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 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 pharmacodynamic (PD) profiles supported once-weekly administration.

Drug-disease and PK/PD modeling and simulations of early phase data leveraged comparator's published literature on the time-course of HbA1c and weight to reduced the uncertainty in predicting responses from short duration studies (28-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 of 1997).

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, multicenter, randomized, double-blind, placebo-controlled, 24-month, parallel clinical trial comparing dula to sitagliptin.
- Patients: T2DM on diet and exercise, stabilized on metformin
- Stage 1: Bayesian adaptive scheme; adaptive dose-finding to enable dula 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 randomised 1:1:3 to placebo, active comparator (sitaglitin 100 mg QD), or 1 of 7 possible once-weekly dula doses (0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0 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
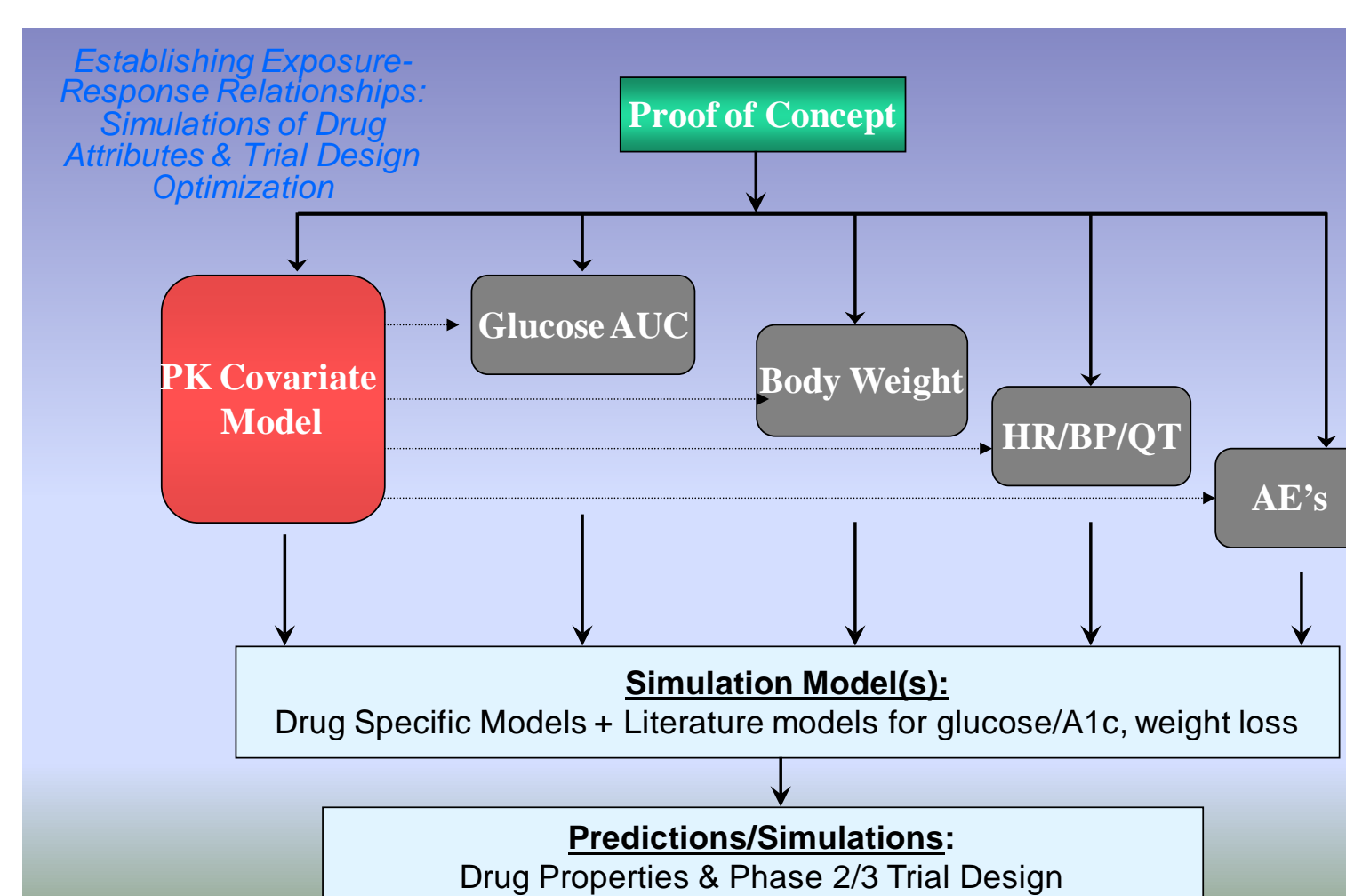
- Combined PK/PD analysis dataset comprised of data from 5 studies: 2 single-dose studies in healthy subjects and patients with T2DM, 2 28-day dose-ranging studies in patients with T2DM and interim data from one Phase 2 dose-titration study in patients.
- Dula PK/PD models were developed using nonlinear mixed effects modeling techniques implemented in NONMEM VI and simulations using R.
- Drug-disease model linking FBG and HbA1c time course and associated inter-patient variability were developed using a large patient level database of Lilly clinical trials of 12 to 104 week treatment duration.

$$FBG = E_{0,FPG} - \left(E_{0,FPG} - E_{max,FBG}\right) \bullet \left(\frac{Dose}{Dose + ED_{50}}\right) \bullet \left(1 - e^{-K_{FPG} \bullet Week}\right) \bullet Trough$$

$$HbA1c = E_{0,A1c} - \left(E_{0,A1c} - E_{max,A1c}\right) \bullet \left(\frac{Dose}{Dose + ED_{50}}\right) \bullet \left(1 - e^{-K_{A1c} \bullet Week}\right)$$

- Time course model of weight loss using summary level data from published clinical trial literature of anti-diabetic agents (e.g., exenatide, sitagliptin, liraglutide).

$$BodyWeight = E_0 \bullet \left[1 + \left(Placebo + Slope \bullet Dose^\gamma\right) \bullet \left(1 - e^{-K \bullet Day}\right)\right]$$
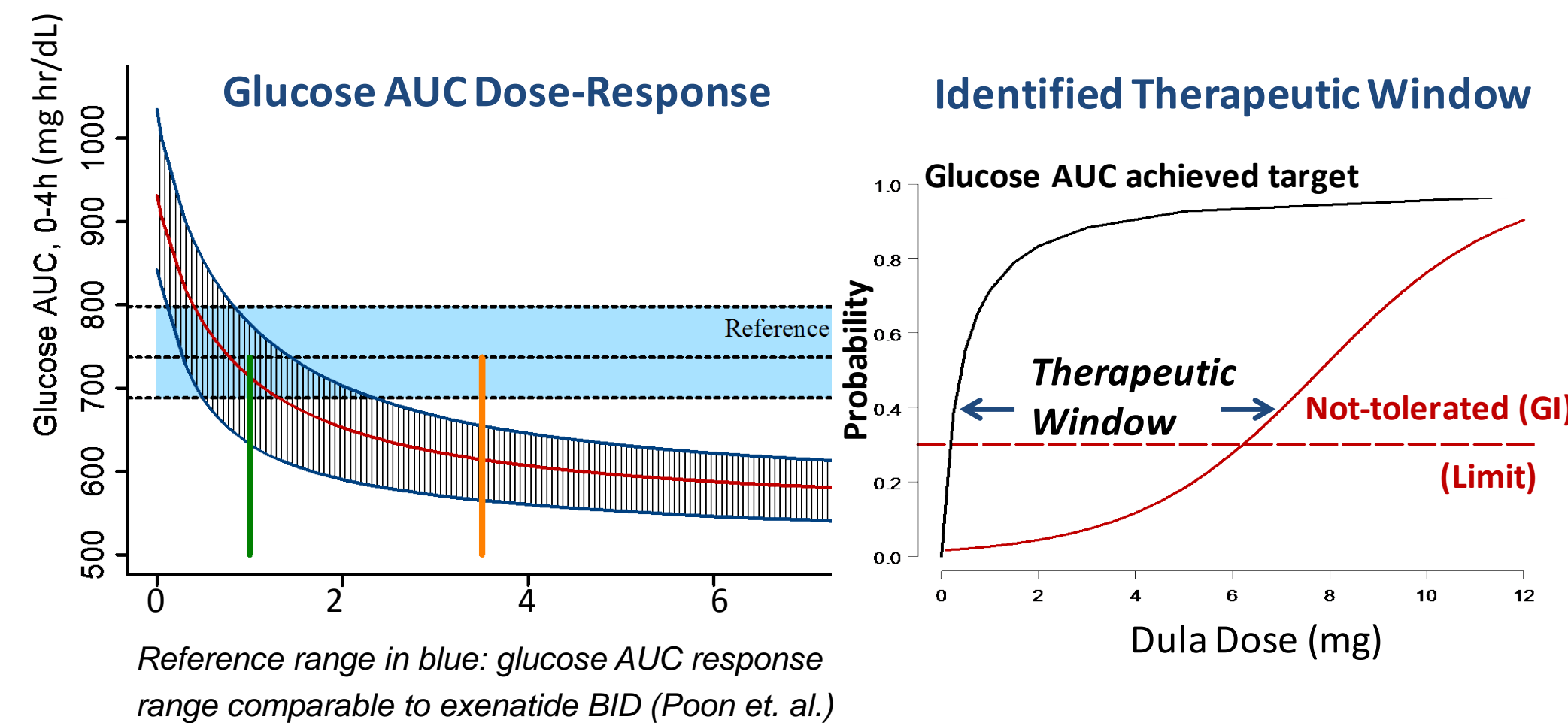
- Dula drug-disease simulation models were used to predict patient responses from a 28-day trial to Phase 2/3 trials long term (6 to 12 month) treatment durations.
- Functions for clinical utility index (CUI) were developed for HbA1c, weight and markers of cardiovascular safety (heart rate and diastolic blood pressure) in collaboration with internal and external medical experts and regulatory agency that take into account risk and benefit trade-offs in Phase 3 dose selection.

RESULTS

Patient Data Disposition

Baseline Covariate	PK	FBG and HbA1c	Weight	Heart Rate	Diastolic Blood Pressure
Number of Subjects	382	314	321	351	351
Dose Range (mg)	(0.05 – 12)	(0 – 8)	(0 – 8)	(0 – 8)	(0 – 8)
Healthy Subject (%)	32%	0	0	0	0
Age (years) Median (range)	55 (19 – 87)	58 (30 – 87)	58 (30 – 87)	58 (30 – 87)	58 (30 – 87)
BMI (Kg/m²) Median (range)	30 (20 – 43)	-	-	32 (18 – 48)	32 (18 – 48)
Body Weight (Kg) Median (range)	84 (45 – 141)	-	92 (46 – 142)	90 (46 – 141)	90 (46 – 141)
Female	43%	49%	49%	47%	47%
Ethnic Origin – Caucasian	43%	53%	51%	45%	45%
Ethnic Origin –African	15%	7%	7%	6%	6%
Ethnic Origin –Asian	13%	7%	8%	19%	19%
Ethnic Origin –Hispanic	27%	33%	32%	29%	29%
CG Creatine CL (mg/dL) Median (range)	115 (48 – 233)	-	-	-	-
Baseline PD Median (range)	NA	FBG: 159 mg/dL (83 – 340 mg/dL) A1C: 8.0 % (5.6 – 11%)	92 Kg (46 – 142 Kg)	73 bpm (52 – 115 bpm)	77 mmHg (48 – 96 mmHg)

Model-based analysis results of Proof of Concept (POC) Study Narrowed Therapeutic Dose Range for AWARD-5

Glucose AUC Dose-Response

Identified Therapeutic Window

Reference range in blue: glucose AUC response range comparable to exenatide BID (Poon et. al.)

- Maximum glucose response (Emax) at dula doses ≥ 3 mg following testmeals.
- Therapeutic window: between 0.25 and 5 mg with low probability of significant gastrointestinal (GI) adverse effects

FPG-HbA1c Linked Model Parameters

Parameter Description	Population Estimate (%SEE)	Inter-patient Variability (%SEE)
Response Rate		
HbA1c-K10 (week⁻¹)	0.104 (3.12)	35.2 (22.0)-
FPG-K10 (week⁻¹)	0.145 (9.22)	69.1 (33.1)
Baselines		
FPG (mg/dL)	162 (1.55)	23.7 (10.1)
HbA1c (%)	8.88 (0.721)	7.14 (13.6)
FPG-HbA1c link [a]	0.408 (5.51)	
Dose Response		
FPG-Emax (mg/dL)	110 (5.71)	32.4 (23.6)
HbA1c-Emax (mg/dL)	5.96 (3.24)	17.1 (20.7)
FPG-Emax X HbA1c Emax	0.0477 (22.6)	
FPG Baseline Effect (mg/dL) [b]	0.371 (9.76)	
HbA1c Baseline Effect (%) [c]	0.359 (9.25)	
Potency		
ED₅₀ (mg)	0.387 (28.5)	
Trough FPG as fraction of peak in 1 week	0.835 (16.8)	---
Residual Error		
Proportional FPG	15.5 (6.71)	
Proportional HbA1c	4.82 (4.96)	

$$^a\ E_{0,A1c} = 8.88*(E_{0,FPG}/200)^{0.408}$$
$$^b\ E_{max,FPG} = 110*(E_{0,FPG}/200)^{0.371}$$
$$^c\ E_{max,A1c} = 5.96*(E_{0,A1c}/8.6)^{0.359}$$

Weight Loss Model Parameters

Parameter Description	Population Estimate (%SEE)	Additive Inter-patient Variability (%SEE)
Baseline Weight		
E0 (Kg)	92.6 (1.07)	0.207 (8.21)
Turnover Rate		
K₁₀ (day⁻¹)	0.0198 (2.70)	---
Placebo Response		
Placebo	0 (FIXED)	
Dose Response		
Slope (mg⁻¹)	0.0197 (12.6)	0.000767 (14.5)
Sigmoidicity	0.471 (27.4)	
Residual Error		
Additive (kg)	0.931 (4.83)	

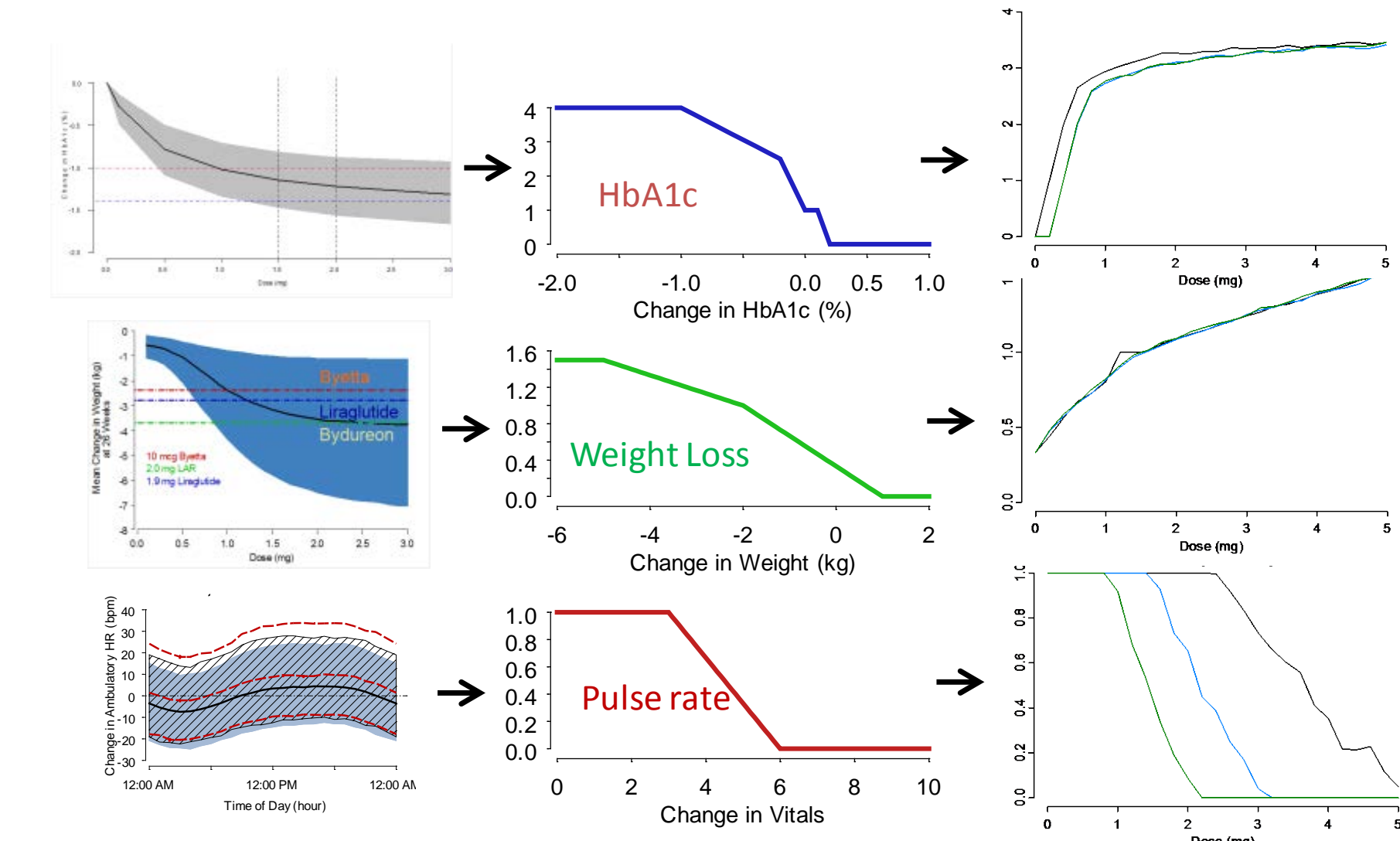### Leverage Literature Data for Time-course Models of HbA1c and Weight Loss

Literature data on marketed drugs
HbA1c lowering half-life ~ 3.5 weeks
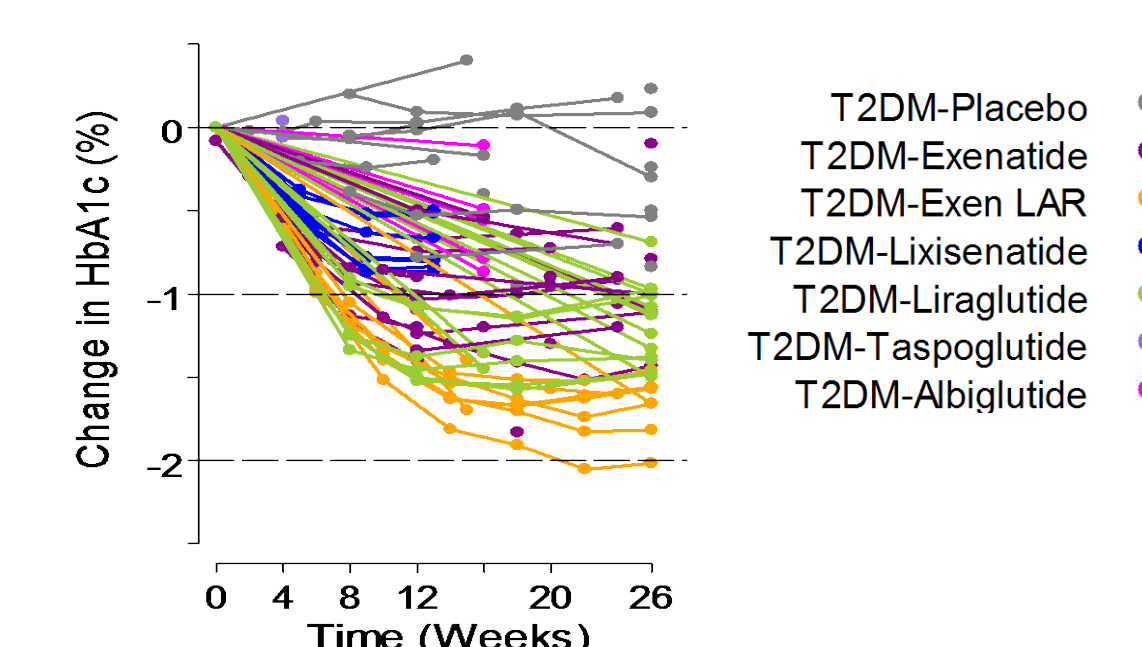
Literature data on marketed drugs
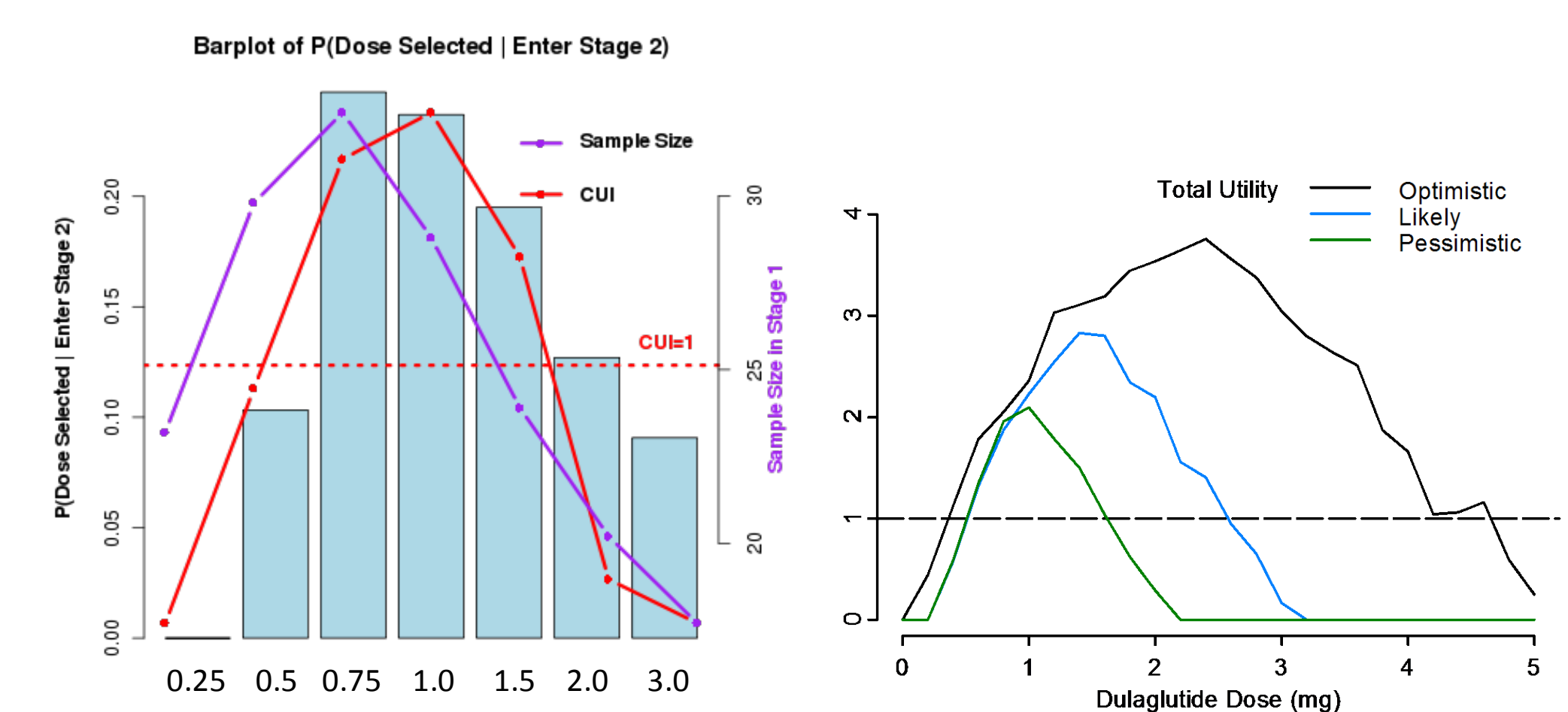Weight loss half-life ~ 8.5 weeks
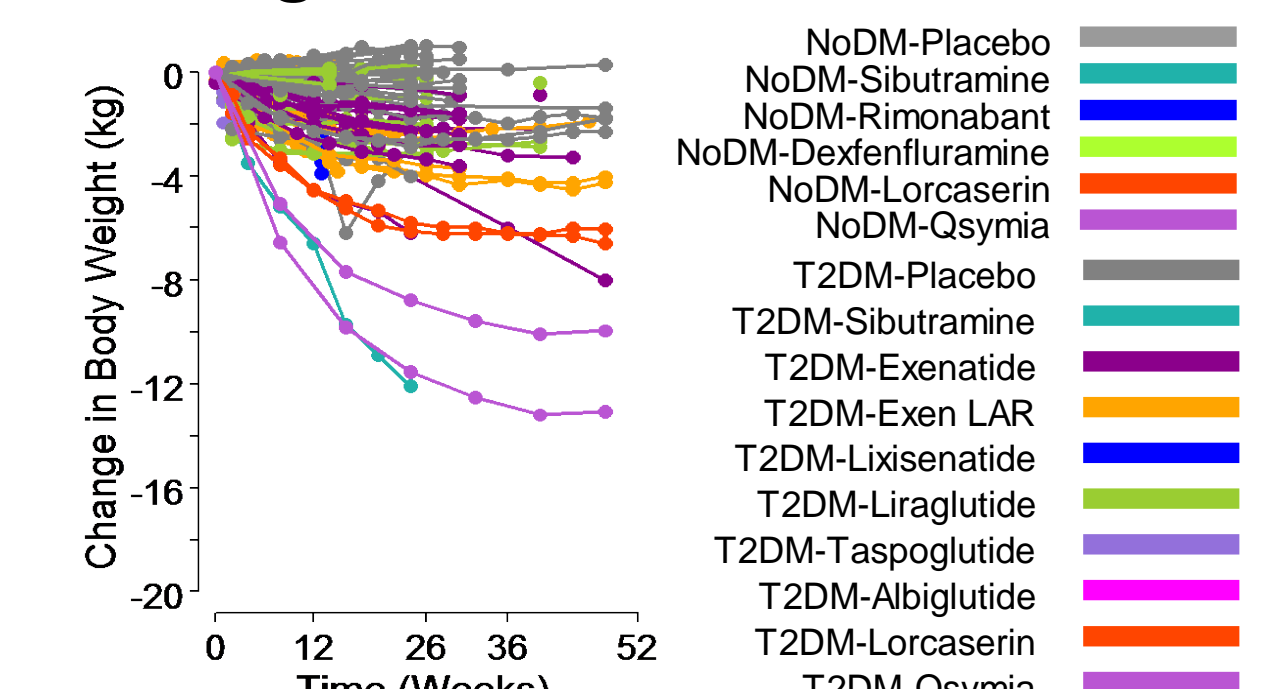
CUI Based on Predicted Drug Response Scenarios (for 3 drug plausible potency assumptions)

Model predicted dose-response (90% CI) 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

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.

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