

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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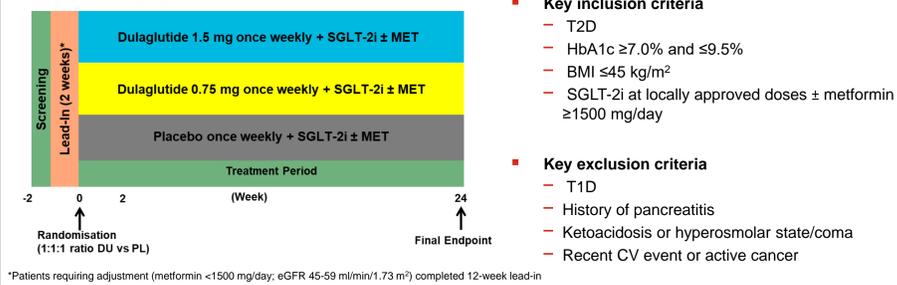
OBJECTIVE

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

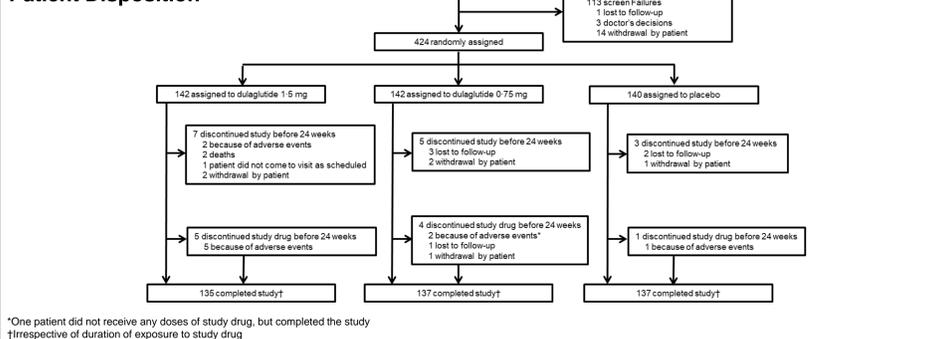
- Combination of GLP-1 RAs and SGLT-2is is of interest because of mostly complementary mechanisms of action
 - GLP-1 RAs enhance insulin secretion^{1,2}, slow gastric emptying³ and reduce body weight³
 - SGLT-2is promote urinary glucose excretion⁴⁻⁶ and reduce body weight⁴⁻⁶
 - They have opposing effect on glucagon
 - GLP-1 RAs inhibit glucagon secretion
 - SGLT-2is increase glucagon secretion
- Agents from both classes have been shown to reduce CV risk⁷⁻⁸

STUDY DESIGN



KEY RESULT

Patient Disposition



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 $\leq 6.5\%$
 - Change in body weight
 - Change in FSG
 - Change in SMPG profile
 - Change in fasting glucagon
- Secondary safety objectives
 - Adverse events, vitals, ECGs, hypoglycaemia
 - 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

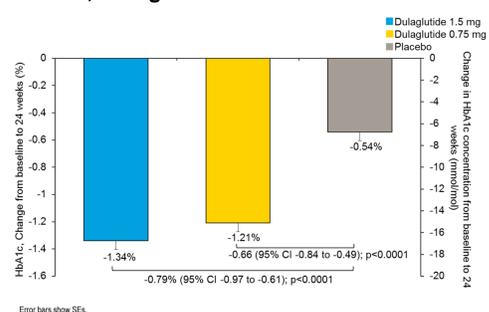
- Graphical testing approach to control for Type 1 error⁹
 - Primary objective
 - Key secondary objectives
- Mixed model for repeated measures (primary analysis model)
 - Body weight
 - SMPG
 - Vital sign data
- Analysis of covariance model
 - FSG
 - Glucagon
- Chi-square test
 - Categorical measures
- Logistic regression model
 - Percentage of patients achieving HbA1c targets
- Generalized linear model with negative binomial distribution
 - Hypoglycaemia rate

Baseline characteristics

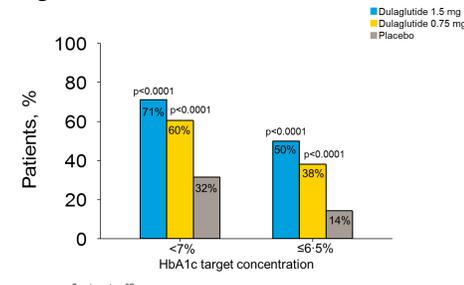
Variable	Dulaglutide 1.5 mg (N=142)	Dulaglutide 0.75 mg (N=141)	Placebo (N=140)
Sex			
Men	77 (54%)	69 (49%)	66 (47%)
Women	65 (46%)	72 (51%)	74 (53%)
Age (years)	56.17 (9.26)	58.55 (9.14)	57.10 (9.59)
Aged ≥ 65 years	23 (16%)	44 (31%)	31 (22%)
Body weight (kg)	92.87 (19.73)	91.07 (20.99)	90.50 (19.47)
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)

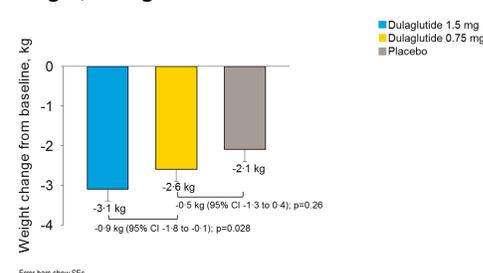
HbA1c, change from baseline to 24 weeks



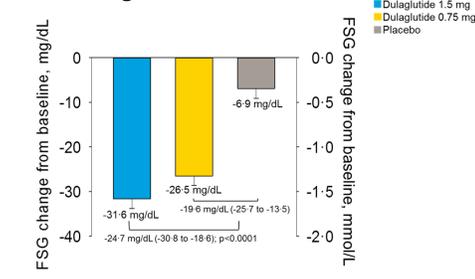
Percentage of patients achieving HbA1c targets at 24 weeks



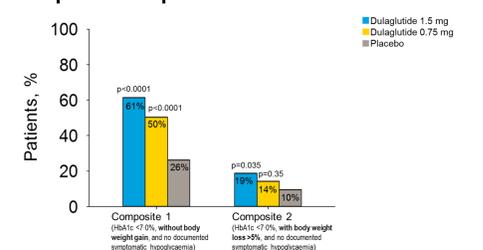
Weight, change to 24 weeks



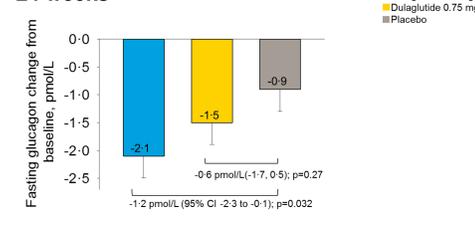
FSG, change from baseline to 24 weeks



Composite endpoints at 24 weeks



Fasting glucagon, change from baseline to 24 weeks



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 event)	95 (67%)	83 (59%)	81 (58%)
Treatment-emergent adverse events ($\geq 5\%$ 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 hypoglycaemia (≤ 70 mg/dL \pm 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 hypoglycaemia, n (%)	0 (0.0)	1 (0.7)	0 (0.0)

Summary of baseline SGLT-2i dose

	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 (%) ^a						
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 glycaemic 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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