Development of Once-Weekly Glucagon-Like-Peptide-1 Receptor Agonist (GLP-1 RA) Dulaglutide For Treatment of Type 2 Diabetes Mellitus

Zvonko Milicevic, MD, PhD, Senior Medical Fellow, Eli Lilly and Co.
Importance Of The GLP-1 Pathway For Future Drug Development

GLP-1=glucagon-like peptide-1.

Liver
- Enzymes
  - Increased glycogen storage

Brain
- Neuroprotection
  - Increased neurogenesis
  - Improved memory

Heart
- Increased myocardial contractility
  - Increased heart rate
  - Increased myocardial glucose uptake
  - Reduced ischemia-induced myocardial damage

Pancreas
- Increased new β-cell formation
  - Reduced β-cell apoptosis
  - Increased insulin biosynthesis

Kidney
- Increased natriuresis

Fat cells
- Increased glucose uptake
  - Increased lipolysis

Skeletal muscle
- Increased glucose uptake

Blood vessel
- Increased endothelial-dependent vasodilation

Abbreviations:
- GLP-1=glucagon-like peptide-1.
Dulaglutide Molecule
Dulaglutide: a GLP-1 IgG Fusion Protein

GLP-1=glucagon-like peptide-1; IgG=immunoglobulin gamma; Fab=fragment antigen binding; Fc=fragment crystalizable


Color code in B is representative of region color in A
Dulaglutide was Designed to Offer Extended Activity\(^1\)

Allows once-weekly administration\(^1,2\)
- Removed and replaced alanine at position 8 with glycine to resist DPP-4 degradation\(^3\)
- Fused 2 GLP-1 analogues to the Fc portion of an IgG4 antibody to decrease renal clearance and increase time-action profile\(^4-5\)
- Inserted optimized amino acid linker to improve binding\(^1,4\)

Fc-fusion protein molecules are used currently to treat a wide range of disease states, such as rheumatoid arthritis, organ rejection, and macular degeneration\(^6\)

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DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1, Fc=fragment crystallizable; IgG4=immunoglobulin G4
Dulaglutide was Designed to be Soluble

Eliminates the need for reconstitution and allows delivery via a small-gauge needle (29G)\(^1\)

♦ Fc fusion-enhanced solubility\(^2\)
♦ In addition to other changes, modified glycine at position 22 in the GLP-1 analogue to glutamic acid to further enhance solubility\(^3\)

3. Data on file, Eli Lilly and Company and/or one of its subsidiaries
Dulaglutide was Designed to Have Low Potential for Immunogenicity

- IgG4 selected to minimize potential for cell-mediated toxicity\(^1,2\)
- Mutations inserted into the IgG4 to minimize potential cytotoxicity\(^1\)
- Replaced an arginine residue with glycine in the GLP-1 analogue to eliminate a potential T-cell epitope\(^1\)

Pharmacokinetic Profile of LY2189265

- BQL: below the quantification limit

Dulaglutide: Across the T2DM Treatment Continuum

- The Phase 3 studies (AWARD-1 through AWARD-6, AWARD-8, and AWARD-9) are complete
- Three additional studies: AWARD-7, AWARD-10, and REWIND are ongoing
  - REWIND is a long-term cardiovascular outcomes study

AWARD=Assessment of Weekly AdministRation of LY2189265 [Dulaglutide] in Diabetes; BID=two times per day; CKD=chronic kidney disease; GLP-1=glucagon-like peptide 1; OAM=oral antihyperglycemic medication; REWIND=Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SGLT2=sodium-glucose co-transporter 2; SU=sulfonylurea; TZD=thiazolidinedione
Efficacy of Dulaglutide
HbA$_1c$ Change from Baseline at Primary Endpoint

Baseline HbA$_1c$ (%)  | 26-week  | 52-week
--- | --- | ---
AWARD-3 | 7.6 | 8.1
AWARD-5 | 7.6 | 8.1
AWARD-6 | 8.1 | 8.1
AWARD-1 | 8.1 | 8.1
AWARD-2 | 8.5 | 8.5
AWARD-4 | Combination with insulin lispro +/- MET

HbA$_1c$ Change from Baseline (mmol/mol)

Data presented are LS means, ITT, LOCF ANCOVA analysis except AWARD-6 (MMRM analysis)

**p<.001 vs placebo**

††p<.025 superiority vs MET

††p<.001 superiority vs SITA

†p<.001 non-inferiority vs LIRA

††p<.001 superiority vs EX BID and placebo

**p<.001 vs placebo**

††superiority, †non-inferiority vs GLAR

††p<.025 superiority vs GLAR

††p<.001 superiority vs MET

††p<.001 non-inferiority vs LIRA

††p<.001 superiority vs GLAR
### Proportion of Patients Achieving HbA$_1c$ Target of $<7\%$ at Primary Time Point

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Patients (%)</th>
<th>26-week</th>
<th>52-week</th>
</tr>
</thead>
<tbody>
<tr>
<td>AWARD-3</td>
<td>Monotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>vs MET</td>
<td>62%</td>
<td></td>
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<tr>
<td></td>
<td>Add-on to MET</td>
<td>58%</td>
<td></td>
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<tr>
<td></td>
<td>Add-on to MET+TZD</td>
<td>68%</td>
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<tr>
<td>AWARD-5</td>
<td>Monotherapy</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>vs SITA</td>
<td>54%</td>
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<td></td>
<td>Add-on to MET</td>
<td>58%</td>
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<tr>
<td></td>
<td>Add-on to MET+TZD</td>
<td>68%</td>
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<tr>
<td>AWARD-6</td>
<td>Monotherapy</td>
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<td></td>
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<tr>
<td></td>
<td>vs LIRA</td>
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<td></td>
<td>Add-on to MET</td>
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<td></td>
<td>Add-on to MET+TZD</td>
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<tr>
<td>AWARD-1</td>
<td>Monotherapy</td>
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<tr>
<td></td>
<td>vs EX BID</td>
<td>78%</td>
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<td>Add-on to MET</td>
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<tr>
<td></td>
<td>Add-on to MET+SU</td>
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<tr>
<td>AWARD-2</td>
<td>Monotherapy</td>
<td></td>
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<tr>
<td></td>
<td>vs GLAR</td>
<td>66%</td>
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<td></td>
<td>Add-on to MET</td>
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<td></td>
<td>Add-on to MET+SU</td>
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<tr>
<td>AWARD-4</td>
<td>Combination with insulin lispro</td>
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<tr>
<td></td>
<td>vs MET</td>
<td>68%</td>
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<td>69%</td>
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<td>Add-on to MET+TZD</td>
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<td></td>
<td>Add-on to MET+SU</td>
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</tbody>
</table>

- **#** $p<.05$ vs MET
- **##** $p<.001$ vs MET
- * $p<.05$ vs placebo
- *** $p<.001$ vs placebo

**ITT, LOCF logistic regression analysis**
Data presented are LS means, ITT, LOCF ANCOVA analysis.
DU=dulaglutide; SITA=sitagliptin
Data presented are LS means ± SE, ITT MMRM analysis
##p<.001 vs sitagliptin, **p<.001 vs placebo

Weinstock et al. Diabetes Obes Metab. 2015 Apr 23. (Ahead of print)
Self-Monitored Plasma Glucose (SMPG) at Baseline and 26 Weeks: AWARD-1

Add-on to MET + TZD

DU=dulaglutide; EX=exenatide; BID=twice per day
Data presented are means, ITT, MMRM analysis
*p<.05, **p<.001 vs. exenatide BID; *p<.05, **p<.001 vs. placebo
Wysham et al. Diabetes Care 2014;37:2159-2167
Change in Fasting Plasma Glucose Over Time: AWARD-1

Baseline FPG = 162 mg/dL (9.0 mmol/L)

DU=dulaglutide; EX=exenatide; BID=twice per day
Data presented are central laboratory measurements and LS means ± SE, ITT, MMRM analysis
#2-sided p<.05, ##p<.001 vs exenatide, *p<.05, **p<.001 vs placebo
Wysham et al. Diabetes Care 2014;37:2159-2167
Change in Postprandial Glucose Over Time: AWARD-1

Baseline PPG = 202 mg/dL (11.2 mmol/L)

- PPG, Change Over Time (mg/dL)
- Time (Weeks)
- Add-on to MET + TZD

**p<.001 vs. placebo
#p<.05 vs. exenatide

DU=dulaglutide; EX=exenatide; BID=twice per day
Data presented are from SMPG and LS means ± SE, ITT, MMRM analysis

Data on file, Eli Lilly and Company and/or one of its subsidiaries
Self-Monitored Plasma Glucose (SMPG) at Baseline and 26 Weeks: AWARD-6

Add-on to MET

SMPG (mg/dL)

240
220
200
180
160
140
120
100

Pre-morning meal
Post-morning meal
Pre-midday meal
Post-midday meal
Pre-evening meal
Post-evening meal
Bed time

DU 1.5 mg
LIRA 1.8 mg

Baseline
26 Weeks

SMPG (mmol/L)

12
10
8
6

DU=dulaglutide; LIRA=liraglutide
Data presented are means, ITT MMRM analysis
Dungan et al. *Lancet* 2014;384:1349-1357
The Phase 3 studies (AWARD-1 through AWARD-6, AWARD-8, and AWARD-9) are complete.

Three additional studies: AWARD-7, AWARD-10, and REWIND are ongoing

- REWIND is a long-term cardiovascular outcomes study

AWARD=Assessment of Weekly Administration of LY2189265 [Dulaglutide] in Diabetes; BID=two times per day; CKD=chronic kidney disease; GLP-1=glucagon-like peptide 1; OAM=oral antihyperglycemic medication; REWIND=Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SGLT2=sodium-glucose co-transporter 2; SU=sulfonylurea; T2D=type 2 diabetes; TZD=thiazolidinedione

#with or without metformin
AWARD 9: Study Design

**Screening:**
3 weeks prior to randomization

**Randomize:**

1:1

**Stabilization:**
Weeks 1-4

**Titration period:**
Weeks 4-28

**Maintenance period:**
Weeks 12-28

**Dulaglutide 1.5 mg once weekly + Insulin glargine once daily**

**Placebo + Insulin glargine once daily**

**Key inclusion criteria**
- T2DM
- Basal insulin with/without metformin ≥1500 mg/day
- A1c ≥7.0% and ≤10.5%
- BMI ≤45 kg/m²
- Stable body weight for ≥3 months

**Key exclusion criteria**
- T1DM
- History of pancreatitis
- Serum calcitonin ≥20 pg/mL

Abbreviations: A1c=glycated hemoglobin; BMI=body mass index; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus.
AWARD-9: Key Outcomes

- Change in A1c:
  - DU 1.5 mg: -1.44 ± 0.09, p < 0.001
  - PL: -0.67 ± 0.09, p < 0.001
  - p-values indicate between group comparisons.

- Change in Body Weight (kg):
  - DU 1.5 mg: -1.91 ± 0.30, p < 0.001
  - PL: 0.50 ± 0.30, p = 0.093

- Patients Achieving A1c ≤ 6.5% and < 7% at Week 28:
  - DU 1.5 mg: 75 (50.0%)
  - PL: 25 (16.7%)
  - A1c < 7%: 100 (66.7%)
  - p-values indicate between group comparisons.

Abbreviations: DU = dulaglutide; LS = least square; PL = placebo; SE = standard error.
Safety of Dulaglutide
Gastrointestinal adverse reactions: The most common gastrointestinal adverse events were nausea, vomiting, and diarrhea, and to a lesser extent constipation and abdominal pain. The incidence of nausea typically peaked within the first 2 weeks of dulaglutide treatment and then rapidly declined1-6.

Hypoglycemia: The incidence of hypoglycemia in dulaglutide-treated patients was similar to or lower than other comparators1-6.

Injection site reaction: 1.9% of patients treated with dulaglutide had injection site reactions7.

ADA: 1.6% dulaglutide-treated patients developed dulaglutide ADAs across 4 Phase 2 and 6 Phase 3 studies7,8.

Acute pancreatitis: The incidence in Phase II and III clinical studies was 0.07% for dulaglutide compared to 0.14% for placebo and 0.19% for comparators with or without additional background antidiabetic therapy8.

Cardiac: Dulaglutide is associated with small mean increases in heart rate of 2–4 beats per minute, and with small mean increases from baseline in PR interval of 2–3 msec and a 1.5–2.4% incidence of first-degree AV block8.

Thyroid: Dulaglutide causes thyroid C-cell tumors in rats. It is unknown whether dulaglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of dulaglutide-induced rodent thyroid C-cell tumors has not been determined8.
Nausea with Dulaglutide is Comparable to Liraglutide 1.8 mg (AWARD-6)

- Liraglutide was titrated according to the label on weeks 1 (0.6 mg/day) and 2 (1.2 mg/day), until full dose (1.8 mg/day)
- Nausea was generally mild to moderate in nature
- Episodes of nausea were reported to peak during the first 2 weeks of treatment and rapidly declined over the next 4 weeks, after which the rate remained relatively constant
- Nausea led to discontinuation for <2% of patients
No Increase of CV Risk was Observed in a Metanalysis of Adjudicated MACE Events Across the Phase 2 and 3 Studies.

**Forest Plot of Primary 4-Component MACE Endpoint by Study**

<table>
<thead>
<tr>
<th>Stratum (Dula/Comparators)</th>
<th>Hazard Ratio and 98.02% CL</th>
<th>HR</th>
<th>LCL</th>
<th>UCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2 trials (1/2)</td>
<td></td>
<td>0.22</td>
<td>0.01</td>
<td>3.77</td>
</tr>
<tr>
<td>AWARD-3_AWARD-6 (9/8)</td>
<td></td>
<td>0.72</td>
<td>0.23</td>
<td>2.23</td>
</tr>
<tr>
<td>AWARD-1 (6/2)</td>
<td></td>
<td>1.49</td>
<td>0.21</td>
<td>10.53</td>
</tr>
<tr>
<td>AWARD-2 (5/5)</td>
<td></td>
<td>0.48</td>
<td>0.11</td>
<td>2.08</td>
</tr>
<tr>
<td>AWARD-4 (6/8)</td>
<td></td>
<td>0.38</td>
<td>0.11</td>
<td>1.35</td>
</tr>
<tr>
<td>Overall (26/25)</td>
<td></td>
<td>0.57</td>
<td>0.30</td>
<td>1.10</td>
</tr>
</tbody>
</table>

MACE = major adverse CV event; HR = hazard ratio; LCL = lower limit of confidence interval; UCL = upper limit of confidence interval.

*AWARD-3 did not have a primary endpoint event in the metformin control arm, therefore, AWARD-3 was combined with AWARD-5 to form a single stratum.*
Prior to completion of the DCE, 92 (37.9%) patients were willing to take injectable T2D medication, while 94 (38.7%) were not willing.

After completion of the DCE, significantly larger number of patients were willing to take medication represented by the dulaglutide profile (77.0%) vs. the liraglutide profile (30.5%) (p<.0001)

<table>
<thead>
<tr>
<th></th>
<th>Dulaglutide profile</th>
<th>Liraglutide profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Willing to take medication</td>
<td>77.0%</td>
<td>30.5%</td>
</tr>
<tr>
<td>Somewhat willing</td>
<td>39.1%</td>
<td>17.7%</td>
</tr>
<tr>
<td>Very willing</td>
<td>37.9%</td>
<td>12.8%</td>
</tr>
</tbody>
</table>
Over post-period index (6 months), 26.2% of dulaglutide patients discontinued treatment compared with 48.4% of patients taking exenatide QW (p<.0001)

The majority of the patients initiated exenatide QW utilizing a pen (72.3% [n=1746]) vs. vial and syringe (27.7% [n = 669])

HR = hazard ratio; CI = confidence interval; QW = once weekly
Kaplan-Meier Persistence Curves of Dulaglutide-Liraglutide

Significantly fewer patients discontinued dulaglutide compared to liraglutide (28.0% vs. 35.6%; p<.0001)

HR (95% CI) = 0.79 (0.71 – 0.88)

HR = hazard ratio; CI = confidence interval; QW = once weekly
Dulaglutide is Delivered via a Ready-to-Use Pen

Characteristics of the ready-to-use pen

♦ Steps to use: uncap, place and unlock, inject
♦ Provides dose confirmation
♦ Dose delivery (5–10 seconds)
♦ Automatically retracts needle following injection
♦ Small (29G, 5 mm injection depth\(^1\)), hidden needle
♦ In a phase 3 study, 99% of people found the pen easy to use\(^1\)

Dulaglutide demonstrated significant, sustained glucose lowering with a dose-dependent weight benefit.

Dulaglutide lowers HbA$_{1c}$ by improving fasting and postprandial glucose.

The safety profile of dulaglutide was comparable to the GLP-1 receptor agonist class, with no new safety signals in up to 2 years of controlled clinical trial data.

Dulaglutide allows for a once weekly subcutaneous injection that does not require reconstitution or preparation by the patient.