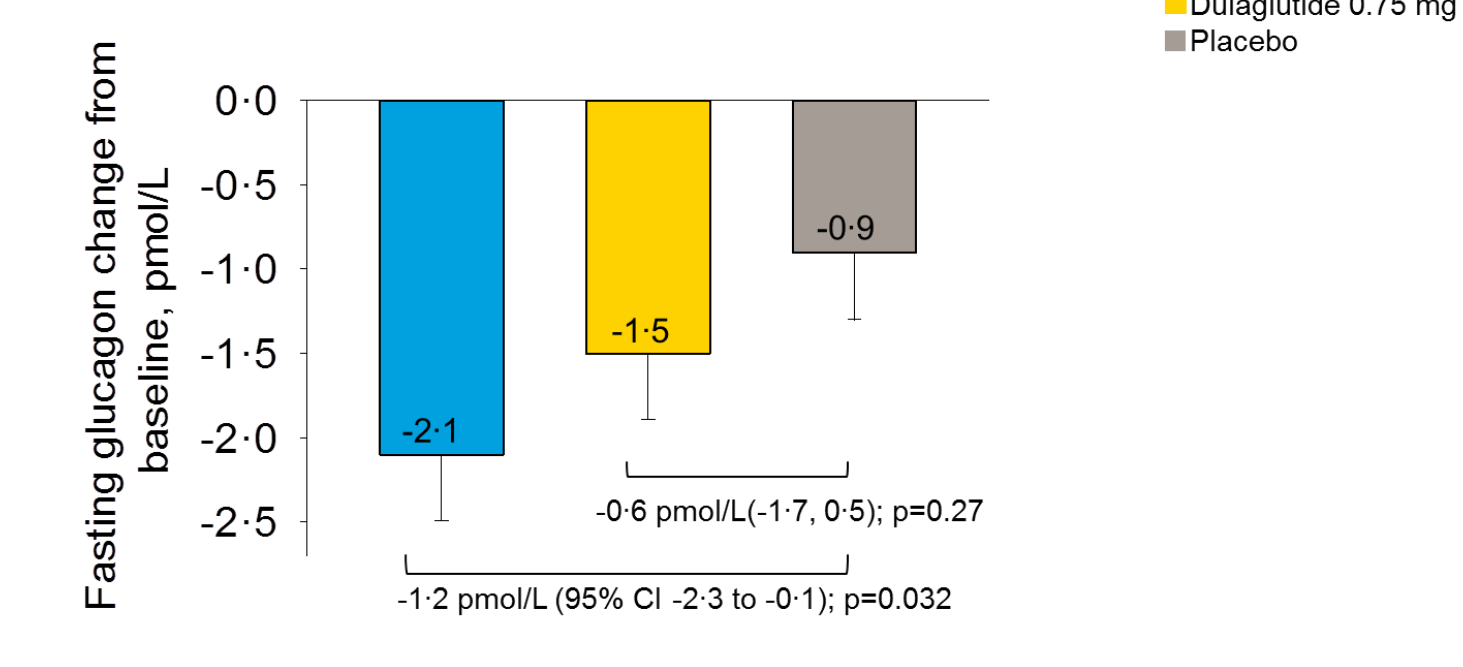


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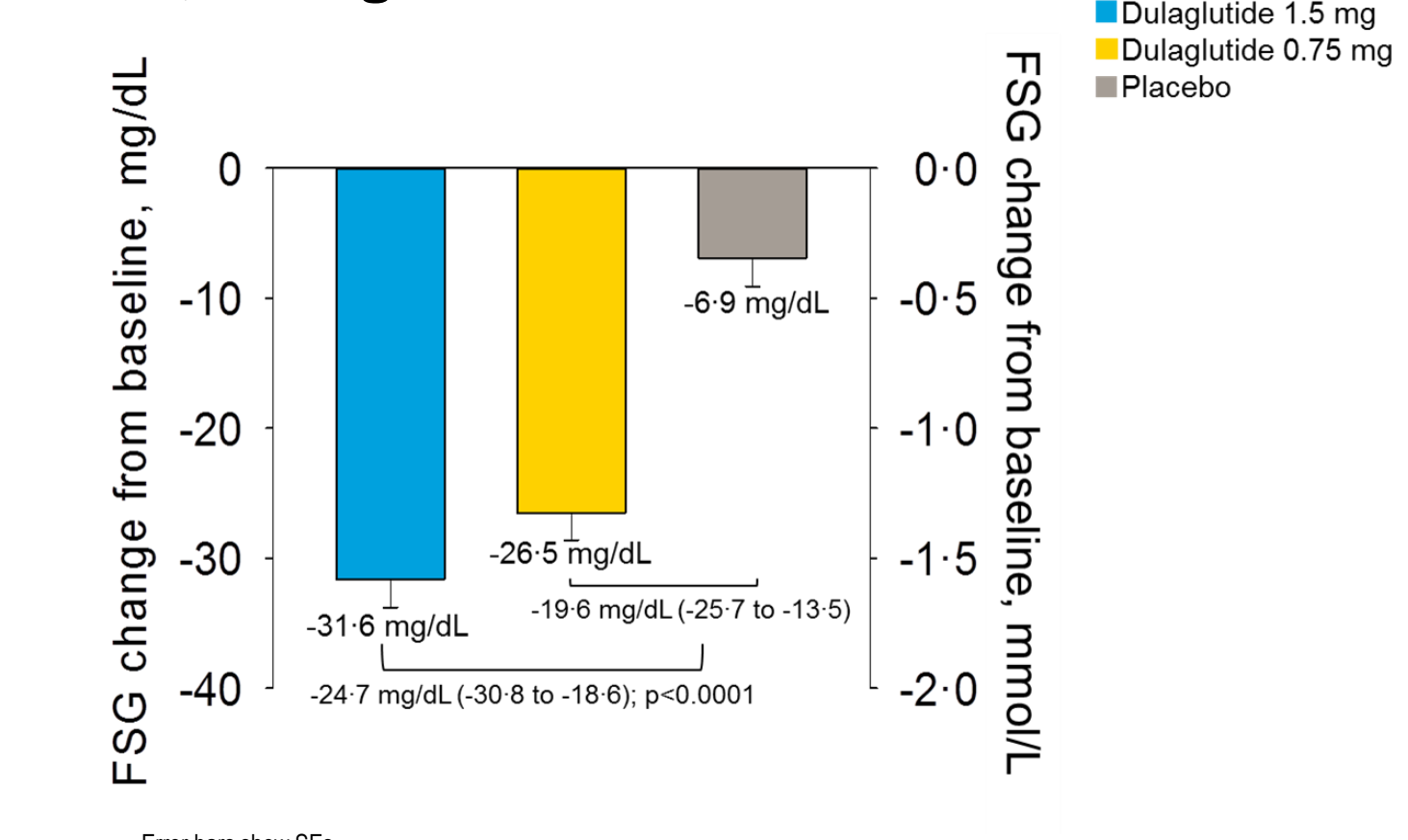
### Composite endpoints at 24 weeks
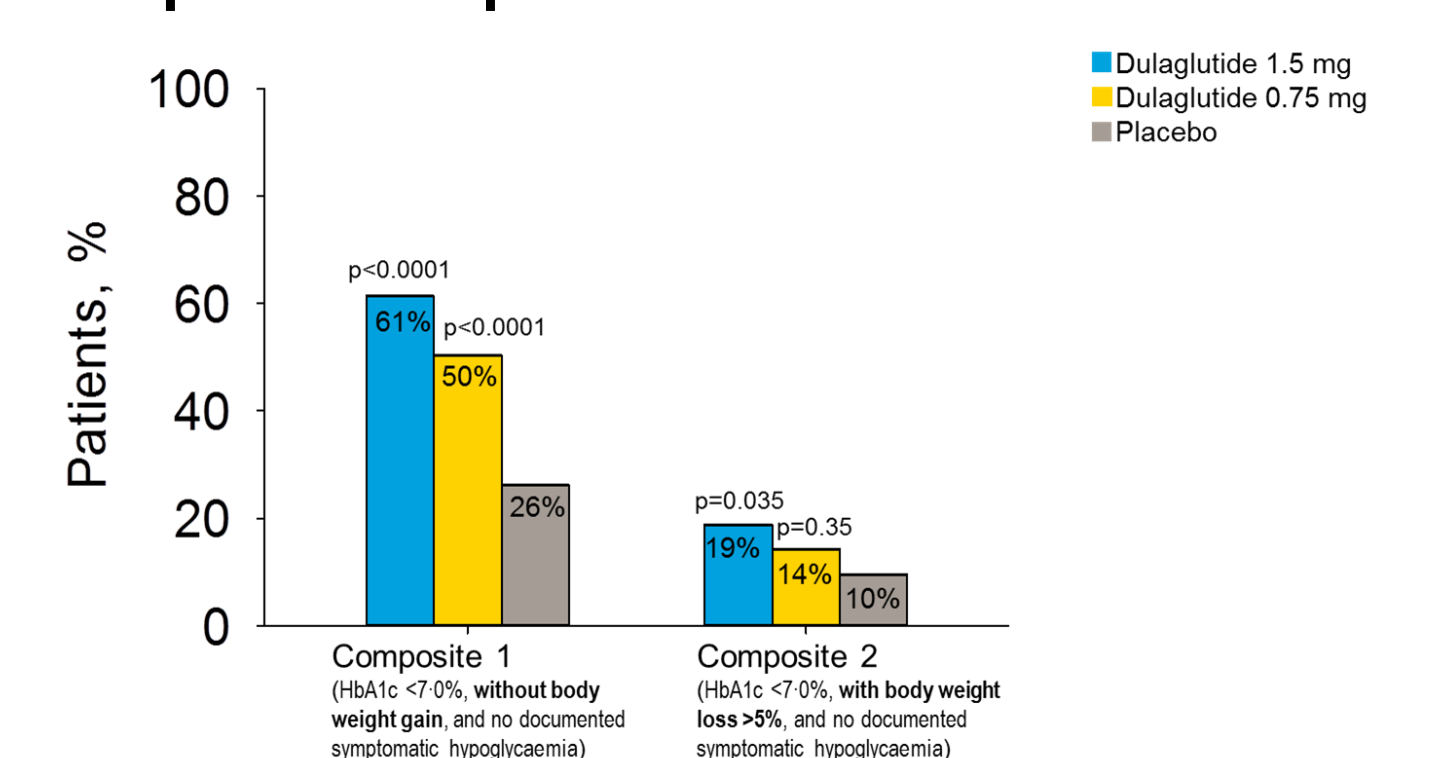


### Fasting glucagon, change from baseline to 24 weeks



### Adverse events through 24 weeks

| Adverse events [n (%)] | Dulaglutide 1·5 mg (N=142) | Dulaglutide 0·75 mg (N=141) | Placebo (N=140) |
|---|---|---|---|
| Deaths | 2 (1%) | 0 | 0 |
| Serious adverse events | 5 (4%) | 3 (2%) | 5 (4%) |
| Treatment-emergent adverse events (Patients with ≥1 adverse event) | 95 (67%) | 83 (59%) | 81 (58%) |
| **Treatment-emergent adverse events (≥5% patients in either group)** | | | |
| Gastrointestinal disorders | 46 (32%) | 29 (21%) | 24 (17%) |
| Nausea | 21 (15%) | 7 (5%) | 5 (4%) |
| Diarrhoea | 8 (6%) | 14 (10%) | 4 (3%) |
| Other | | | |
| Back pain | 13 (9%) | 12 (9%) | 10 (7%) |
| Headache | 8 (6%) | 5 (4%) | 13 (9%) |
| Study and/or study drug discontinuation due to adverse events | 4 (3%) | 0 | 0 |
| **Variables** | | | |
| **Adjudication confirmed** | | | |
| Pancreatitis | 0 | 0 | 0 |
| CV events | 0 | 0 | 3 (2%) |
| CV death | 0 | 0 | 0 |
| Non-fatal MI | 0 | 0 | 2 (1%) |
| Unstable angina | 0 | 0 | 1 (1%) |
| **Adverse events of interest associated with SGLT-2is** | | | |
| Amputation | 0 | 0 | 0 |
| Diabetic ketoacidosis | 0 | 0 | 0 |
| Hypotensive episodes/ syncope | 0 | 1 (1%) | 1 (1%) |
| Genital infections | 0 | 0 | 1 (1%) |
| Fractures | 1 (1%) | 1 (1%) | 1 (1%) |

### Hypoglycaemia through 24 weeks

| Through 24 weeks | Dulaglutide 1.5 mg (N=142) | Dulaglutide 0.75 mg (N=141) | Placebo (N=140) |
|---|---|---|---|
| **Total hypoglycemia (≤70 mg/dL ± symptoms)** | | | |
| Incidence n (%) | 5 (3.5) | 5 (3.6) | 4 (2.9) |
| Rate (events/pt/year), mean (SD) | 0.31 (2.22) | 0.26 (1.67) | 0.21 (1.61) |
| 30-day rate, mean (SD) | 0.03 (0.18) | 0.02 (0.14) | 0.02 (0.13) |
| **Documented symptomatic (≤70 mg/dL)** | | | |
| Incidence n (%) | 2 (1.4) | 3 (2.1) | 3 (2.1) |
| Rate (events/pt/year), mean (SD) | 0.16 (1.71) | 0.16 (1.25) | 0.12 (1.09) |
| 30-day rate, mean (SD) | 0.01 (0.14) | 0.01 (0.10) | 0.01 (0.09) |
| **Nocturnal (≤70 mg/dL)** | | | |
| Incidence n (%) | 1 (0.7) | 2 (1.4) | 0 (0.0) |
| Rate (events/pt/year), mean (SD) | 0.03 (0.35) | 0.11 (1.00) | 0.00 (0.00) |
| 30-day rate, mean (SD) | 0.002 (0.03) | 0.01 (0.08) | 0.00 (0.00) |
| Severe hypoglycemia, n (%) | 0 (0.0) | 1 (0.7) | 0 (0.0) |

### Summary of baseline SGLT-2i dose

| Patients, n (%)ª | Dulaglutide 1·5 mg (N=142) | | Dulaglutide 0·75 mg (N=141) | | Placebo (N=140) | |
|---|---|---|---|---|---|---|
| | Low Dose | High Dose | Low Dose | High Dose | Low Dose | High Dose |
| Canagliflozin | 12 (8.5) | 9 (6.3) | 10 (7.1) | 9 (6.4) | 15 (10.7) | 4 (2.9) |
| Dapagliflozin | 4 (2.8) | 59 (41.5) | 3 (2.1) | 58 (41.1) | 4 (2.9) | 68 (48.6) |
| Empagliflozin | 34 (23.9) | 24 (16.9) | 33 (23.4) | 28 (19.9) | 27 (19.3) | 22 (15.7) |

## Summary

- The addition of dulaglutide to ongoing SGLT-2i treatment ± metformin resulted in statistically significant and clinically relevant reduction in HbA1c and FSG, compared to the addition of placebo. A significantly greater proportion of patients reached target HbA1c of <7%
- Dulaglutide 1.5 mg dose resulted in significantly greater reduction in body weight versus placebo
- Treatment with dulaglutide was associated with higher incidence of gastrointestinal adverse events
- Dulaglutide 1.5 mg significantly decreased SBP from baseline versus placebo

## Limitations

- Short duration (24 weeks)
- Patients were inadequately controlled on SGLT-2i ± metformin ≥1500 mg/day as tolerated, thus the results cannot be generalised to patients who do not meet these criteria
- Most patients had been taking a SGLT-2i for less than six months prior to enrolling in the study, which may partially explain a statistically significant change from baseline for HbA1c and weight in the placebo group
- This study did not include a placebo-only group (all treatment groups received SGLT-2i ± metformin) to inform the contributions of medications to the results observed
  - A substantial change from baseline for HbA1c in the placebo group was observed

## CONCLUSIONS

- In AWARD-10 once weekly dulaglutide as add-on to SGLT-2i ± metformin improved glycaemic control, reduced body weight and SBP, with acceptable tolerability
- These results showed that in patients with T2D and inadequate glycemic control on SGLT-2is, the addition of dulaglutide is an effective and safe treatment option

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