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CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Challenges and Opportunities of Bayesian Adaptive Trials: Regulatory and Pharmacometrics Perspectives

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Disclaimer: My remarks today are my own personal views and do not represent those of the FDA

Outline

- Overview
- Review case study
- Summary

Adaptive Trials

- **FDA guidance**
  - **CDER: Adaptive Design Clinical Trials for Drugs and Biologics, 2010**
  - **CDRH: Adaptive Designs for Medical Device Clinical Studies, 2016**
- **Many features can be modified or adaptive**
- **Bayesian or not Bayesian**
- **Bayesian adaptive trials are not common for drugs and biologics programs**

https://www.fda.gov/downloads/drugs/guidances/ucm201790.pdf
https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446729.pdf

Therapeutic Areas

- Diabetes
- Epilepsy
- Pulmonary arterial hypertension
- Smoking cessation
- Spinal muscular atrophy
- Acute spinal cord injuries
- Athsma/COPD
- Cancer

Dulaglutide

- **A glucagon-like peptide (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.**
- **The recommended initiating dose is 0.75 mg once weekly. The dose may be increased to 1.5 mg once weekly for additional glycemic control. The maximum recommended dose is 1.5 mg once weekly.**
- **Initial approval in US: 2014**

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125469Orig1s000Lbl.pdf

Development History

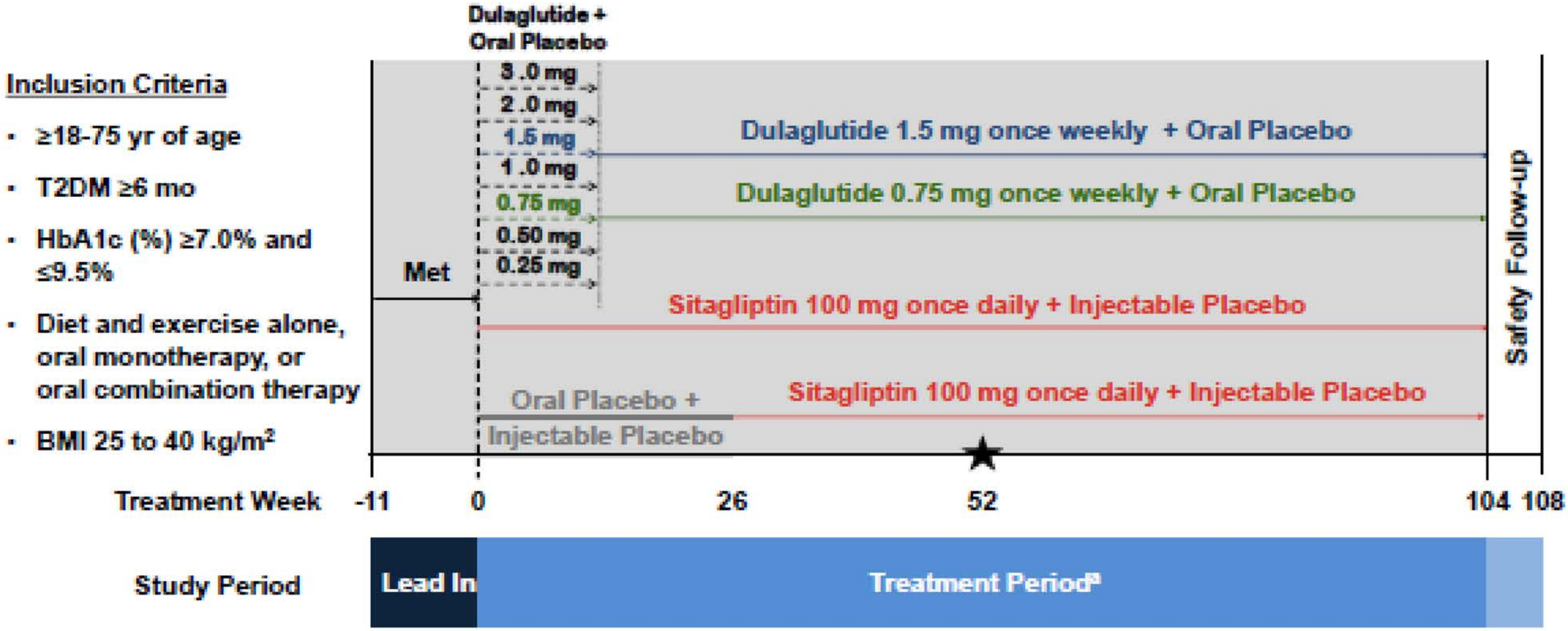
- **IND initiated in 2005**
- **Adaptive randomization, seamless phase 2/3 trial proposed in 2007**
- **FDA response: "FDA agreed that Lilly can conduct and analyze the trial as proposed, understanding that FDA may only consider data from patients enrolled in Stage 2 as confirmatory." in 2008**
- **End-of-Phase 2 (EOP2) meeting in 2009**
- **Adaptive trial conduct: August 2008 – July 2012**
- **BLA submission in 2013**
- **Approval in 2014**

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125469Orig1s000StatR.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125469Orig1s000SumR.pdf
https://clinicaltrials.gov/ct2/show/NCT00734474

Publications Related to the Adaptive Trial

- Spencer K, Colvin K, Braunecker B et al. Operational challenges and solutions with implementation of an adaptive seamless phase 2/3 study. J Diabetes Sci Technol 2012; 6: 1296–1304.
- Skrivanek Z, Berry S, Berry D et al. Application of adaptive design methodology in development of a long-acting glucagon-like Peptide-1 analog (dulaglutide): statistical design and simulations. J Diabetes Sci Technol 2012; 6: 1305–1318
- Geiger MJ, Skrivanek Z, Gaydos B, Chien J, Berry S, Berry D. An adaptive, dose-finding, seamless phase 2/3 study of a long-acting glucagon-like Peptide-1 analog (dulaglutide): trial design and baseline characteristics. J Diabetes Sci Technol 2012; 6: 1319–1327.
- Skrivanek Z, Chien J, Gaydos B, Heathman M, Geiger MJ, Milicevic Z, Dose-finding results in an adaptive trial of dulaglutide combined with metformin in type 2 diabetes (AWARD-5). Diabetes 2013; 62(Suppl 1):A269
- Skrivanek Z, Gaydos BL, Chien JY, Geiger MJ, Heathman MA, Berry S, Anderson JH, Forst T, Milicevic Z, Berry D. Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5). Diabetes Obes Metab. 2014 Aug;16(8):748-56
- Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivanek Z, Milicevic Z, Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5), Diabetes Care. 2014 Aug;37(8):2149-58
- Weinstock RS, Guerci B, Umpierrez G, Nauck MA, Skrivanek Z, Milicevic Z. Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2 years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study. Diabetes Obes Metab. 2015 Sep;17(9):849-58

Study Design of the Adaptive Trial



Inclusion Criteria

- ≥18-75 yr of age
- T2DM ≥6 mo
- HbA1c (%) ≥7.0% and ≤9.5%
- Diet and exercise alone, oral monotherapy, or oral combination therapy
- BMI 25 to 40 kg/m^2

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125469Orig1s000MedRedt.pdf

Stage 1: Adaptive Allocation

- Placebo (0.2), active control (0.2), and 7 dose levels of dulaglutide (0.6)
- Four endpoints (HbA1c at 12 months, weight, pulse rate and diastolic blood pressure at 6 months) were combined to form a clinical utility index (CUI) to be used in the adaptive treatment algorithm
- Safety and efficacy data drive the randomization scheme (by means of CUI) to allocate more patients to the most beneficial doses and fewer patients to less beneficial doses.
- During each biweekly interim assessment to support the adaptive algorithm, the dose with the highest posterior probability of having the largest CUI was designated the maximum utility dose (MUD)
- If the MUD met predefined selection criteria (CUI ≥0.6 and predictive probability of non-inferiority versus sitagliptin at 52weeks for HbA1c change from baseline ≥0.85) at one of the interim assessments, that dose and possibly a lower dose would be selected.
- This second dose was required to have a CUI ≥0.6 and be ≤50% of the MUD.
- Two decision rules after 200 subjects were randomized: (1) to stop for futility, based on both safety and efficacy; or (2) to start stage 2 with up to two doses selected from stage 1, based on predefined decision rules.
- If there is insufficient evidence to make either of these decisions, patients continue to be randomized in stage 1. If sufficient evidence cannot be gathered to make either decision after 400 patients are enrolled, the study will be terminated.

Skrivanek Z, et al. Application of adaptive design methodology in development of a long-acting glucagon-like Peptide-1 analog (dulaglutide): statistical design and simulations. J Diabetes Sci Technol 2012; 6: 1305–1318
Skrivanek Z, et al. Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5). Diabetes Obes Metab. 2014 Aug;16(8):748-56

Extensive Modelling and Simulation

- **Dose/exposure-response longitudinal models were developed for four endpoint (HbA1c, weight, pulse rate and diastolic blood pressure)**

- **These models were used to**
  1. **Justify the doses selected in the adaptive trial**
  2. **Provide prior information for the development of adaptive statistical analysis models**
  3. **Simulate the efficacy and safety responses of the virtual patients under various trial scenarios (e.g., “no dose response”, “most likely response”, “optimistic” and “pessimistic” dose-response) to evaluate operating characteristics of the adaptive trial design**
  4. **Simulate conventional dose-finding Phase 2 trial designs to be compared with the adaptive design**

Skrivanek Z, et al. Application of adaptive design methodology in development of a long-acting glucagon-like Peptide-1 analog (dulaglutide): statistical design and simulations. J Diabetes Sci Technol 2012; 6: 1305–1318

Analysis Models for Adaptive Allocation

- **Dose-response: normal dynamic linear models (NDLM)**
  - **A nonparametric approach to model correlated data, NDLM "borrows" information from neighboring doses but does not force any particular shape to the overall response curve**
- **Longitudinal models serve as a bridge between the early and later time periods**
  - **$\exp(\gamma_t)\ \theta(d)$ where $\exp(\gamma_t)$ determines the fraction of mean HbA1c at time t relative to $\theta(d)$, the mean HbA1c at 12 months for dose "d"**
- **Normal prior distribution assumed**

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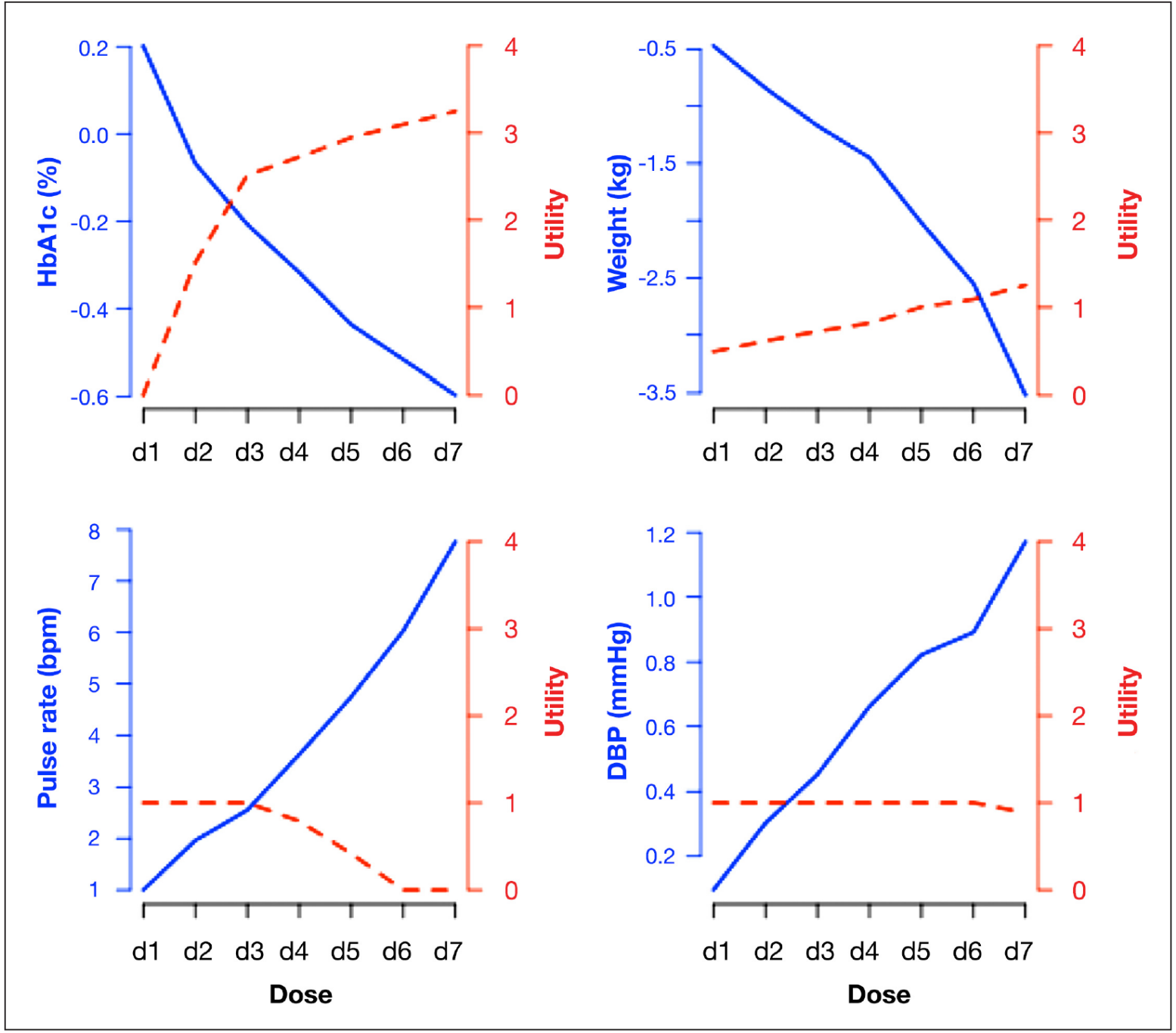

Figure 2. Change from baseline relative to comparator and corresponding values from utility components. Plot of the change from baseline of HbA1c, weight, HR, and DBP based on the most likely model and the corresponding utility component values.

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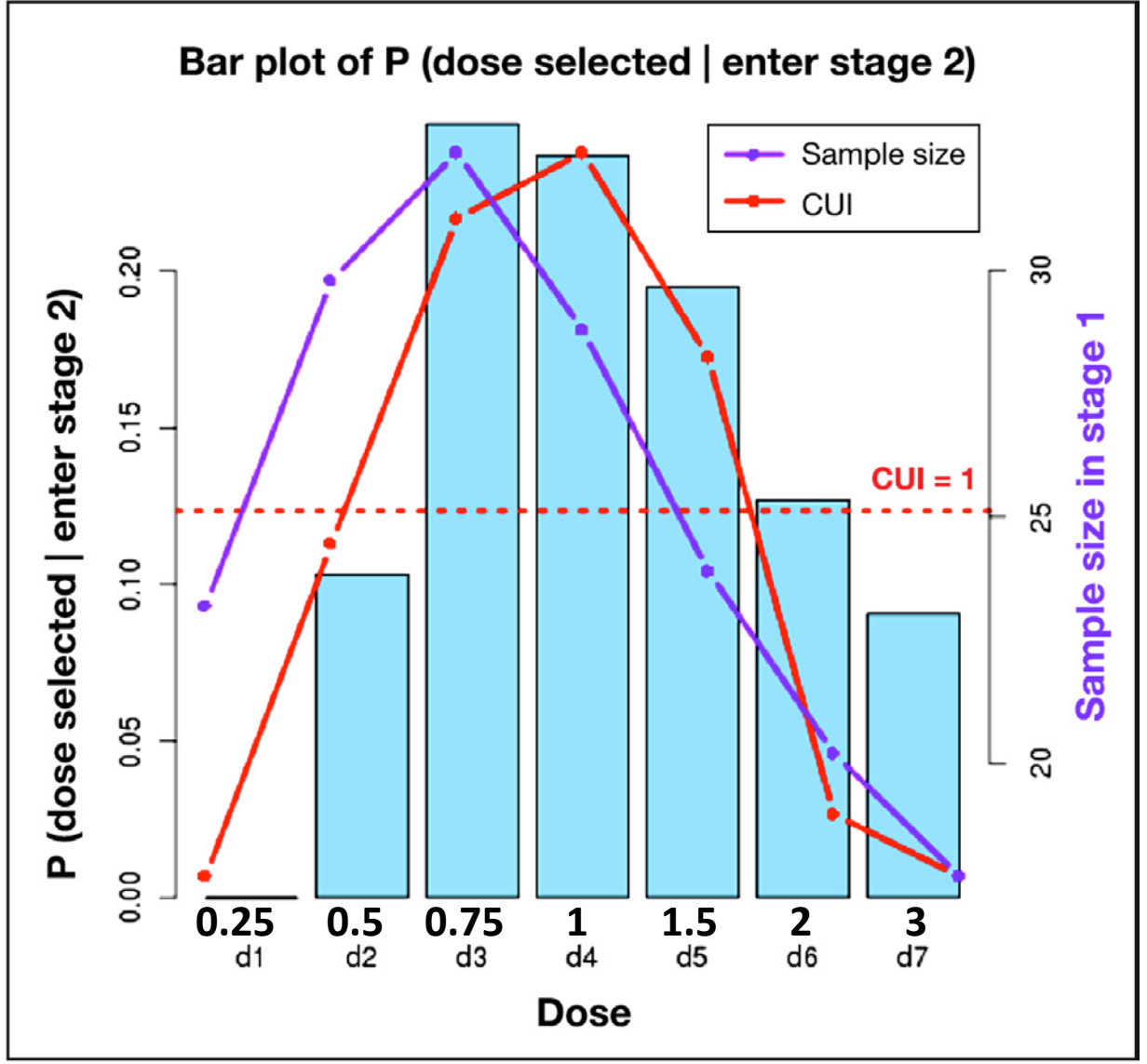


Figure 4. Plot of operating characteristics of the adaptive algorithm for the most likely model. A bar plot of the P (dose is selected given that stage 2 was conducted) is given with the scale on the left *y*-axis. The purple line plots the sample size with the corresponding scale given on the right *y*-axis. The CUI is plotted in red with no scale given. A reference line for CUI = 1 is provided.

Skrivanek Z, et al. Application of adaptive design methodology in development of a long-acting glucagon-like Peptide-1 analog (dulaglutide): statistical design and simulations. J Diabetes Sci Technol 2012; 6: 1305–1318

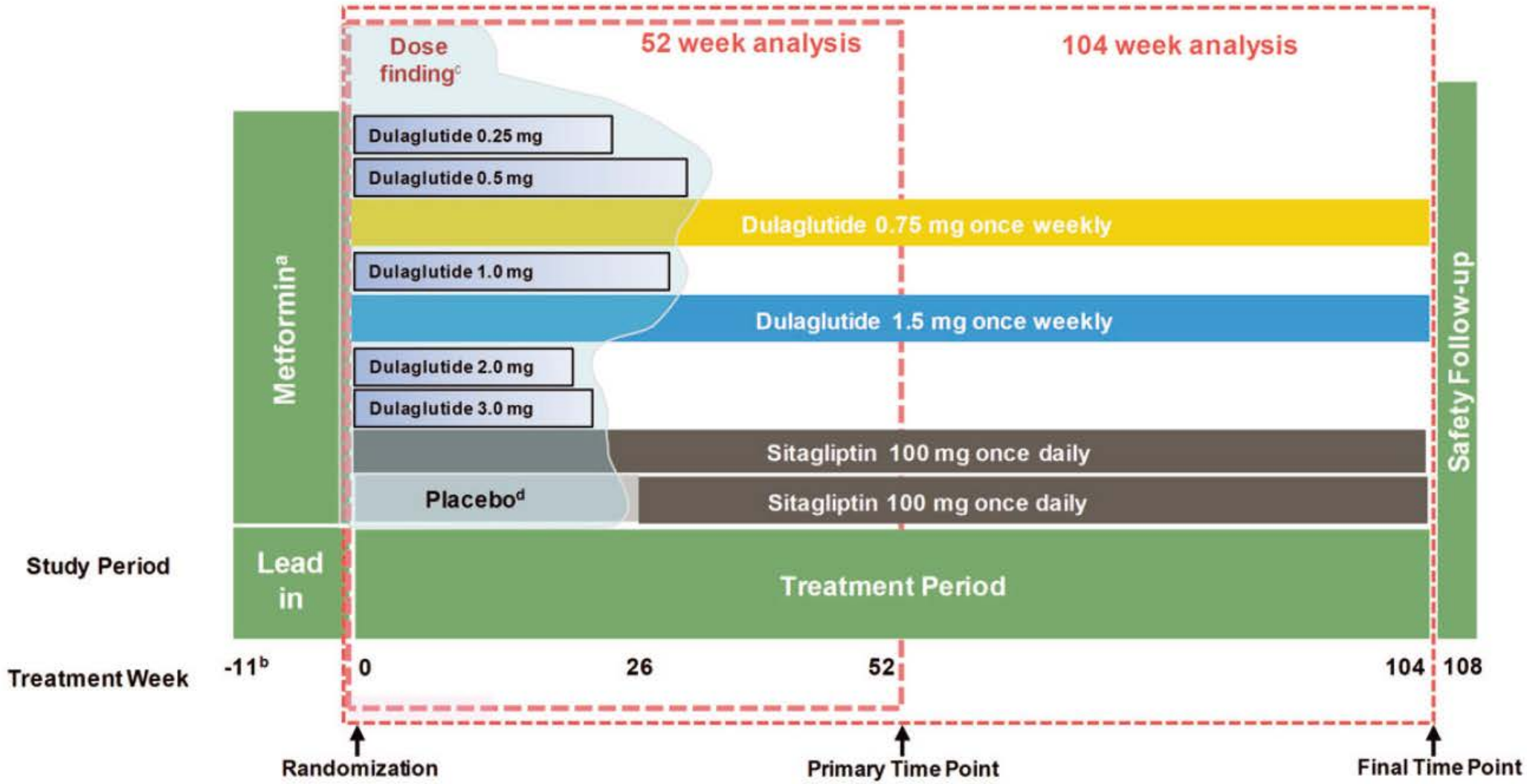


Figure 1. Study design. [a]Metformin concomitant therapy from lead-in through treatment period (≥1500 mg/day). [b]Lead-in period lasted up to 11 weeks. [c]The dose finding period (indicated by the blue area) ended at the decision point (29 April 2009) resulting in different exposures within and across treatment groups. [d]After 26 weeks, patients in the placebo arm transitioned to sitagliptin in a blinded fashion.

Skrivanek Z, et al. Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5). Diabetes Obes Metab. 2014 Aug;16(8):748-56

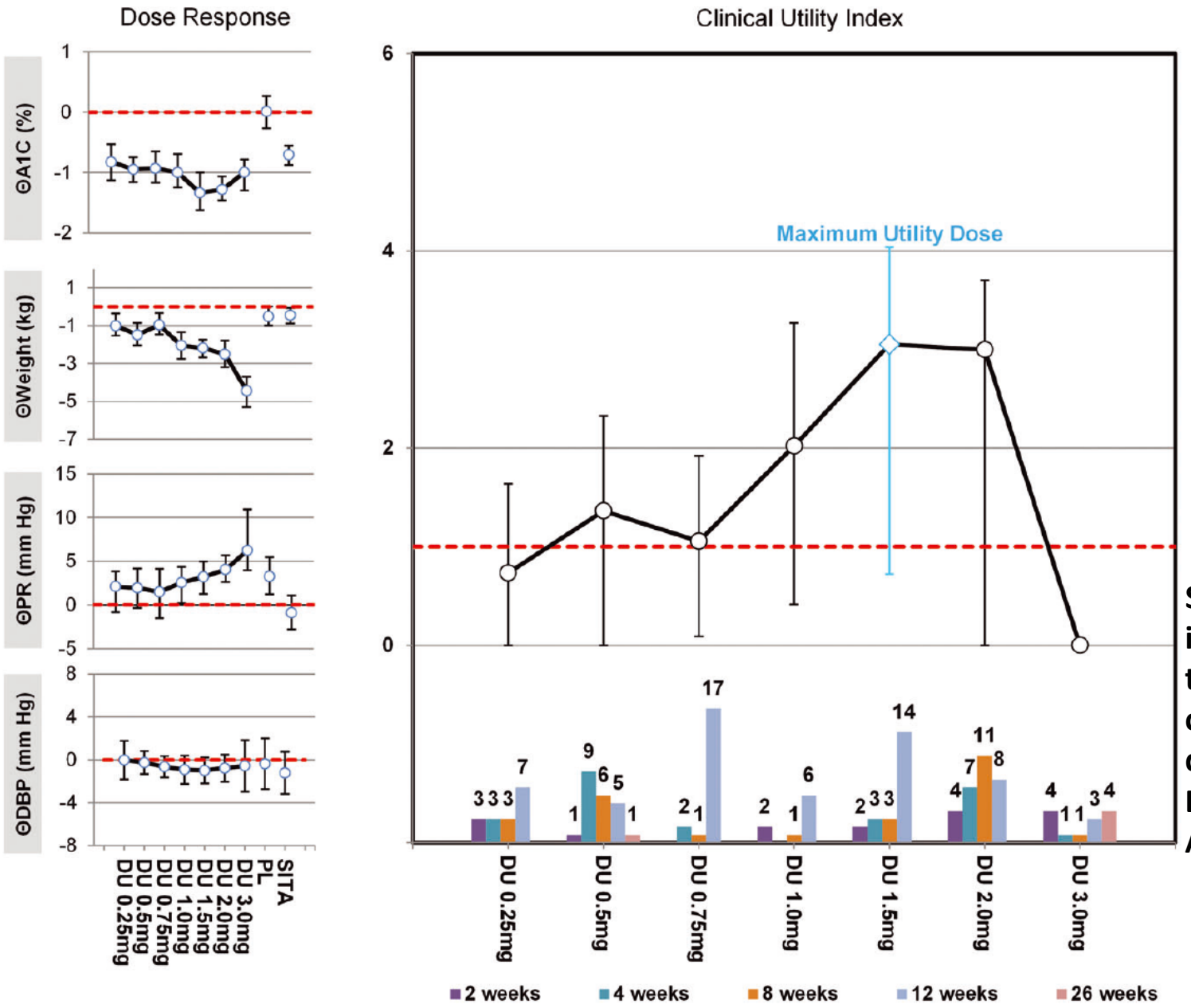


Figure 2. Dose–response model and CUI. CUI and change from baseline in CUI components, posterior means and 95% credible intervals at 6 months (DBP, PR and weight) and 12 months (HbA1c) (data available at decision point, the 10th Interim, 29 April 2009). bpm, beats per minute; CUI, clinical utility index; DBP, diastolic blood pressure; DU, dulaglutide; HbA1c, glycosylated haemoglobin A1C; PK/PD, pharmacokinetic/pharmacodynamics; PL, placebo; PR, pulse rate; SITA, sitagliptin.

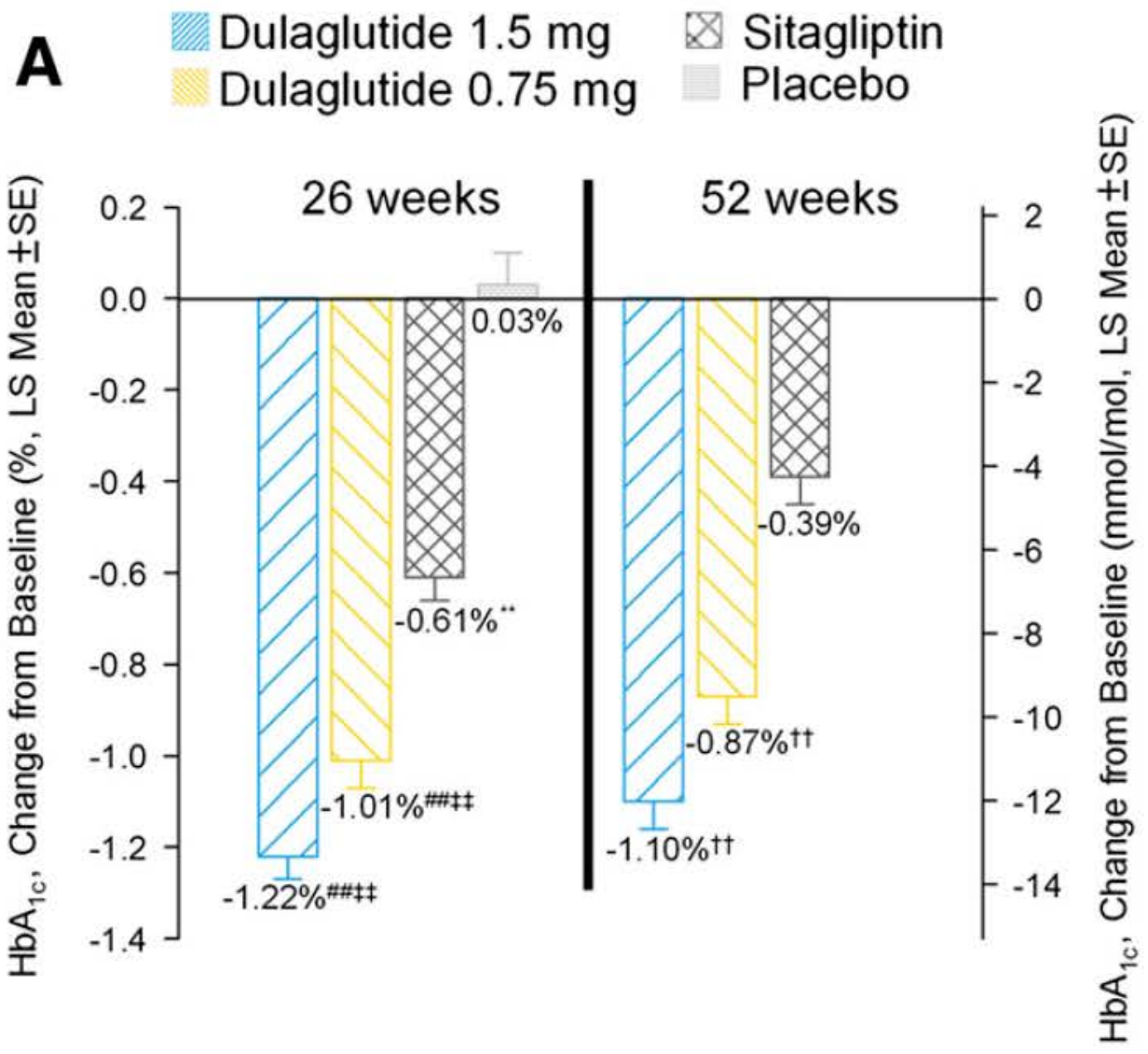
Skrivanek Z, et al. Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5). Diabetes Obes Metab. 2014 Aug;16(8):748-56

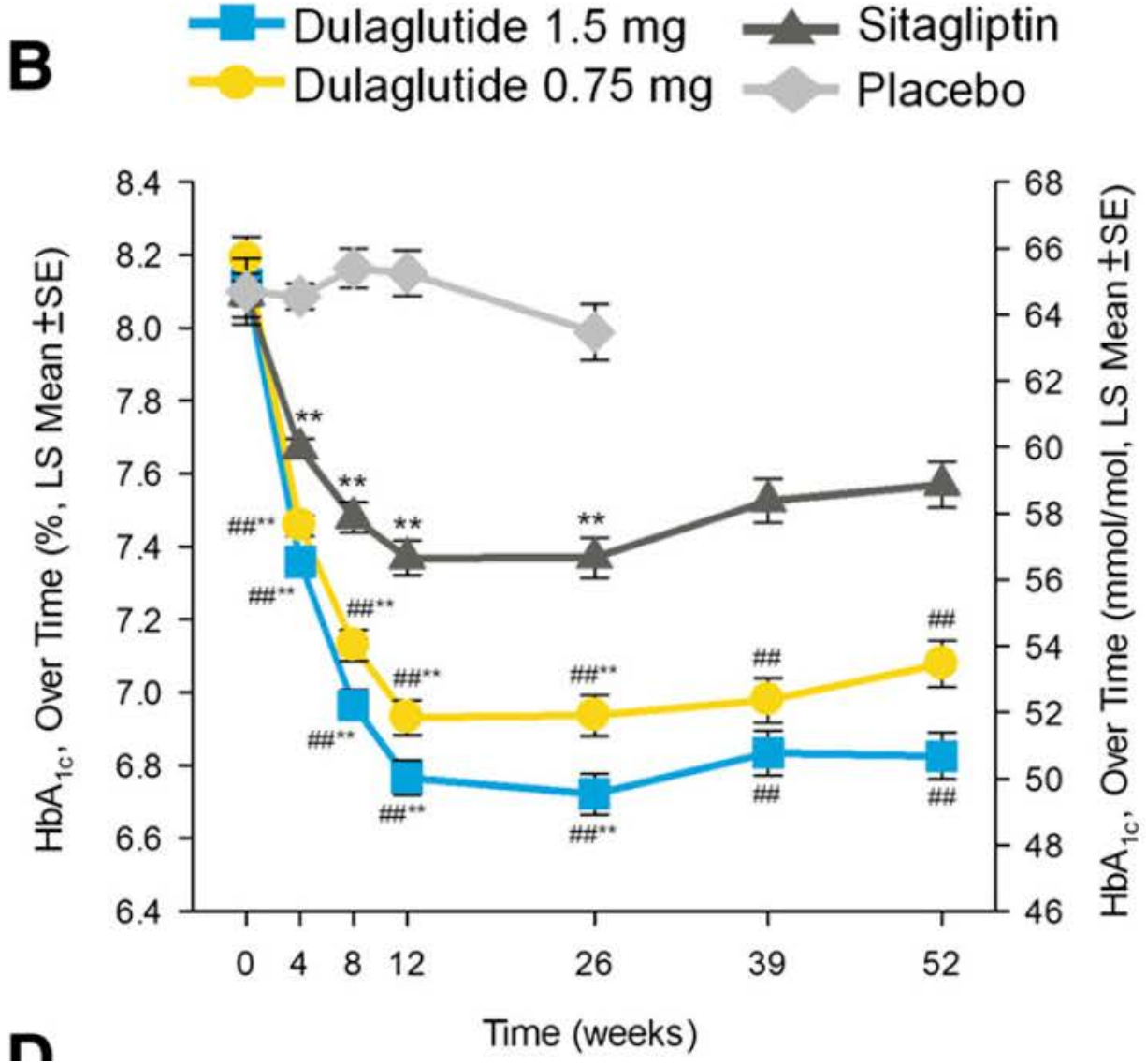
Table 1.
Operational Considerations: Adaptive, Seamless Trial versus Two Separate Studies

	Adaptive, seamless phase 2/3 study	Separate phase 2 and phase 3 studies
Resources	• More upfront planning and cross functional integration	• Traditional planning
Documentation	• Design sufficiently described in protocol • All adaptations had to be prespecified and documented • Additional design documentation needed for clarity: ERB supplement, trial simulation report, DMC charter	• Designs sufficiently described in separate protocols
Communication plans	• Prespecified to manage adaptations and seamless transition	• Additional plans not required
Enrollment rate	• Enrollment rate targeted to optimize performance of adaptive algorithm • Need to monitor and manage enrollment rate	• Enrollment may proceed as quickly as feasible
Seamless design feature	• Initiating regulatory approval processes for new sites at risk (for stage 2) • Uncertainty of timing of these activities • Need to minimize operational bias	• Studies are conducted separately • Potential lag time of 9 to 12 months between studies
Data acquisition and management	• Rapid data entry needed • Frequent data transfers and data validation to ensure quality of data • Rapid data integration, extraction, and reporting required • Need for highly integrated data flow system	• Standard time frames for data acquisition and transfers
Randomization	• Flexible system needed to accommodate adaptive and fixed randomization schemes • Developed jointly with data analyses processes	• Traditional systems for fixed dose designs may suffice
Drug supply and management	• Accelerated formulation needed • Plans needed for managing adaptations • Greater quantity and more dosage strengths needed • Significant material wastage encountered	• Acceleration of formulation not necessary • Less quantity and material wastage
DMC	• Required statistical expertise to monitor adaptive algorithm • Responsible to oversee patient safety • Involved in decision-making processes • Proposed role for limited sponsor involvement • Document and implement restrictive firewalls	• May be utilized for a phase 3 study, depending on the study objectives, to oversee patient safety

Spencer K, et al. Operational challenges and solutions with implementation of an adaptive seamless phase 2/3 study. J Diabetes Sci Technol 2012; 6: 1296–1304

Sponsor's Analysis





Nauck M, et al. Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5), Diabetes Care. 2014 Aug;37(8):2149-58

FDA's Analysis

- **"Combining data from both Stages presents non-trivial statistical issues impacting the ability to strongly control type I error and reliably estimate the treatment effect. Due to these considerations this review considers subject that enrolled during the confirmatory phase. The sponsor's primary analysis combines data from both stages."**

Table 7. Change in HbA1c at Weeks 26, 52 (Trial GBCF, Stage II)

	Dulaglutide			
	0.75 mg	1.5 mg	Placebo	Sitagliptin
Primary Analysis Model: ANCOVA w/LOCF				
Adj. Mean Change (95% CI)				
Week 26	-0.99 (-1.11, -0.88)	-1.18 (-1.29, -1.07)	0.05 (-0.10, 0.20)	-0.58 (-0.70, -0.47)
Week 52	-0.86 (-0.99, -0.73)	-1.07 (-1.19, -0.94)	-	-0.36 (-0.49, -0.23)
Dulaglutide - Placebo (95% CI)				
Week 26	-1.04 (-1.22, -0.86)	-1.23 (-1.41, -1.05)		
p-value (1-sided): SUP	< 0.001	< 0.001		
Dulaglutide - Sitagliptin (95% CI)				
Week 26	-0.41 (-0.56, -0.26)	-0.60 (-0.74, -0.45)		
Week 52	-0.50 (-0.67, -0.33)	-0.71 (-0.87, -0.54)		
p-value (1-sided): NI	< 0.001	< 0.001		
p-value (1-sided): SUP	< 0.001	< 0.001		

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125469Orig1s000StatR.pdf

Summary

- Adaptive designs are attractive from both ethical standpoint and efficiency perspective.
- There is more regulatory acceptance of adaptive designs for early clinical trials.
- Bayesian philosophy has been common in Pharmacometrics.
- Efficiency can be further improved if more mechanistic pharmacometric models are applied.
- Challenges remain for a wide application of Bayesian adaptive trials.

Acknowledgements

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THANK YOU

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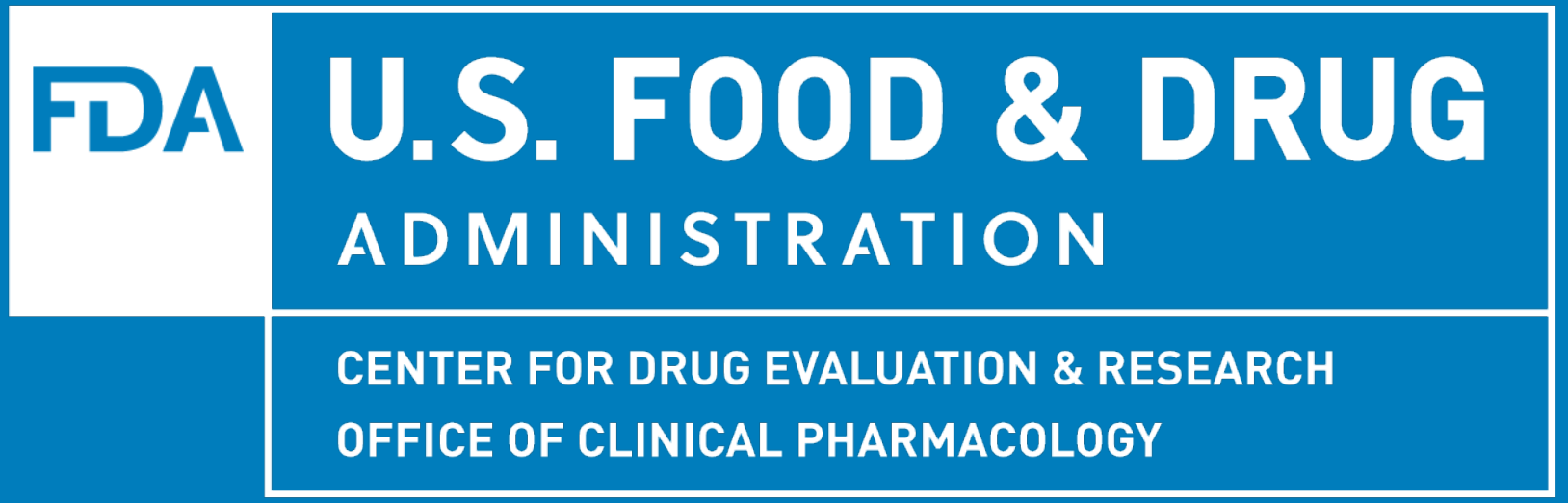
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