CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125469Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Jean-Marc Guettier, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	BLA 125469
Applicant Name	Eli Lilly and Company
Date of Submission	September 18, 2013
PDUFA Goal Date	September 18, 2014
Proprietary Name / **Established (USAN) Name**	Trulicity/dulaglutide
Dosage Forms / Strength **/Presentation**	Injection, for subcutaneous use once weekly/0.75 mg and 1.5 mg/single-dose pen or single-dose syringe
Proposed Indication(s)	1. As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Suchitra Balakrishnan, MD PhD
Statistical Review	Bradley McEvoy, PhD
Pharmacology Toxicology Review	Timothy Hummer, PhD
CMC Review/OBP Review	Joel Welch, PhD
Microbiology Review	Bo Chi, PhD and Colleen Thomas, PhD
Clinical Pharmacology Review	Sang Chung, PhD
DDMAC	Tara Turner
DSI	Cynthia Kleppinger, MD
CDTL Review	Bill Chong, MD
OSE/DMEPA	Sara Vee, PharmD
OSE/DDRE	Debra Ryan, PharmD
OSE/DRISK	Naomi Redd, PharmD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

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1. Introduction

On September 18, 2013 Eli Lilly and Company submitted a Biologics License Application (BLA) for Trulicity under section 351 of the Public Health Service Act. The applicant is seeking to indicate Trulicity as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Trulicity is a solution for injection containing either 0.75 or 1.5 mg of dulaglutide [i.e., a glucagon-like peptide 1 (GLP-1) receptor agonist]. Trulicity is to be administered by subcutaneous injection at once weekly intervals. Once approved, Trulicity will be the fifth GLP-1 agonist indicated for use in the management of patients with type 2 diabetes mellitus in the United States.

This document serves as the division director's memorandum for the application.

2. Background

The drug substance in Trulicity is dulaglutide. In this memorandum, I will use Trulicity and dulaglutide interchangeably. Dulaglutide is a homodimer that consists of two identical polypeptide chains linked to each other by a disulfide bond. The polypeptide chain is a fusion protein that consists of a glucagon-like peptide 1 (GLP-1) variant, a linker, and the Fc portion of a human IgG4 variant antibody. The GLP-1 analog portion of dulaglutide is (b) (4) homologous to native human GLP-1 (7-37) (b) (4)

(b) (4)

Dulaglutide was demonstrated to bind and activate the GLP-1 receptor. The biological effects of endogenous GLP-1 on glucose homeostasis include augmentation of glucose stimulated insulin secretion, inhibition of glucagon release, and delay of gastric emptying. These effects in concert are believed to contribute to the glucose lowering effect of exogenously administered GLP-1 agonists in general and dulaglutide specifically.

Potential and labelled risks of currently available long-acting GLP-1 therapies include: The theoretical risk of thyroid C-cell tumors including medullary thyroid carcinoma, the risk of acute pancreatitis, the risk of worsening renal function precipitated by dehydration, the risk of hypoglycemia when used with drugs known to cause hypoglycemia (i.e., sulfonylurea or insulin), and the risks of hypersensitivity and injection site reactions. Common adverse reactions reported for this class include gastrointestinal tolerability issues and increased heart rate. Risks for currently approved products are managed through product labeling and Risk Evaluation and Mitigation Strategies (REMS) to ensure that in patients prescribed long acting GLP-1 therapies benefits related to improved glycemic control of the drug are not outweighed by these risks.

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The phase III clinical development program for dulaglutide was discussed with the Division of Metabolism and Endocrinology Products (DMEP) at an End of Phase II (EOP2) Meeting on November 10, 2009. In Phase III development, specific issues regarding particular aspects of the program were handled in the form of written correspondences or teleconferences. At the EOP2 meeting the applicant was asked to carry out a dedicated study in patients with renal impairment to adequately evaluate the risk of Trulicity in this population. This request stemmed from an emerging post-marketing signal (acute renal failure in the setting of severe gastrointestinal reactions) associated several members of the approved GLP-1 agonist drugs. The Phase III program employed a phase 2/3 trial design (trial GBCF) that includes adaptive randomization (novel paradigm reviewed under The Critical Path Initiative). This trial was used for the purpose of dose selection and efficacy determination. This trial and Agency interactions pertaining to statistical issues with this type of design have been reviewed in details by Dr. McEvoy. The development program also included a prospective proposal to assess cardiovascular risk associated with dulaglutide use to satisfy the requirements stipulated in the 2008 FDA Guidance for Industry entitled: *Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.* The proposed plan was reviewed by DMEP as reflected in an advice letters issued on 31 August, 2011, 16 September, 2011 and a response from the sponsor received on 13 August, 2012. In preparation for filing the biologic licensing application a meeting was held on 9 July 2013 and minutes issued on July 30th 2013.

3. CMC/Device

The drug substance is described in the background section above. The dulaglutide drug substance is manufactured using a mammalian-cell based recombinant expression system (i.e., (b) (4)) and each polypeptide chain contains an (b) (4) . The drug substance and product manufacturing processes and in process controls were reviewed in details by Drs. Joel Welch, Bo Chi, and Colleen Thomas.

I concur with the conclusions reached by the product quality teams (Drs. Welch, Chi and Thomas) regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiration date of 24 months for the finished drug product (both 1.5 mg/0.5 mL and 0.75 mg/0.5 mL dosage strengths) when stored at 2-8°C. There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

Dr. Chong has summarized the main nonclinical toxicology findings. Dr. Hummer has reviewed nonclinical pharmacology and toxicology studies in details. The main nonclinical findings relate to the effect of dulaglutide on thyroid C-cells in life-long rodent studies (i.e., carcinogenicity studies). This effect is recognized as a class effect for longer acting GLP-1

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receptor agonists. In the two-year rat study, increases in incident thyroid C-cell ademonas (at 7-fold the clinical exposure) and thyroid C-cell carcinomas (at 58-fold the clinical exposure) were observed to occur. An increase in C-cell volume was noted in a second carcinogenicity study [i.e., six month study carried out in a transgenic mouse model (TgRas)] but no increased incidence of adenomas or carcinomas was observed. A one year Cynomologus monkey study evaluating a dose 474 –fold higher than the clinical dose was also carried out to evaluate thyroid and pancreatic toxicity in a non-human primate model. After one-year of exposure, no microscopic findings in the thyroid suggestive of thyroid C-cell hyperplasia/tumor and no evidence of pancreatic inflammation and/or proliferation were observed. The non-clinical findings are consistent with other members of the class and the approach to labeling, risk evaluation and mitigation strategy as well as post marketing surveillance will be consistent with other members of the class. I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer (Dr. Sang Chung) that there are no outstanding clinical pharmacology issues that preclude approval. Dulaglutide was observed to have a prolonged terminal half-life of approximately 4.7 days and reaches steady-state exposures between the 2^{nd} and 4^{th} dose of once-weekly administration. The exposure to dulaglutide increased less than proportionally with increasing dose in the 0.5 mg to 1.5 mg dose range. Elimination occurs through protein catabolism and the product is no longer detectable in blood 14 days after last administration. Subcutaneous administration of dulaglutide in the abdomen, thigh, or upper arm result in similar exposure and dulaglutide can be administered in either site. No dose adjustment is needed based on body weight, age, sex, race, ethnicity, or renal or hepatic impairment. The lower dose 0.75 mg was also recommended for approval because of evidence from Phase III trials of a dose-dependent difference on heart rate and gastrointestinal tolerability between the 0.75 mg and 1.5 mg dose.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewers (Drs. Chi and Thomas) that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

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To support the indication of improved glycemic control, the medium to long term glucose lowering effect of dulaglutide 0.75 mg and 1.5 mg was evaluated in 5 completed phase 3 clinical trials.

The pivotal trials were multi-center, multi-national, multi-arm, randomized, double-blind (n=2) or open-labeled (n=3). Studies were generally divided into four periods comprising a screening period, a lead-in/stabilization period, a treatment period and a four weeks post-treatment follow-up period.

Population selected for inclusion in the trial varied with regard to baseline background therapies, duration of disease and level glycemic control (refer to synopsis below). Patient with known gastric emptying abnormalities (e.g., gastroparesis), cardiovascular disease in the past six months, poorly controlled hypertension, QT or PR interval abnormality on baseline electrocardiogram (ECG), known liver disease, and impaired renal function (eGFR < or equal to 30 mL/min/1.72 m^2) were excluded from the studies.

All five trials had an active control arm and two trials had a placebo control arm. Multiple pre-specified hypotheses were tested in each of the five trials. In general, the applicant tested hypotheses of non-inferiority and superiority to active comparator across the two doses sequentially. A gate-keeping strategy was used to control study-wise type 1 error rate at 5% across the multiple pre-specified hypotheses in each study. Dr. McEvoy's review summarizes the pre-specified hypotheses and alpha adjustment across each set of hypotheses tested for each of the five trials (e.g., refer to Table 3 in his review).

The efficacy of dulaglutide was assessed in the following clinically relevant use settings;

- Dulaglutide used as **monotherapy** in adult subjects with type 2 DM not optimally controlled (i.e., inclusion HbA1c[1] between 6.5 and 9.5%) at baseline on diet and exercise alone or one oral anti-diabetic medication[2] (i.e., OAM).

    - Double Blind **Trial H9X-MC-GBDC-**Efficacy assessments at **26 weeks**
    - Compared **dulaglutide** 0.75 mg and 1.5 mg weekly to **metformin**
    - All subjects continued in a 26 weeks double-blind controlled extension

- Dulaglutide used as **add-on therapy to background metformin (≥1500 mg per day)** in adult subjects with type 2 DM not optimally controlled (i.e., inclusion HbA1c between 7.0 and 9.5%) at baseline on diet and exercise alone, one OAM, or one OAM used in combination with metformin.

    - Double Blind **H9X-MC-GBDF-** Efficacy assessments at **26 weeks and 52 weeks**

[1] HbA1c = Hemoglobin A1c
[2] OAM = Oral anti-diabetic medication.

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  - Compared **dulaglutide** 0.75 mg and 1.5 mg weekly to **placebo (26 weeks) and to sitagliptin 100 mg (52 weeks).**
  - All subjects continued in a 52 weeks double-blind controlled extension

- Dulaglutide used as **add-on therapy to background metformin (≥**1500 mg/day) **and a sulfonylurea** (glimepiride ≥ 4 mg/day) in adult subjects with type 2 DM not optimally controlled at baseline (inclusion HbA1c between 7 and 11%) on up to three OAMs with at least one being either metformin or a sulfonylurea.

  - Open Label **H9X-MC-GBDB-** Efficacy assessment at **52 weeks**
  - Compared **dulaglutide** 0.75 mg and 1.5 mg weekly to **insulin glargine dose-titrated to a goal fasting plasma glucose of <100 mg/dL**.
  - All subjects continued in a 26 weeks open label controlled extension

- Dulaglutide used as **add-on therapy to background metformin (≥**1500 mg/day) **and pioglitazone** (up to 45 mg/day) in adult subjects with type 2 DM not optimally controlled at baseline (inclusion HbA1c between 7 and 11%) on up to three OAMs.

  - Double-Blind/Open-label **H9X-MC-GBDA-** Efficacy assessment at **26 weeks**
  - Compared **dulaglutide** 0.75 mg and 1.5 mg weekly to **placebo (double blind)** and **exenatide [open label (10 mcg twice daily)**]
  - All subjects continued in a 26 weeks controlled extension

- Dulaglutide used as **add-on therapy to Lispro** in adult subjects with type 2 DM not optimally controlled at baseline (inclusion HbA1c between 7 and 11%) on a conventional insulin regimen (less than two doses per day) alone or in combination with OAMs.

  - Double-Blind/Open-label **H9X-MC-GBDD-** Efficacy assessment at **26 weeks**
  - Compared **dulaglutide** 0.75 mg and 1.5 mg weekly to **insulin glargine dose-titrated to a goal fasting plasma glucose of <100 mg/dL**
  - All subjects continued in a 26 weeks controlled extension

The applicant had pre-specified the primary efficacy assessment to be the change in hemoglobin A1c (i.e., HbA1c) from baseline to the landmark visit, designated as either 26 weeks or 52 weeks, depending on the trial. Dr. McEvoy notes that the endpoint analyzed was not strictly speaking the change in HbA1c from baseline to the landmark visit but in actuality could reflect the change from baseline to either the landmark visit, the onset of rescue (for subjects rescued) or the last on study visit (for subjects who discontinued prior to the landmark visit). In his review, he describes how assumptions made in handling data in this way could lead to a biased estimate of the treatment effect.

I will use the dulaglutide 0.75 mg to metformin comparison to illustrate this. For this comparison, the superiority of dulaglutide 0.75 mg to metformin in HbA1c reduction at week 26 was not supported by the prespecified MMRM analysis or the ANCOVA model using LOCF

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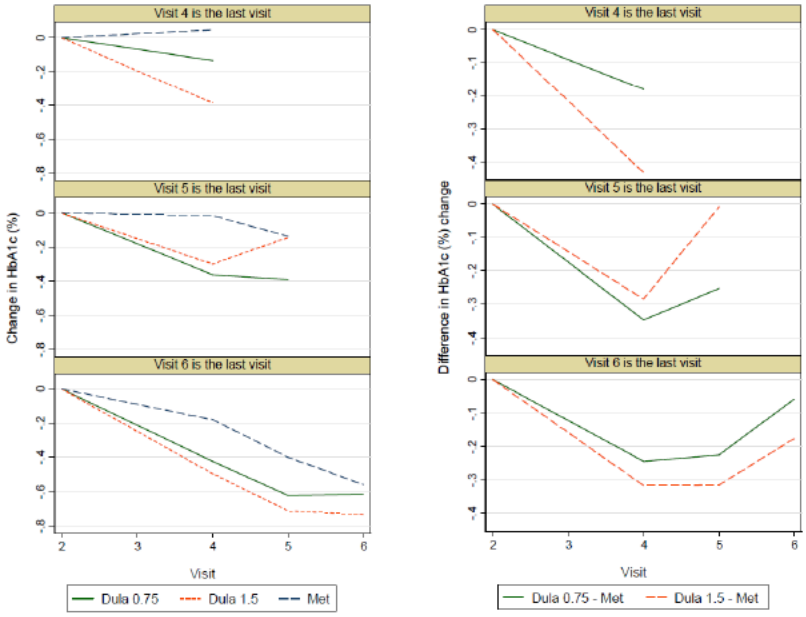
instead of Last pre-rescue Observation Carried Forward (LprOCF) or using the subgroup with an HbA1c assessment at the week 26 visit. Dr. McEvoy notes that in the group of patients with an HbA1c assessment at week 26, the estimated reduction in HbA1c for both dulaglutide groups compared to metformin was not as large as observed in the primary analysis. The difference in HbA1c reduction between this analysis and the primary analysis could be explained by the fact that mean reduction in HbA1c tended to be more favorable at the last available visit for dulaglutide in the subset of individuals with their last HbA1c not at the primary landmark visit. This is illustrated in Figure 4 of his review (copied below) where HbA1c change and difference in HbA1c change are plotted across subsets of individuals with an HbA1c assessment at week 4, 13 and 26 (i.e., primary landmark visit) respectively. He concludes by stating that "given the mechanics of LOCF, it is of concern that the estimated treatment effect may have been inflated due the exploitation of the early differences which could be attenuated by week 26". To assess the impact of missing data and rescue medication on the robustness of the study conclusions Dr. McEvoy performed several sensitivity analyses on all pivotal trials and dose comparisons and the reader is referred to his review for full details of these analyses.

Figure 4. Unadjusted means and difference in means across visits by last available observation (Trial GBDC)



Dr. McEvoy also highlights that the analysis population (i.e., modified intent to treat population consisting of individuals randomized who received at least one dose of therapy and had at least one post-baseline value) may not preserve the integrity of randomization because subjects in the analysis are selected on the basis of a post-randomization event (i.e., whether they took at least one dose and had a post-baseline value).

The applicant's efficacy results across the five trials are summarized in Table 1 of Dr. McEvoy's review and are re-copied immediately below. Subjects included in the analysis are

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a subset of the ITT population that had at least one post-baseline assessment. Last observation carried forward (LOCF) was used to impute missing data. The difference in Last-squares mean (LS Mean) HbA1c reduction adjusted for baseline value and other stratification factors is shown.

Table 1. Summary of Study Findings on the Primary Endpoint

Study	Comparator (endpoint visit)	Dula 0.75 - Comparator LS Mean (95% CI)	Dula 1.5 - Comparator LS Mean (95% CI)
Metformin add-on			
GBCF	Placebo (wk 26) Sitaglitpin (wk 52)	-1.04 (-1.22, -0.86)† -0.50 (-0.67, -0.33)‡†	-1.23 (-1.41, -1.05)† -0.71 (-0.87, -0.54)‡†
Monotherapy			
GBDC	Metformin (wk 26)	-0.15 (-0.29, -0.01)‡†	-0.22 (-0.36, -0.08)‡†
Metformin and Pioglitazone add-on			
GBDA	Placebo (wk 26) Exenatide (wk 26)	-0.84 (-1.01, -0.67)† -0.31 (-0.44, -0.18)‡†	-1.05 (-1.22, -0.88)† -0.52 (-0.66, -0.39)‡†
Metformin and Sulfonylurea add-on			
GBDB	Insulin Glargine (wk 52)	-0.13 (-0.29, 0.02)‡	-0.45 (-0.60, -0.29)‡†
Insulin Lispro add-on			
GBDD	Insulin Glargine (wk 26)	-0.17 (-0.33, -0.02)‡†	-0.22 (-0.38, -0.07)‡†

‡ - Prespecified test for non-inferiority statistically significant
† - Prespecified test for superiority statistically significant

In the pivotal trials, the applicant's analyses showed that dulaglutide 0.75 mg and 1.5 mg resulted in statistically significant improvement in HbA1c compared to metformin ≥ 1500 mg once daily in the monotherapy setting, sitagliptin 100 mg once daily and placebo in the add-on to metformin setting, exenetide 10 mcg twice daily and placebo in the add-on to metformin and pioglitazone setting and titratable insulin glargine in both the add-on to metformin and sulfonylurea and add-on to lispro settings.

Sensitivity analyses performed by Dr. McEvoy's revealed that conclusions of non-inferiority of high and low dose dulaglutide to active comparators were not impacted by the underlying assumptions inherent to the primary method selected for the handling of data missing at the landmark visit (i.e., LOCF). However, these additional analyses called into question the robustness of the analyses demonstrating superiority of dulaglutide to select active controls, namely metformin for both dulaglutide doses and glargine for the high dulaglutide dose.

There a several non-statistical issues related to the superiority claim against metformin and glargine that warrant further discussion.

In Study GBDC comparing dulaglutide to metformin patients were required to have T2DM diagnosed between 3 months and 5 years prior to the screening visit. Patients were eligible if they were treatment naïve (i.e., on no oral anti-diabetic medications 3 months prior to screening) or if they were on a sub-optimal dose of only one oral anti-diabetic medication (OAM) [i.e., ≤50% of the recommended maximum daily dose (per the local label) for at least 3

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months prior to screening]. The OAM was to be discontinued at the screening visit and patients entered a two week washout prior to randomization.

Table GBDC.14.11 of the study report, which is based on electronic Case Report Form data (eCRF), shows that 60% (476/807) of patients who entered the trial were on one OAM at the screening visit. The majority of these patients 53% (n=425/807) were on metformin pre-trial and 7% (n=51) on sulfonylurea (Table GBDC.16.16 in study report). The applicant did not systematically collect dose information for pre-trial medication but had this information for the 425 patients identified as being on metformin pre-trial from eCRF data. In these patients, the median (IQR) daily metformin dose for these 425 patients was 1000 (850, 1250) mg (source: information request received 9/17/2014). The sponsor also acknowledges that case report form data are not entirely consistent with interactive voice response system (IVRS) data used for randomization (stratification). According to IVRS data an even higher number of individuals were reported to have been on an OAM at screening [i.e., up to 75% (606/807): see Table GBDC.14.94 in study report]. The applicant's report does not address this discrepancy.

Regardless of which number is correct, it suggests that a majority (i.e., at least 53%) of patients selected for this trial were selected on the basis of having failed metformin albeit at a submaximal dose. This type of enrichment could bias the treatment effect estimate in dulaglutide's favor (i.e., after a brief washout some patients are randomized to a drug with an entirely new mechanism of action and some patients to their old drug at a higher dose). In light of this fact, it is not surprising that dulaglutide performed better than what amounts to be a dose increase of metformin for the majority of the trial population. The comparison in GBDC is thus not a comparison of dulaglutide to metformin in treatment naïve individuals (b) (4)

Due to the theoretical risk of thyroid c-cell tumors, long acting GLP-1 receptor agonists, dulaglutide included, carry a Limitations of Use statement recommending these agents not be used as first line therapy in patients with type 2 diabetes. We regard this statement as important for the safe use of the drug for this indication. Metformin is the most commonly used first line agent in the United States. A trial in Section 14 of the label (b) (4) in the context of the above limitations would be contradictory to the Limitations of Use statement and may go a long way to render the Limitations of Use statement ineffective. In light of the statistical and trial design issues mentioned above, I recommend against (b) (4).

(b) (4) In trials GBDB and GBDD it is clear that insulin glargine titration was not optimized. At most 24% and 38% of patients in GBDB and GBDD respectively were titrated to the intended fasting plasma glucose target goal (less than 100 mg/dL) at any time in the entire trial. In other insulin clinical trials, much higher goals have been attained with

similar intensity of insulin titration (e.g., in the ORIGIN trial for example 50% of enrollees were within FPG goal of 95 mg/dL at one year[3]). Achievement of titration goal is likely to be dependent on the adequacy of trial monitoring and on the willingness and motivation of investigators and participants to follow protocol mandated titration algorithms (i.e., in ORIGIN investigators were likely motivated to achieve titration goals because the intervention was normalization of glycemia). I do not believe that a safety argument based on hypoglycemia can explain the low achievement of glucose targets in this trial. Indeed only 2 events of severe hypoglycemia were seen at Week 26 in GBDB (refer to Table 33 in Dr. McEvoy's review). Finally, in a short term highly monitored clinical trial setting where frequent visit and contact with providers is the norm, titration should be attained in a greater proportion of individuals than was seen in this trial.

In addition, in GBDD (add-on to lispro trial), a significant proportion of the populations (~ 38%) were inadequately controlled on a twice daily pre-mixed insulin regimen at baseline. Patients randomized to glargine and lispro three times daily were essentially randomized to their baseline regimen with the addition of one extra meal time insulin dose. Issues of selection bias that pertain to selection of a population suboptimally controlled on a baseline regimen and re-randomized to a variant of that regimen may also apply here (refer to discussion above for metformin comparator trial). Finally lispro dose (the background insulin) throughout the trial was higher in the two arms receiving dulaglutide which may confound the estimate.

In light of the statistical and trial design and conduct issues resulting in suboptimal dose titration of the comparator in these open-label trials, I recommend against (b) (4) . This recommendation is in line with the Guidance for Industry entitled:

(b) (4)

Analyses of HbA1c response by subgroups defined by gender, race (White, non-White), age (≤ 65 years, > 65 years), region (US, non-US), baseline HbA1c (≤ 8.5%, > 8.5%), and baseline BMI (≤ 30, > 30) for each trial did not reveal notable differences in dulaglutide's effect across these subgroups.

8. Safety

Drs. Chong and Balakrishnan have summarized the general safety findings in the application and Dr. Charles the cardiovascular risk analyses specifically. Three major overlapping groupings were used to analyze safety. One grouping, referred to as the AS1 grouping,

[3] N Engl J Med 2012; 367:319-328

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pooled safety information collected for exposures of up to 26 weeks in three Phase 2 and 3 placebo-controlled trials. This grouping was used to define common adverse reactions associated with the product and explore dose response relationships. Another grouping, referred to as AS3, pooled safety information collected for the full extent of exposure from six Phase 2 and 3 controlled trials across the two dulaglutide doses. This grouping was used to analyze dose response relationships. A third grouping, referred to as AS7, pooled safety information collected for the full extent of exposure across six Phase 2 and 3 trials placebo and active controlled trials (exposure to dulaglutide was similar to AS3 in this grouping).

Table 2: Number of Subjects Exposed to Dulaglutide 0.75 mg and 1.5 mg by Defined Duration of Exposure in the All Comparator Safety Pool AS3-grouping (Source: Table 2.7.4.7; Clinical Safety Summary)

	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Combined Dulaglutide
≥ 0 months	1671	1671	3342
≥ 6 months	1404	1357	2761
≥ 12 months	813	782	1595
≥ 18 months	574	577	642
≥ 24 months	74	83	157

Deaths and serious adverse events were balanced and Dr. Balakrishnan did not note an imbalance for one particular type of serious adverse event. In general, the overall safety profile of dulaglutide was found to be similar to the safety profiles of other members of the class. Specific issues reviewed in details in Dr. Chong's CDTL memorandum include: gastrointestinal adverse reactions, immunogenicity and hypersensitivity reactions, injection site reactions, pancreatitis, pancreatic cancer, thyroid C-cell proliferation/neoplasm, calcitonin changes, renal function changes, rate of hypoglycemia, changes in heart rate and tachycardia-related adverse reaction and PR prolongation as well as bradycardia related adverse reactions.

Elements identified in the review that suggest a causal link between dulaglutide and; injection site, hypersensitivity, gastro-intestinal, and arrhythmia related adverse reactions as well as increases in amylase and lipase levels 3-fold above the upper limit of normal included; a close temporal association of dulaglutide-treatment onset with reaction onset for some events (e.g., gastrointestinal reaction, hypersensitivity reactions), a strong association between these events and drug for some events (e.g., relative risk increase of 2-fold and 4-fold above placebo for nausea at the 0.75 and 1.5 mg dose), a dose-response relationship for some events (e.g., gastro-intestinal reactions, tachycardia related adverse reactions, and amylase and lipase increases), a positive de-challenge for some events (e.g., amylase and lipase increases), and biological plausibility for some events (e.g., increased heart rate and tachyarrhythmia related adverse reactions). For some reactions, multiple of the above listed elements suggesting causality were identified. The above listed adverse reactions do not preclude approval, can be mitigated through appropriate patient selection and will be described in product labeling. A small imbalance not favoring dulaglutide for pancreatitis

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adverse events, consistent with observations made in development programs for members of the DPP-4 inhibitor and GLP-1 agonist classes of drugs, was noted. This adverse reaction is labeled in the Warning and Precautions section of product labeling and will be included in the Trulicity label. Two cases of pancreatic cancers were identified in the original submission and both individuals were exposed to dulaglutide for < 6 months (one diagnosed one week after randomization) making tumor initiation unlikely. An abdominal pain event prompted the work-up. In these cases either tobacco use history, presence of diabetes and obesity further confound a drug causality assessment. At the four months safety update two additional pancreatic cancers were reported in patients exposed to dulaglutide for less than six months and two pancreatic cancers occurred in placebo treated patients. Overall, no new adverse reaction that would preclude approval was identified in this program[4] and the reader is referred to Drs. Chong and Balakrishnan's reviews for detailed discussions of the safety analyses.

Cardiovascular risk

To meet the requirements outlined in the Guidance to Industry: *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*, the Applicant performed a meta-analysis of nine completed phase 2 and phase 3 studies based on prospectively defined, collected and adjudicated CV-safety data. The plan for the CV-risk assessment had been pre-specified, reviewed and agreed-upon by DMEP in 2012. The meta-analysis was based on 3,885 patients randomized to dulaglutide and 2,125 patient randomized to comparator. The primary endpoint was the time to first major adverse cardiovascular event (MACE) of CV-death, non-fatal myocardial infarction, non-fatal stroke and unstable angina (i.e., MACE+). A total of 51 adjudicated MACE+ events occurred in the nine trials included in the meta-analysis (26 [0.7%] in dulaglutide-treated patients and 25 [1.2%] in comparator-treated patients). The estimated hazard ratio for MACE+ was 0.57 and the upper limit of risk defined by using the upper 98.02% confidence interval around the estimated hazard ratio was 1.10. Analysis for MACE yielded similar results (see Table 1 of Dr. Charles' review). The results of this analysis do not suggest that dulaglutide-use is associated with excess CV-risk, as defined in the Guidance, compared to a pool of comparators in the population studied in the Phase 2 and 3 program (relatively low risk population). In light of the above-mentioned arrhythmia related adverse reactions, I will note that CV-death, which would be expected to capture potential arrhythmogenic deaths, occurred less frequently in dulaglutide treated patients; though numbers of CV-deaths are small. An ongoing cardiovascular outcomes trial comparing dulaglutide to placebo in a population of patients with type 2 diabetes with established cardiovascular disease or at high baseline risk of cardiovascular disease is ongoing and will provide further reassurance regarding the cardiovascular safety of this product. No cardiovascular safety issues preclude approval of the product.

[4] Note increases in heart Rate and atrial fibrillation are labeled adverse reactions for liraglutide and albiglutide respectively.

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9. Advisory Committee Meeting

Dulaglutide is the fifth member of the GLP-1 agonist class of anti-diabetic drugs. No new efficacy or safety issue identified in the application rose to the level of requiring the input from an advisory panel. Therefore no advisory committee was convened.

10. Pediatrics

This has been reviewed by Drs. Chong and Balakrishnan and the reader is referred to their reviews for details.

11. Other Relevant Regulatory Issues

These have been reviewed by Drs. Chong and Balakrishnan and the reader is referred to their reviews for details. No regulatory issues that would preclude product approval were identified.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

Benefits Assessment: The applicant has demonstrated in two adequate and well controlled trials that dulaglutide 0.75 and 1.5 mg administered subcutaneously once weekly result in clinically meaningful improvement glycemic control compared to placebo. The applicant has also compared the effect of dulaglutide to several active comparators in patients with early (i.e., one agent used for type 2 diabetes management) and more advanced disease (three agents used for type 2 diabetes management). In these comparisons, dulaglutide administered as monotherapy or co-administered atop optimized background anti-diabetic therapy (ies) was shown to provide a glucose lowering effect non-inferior to that of metformin ≥ 1500 mg once daily at 26 weeks in one trial, superior to that of sitaglitpin 100 mg once daily at 26 and 52 weeks in one trial, superior to exenatide 10 mcg twice daily at 26 weeks in one trial, and non-inferior to dose-titrated insulin glargine at 26 and 52 weeks in two trials. (b) (4) statistical, design and conduct issues (b) (4) were identified and are summarized in the efficacy section of this memorandum. This will be reflected in product labeling. Glucose lowering with dulaglutide was weight neutral and was not associated with a high risk of hypoglycemia compared to placebo. In contrast, weight gain and hypoglycemia are well recognized adverse reactions associated with insulin and sulfonylurea use. Dulaglutide offers the convenience of a once weekly, simple, dosing administration schedule.

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Risks Assessment: Glucose lowering with dulaglutide is not associated with an inherently high risk of hypoglycemia. The risk of hypoglycemia increases when dulaglutide is added to drugs known to cause hypoglycemia (e.g., sulfonylurea and insulin). Some of the potential drug-related risks identified in the application (Thyroid C-cell tumors, pancreatitis, renal impairment in patients experiencing severe gastrointestinal reactions) are real or potential serious risks associated with this class of glucose lowering agents and are currently mitigated through product labeling and REMS (i.e., REMS apply to Thyroid C-cell tumors and pancreatitis only). No data in the application suggest the presence of qualitative or quantitative differences for these risks when comparing dulaglutide to other currently approved long-acting GLP-1 products. Common product related adverse reactions were consistent with the drug's pharmacological effect on intestinal motility (gastro-intestinal adverse reactions) or the route of administration (injection site reactions). The applicant's pre-marketing CV-risk analysis excludes an excess CV-risk of 1.8. No identified safety issues preclude approval of this application at this time.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

Dulaglutide will be approved with a Risk Evaluation and Mitigation Strategy (REMS), which consists of a communication plan to inform health care providers about the serious risks of thyroid C-cell tumors and pancreatitis.

- Recommendation for other Postmarketing Requirements and Commitments

FDA is requiring postmarketing studies for Trulicity to include a pediatric study to evaluate dosing, efficacy, and safety in pediatric patients; a study to evaluate toxicity in immature rats; a medullary thyroid carcinoma (MTC) case registry of at least 15 years duration to identify any increase in MTC incidence related to Trulicity; a clinical trial comparing Trulicity with insulin glargine on glycemic control in patients with type 2 diabetes and moderate or severe renal impairment; and a cardiovascular outcomes trial. These have been negotiated and agreed to by the applicant and are summarized in Dr. Jennifer Pippins memorandum.

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/s/

JEAN-MARC P GUETTIER
09/18/2014