The Application of Drug-Disease and Clinical Utility Models in the Design of AWARD-5: an Adaptive Seamless Phase 2/3 Study

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BACKGROUND

Dulaglutide (dula) is a novel once-weekly glucagon-like peptide 1 analog in development for the treatment of type 2 diabetes, as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

Early Phase 1 and Phase 2 studies demonstrated tolerable time-linear pharmacokinetics (PK) with steady-state attained after the 2nd dose of dula. Low peak-to-trough variability and sustained drug concentration-time and pharmaco-dynamic (PD) profiles supported once-weekly administration.

Drug-disease and PK/PD modeling and simulations of early phase data demonstrated clinically meaningful benefit and weight to reduced the uncertainty in predicting responses from short duration studies (30-day) to long term clinical effectiveness (6 to 12 months). Patient response and trial simulations were applied as efficient approaches to evaluate trial design and the placement of doses to optimize Phase 3 dose selection with high probability of success.

AWARD-5 is an adaptive dose-finding, inferentially seamless phase 2/3 study, designed in partnership with the FDA as part of the "Critical Path Initiative" (FDA Modernization Act of1997).

INTRODUCTION

Objectives

- Develop dose- and exposure-response models of prospectively selected clinical safety and efficacy endpoints using available clinical trial and literature data
- Simulate patient populations and trials to evaluate – Dose selection algorithms for dose-finding in patients with type 2 diabetes stabilized on diet, exercise and metformin
- Application of clinical utility functions to select the right dose
- Probability of trial success under alternative drug response scenarios

Study Design

AWARD-5 was an adaptive dose-finding, inferentially seamless phase 2/3 study in the clinical development of dula.

- Two-stage, multi-center, randomized, double-blind, placebo-controlled, 24-month, parallel clinical trial comparing dula to exenatide.
- Patients: T2DM on diet and exercise, stabilized on metformin
- Stage 1: Bayesian adaptive scheme: adaptive dose-finding to enable dose selection decision or early study termination due to futility: the adaptive randomization algorithm was applied until a dose with the maximum CUI demonstrated clinically meaningful benefit and meet pre-specified selection criteria to proceed to Stage 2 seamlessly
- Adaptive dose allocation: patients were randomized 1:1:1:1:1 to placebo, active comparator (exenatide 100 mg/day), or 1:1:1:1:1 if possible once-weekly dula doses of 0.25, 0.5, 0.75, 1.5, 2.0, 2.5 mg. Allocation of new patients to dula doses occurred with adaptive randomization bi-weekly using CUI
- Stage 2: Fixed dose allocation scheme: continued evaluation of the selected dula doses with maximum CUI values.

METHODS

Simulation models developed to design Phase 2/3 AWARD-5

- Combining PK/PD analysis dataset comprised of data from 5 studies: 2 single-dose studies in healthy subjects and patients with T2DM, 2 28-day dose-ranging studies in patients with T2DM and interim data from one Phase 2 dose-finding study in patients.
- Dula PK/PD models were developed using nonlinear mixed effects modeling techniques implemented in NONMEM VI and simulations using R.
- Drug-disease and clinical utility models (for 3 drug plausible potency assumptions)
- Dula-drug disease simulation models were used to predict patient responses from a 28-day trial to Phase 3 trials long term (6 to 12 month) treatment durations.
- Functions for clinical utility index (CUI) were developed for HbA1c, weight and maintained comparator’s published literature on the time course of HbA1c in collaboration with internal and external medical experts and regulatory agency that take into account information and benefit trade-offs in Phase 3 dose selection.

RESULTS

Patient Data Disposition

<table>
<thead>
<tr>
<th>Baseline Correlation</th>
<th>PK</th>
<th>FPG and HbA1c</th>
<th>Weight</th>
<th>Heart Rate</th>
<th>CUI Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>88</td>
<td>104</td>
<td>88</td>
<td>88</td>
<td>104</td>
</tr>
<tr>
<td>Dose Range (mg)</td>
<td>(50 – 122)</td>
<td>(9 – 8)</td>
<td>(50 – 122)</td>
<td>(9 – 8)</td>
<td>(9 – 8)</td>
</tr>
<tr>
<td>Baseline HbA1c (%)</td>
<td>12%</td>
<td>12%</td>
<td>12%</td>
<td>12%</td>
<td>12%</td>
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<tr>
<td>Patient Age (y)</td>
<td>50</td>
<td>50</td>
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<tr>
<td>Median (range)</td>
<td>(39 – 87)</td>
<td>(39 – 87)</td>
<td>(39 – 87)</td>
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<tr>
<td>BMI (Kg/m²)</td>
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<tr>
<td>Median (range)</td>
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<td>(20 – 41)</td>
<td>(20 – 41)</td>
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</tr>
<tr>
<td>Body Weight (Kg)</td>
<td>94</td>
<td>94</td>
<td>94</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Median (range)</td>
<td>(94 – 141)</td>
<td>(94 – 141)</td>
<td>(94 – 141)</td>
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<tr>
<td>Female</td>
<td>64%</td>
<td>64%</td>
<td>44%</td>
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</tr>
<tr>
<td>Median (range)</td>
<td>(50 – 122)</td>
<td>(9 – 8)</td>
<td>(50 – 122)</td>
<td>(9 – 8)</td>
<td>(9 – 8)</td>
</tr>
<tr>
<td>Ethnic Origin - Asian</td>
<td>13%</td>
<td>13%</td>
<td>13%</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Median (range)</td>
<td>(94 – 141)</td>
<td>(94 – 141)</td>
<td>(94 – 141)</td>
<td>(94 – 141)</td>
<td></td>
</tr>
</tbody>
</table>

Study Design

Model-based analysis results of Proof of Concept (POC) Study

Narrowed Therapeutic Dose Range for AWARD-5

- Therapeutic window: between 0.25 and 5 mg with low probability of significant
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- Narrowed Therapeutic Dose Range for AWARD-5

- Model predicted dose-response (95% C.I) of HbA1c and weight change from baseline at 6 months: dose to achieve target HbA1c was predicted ≥ 0.5 mg

CONCLUSIONS

- Drug-Disease and PK/PD model-based trial simulation supported the selection of optimal dose range with high probability of trial success for the adaptive seamless Phase 2/3 dose-finding AWARD-5 trial.
- CUI function predicted the likely Phase 3 dose between 0.5 and 2 mg for further confirmation of safety and efficacy in Phase 3.
- Model-based trial simulation streamlined dula clinical plan and supported the design of AWARD-5, an adaptive seamless Phase 2/3 dose-finding study.
- Drug-disease models developed using Limited Phase 1 and literature data are efficient tools for streamlining drug development. Model-based trial simulations allow systematic and robust evaluation of trial design and assessment of probability of trial success.

Leverage Literature Data for Time-course Models of HbA1c and Weight Loss

Literature data on marketed drugs

HbA1c lowering half-life ~ 3.5 weeks

Weight loss half-life ~ 8.5 weeks

Clinical Utility Index Based Dose Allocation

CUI Based on Predicted Drug Response Scenarios for (3 drug plausible potency assumptions)

- Model predicted dose-response (95% C.I) of HbA1c and weight change from baseline at 6 months: dose to achieve target HbA1c was predicted ≥ 0.5 mg

- Clinical Utility Index Based Dose Allocation

- CUI identified an optimal dose range between 0.5 to 2 mg with utility ≥ 1 to proceed to Stage 2 for further evaluation

References: Lilly internal literature database (courtesy of GVK).

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