original article

Diabetes, Obesity and Metabolism 16: 748–756, 2014.
© 2014 John Wiley & Sons Ltd

ORIGINAL ARTICLE

Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5)

Z. Skrivanek[1], B. L. Gaydos[1], J. Y. Chien[1], M. J. Geiger[2], M. A. Heathman[1], S. Berry[3], J. H. Anderson[4], T. Forst[5], Z. Milicevic[1] & D. Berry[3]

[1] *Lilly Diabetes, Eli Lilly and Company, Indianapolis, IN, USA*
[2] *Cardiovascular & Metabolism Therapeutics, Regeneron Pharmaceuticals Inc, Tarrytown, NY, USA*
[3] *Berry Consultants, Austin, TX, USA*
[4] *Diabetes and Cardiometabolic Medicine, Carmel, IN, USA*
[5] *Profil, Hellersbergstrasse, Neuss, Germany*

Aims: AWARD-5 was an adaptive, seamless, double-blind study comparing dulaglutide, a once-weekly glucagon-like peptide-1 (GLP-1) receptor agonist, with placebo at 26 weeks and sitagliptin up to 104 weeks. The study also included a dose-finding portion whose results are presented here.

Methods: Type 2 diabetes (T2D) patients on metformin were randomized 3 : 1 : 1 to seven dulaglutide doses, sitagliptin (100 mg), or placebo. A Bayesian algorithm was used for randomization and dose selection. Patients were adaptively randomized to dulaglutide doses using available data on the basis of a clinical utility index (CUI) of glycosylated haemoglobin A1c (HbA1c) versus sitagliptin at 52 weeks and weight, pulse rate (PR) and diastolic blood pressure (DBP) versus placebo at 26 weeks. The algorithm randomly assigned patients until two doses were selected.

Results: Dulaglutide 1.5 mg was determined to be the optimal dose. Dulaglutide 0.75 mg met criteria for the second dose. Dulaglutide 1.5 mg showed the greatest Bayesian mean change from baseline (95% credible interval) in HbA1c versus sitagliptin at 52 weeks −0.63 (−0.98 to −0.20)%. Dulaglutide 2.0 mg showed the greatest placebo-adjusted mean change in weight [−1.99 (−2.88 to −1.20) kg] and in PR [0.78 (-2.10 to 3.80) bpm]. Dulaglutide 1.5 mg showed the greatest placebo-adjusted mean change in DBP [−0.62 (−3.40 to 2.30) mmHg].

Conclusions: The Bayesian algorithm allowed for an efficient exploration of a large number of doses and selected dulaglutide doses of 1.5 and 0.75 mg for further investigation in this trial.

Keywords: AWARD-5, Bayesian adaptive, dose finding, dulaglutide dose, GLP-1, GLP-1 receptor agonist, metformin, type 2 diabetes

Date submitted 24 February 2014; date of first decision 12 March 2014; date of final acceptance 18 April 2014

Introduction

Dulaglutide is a long-acting human GLP-1 receptor agonist in development as a once-weekly subcutaneous injection for the treatment of type 2 diabetes (T2D) [1–3]. The molecule consists of two identical, disulphide-linked chains, each containing an N-terminal GLP-1 analogue sequence covalently linked to a modified human immunoglobulin G4 heavy chain by a small peptide linker [1]. Dulaglutide exhibits GLP-1-mediated effects, including glucose-dependent potentiation of insulin secretion, inhibition of glucagon secretion, delay of gastric emptying and weight loss [1–4].

Dose selection for the dulaglutide clinical development programme utilized an adaptive design within the first confirmatory dulaglutide trial (AWARD-5) that enabled exploration of seven doses in a dose-finding portion, and possible selection of up to two doses. The primary and secondary objectives compared the efficacy and safety of selected dulaglutide dose(s) with sitagliptin at 52 and 104 weeks, and with placebo at 26 weeks [5,6]. The results of dose-finding are presented here.

Correspondence to: Zachary Skrivanek, PhD, Eli Lilly Corporate Center, Lilly Diabetes, Indianapolis, IN 46285, USA.
e-mail: skrivanek_zachary@lilly.com

Research Design and Methods

Eligible patients (18–75 years) had T2D (≥6 months) and glycosylated haemoglobin A1c (HbA1c) of >8.0% if on diet and exercise alone, or HbA1c of ≥7.0 and ≤9.5% if on oral antihyperglycaemic medications (OAM) (any OAM monotherapy, or combination of metformin with another OAM) and a BMI between 25 and 40 kg/m^2. The protocol was approved by local ethical review boards, and all patients provided written informed consent before trial-related activity. The study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization guideline on good clinical practices [7].

AWARD-5 was a multicentre, randomized, double-blind, 104-week, parallel-arm trial in T2D patients treated with metformin, and included an initial dose-finding portion (Figure 1). The study design and statistical methodologies were previously published [8–10]. Eligible patients entered a lead-in period (≤11 weeks). Patients were required to be treated with metformin (≥1500 mg/day) for ≥6 weeks prior to randomization; other OAMs were discontinued. After lead-in, patients were randomized to dulaglutide injection (seven doses during dose-finding; only selected dose(s) after dose selection occurred), sitagliptin 100 mg once daily or placebo (injectable and oral), all in combination with metformin.

The objective of the dose-finding portion was to identify a dulaglutide dose with an optimal efficacy and safety profile, and possibly one lower dose to be available in case of an observed, unforeseen safety signal with the optimal dose during subsequent clinical development. For that purpose, a Bayesian adaptive algorithm was used. The algorithm involved adaptive randomization of patients to dulaglutide doses and evaluation of predefined dose decision rules on a biweekly basis. The decisions made by the algorithm were based on the posterior probability distributions available for each analysis. Posterior probability distributions changed with each analysis based on the additional data that had accrued in the interim. Patients were adaptively randomized to 1 of seven once-weekly dulaglutide doses (0.25, 0.50, 0.75, 1.0, 1.5, 2.0 and 3.0 mg), preferentially assigning higher probabilities to doses considered to have a more favourable clinical profile, and randomization to sitagliptin or placebo at 20% each; 3 : 1 : 1 ratio, respectively (Figure 1).

Four efficacy and safety measures were considered important for dose selection based on early phase dulaglutide data: HbA1c, weight, pulse rate (PR) and diastolic blood pressure (DBP) [1]. These measures were used to define criteria for dose selection. The selected dulaglutide dose(s) had to have a mean change of ≤+5 beats per minute (bpm) for PR and ≤+2 mmHg for DBP relative to placebo at 26 weeks. In addition, if a dose was weight neutral versus placebo, it had to show HbA1c reduction ≥1.0% and/or be superior to sitagliptin at 52 weeks. If a dose reduced weight relative to placebo ≥2.5 kg, then non-inferiority to sitagliptin would be acceptable.

A clinical utility index (CUI) was incorporated in the algorithm to facilitate adaptive randomization and dose selection [8,9] based on the same parameters used to define dose-selection criteria described above. Longitudinal models were utilized to estimate HbA1c at 52 weeks and weight, PR and DBP at 26 weeks. The CUI was applied to estimate for HbA1c, weight, DBP and PR. A posterior probability distribution for the CUI and its components were calculated every 2 weeks. The CUI was a multiplicative index with a range of possible values from 0 to 6, with larger values reflecting a favourable clinical profile [9]. Zero values resulted if at least one component reached prespecified thresholds for a clinically unacceptable outcome (i.e. posterior mean increase in DBP ≥2.5 mmHg). Decision rules were based on posterior probability thresholds and predictive probabilities for meeting the primary study objective.

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). After 200 patients were randomized (the minimum sample size required for dose selection), if the MUD met predefined selection criteria (CUI ≥0.6 and predictive probability of non-inferiority versus sitagliptin at 52 weeks for HbA1c change from baseline ≥0.85) at one of the interim assessments, that dose and possibly a lower dose would be selected. The lower dose was the next highest dose with an acceptable CUI ≥0.6 and ≤50% the dose

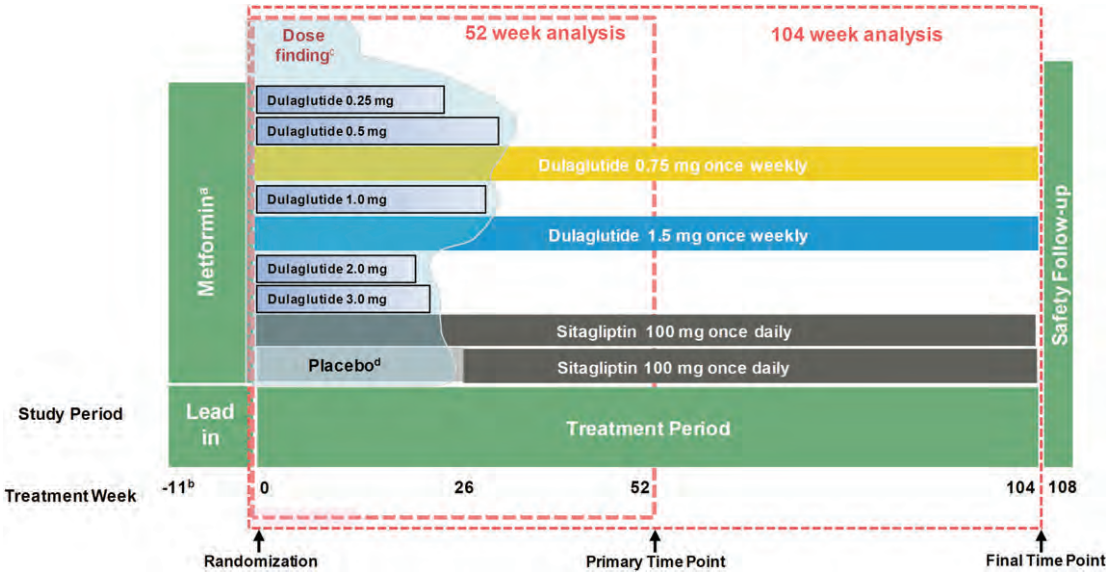

Figure 1. Study design. [a]Metformin concomitant therapy from lead-in through treatment period (≥1500 mg/day). [b]Lead-in period lasted up to 11 weeks. [c]The dose finding period (indicated by the blue area) ended at the decision point (29 April 2009) resulting in different exposures within and across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

MPI EXHIBIT 1113 PAGE 2

strength of the MUD to ensure minimal overlap of dulaglutide exposure. If there was strong evidence that no optimal dose existed (i.e. no therapeutic window), the algorithm would determine the study should be stopped because of 'futility'.

The potential decision point was also adaptive (could have happened any time after 200 patients were randomized and up until 400 patients were randomized) (Figure 1). If data at the decision point supported selection of 1 or 2 doses, patients randomized to those specific doses and the comparator arms would continue the study, whereas patients assigned to non-selected dulaglutide doses would be discontinued. Additional patients would be randomized to selected doses and comparator arms using a fixed-allocation scheme to test the primary objective. The primary objective was to show non-inferiority (margin of 0.25%) of the selected optimal dulaglutide dose to sitagliptin in HbA1c change from baseline at 52 weeks [11]. Patients followed the same visit schedule and testing procedures, irrespective of when they were randomized into the trial

An independent Data Monitoring Committee (DMC) external to Lilly provided oversight of the implementation of the adaptive algorithm and monitored study safety. The DMC fulfilled this role during the dose-finding portion, and continued monitoring after dose selection until an interim database lock at 52 weeks, at which time the study was unblinded to assess the primary objectives. Sites and patients continued to be blinded to the treatment allocation until the completion of the study. The DMC was not allowed to intervene with the design operations. A Lilly Internal Review Committee (IRC), independent of the study team, would meet if the DMC recommended the study to be modified. The role of the IRC was to make the final decision regarding the DMC's recommendation. The external Statistical Analysis Center (SAC) performed all interim data analyses for the DMC, evaluated the decision rules and provided the randomization updates for the adaptive algorithm.

The DMC reviewed additional efficacy measures including fasting serum glucose and fasting plasma insulin; β-cell function and insulin sensitivity indices [updated Homeostasis Model Assessment (HOMA2)]; and lipids. Safety assessments included vital signs, adverse events, laboratory parameters, hypoglycaemic episodes, electrocardiograms (ECGs) and dulaglutide antidrug antibodies. Pancreatic enzyme measurements began approximately 7 months after study initiation, per regulatory guidance for GLP-1 receptor agonists.

Statistical Analysis

Interim analyses included all patients randomized and were based on all available data in the clinical trial database at the time of data transfers. After initiation of the adaptive algorithm, updated randomization probabilities were provided in a biweekly report by the SAC. The report summarized the exposure and the randomization probabilities for the next 2 weeks. Raw data and Bayesian estimates (posterior means, posterior probabilities and posterior predictive probabilities) for the four CUI components, the CUI and Bayesian parameters related to the algorithm were plotted and tabulated. Posterior probability distributions at an interim analysis represent the current knowledge about the parameter of interest. This Bayesian approach is referred to as 'active learning', which updates posterior distributions with data from the interim to help with decision making [9]. Ninety-five percentage credible intervals were calculated by taking the 2.5th and 97.5th percentiles of the corresponding posterior probability distributions. The DMC chair and the lead SAC statistician reviewed these reports and were tasked to convene an unscheduled DMC meeting if an issue was identified with the algorithm or the decision point was triggered.

Additional interim safety reports were generated for DMC meetings. These reports included summary tables of adverse events, serious adverse events, vital signs, ECG parameters, hypoglycaemic events, laboratory parameters and antihypertensive medications.

After final database lock at 104 weeks, data from patients randomized in the dose-finding portion were reassessed for robustness of the dose-finding results (Appendix S1 for methods, Supporting information and Table S2 for results) Statistical analyses were performed using the SAS SYSTEM® version 8.2 or higher and Fortran 77.

Results

Patient Disposition and Exposure

Patients were adaptively randomized to the seven dulaglutide doses during the dose-finding portion (Table S1). A total of 230 patients were enrolled prior to the decision point. Of these, 199 patients had post-randomization data available to contribute to the evaluation of the decision rules. The other 31 patients enrolled shortly before the decision point, and thus, had no available post-randomization data. The number of patients randomized to treatment arms and their baseline characteristics are provided in Table 1. Sponsor decision was the most common reason for early study discontinuation (Figure S1); this included all patients from dulaglutide arms who were discontinued at decision point because their respective doses were not selected.

At decision point (10th biweekly interim analysis), mean exposure in all dulaglutide-treated patients was 11.1 ± 7.5 weeks; placebo- and sitagliptin- treated patients had been exposed to study drug for (mean $\pm$ SD) 9.2 ± 7.2 and 10.7 ± 7.6 weeks, respectively (Table 2).

Dose Selection

The results of the first nine interim analyses were used only for adjustment of the dulaglutide randomization probabilities as specified in the protocol. After the ninth interim, the DMC recommended ceasing randomization to dulaglutide 3.0 mg because of safety concerns (additional data presented below); the IRC endorsed that recommendation. The decision rules were applied for the first time at the 10th interim, after 200 patients had been enrolled. Results of the posterior unadjusted mean changes from baseline and mean changes from baseline adjusted for comparators for the four components of the CUI at this interim are shown in Tables 2 and 3, respectively. Figure 2

MPI EXHIBIT 1113 PAGE 3

Table 1. Baseline characteristics, demographics and disposition of randomized patients.

Variable	Dulaglutide 0.25 mg (n = 24)	Dulaglutide 0.5 mg (n = 25)	Dulaglutide 0.75 mg (n = 21)	Dulaglutide 1.0 mg (n = 10)	Dulaglutide 1.5 mg (n = 25)	Dulaglutide 2.0 mg (n = 30)	Dulaglutide 3.0 mg (n = 15)	Sitagliptin (n = 42)	Placebo (n = 38)
Sex, n (%)									
Men	9 (38)	13 (52)	10 (48)	3 (30)	10 (40)	8 (27)	5 (33)	21 (50)	12 (32)
Women	15 (63)	12 (48)	11 (52)	7 (70)	15 (60)	22 (73)	10 (67)	21 (50)	26 (68)
Age (years)	57 (7)	55 (10)	52 (11)	55 (9)	53 (11)	53(11)	53 (11)	53 (12)	53 (10)
Race, n (%)									
Black	0 (0)	2 (8)	0 (0)	0 (0)	2 (8)	3 (10)	1 (7)	2 (5)	2 (5)
White	12 (50)	9 (36)	13 (62)	4 (40)	10 (40)	13 (43)	7 (47)	20 (48)	15 (40)
East Asian	5 (21)	0 (0)	1 (5)	0 (0)	2 (8)	6 (20)	0 (0)	4 (10)	4 (11)
Hispanic	6 (25)	14 (56)	7 (33)	6 (60)	11 (44)	8 (27)	7 (47)	16 (38)	17 (45)
Others	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BMI (kg/m^2)	31 (4)	33 (5)	33 (5)	34 (4)	32 (5)	31 (5)	31 (5)	32 (4)	32 (4)
Duration of diabetes (years)	7 (4)	7 (4)	7 (5)	7 (5)	9 (7)	7 (5)	7 (6)	9 (5)	7 (6)
HbA1c [%, (mmol/mol)]	7.8 (0.8) [62 (9)]	8.3 (1.3) [67 (14)]	8.2 (1.1) [66 (12)]	7.9 (0.6) [63 (7)]	8.7 (1.5) [72 (16)]	8.4 (1.0) [68 (11)]	8.0 (1.1) [64 (12)]	8.4 (1.1) [68 (12)]	8.1 (1.1) [65 (12)]
SBP (mm Hg)	130 (15)	125 (16)	133 (16)	134 (13)	127 (16)	127 (15)	128 (17)	128 (12)	127 (12)
DBP (mm Hg)	78 (9)	76 (7)	82 (8)	79 (10)	77 (8)	79 (8)	76 (9)	77 (6)	78 (8)

Data are means (SD) or n (%) unless otherwise indicated. BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycosylated haemoglobin A1C; SBP, systolic blood pressure; SD, standard deviation.

provides the Bayesian estimates for the CUI and for each individual component. All results presented are based on data accrued up until the time of dose selection, the decision point.

Posterior mean (95% credible interval) changes from baseline in HbA1c at 52 weeks ranged from 0.82 (−1.13, −0.53)% for dulaglutide 0.25 mg to −1.33 (−1.62, −1.00)% for dulaglutide 1.5 mg (Table 2 and Figure 2). The posterior mean change for sitagliptin was −0.70 (−0.87, −0.56)%. Dulaglutide 1.5 mg showed the greatest posterior mean change compared to sitagliptin at 52 weeks −0.63 (−0.98, −0.20)% (Table 3).

Posterior mean (95% credible interval) changes from baseline in weight at 26 weeks ranged from −0.96 (−1.47, −0.33) kg for dulaglutide 0.75 mg to −4.45 (−5.30, −3.70) kg for dulaglutide 3.0 mg (Table 2 and Figure 2). The posterior mean change from baseline for placebo was −0.52 (−0.99, 0.01) kg (Table 2 and Figure 2). Across the range of dulaglutide doses (excluding discontinued 3.0 mg dose), dulaglutide 2.0 mg showed the greatest posterior mean change in weight compared to placebo at 26 weeks [−1.99 (−2.88, −1.20) kg] (Table 3).

For PR, the posterior mean (95% credible interval) changes from baseline to 26 weeks for dulaglutide doses ranged from 1.47 (−1.50, 4.13) bpm for dulaglutide 0.5 mg to 6.26 (3.95, 10.95) bpm for dulaglutide 3.0 mg (Table 2 and Figure 2). The posterior mean change for placebo was 3.27 (1.23, 5.47) bpm (Table 2 and Figure 2). Across the range of dulaglutide doses (excluding discontinued 3.0 mg dose), dulaglutide 2.0 mg showed the greatest posterior mean change in PR compared to placebo at 26 weeks 0.78 (−2.10, 3.80) bpm (Table 3).

The posterior mean (95% credible interval) changes from baseline to 26 weeks in DBP for dulaglutide doses ranged from −0.02 (−1.74, 1.78) mmHg for dulaglutide 0.25 mg to −0.99 (−2.22, 0.20) mmHg for dulaglutide 1.5 mg (Table 2 and Figure 2). The posterior mean change for placebo was −0.37 (−2.88, 1.99) mmHg (Table 2 and Figure 2). Across the range of dulaglutide doses (excluding discontinued 3.0 mg dose), dulaglutide 1.5 mg showed the greatest posterior mean change in DBP compared to placebo at 26 weeks [−0.62 (−3.40, 2.30) mmHg] (Table 3).

Dulaglutide 1.5 mg was determined to be the MUD [3.1 (0.7, 4.0)] at the 10th interim assessment (Figure 2). The posterior probability that the CUI for this dose of ≥0.6 sample size was 0.982 and the posterior predictive probability that dulaglutide 1.5 mg would show non-inferiority to sitagliptin at 52 weeks, based on a total sample size of 263 in each arm, was >0.99 (Figure 2). On the basis of these results, the algorithm determined the decision point had been reached, and selected two doses: dulaglutide 1.5 mg as the optimal dose and dulaglutide 0.75 mg as the second, lower dose (CUI = 1.054). It also determined the total sample size for each treatment arm in the trial based on the data from the dose-finding portion.

The population PK/PD results supported the Bayesian-based results. A summary of the range of expected responses predicted by population PK/PD exposure-response models is provided in the Table S2 (Appendix S1 for details in method). These model-predicted responses and CUI values supported the Bayesian-based results shown in Figure 2. Dulaglutide 1.5 mg was associated with a similar effect on HbA1c (mean; 90% confidence interval) −1.27 (−1.72 to −0.84)% and weight −3.49 (−5.32 to 2.07) kg to that estimated during the dose-finding portion. Dulaglutide 1.5 mg also met the prespecified requirements of change in PR ≤5 bpm. No concentration-response relationship was identified for DBP, hence, there are no results presented for this CUI component.

Data for all nine treatment arms from the final database up to the decision point were summarized for each component of the CUI. These reports (data not shown) were consistent with the results of assessments based on the datasets used for adaptation by the SAC.

MPI EXHIBIT 1113 PAGE 4

Table 2. Bayesian posterior mean (95% credible interval) changes from baseline and exposure.

Dose (mg)	HbA1c (%) 52 weeks	Weight (kg) 26 weeks	Pulse rate (bpm) 26 weeks	DBP (mm Hg) 26 weeks	Mean utility	Exposure (weeks) mean ± SD
Dulaglutide 0.25	−0.82 (−1.13; −0.53) n = 13	−1.01 (−1.53; −0.35) n = 16	2.12 (−0.83; 3.84) n = 16	−0.02 (−1.74; 1.78) n = 16	0.733 (0, 1.639)	8.9 ± 8.5
Dulaglutide 0.5	−0.95 (−1.16; −0.75) n = 16	−1.48 (−2.04; −0.86) n = 22	1.95 (−0.35; 4.15) n = 22	−0.26 (−1.67; 0.81) n = 22	1.362 (0, 2.326)	9.7 ± 7.1
Dulaglutide 0.75	−0.93 (−1.17; −0.65) n = 20	−0.96 (−1.47; −0.33) n = 20	1.47 (−1.50; 4.13) n = 20	−0.65 (−1.92; 0.34) n = 20	1.054 (0.090, 1.923)	15.7 ± 6.2
Dulaglutide 1.0	−1.00 (−1.25; −0.69) n = 8	−2.05 (−2.75; −1.34) n = 9	2.56 (0.19; 4.34) n = 9	−0.92 (−2.36; 0.38) n = 9	2.021 (0.415, 3.267)	13.0 ± 8.8
Dulaglutide 1.5	−1.33 (−1.62; −1.00) n = 18	−2.18 (−2.68; −1.74) n = 22	3.2 (1.25; 4.99) n = 22	−0.99 (−2.22; 0.20) n = 22	3.052 (0.721, 4.037)	12.5 ± 7.4
Dulaglutide 2.0	−1.28 (−1.46; −1.07) n = 24	−2.50 (−3.20; −1.78) n = 29	4.05 (2.63; 5.70) n = 29	−0.78 (−2.05; 0.47) n = 29	2.996 (0, 3.702)	10.0 ± 5.2
Dulaglutide 3.0	−1.00 (−1.30; −0.78) n = 10	−4.45 (−5.30; −3.70) n = 13	6.26 (3.95; 10.95) n = 13	−0.57 (−2.70; 1.85) n = 13	Not applicable	9.2 ± .8.8
Sitaglitpin	−0.70 (−0.87; −0.56) n = 25	−0.45 (−0.89; 0.06) n = 35	−0.90 (−2.80; 1.09) n = 35	−1.22 (−3.52; 0.75) n = 35	Not applicable	10.7 ± 7.6
Placebo	0.01 (−0.27; 0.27) n = 28	−0.52 (−0.99; 0.01) n = 33	3.27 1.23; 5.47) n = 33	−0.37 (−2.88; 1.99) n = 33	Not applicable	9.2 ± 7.2

Statistics presented are posterior means and 95% credible intervals based on data available at the decision point (10th Interim, 29 April 2009). bpm, beats per minute; DBP, diastolic blood pressure; HbA1c, glycosylated haemoglobin A1c; SD, standard deviation.

Safety

The most common adverse events reported during dose-finding were gastrointestinal (including nausea, diarrhoea and vomiting) and urinary tract infection (Table S3). Nausea and vomiting were more common with dulaglutide than sitagliptin and placebo. The highest incidence was observed in patients with doses ≥1.0 mg. There were a total of three serious adverse events (SAEs) (dulaglutide 0.5 mg: pneumonia [1]; dulaglutide 3.0 mg: gastroenteritis [1] and placebo: cervical dysplasia [1]). Approximately 1 year after study discontinuation, a patient exposed to dulaglutide 2.0 mg for 6 months was diagnosed with an SAE of medullary thyroid carcinoma (MTC). The patient had increased calcitonin levels before randomization [91.5 pg/ml (reference range 0–11.5 pg/ml), evaluated retrospectively] which decreased upon exposure to dulaglutide. At the time of dulaglutide discontinuation and 3 months thereafter, the patient's calcitonin was 61.7 and 82.8 pg/ml, respectively. Subsequently, this patient was also found to be positive for the *RET* proto-oncogene mutation, indicating a preexisting neoplasm in an individual with high risk of MTC. At the time of this patient's randomization, there were no exclusionary criteria for patients at increased risk of C-cell neoplasm. Four patients each in the dulaglutide 2.0 mg, dulaglutide 3.0 mg, and placebo arms, and 1 each in the dulaglutide 0.25 mg and dulaglutide 1.0 mg arms, discontinued the study because of adverse events. Nausea was the most commonly reported adverse event that led to discontinuation with dulaglutide (2.0 mg: one patient; 3.0 mg: three patients). In the placebo group, hyperglycaemia was the most common adverse event resulting in discontinuation (two patients).

The proportion of patients with post-baseline lipase levels greater than ×3 upper limit of normal (ULN) was 2.5% (dulaglutide 3.0 mg one patient; dulaglutide 2.0 mg two patients; sitagliptin one patient). Increase in lipase above ULN was the most common treatment-emergent abnormal laboratory finding and ranged from 13% for placebo to 46% for dulaglutide 2.0 mg. Similar increases in pancreatic amylase were reported, but were lower in frequency. There were no events of pancreatitis reported during dose-finding.

Dulaglutide 3.0 mg was discontinued because of increase in PR (posterior mean for PR >5 bpm) and higher incidence of gastrointestinal adverse events (nausea and vomiting) with/without higher increases in pancreatic enzymes compared to lower doses.

Discussion

AWARD-5 was the first Phase 3 trial of dulaglutide. The first portion of the trial served as the dose finding and dose selection trial for the dulaglutide development programme. An algorithm was employed to adaptively randomize patients to

MPI EXHIBIT 1113 PAGE 5

Table 3. Bayesian posterior adjusted mean (95% credible interval) changes from baseline.

Dose (mg)	HbA1c (%) 52-week sitagliptin-adjusted	Weight (kg) 26-week placebo-adjusted	Pulse rate (bpm) 26-week placebo-adjusted	DBP (mm Hg) 26-week placebo-adjusted	Mean utility
Dulaglutide 0.25	−0.12 (−0.38; 0.20) n = 13	−0.49 (−1.36; 0.44) n = 16	−1.16 (−4.40; 1.90) n = 16	0.35 (−2.60; 3.60) n = 16	0.733 (0, 1.639)
Dulaglutide 0.5	−0.24 (−0.44; 0.02) n = 16	−0.97 (−1.80; −0.12) n = 22	−1.32 (−4.30; 1.80) n = 22	0.11 (−2.40; 3.20) n = 22	1.362 (0, 2.326)
Dulaglutide 0.75	−0.23 (−0.44; 0.08) n = 20	−0.44 (−1.16; 0.44) n = 20	−1.80 (−5.50; 2.10) n = 20	−0.27 (−3.00; 2.50) n = 20	1.054 (0.090, 1.923)
Dulaglutide 1.0	−0.30 (−0.58; 0.08) n = 8	−1.53 (−2.44; −0.60) n = 9	−0.71 (−4.00; 2.50) n = 9	−0.55 (−3.90; 2.20) n = 9	2.021 (0.414, 3.267)
Dulaglutide 1.5	−0.63 (−0.98; −0.20) n = 18	−1.67 (−2.48; −0.92) n = 22	−0.07 (−3.20; 2.70) n = 22	−0.62 (−3.40; 2.30) n = 22	3.052 (0.721, 4.037)
Dulaglutide 2.0	−0.58 (−0.76; −0.32) n = 24	−1.99 (−2.88; −1.20) n = 29	0.78 (−2.10; 3.80) n = 29	−0.41 (−2.60; 3.20) n = 29	2.996 (0, 3.702)
Dulaglutide 3.0	−0.29 (−0.62; −0.02) n = 10	−3.93 (−4.84; −2.88) n = 13	2.98 (−0.60; 8.70) n = 13	−0.19 (−2.70; 2.80) n = 13	Not applicable

Statistics presented are model predicted means and 95% credible intervals based data available at the decision point. bpm, beats per minute; DBP, diastolic blood pressure; HbA1c, glycosylated haemoglobin A1c.

a range of seven dulaglutide doses and to select up to two doses. This design enabled simultaneous assessment of efficacy and safety measures deemed relevant for dose selection based on the results of the completed clinical pharmacology studies, optimized patient allocation using data accumulated during the dose-finding portion and selected the optimal dose when enough data to reach a decision were available. Dulaglutide 1.5 mg was selected as the optimal dose and dulaglutide 0.75 mg was selected as the lower dose for further assessment.

The data met the protocol prespecified conditions for dose selection and the assignment algorithm dropped all but two active doses, dulaglutide 1.5 and 0.75 mg, at the 10th interim analysis. Dulaglutide 1.5 mg had the highest posterior probability of being the MUD. Assessment of the effects of dulaglutide 1.5 mg on the posterior probability distributions for the four components of the CUI showed that this dose had robust glucose and weight lowering effects, and was associated with an increase in PR that was smaller than the effect of the adjacent 2.0 mg dose. These observations explain the selection of the 1.5 mg dose. The 0.75 mg dose met the prespecified criteria for a lower dulaglutide dose. The selection of the dulaglutide 1.5 and 0.75 mg doses were also supported by PK/PD model-based analyses and the results of the efficacy and safety assessments up to 104 weeks [5,6,12–16].

The dose responses for PR and weight are different than for HbA1c. It appears, based on this study (Table 2) and previous studies [1], that the dose-response attenuates around 1.5 mg for HbA1c but continues for weight and PR. This closely linked dose effect for weight loss is in line with expectations for the GLP-1 receptor agonist class and may have significant value in combination with other antidiabetes therapies that cause weight gain (e.g. insulin).

Although dulaglutide was commonly associated with GI effects in earlier Phase 1 studies, that effect was not considered to be dose limiting in the dose range included in the AWARD-5 study. Phase 1 data indicated that PR and DBP would be dose limiting before GI would become a factor in dose selection. Because there was no indication of potential dose–response effect for SBP, PR and DBP were included in the CUI. In this study we did not observe any dose response with DBP, but PR was indeed dose limiting. There were no DMC concerns related to GI issues with the selected doses.

After the ninth interim data assessment, the DMC recommended discontinuing the dulaglutide 3.0 mg dose because of increases in PR, higher incidence of GI adverse events, and higher incidence in pancreatic enzyme values above ULN. These changes were not unexpected based on the known dose-response effects of the GLP-1 receptor agonist class, and observations from completed dulaglutide trials [1,12,17,18]. Although the changes in pancreatic enzymes have not been completely understood, recent reports have showed an increased incidence of asymptomatic increases above upper limit of the normal range in lipase and amylase in patients with T2D [19–23]. The incidence increases further with exposure to GLP-1 receptor agonists; these asymptomatic findings have not been associated with any adverse outcome in clinical trials [24,25].

The Bayesian adaptive approach used in AWARD-5 has not been used often in drug development, although it offers substantial benefits in terms of accuracy and efficiency in

MPI EXHIBIT 1113 PAGE 6

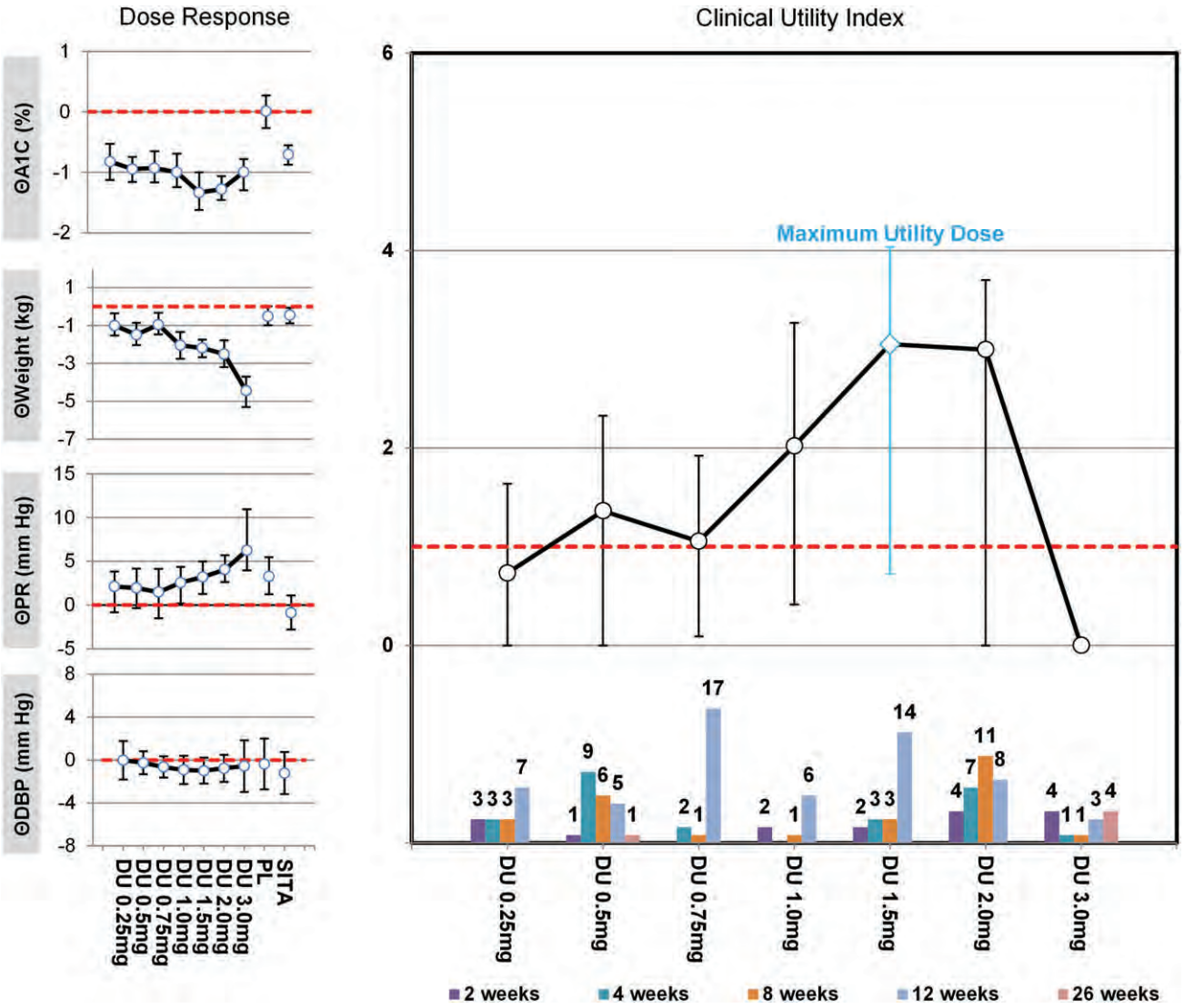

Figure 2. Dose–response model and CUI. CUI and change from baseline in CUI components, posterior means and 95% credible intervals at 6 months (DBP, PR and weight) and 12 months (HbA1c) (data available at decision point, the 10th Interim, 29 April 2009). bpm, beats per minute; CUI, clinical utility index;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

comparison to a fixed design [26,27]. Several design aspects [use of prior information (information gained from Phase 1 studies, the mechanism of action and general knowledge about the class), adaptive randomization and dose selection] were utilized to increase the efficiency and quality of dose-finding. First, the Bayesian approach explicitly used prior information to inform the dose response and the longitudinal profiles of the treatment arms. This decreased the uncertainty of the CUI, allowing for earlier adaptations and decision making. Second, the adaptive randomization enabled exploration of more dulaglutide doses than would be possible with a traditional fixed-allocation strategy, given total sample size constraints. This was achieved by allowing data accumulating during the trial to drive randomization probabilities, in effect, shifting patients away from doses with a less favourable clinical profile to doses more probably to meet target clinical profiles (Figure 2). Finally, the adaptive algorithm selected doses when it determined adequate safety and efficacy information was collected; whereas a fixed design would stop after a predetermined study length irrespective of whether there was sufficient information to make a decision. The efficiency of the utilized design is showed by the relatively small sample size (230 patients) and short exposures (median exposure: 4–16 weeks) needed to accumulate enough data to select doses. This sample size and exposure duration are similar to trials with traditional designs, despite the greater number of doses of investigational drug included in this trial [28,29].

There are limitations to this study. It is possible that factors other than those included in the CUI could have been important for dose selection. To mitigate this risk, the study included additional safety assessments and regular reviews by the DMC; and for final confirmation, larger Phase 3 clinical trials have

MPI EXHIBIT 1113 PAGE 7

been subsequently completed. Another possible concern is the potential interaction between metformin and dulaglutide that may affect the dulaglutide dose-response curve. This issue was addressed in a separate monotherapy dose-response study which showed similar results to those described here [11]. The completed Phase 2 studies, as well as data from larger Phase 3 studies that include different patient populations with respect to prestudy therapy and active comparators, provide further support for the dulaglutide dose selection in AWARD-5 [5,6,12–16].

In conclusion, an adaptive design was utilized within the first dulaglutide Phase 3 trial, AWARD-5, to select the optimal once-weekly dulaglutide 1.5 mg dose and 1 lower dose (0.75 mg) for further clinical development. This novel approach allowed assessment of multiple doses with a relatively small sample size and limited exposure. The robustness of the results is supported by consistency across multiple sets of analyses provided during and after completion of the dose-finding portion of AWARD-5.

Acknowledgements

The authors acknowledge and thank the AWARD-5 team and their staff for conducting this study; and Oralee Johnson Varnado, PhD for writing assistance. This work is sponsored by Eli Lilly and Company. Additional details of this study, entitled "A Study of LY2189265 Compared to Sitagliptin in Patients With Type 2 Diabetes Mellitus on Metformin," can be found at http://clinicaltrials.gov as NCT00734474.

Conflict of Interest

D. B., M. G., S. B., Z. M., Z. S., contributed to the design, conduct, analysis and manuscript writing. B. G., J. A., J. C., J. H. and T. F. contributed to the design, conduct, and data analysis and made intellectual contributions to the manuscript writing. D. B. and S. B. are consultants to Eli Lilly and Company through contracts between Eli Lilly and Company and Berry Consultants, LLC. T. F. worked as a consultant to Eli Lilly and Company. J. A. owns stock or stock options for Eli Lilly and Company. M. G., a former Lilly employee, is now at Regeneron Pharmaceuticals. B. G., J. C., M. H., Z. S., and Z. M. are full-time employees of and own stock or stock options for Eli Lilly and Company. Donald Berry and Scott Berry are consultants to Eli Lilly and Company through contracts between Eli Lilly and Company and Berry Consultants, LLC. TF worked as a consultant for Eli Lilly and company. JA owns stock or stock options for Eli Lilly and Company. MG, a former Lilly employee, is now at Regeneron Pharmaceuticals. B. G., J. C., M. H., Z. S. and Z. M. are full-time employees of and own stock or stock options for Eli Lilly and Company.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Pharmacokinetic/pharmacodynamics (PK/PD) sample collection and methods for PK/PD model-based responses for glycosylated haemoglobin A1c (HbA1c), fasting serum glucose, weight and sitting pulse rate (PR) for dose assessment.

Figure S1. Patient disposition.

Table S1. Randomization probabilities.

Table S2. Pharmacokinetic/pharmacodynamics (PK/PD) model-based responses for glycosylated haemoglobin A1c (HbA1c), fasting serum glucose, weight and sitting pulse rate (PR) for dose assessment.

Table S3. Incidence of the most common side effects for dulaglutide post-baseline to decision point.

References

1. Barrington P, Chien JY, Showalter HD et al. A 5-week study of the pharmacokinetics and pharmacodynamics of LY2189265, a novel, long-acting glucagon-like peptide-1 analogue, in patients with type 2 diabetes. Diabetes Obes Metab 2011; **13**: 426–433.
2. Barrington P, Chien JY, Tibaldi F, Showalter HD, Schneck K, Ellis B. LY2189265, a long-acting glucagon-like peptide-1 analogue, showed a dose-dependent effect on insulin secretion in healthy subjects. Diabetes Obes Metab 2011; **13**: 434–438.
3. Glaesner W, Vick AM, Millican R et al. Engineering and characterization of the long-acting glucagon-like peptide-1 analogue LY2189265, an Fc fusion protein. Diabetes Metab Res Rev 2010; **26**: 287–296.
4. Umpierrez G, Povedano ST, Manghi FP, Shurzinske L, Pechtner V. Efficacy and safety of dulaglutide monotherapy vs metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). Diabetes Care 2014; in press.
5. Nauck M, Weinstock R, Umpierrez G et al. Efficacy and safety of dulaglutide vs. sitagliptin after 52 weeks in type 2 diabetes (AWARD-5). Diabetes 2013; **62**(Suppl 1): A17.
6. Weinstock R, Umpierrez G, Guerci B et al. Safety and efficacy of dulaglutide vs. sitagliptin after 104 weeks in type 2 diabetes (AWARD-5). Diabetes 2013; **62**(Suppl 1): A258.
7. WMA. World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. JAMA 1997; **277**: 925–926.
8. 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.
9. 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.
10. 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.
11. 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.
12. Grunberger G, Chang A, Garcia Soria G, Botros FT, Bsharat R, Milicevic Z. Monotherapy with the once-weekly GLP-1 analogue dulaglutide for 12 weeks in patients with Type 2 diabetes: dose-dependent effects on glycaemic control in a randomized, double-blind, placebo-controlled study. Diabet Med 2012; **29**: 1260–1267.
13. Umpierrez G, Manghi F, Perez M, Tofé PS, Shurzinske L, Pechtner V. Efficacy and safety of dulaglutide vs. metformin in type 2 diabetes (AWARD-3). Diabetes 2013; **62**(Suppl 1): A17.

MPI EXHIBIT 1113 PAGE 8

14. Wysham C, Blevins T, Arakaki R et al. Efficacy and safety of dulaglutide versus placebo and exenatide in type 2 diabetes (AWARD-1). Diabetes 2013; **62**(Suppl 1): A16.
15. Umpierrez G, Blevins T, Rosenstock J, Cheng C, Anderson JH, Bastyr E. The effects of LY2189265, a long-acting glucagon-like peptide-1 analog, in a randomized, placebo-controlled, double-blind study of overweight/obese patients with type 2 diabetes: the EGO study. Diabetes Obes Metab 2011; **13**: 418–425.
16. Ferdinand K, Calhoun D, Lonn E et al. Long-term effects of dulaglutide, a novel GLP-1 agonist, on ambulatory blood pressure and heart rate in patients with type 2 diabetes. J Clin Hypertens 2012; **14**: 488.
17. Pratley RE, Nauck M, Bailey T et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet 2010; **375**: 1447–1456.
18. Bergenstal RM, Wysham C, Macconell L et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet 2010; **376**: 431–439.
19. Blevins T, Pullman J, Malloy J et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. J Clin Endocrinol Metab 2011; **96**: 1301–1310.
20. Buse JB, Nauck M, Forst T et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet 2013; **381**: 117–124.
21. Diamant M, Van Gaal L, Stranks S et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet 2010; **375**: 2234–2243.
22. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 2012; **8**: 728–742.
23. Malloy J, Gurney K, Shan K, Yan P, Chen S. Increased variability and abnormalities in pancreatic enzyme concentrations in otherwise asymptomatic subjects with type 2 diabetes. Diabetes Metab Syndr Obes 2012; **5**: 419–424.
24. Steinberg WDJ, Wadden T, Jensen C, Svendsen C, Rosenstock J (eds). Longitudinal Monitoring of Lipase and Amylase in Adults With Type 2 Diabetes and Obesity: Evidence From Two Phase 3 Randomized Clinical TrialsWith the Once-Daily GLP-1 Analog Liraglutide. Miami, FL: American Gastroenterological Association; 2013, 2012.
25. Lando HM, Alattar M, Dua AP. Elevated amylase and lipase levels in patients using glucagonlike peptide-1 receptor agonists or dipeptidyl-peptidase-4 inhibitors in the outpatient setting. Endocr Pract 2012; **18**: 472–477.
26. Berry D. Bayesian clinical trials. Nat Rev Drug Discov 2006; **5**: 27–36.
27. Berry S, Carlin B, Lee J, Mueller P. Bayesian Adaptive Methods for Clinical Trials, Vol. **38**. New York: Chapman & Hall/CRC Biostatistics Series, 2010.
28. Moretto TJ, Milton DR, Ridge TD et al. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naive patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther 2008; **30**: 1448–1460.
29. Vilsboll T, Brock B, Perrild H et al. Liraglutide, a once-daily human GLP-1 analogue, improves pancreatic B-cell function and arginine-stimulated insulin secretion during hyperglycaemia in patients with Type 2 diabetes mellitus. Diabet Med 2008; **25**: 152–156.

MPI EXHIBIT 1113 PAGE 9