

## 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**

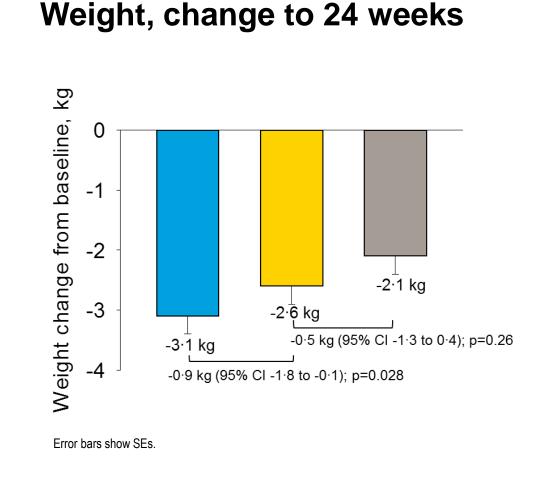
The AWARD-10 study was designed to assess the effects of once weekly dulaglutide (1.5 mg and 0.75 mg) on HbA1c, weight, FSG, and safety, when added on to stable doses of an SGLT-2i ± metformin in patients with inadequately controlled type 2 diabetes

#### 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<sup>1-2</sup>, slow gastric emptying<sup>3</sup> and reduce body weight<sup>3</sup>
- SGLT-2is promote urinary glucose excretion<sup>4-6</sup> and reduce body weight<sup>4-6</sup>
- 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<sup>7-8</sup>

### **STUDY DESIGN**



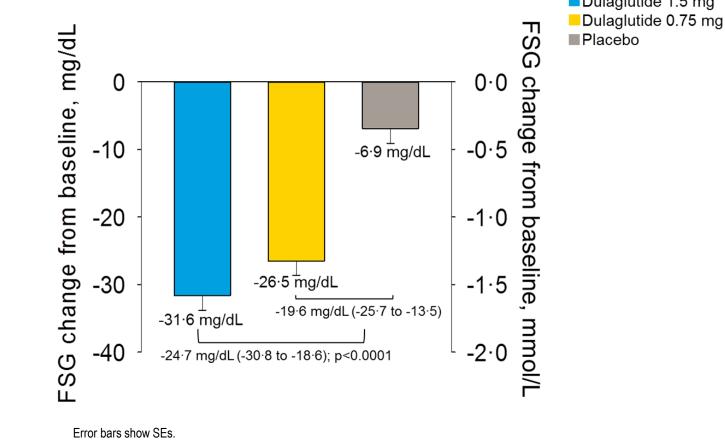
#### Composite endpoints at 24 weeks

Dulaglutide 1.5 mg
Dulaglutide 0.75 mg

Dulaglutide 1.5 mg Dulaglutide 0.75 mg

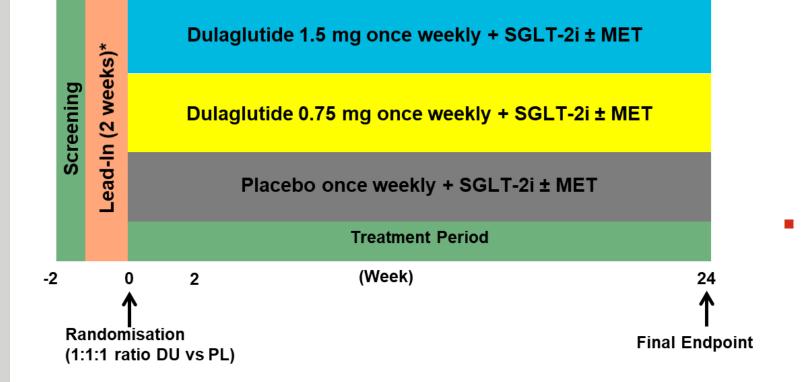
Placebo

### FSG, change from baseline to 24 weeks



# Fasting glucagon, change from baseline to 24 weeks Dulaglutide 1.5 mg Dulaglutide 0.75 mg

Placebo

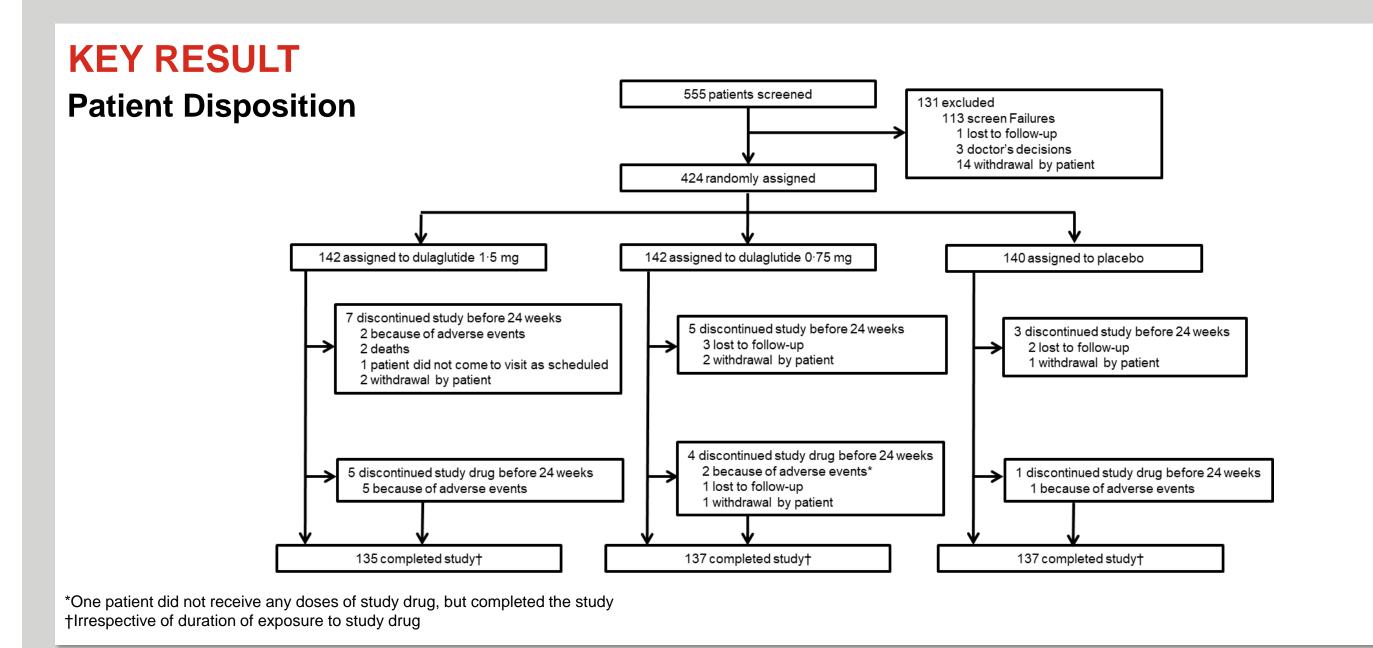


- T2D
- HbA1c ≥7.0% and ≤9.5%
- BMI ≤45 kg/m<sup>2</sup>

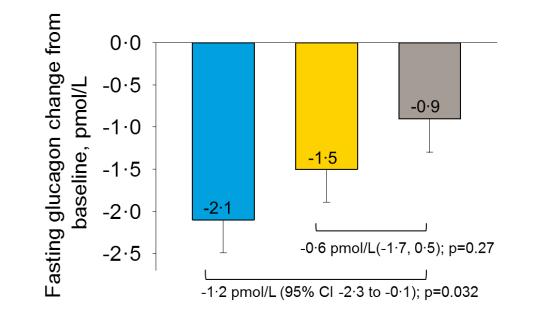
Key inclusion criteria

- 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<sup>2</sup>) completed 12-week lead-in



100 Placebo 80 % p<0.0001 Patients, 60 p<0.0001 40 p=0.035 20 Composite 1 Composite 2 (HbA1c <7.0%, without body (HbA1c <7.0%, with body weight loss >5%, and no documented weight gain, and no documented symptomatic hypoglycaemia) symptomatic hypoglycaemia



#### Adverse events through 24 weeks

	Dulaglutide 1·5 mg (N=142)	Dulaglutide 0·75 mg (N=141)	Placebo (N=140)
Adverse events [n (%)]			
Deaths	2 (1%)	0	0
Serious adverse events	5 (4%)	3 (2%)	5 (4%)
Treatment-emergent adverse events (Patients with ≥1 adverse e	vent)		
	95 (67%)	83 (59%)	81 (58%)
Treatment-emergent adverse events (≥5% patients in either grou	ıp)		
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 (1.09)	
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)	

#### **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

#### **Statistical analysis**

- Graphical testing approach to control for Type 1 error<sup>9</sup>
  - 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

#### **Baseline characteristics**

Variable	Dulaglutide 1·5 mg	Dulaglutide 0·75 mg	Placebo	
variable	(N=142)	(N=141)	(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/m²)	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%)	

- 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
- Chi-square test
- Categorical measures
- Logistic regression model
- Percentage of patients achieving HbA1c targets
- Generalized linear model with negative binomial distribution
  - Hypoglycaemia rate

#### Summary of baseline SGLT-2i dose

	Dulaglı	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	
Patients, n (%) <sup>a</sup>							
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%</p>
- 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

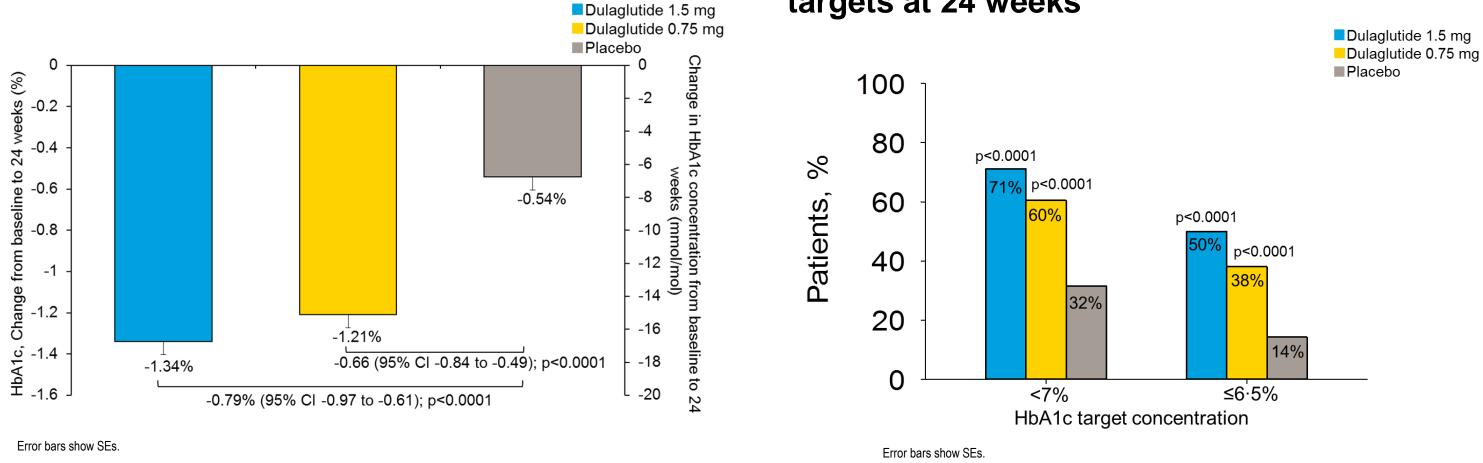
#### Limitations

- 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

Data are n (%) or mean (SD)

#### HbA1c, change from baseline to 24 weeks





## **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

Abbreviations: BMI=body mass index; CV=cardiovascular; DBP=diastolic blood pressure; ECG=electrocardiogram; FSG=fasting serum glucose; GLP-1RA=glucagon-like peptide-1 receptor agonists; HbA1c=glycated haemoglobin; MET=metformin; SBP=systolic blood pressure; SE=standard error; SGLT-2is=sodium-glucose co-transporter-2 inhibitors; SMPG=self-monitored plasma glucose; T2D=type 2 diabetes

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