CDTL Review and
Division Summary Memo for Regulatory Action

Date	November 16, 2022
From	Patrick Archdeacon, M.D. Deputy Director Division of Diabetes, Lipid Disorders, and Obesity
BLA # / Sequence #	125469/S-051
Applicant	Eli Lilly and Company
Date of Submission Receipt	May 17, 2022
PDUFA Goal Date	November 17, 2022
Non-proprietary name	Dulaglutide
Trade name	Trulicity
Dosage forms / Strength	Single dose pen for subcutaneous injection 0.75 mg and 1.5 mg once weekly
Proposed Indication	As an adjunct to diet and exercise to improve glycemic control in patients aged 10 years and older with type 2 diabetes mellitus (T2D)
Recommended Action	Approval of proposed new indication; discharge PMR 2781-1; grant pediatric exclusivity
Recommended Indication/Population	As an adjunct to diet and exercise to improve glycemic control in patients aged 10 years and older with type 2 diabetes mellitus (T2D)

1. Introduction

This document contains the 'Summary Basis for Regulatory Action' memo for Supplement 051 to Biologics License Application (BLA) 125469 (Trulicity; dulaglutide), received May 17, 2022. The memo includes the basis for the decision to approve the proposal to expand the indication of the 0.75 mg sc/week and 1.5 mg sc/week doses to improve glycemic control in adults with type 2 diabetes mellitus (T2D) to include patients aged 10 years and older with T2D an indication to improve glycemic control in adults and pediatric patients with diabetes mellitus. The memo also includes the basis for the decision to discharge PREA PMR 2781-1 (requiring a study of the safety, efficacy and pharmacokinetics of the 0.75 mg sc/week and 1.5 mg sc/week dose regimens of dulaglutide in pediatric patients ages 10-17 years, inclusive) based on the results of Study GBGC. The memo also documents the recommendation of the Pediatric Research Committee (PeRC) to grant pediatric exclusivity based on their determination that the results of Study GBGC fulfilled the terms of the written request issued August 31, 2016.

This memo relies on the following documents/sources:

Subject		Date
Clinical	Suchitra Balakrishnan	November 14, 2022
Statistics	Roberto Crackel	November 19, 2022
Clinical Pharmacology	Mohamad Kronfol	October 26, 2022
Nonclinical	Ronald Wange	March 7, 2016
DMEPA Labeling	Ariane Conrad	October 15, 2022
DMEPA Human Factors	Avani Bhalodia	October 12, 2022
Patient Labeling Review	Mary Carroll	October 31, 2022
Pediatric Exclusivity Determination Checklist	Meshaun Payne, Mary Thanh Hai	October 4, 2022
OPDP Review	Charuni Shah	November 3, 2022
OSI CIS Summary	Ling Yang	October 4, 2022
OPDP: Office of Prescription Drug Promotion; DMEPA: Division of Medication Error and Prevention Analysis		

2. Background and Executive Summary

Dulaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) analog comprising two peptide sequences with 90% homology to human GLP-1 (7-37), each covalently linked to an Fc fragment of human IgG4. Dulaglutide was initially approved on September 18, 2014 for two dose regimens (0.75 mg administered subcutaneously once weekly; 1.5 mg administered subcutaneously once weekly) as an adjunct to diet and exercise to improve glycemic control in adults with T2D. At the time of the initial approval, post-marketing requirement (PMR) 2781-1 was issued; the PMR required a randomized controlled study of the safety, efficacy, and pharmacokinetics of dulaglutide in pediatric patients ages 10 to 17 years (inclusive) with T2D. Subsequently, a Written Request (WR) was issued in accordance with the Best Pharmaceuticals for Children Act (BPCA). The Applicant has accordingly submitted sBLA 125469/S-051—the submission includes the results from Study GBGC, which was designed and conducted in keeping with PMR 2781-1 and the WR.

Based on their review of the results of GBGC, the FDA review team recommends expanding the glycemic control indication for the 0.75 mg and 1.5 mg dose to include patients with T2D aged 10 and above, discharging PMR 2781-1, and granting pediatric exclusivity for the 0.75 mg and 1.5 mg doses. I concur with the recommendations of the review team. The Pediatric Research Committee and Dr. Mary Thanh Hai (Deputy Director of the Office of New Drugs) also concurred with the recommendation to grant pediatric exclusivity.

In September of 2020, two additional doses of dulaglutide (3.0 mg subcutaneously once weekly; 4.5 mg subcutaneously once weekly) were approved in adults with T2D. Another PMR (PMR 3931-1) was issued at that time for a randomized controlled study of the safety, efficacy, and pharmacokinetics of new doses of dulaglutide in pediatric patients ages 10 to 17 years (inclusive) with T2D. The Applicant does not propose that sBLA 125469/S-051 addresses PMR 3931-1 and that PMR remains in effect. Incidentally, in February of 2020, dulaglutide was approved to reduce the risk of major cardiovascular events (MACE) in adults with T2D who have established cardiovascular disease or multiple cardiovascular risk factors. As cardiovascular disease is not a condition typically observed in pediatric patients with T2D, no PMRs were issued in association with the approval of the MACE indication.

3. CMC/Device

sBLA 125469/S-051 contains no new CMC or device data. For that reason, OPQ and CDRH did not participate in the review.

The submission includes the results of a Human Factors (HF) study, which was conducted to establish that pediatric patients may administer dulaglutide using the single-dose pens (the only marketed presentation of dulaglutide) without the assistance of an adult.

The Human Factors study was reviewed by Avani Bhalodia, Murewa Oguntimein, and Jason Flint of the Division of Medication Error Prevention and Analysis (DMEPA). The reviewers from DMEPA noted some deficiencies in the conduct and results of the HF study. Based on their review, they identified several use errors with critical tasks that could result in harm. DMEPA identified risk mitigations to address the use errors and provided recommendations to improve its Instructions for Use (IFU). The Applicant revised its IFU accordingly. I concur

that, given the revisions to the IFU, the data and information in sBLA 125469/S-051 suffice to support the proposed pediatric dosage and administration components of the labeling.

4. Nonclinical Pharmacology/Toxicology

sBLA 125469/S-051 contains no new nonclinical data. For that reason, nonclinical did not review the submission. However, an internal memorandum written by the nonclinical review team (Dr Ronald Wange, Dr. Todd Bourcier, and Dr Lee Elmore) and finalized in DARRTS on March 7, 2016 regarding the class of long-acting GLP-1 RAs is relevant to the submission. As described in the memorandum, non-clinical data exist that suggest that the class may be associated with accelerated testicular development in male monkeys. The non-clinical data, in conjunction with additional data in the scientific literature, suggested a hypothesis that long-acting GLP-1 RAs may have the potential to accelerate entry into (and/or progression through) puberty. For that reason, juvenile toxicity studies in rats were required and reviewed for four long-acting GLP-1 RAs (liraglutide, exenatide LAR, dulaglutide, and lixisenatide): none of the four studies revealed evidence of accelerated sexual maturation. Rather, the liraglutide, exenatide LAR, and lixisenatide studies showed signs of delay of sexual maturation. The nonclinical review team concluded the observed delay of sexual maturation is likely explained by a marked reduction in body weight induced by the investigational products. The dulaglutide program attempted to control for the confounding effects of change in body weight using a pair-feeding protocol. Under aggressive dosing and the pair-feeding protocol, dulaglutide demonstrated a small, statistically-significant acceleration of sexual maturity in female rats. However, there was no discernable affect on sexual maturation of male rats and all values for measures of sexual maturation in female rats. The nonclinical reviewer concluded that subcutaneously administered GLP-1 RAs have limited capacity to accelerate sexual maturation and that the nonclinical data indicate it is unlikely that a biologically significant acceleration of entry into puberty will occur in human children. See the Nonclinical Memorandum for additional details.

CDTL comment: I concur with the conclusion from the 2016 nonclinical memorandum. Although the data collected in Study GBGC regarding growth and puberty have limited value (see the Clinical Review by Dr. Suchitra Balakrishnan for a full discussion of those data), the hypothesis that dulaglutide could have a clinically meaningful effect on growth and puberty is adequately refuted by the data from the nonclinical GLP-1 RA programs.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Mohamad Kronfol, Dr. Hezhen Wang, Dr Justin Earp, and Dr. Edwin Chow from the Office of Clinical Pharmacology (OCP) reviewed the clinical pharmacology data from sBLA 125469/S-051. They concluded, and I concur, that the application contains sufficient data to support approval from a clinical pharmacology perspective and that PREA PMR 2781-1 is considered fulfilled from a clinical pharmacology perspective. For details, see the full clinical pharmacology review in DARRTS.

In brief, the clinical pharmacology data derived from Study GBGC were used to evaluate the pediatric exposure associated with the doses of dulaglutide 0.75 mg/week and dulaglutide 1.5 mg/week. The data indicated that the exposure in pediatric patients aged 10-17 was approximately 37% lower than that in adults; further, the data indicated that the exposure in male pediatric patients was approximately 36% lower than the exposure in female pediatric patients. The OCP reviewers also evaluated the immunogenicity data. Based on their review, they provided labeling recommendations, describing the observed rates of anti-drug antibodies and neutralizing antibodies (both were very infrequent) and stated that the effect of immunogenicity on efficacy, safety, and exposure remained unknown. I concur with the labeling recommendations provided by OCP.

CDTL comment: Neither the Applicant nor the FDA pharmacology reviewers offered a biological explanation for the reported differences in exposures between adults and children aged 10-17 nor between males aged 10-17 and females aged 10-17. However, efficacy was convincingly demonstrated for both the 0.75 mg and 1.5 mg dose for children aged 10-17 (see Table 2) *and males aged 10-17 were observed to have a numerically larger treatment effect size than females aged 10-17 (see* Figure 2*). I concur with the recommendation to report the differences in exposures between children and adults. Interestingly, the pharmacometrics modeling by the Applicant prior to conducting Study GBGC predicted that children would have higher exposure (rather than the lower exposure observed) than adults when given the same dose. The Applicant offered a rather circular argument when asked to explain their statement that the exposures in children and adults were comparable – the Applicant simply noted that the clinical outcomes observed were comparable, so they concluded that the exposures were comparable. While there is a certain truth in that argument, it elides the fact that the clinical pharmacology data then appear not useful for labeling or other potential purposes. Certainly, given the lack of clarity around the results, I do not currently consider potential pharmacometrics approaches such as "exposure matching" or modeling as useful or reliable, at least with respect to dulaglutide. Because the clinical efficacy and safety data stand on their own, however, my concerns that the PK data from Study GBGC have not been fully explained do not undermine any of the recommendations for regulatory action I have made for sBLA 125469/S-051.*

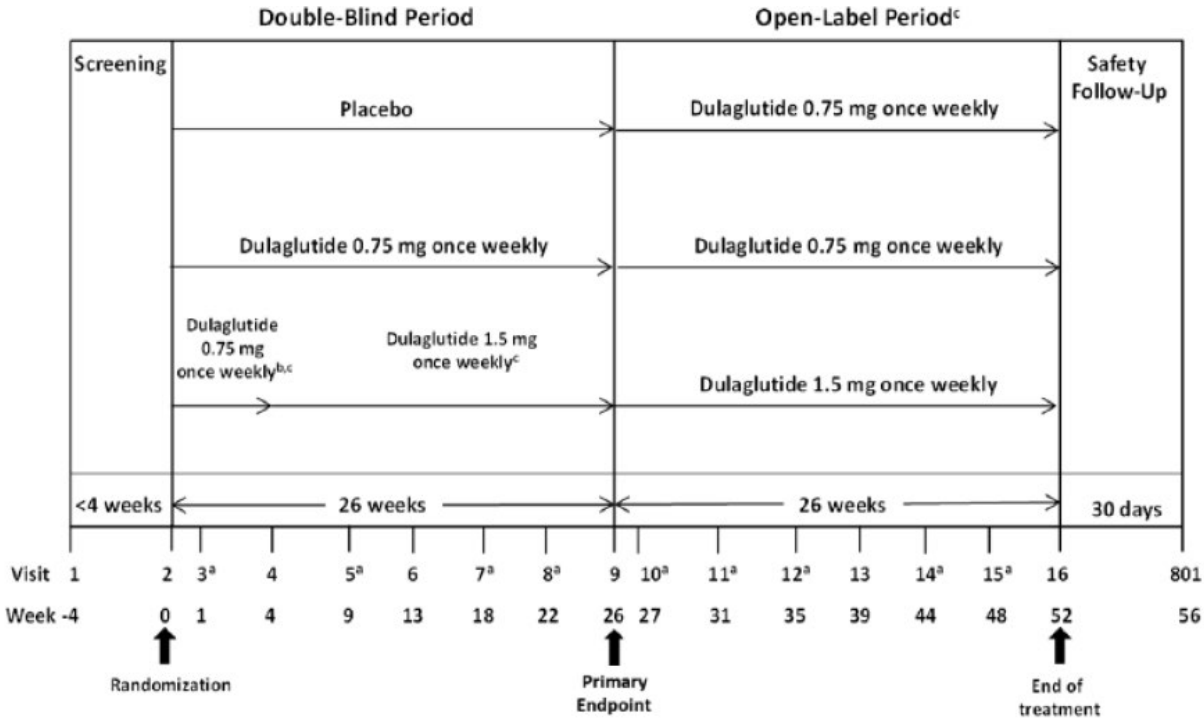
6. Clinical/Statistical- Efficacy

Dr. Roberto Crackel from the Division of Biometrics II and Dr. Suchitra Balakrishnan from the Division of Diabetes, Lipid Disorders, and Obesity reviewed the data from Study GBGC to determine whether the efficacy of dulaglutide had been demonstrated in pediatric patients with T2D aged 10-17 years, inclusive. They concluded, and I concur, that the results from Study CBGC sufficed to support expanding the glycemic control indication to include all patients with T2D aged 10 and older. See the reviews by Dr. Crackel and Dr. Balakrishnan for details.

In brief, Study GBGC was a Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group study. The study included a 4-week screening period, a 26-week double-blind period, a 26-week open-label period, and 30 days of additional safety follow-up. Patients were randomized 1:1:1 to dulaglutide 0.75 mg, dulaglutide 1.5 mg, or placebo. The

primary endpoint was change from baseline to Week 26 in HbA1c. The primary comparison was pooled dulaglutide vs placebo, followed by the individual treatment arm versus placebo.

Figure 1: Design of Study GBGC



a Phone visits.
b Patients who tolerate the 0.75 mg/week dose in the opinion of the investigator will be changed to dulaglutide 1.5 mg/week at Week 4.
c If patients do not tolerate the higher dose, they will be allowed to go back to the previous dose.

Source: Clinical Study Report, page 33

The study enrolled a total of 154 patients (52 were randomized to dulaglutide 1.5 mg, 51 were randomized to dulaglutide 0.75 mg, and 51 were randomized to placebo). The study population was 71.4% female and 54.5% white; 47.4% of subjects were from the United States (see Table 1). For the most part, the demographics were balanced across treatment groups, though the placebo treatment arm did have lower percentages of males (19.6% compared to 34.6% in the dulaglutide treatment 1.5 mg arm and 31.4% in the dulaglutide 0.75 treatment arm) and patients aged 14-17 (51% vs 63.5% and 68.6%, respectively) and somewhat higher percentage of Asians (21.6% vs 7.7% and 7.8%, respectively).

CDTL Comment: Although worth noting, I do not believe that the small demographic imbalances described above meaningfully limit the interpretability of Study GBGC

Table 1: Demographics of Study GBGC

	Dula 1.5 mg (N=52)	Dula 0.75 mg (N=51)	Placebo (N=51)	Total (N=154)
Sex [n(%)]				
Male	18 (34.6)	16 (31.4)	10 (19.6)	44 (28.6)
Female	34 (65.4)	35 (68.6)	41 (80.4)	110 (71.4)
Age (years)				
Mean (SD)	14.7 (1.8)	14.7 (2.2)	14.2 (2.1)	14.5 (2.0)
Age Group [n(%)]				
< 14	19 (36.5)	16 (31.4)	25 (49.0)	60 (39.0)
≥ 14	33 (63.5)	35 (68.6)	26 (51.0)	94 (61.0)
Race [n(%)]				
American Indian or Alaska Native	4 (7.7)	6 (11.8)	6 (11.8)	16 (10.4)
Asian	4 (7.7)	4 (7.8)	11 (21.6)	19 (12.3)
Black or African American	9 (17.3)	9 (17.6)	5 (9.8)	23 (14.9)
Native Hawaiian or other Pacific Islander	0	0	1 (2.0)	1 (0.6)
White	30 (57.7)	29 (56.9)	25 (49.0)	84 (54.5)
Multiple	3 (5.8)	1 (2.0)	3 (5.9)	7 (4.5)
Missing	2 (3.8)	2 (3.9)	0	4 (2.6)
Region [n(%)]				
US	29 (55.8)	22 (43.1)	22 (43.1)	73 (47.4)
Non-US	23 (44.2)	29 (56.9)	29 (56.9)	81 (52.6)
Metformin [n(%)]				
Yes	46 (88.5)	44 (86.3)	46 (90.2)	136 (88.3)
No	6 (11.5)	7 (13.7)	5 (9.8)	18 (11.7)
Insulin [n(%)]				
Yes	15 (28.8)	13 (25.5)	15 (29.4)	43 (27.9)
No	37 (71.2)	38 (74.5)	36 (70.6)	111 (72.1)
HbA1c (%)				
Mean (SD)	8.16 (1.39)	7.92 (1.27)	8.14 (1.12)	8.08 (1.26)
Min, max	(6.3, 12.5)	(5.4, 11.4)	(6.5, 10.7)	(5.4, 12.5)
HbA1c category [n(%)]				
< 8.0%	25 (48.1)	25 (49.0)	20 (39.2)	70 (45.5)
≥ 8.0%	27 (51.9)	26 (51.0)	31 (60.8)	84 (54.5)
Duration of diabetes (years)				
Mean (SD)	2.1 (1.6)	1.8 (1.8)	2.0 (1.8)	2.0 (1.7)
Min, max	(0, 6)	(0, 7)	(0, 9)	(0, 9)

Source: Statistical Reviewer's Analysis and CSR Page 55

Loss to follow up was minimal – the percent of overall missing data was 7.8%. The primary efficacy endpoint was calculated using a multiple imputation placebo wash-out model: 1000 datasets were generated, and each dataset was analyzed with ANCOVA using treatment, insulin use, and metformin use as fixed effects and baseline HbA1c as a covariate. The treatment effect of pooled dulaglutide relative to placebo was -1.25% with 95% CI (-1.87, -0.84) and p-value < 0.001. The treatment effect of dulaglutide 1.5 mg relative to placebo is -1.51% with 95% CI (-2.10, -0.92) and the treatment effect of dulaglutide 0.75 mg relative to placebo was -1.19% with 95% CI (-1.78, -0.60). See Table 2

Table 2: Results for HbA1c(%) at Week 26

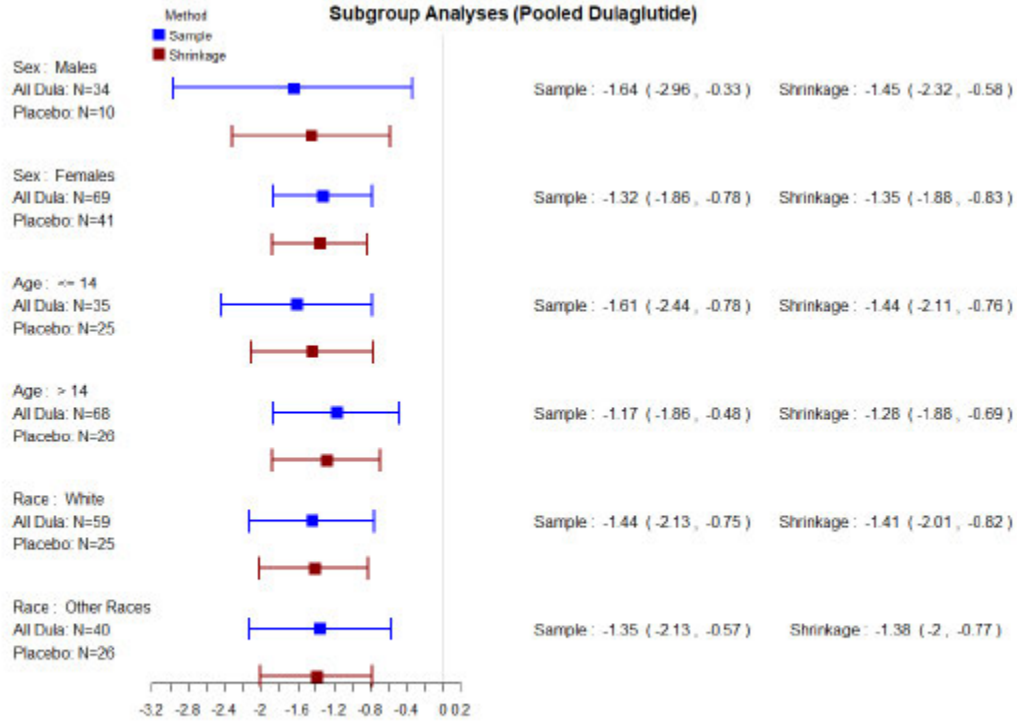
	Dula 1.5 mg (N=52)	Dula 0.75 mg (N=51)	Dula Pooled (N=103)	Placebo (N=51)
Baseline mean (SD)	8.2 (1.39)	7.9 (1.27)	8.0 (1.33)	8.1 (1.12)
Change from baseline				
LS Mean (SE)	-0.94 (0.21)	-0.62 (0.21)	-0.78 (0.15)	0.57 (0.21)
Comparison to Placebo				
LS Mean	-1.51	-1.19	-1.35	
95% C.I.	(-2.10, -0.92)	(-1.78, -0.60)	(-1.87, -0.84)	
P-value[a]	< 0.001	< 0.001	< 0.001	

a P-value (2-sided) for superiority

Source: Statistical Reviewer's Analysis and the sponsor's clinical study report (CSR) Page 67-69, 184

Subgroup analyses of sex, age, and race did not suggest differences in treatment effects across subgroups (see Figure 2).

Figure 2: Forest Plot of Subgroup Analyses: Pooled Dulaglutide for Sex, Age, and Race



Values less than 0 favor Pooled Dulaglutide
Parentheses indicate 95% Confidence/Credible intervals for sample and shrinkage estimates, respectively
Source: Statistical Reviewer's Analysis

CDTL Comment: Despite the finding that dulaglutide exposures were lower in pediatric male patients than pediatric female patients, the observed treatment effect in pediatric males and pediatric females was similar. Indeed, the point estimate of the treatment effect for pediatric males is numerically larger than the point estimate of the treatment effect for pediatric

females. If there is indeed a difference in dulaglutide exposures in males and females, the difference does not appear clinically meaningful.

7. Clinical Safety

Dr. Suchitra Balakrishnan also reviewed Study GBGC from the perspective of clinical safety. She concluded, and I concur, that the data did not indicate any new safety issues not previously identified in the adult development program. Overall, the safety profile observed in children is comparable to the safety profile observed in adults, other than a slightly higher rate of infusion site reactions in children. For details, see Dr. Balakrishnan's review.

In brief, the study collected safety data through the first 26-week double-blind treatment period and the second 26-week open-label treatment period, for a total exposure to dulaglutide of 96.1 patient-years (see Table 3.

Table 3: Summary of Exposure by Treatment, ITT

Days of exposure n (%)	Dulaglutide 0.75 mg; (N=51)	Dulaglutide 1.5 mg (N=51)	Placebo/Dulaglutide 0.75 mg; (N=51)
≥7 Days	50 (98.0)	52 (100)	50 (98.0)
≥14Days	50 (98.0)	52 (100)	50 (98.0)
≥30 Days	50 (98.0)	51 (98.1)	49 (96.1)
≥90 Days	50 (98.0)	51 (98.1)	47 (92.2)
≥180 Days	48 (94.1)	50 (96.2)	47 (92.2)
≥252 Days	46 (90.2)	49 (94.2)	46 (90.2)
≥320 Days	44 (86.2)	46 (88.5)	45 (88.2)
≥350 Days	44 (86.2)	43 (82.7)	43 (84.3)
≥365 Days	21 (41.2)	16 (30.8)	21 (41.2)

Source: FDA Clinical Review

There were no deaths and few serious adverse events observed in Study GBGC (see Table 4). Review of the serious adverse event narratives did not suggest a causal association of dulaglutide with any new adverse reaction. The most common treatment-emergent adverse events observed in Study GBGC were GI adverse events, which have a well-known and well-characterized association with the GLP-1 RA class (see Table 5).

Table 4: Serious Adverse Events by Treatment Group through Week 52

Preferred Term	Dulaglutide 1.5 mg; (N=52) n(%)	Dulaglutide 0.75mg (N=51) n(%)	Placebo/Dulaglutide 0.75 mg; (N=51) n(%)
Subjects with ≥1 SAE	3 (5.8)	2 (3.9)	3 (5.9)
Diabetic ketoacidosis			1 (2.0)
Genital herpes			1 (2.0)
Nonalcoholic fatty liver disease		1 (2.0)	
Pilonidal cyst		1 (2.0)	
Pulmonary embolism			1 (2.0)
Respiratory failure			1 (2.0)
Right ventricular failure			1 (2.0)
Stress Fracture	1 (1.9)		
Pyelonephritis	1 (1.9)		
Carbon Monoxide Poisoning	1 (1.9)		

Source: FDA Clinical Review

Table 5: Common Treatment-Emergent Adverese Events Through Week 26

Preferred Term	Dulaglutide 1.5 mg; (N=52) n(%)	Dulaglutide 0.75mg (N=51) n(%)	Placebo/Dulaglutide 0.75 mg; (N=51) n(%)
Patients with ≥1 TEAE, n (%)	38 (73.1)	38 (74.5)	35 (68.6)
Diarrhea	11 (21.2)	8 (15.7)	7 (13.7)
Vomiting	7 (13.5)	9 (17.6)	2 (3.9)
Nausea	8 (15.4)	7 (13.7)	4 (7.8)
Headache	8 (15.4)	7 (13.7)	5 (9.8)
Abdominal pain upper	5 (9.6)	3 (5.9)	4 (7.8)
Upper respiratory tract infection	6 (11.5)	2 (3.9)	4 (7.8)
Nasopharyngitis	2 (3.8)	5 (9.8)	3 (5.9)
Abdominal pain	1 (1.9)	4 (7.8)	3 (5.9)

Events Occurring in ≥5% of patients are shown

Source: FDA Clinical Review

Notable findings of the safety review included the results related to injection site reactions and hypoglycemia (see Table 6 and Table 7).

Table 6: Injection Site Reactions through Week 52

Preferred Term	Dulaglutide 1.5 mg; (N=52) n(%)	Dulaglutide 0.75mg (N=51) n(%)	Placebo/Dulaglutide 0.75 mg; (N=51) n(%)	All Dulaglutide (N=103), n (%)
Injection site reaction through week 26				
Any Injection Site Reactions	4 (7.7)	5 (9.8)	5 (9.8)	9 (8.7)
Potentially Immune Mediated	2 (3.8)	2 (3.9)	1 (2.0)	4 (3.9)
Injection site erythema	1 (1.9)	0	1 (2.0)	1 (1.0)
Injection site hypersensitivity	1 (1.9)	0	1 (2.0)	1 (1.0)
Injection site induration	0	1 (2.0)	0	1 (1.0)
Injection site pruritus	0	1 (2.0)	0	1 (1.0)
Injection site urticaria	0	1 (2.0)	0	1 (1.0)
Injection site reaction through week 52				
Any Injection Site Reactions	5 (9.6)	7 (13.7)	6 (11.8)	12 (11.7)
Potentially Immune Mediated	2 (3.8)	2 (3.9)	2 (3.9)	4 (3.9)
Injection site erythema	0	1 (2.0)	2 (3.9)	

Source: FDA Clinical Review

Table 7: Hypoglycemia Incidence through Week 26

Hypoglycemia Category	N	Incidence n (%)	Episodes (count)	Aggregated Rate per Year
Hypoglycemia with plasma Glucose < 54 mg/dL (Level 2),				
Placebo	51	1 (1.96)	1	0.04
Dula 0.75	51	2 (3.92	27	1.04
Dula 1.5	52	2 (3.85)	2	0.08
All Dulaglutide	103	4 (3.88)	29	0.56
Hypoglycemia with PG <54 mg/dL, with insulin use at baseline, without post-rescue data				
Placebo	15	1 (6.67)	1	0.13
Dula 0.75	13	2 (15.38)	27	4.18
Dula 1.5	15	1 (6.67)	1	0.13
All Dulaglutide	28	3 (10.71)	28	2.0
Hypoglycemia with PG <54 mg/dL, with no insulin use at baseline, without post-rescue data				
Placebo	36	0	0	0
Dula 0.75	38	0	0	0
Dula 1.5	37	1 (2.70)	1	0.055
All Dulaglutide	75	1 (1.33)	1	0.027
Documented symptomatic hypoglycemia with plasma Glucose <70 mg/dl excluding post-rescue data				
Placebo	51	6 (11.76)	6	0.27
Dula 0.75	51	5 (9.80)	34	1.36
Dula 1.5	52	3 (5.77)	4	0.16
All Dulaglutide	103	8 (7.77)	38	0.75

Source: FDA Clinical Review

CDTL Comment: Injection site reactions and hypoglycemia are known adverse reactions of dulaglutide. As in adults, the risk of hypoglycemia in the pediatric study was observed to be the greatest among patients who also use exogenous insulin. I concur with including these data in Section 6 of the Prescribing Information.

8. Advisory Committee Meeting

No new efficacy or safety issue rose to the level of requiring the input from an advisory panel. Therefore, an advisory committee meeting was *not* convened for sBLA 125469/S-051.

9. Pediatrics

As described above, the review of the data and information in sBLA 125469/S-051 has been determined to suffice to expand the glycemic control indication for the 0.75 mg and 1.5 mg dose to include patients with T2D aged 10 and above, to discharge PMR 2781-1, and to grant pediatric exclusivity for the 0.75 mg and 1.5 mg doses.

sBLA 125469/S-051 does not trigger any new PREA PMRs.

However, PMR 3931-1 remains outstanding. PMR 3931-1, issued at the time of the approval of the 3.0 mg and 4.5 mg doses to improve glycemic control in adults with T2D, requires a randomized controlled study of the safety, efficacy, and pharmacokinetics of the 3.0 mg and 4.5 mg doses of dulaglutide in pediatric patients ages 10 to 17 years (inclusive) with T2D.

10. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA), the Patient Labeling Team in the Division of Medical Policy Programs (DMPP), and the Office of Prescription Drug Promotion (OPDP) all reviewed sBLA 125469/S-051. See their reviews for additional details regarding their input to labeling.

I participated in the revision of the labeling and concur with the labeling recommendations of the FDA review team.

In brief, modifications to the labeling include:

- Indication: Expanding the glycemic control indication to include pediatric patients 10 years and older
- Dosage and Administration: the recommended pediatric dosage is provided as follows
    - The recommended starting dosage of TRULICITY is 0.75 mg injected subcutaneously once weekly.
    - If additional glycemic control is needed, increase the dosage to the maximum recommended dosage of 1.5 mg once weekly after at least 4 weeks on the 0.75 mg dosage.

- Adverse Reactions: updated with the information that the safety profile in children and adults is similar, except for injection site reactions (which were numerically more common in children relative to adults)
- Immunogenicity (Section 12): The labeling reports the frequency of anti-dulaglutide antibodies observed in the pediatric study and notes that the effects of these antibodies on PK, PD, safety, and/or effectiveness is unknown in pediatric patients

11. Recommendations/Risk Benefit Assessment

I recommend **Approval** of sBLA 125469/S-051 to expand the glycemic control indication of dulaglutide to include pediatric patients

I recommend discharging PREA PMR 2781-1 and granting pediatric exclusivity for the 0.75 mg and 1.5 mg doses.

PMR 3931-1 remains outstanding. PMR 3931-1, issued at the time of the approval of the 3.0 mg and 4.5 mg doses to improve glycemic control in adults with T2D, requires a randomized controlled study of the safety, efficacy, and pharmacokinetics of the 3.0 mg and 4.5 mg doses of dulaglutide in pediatric patients ages 10 to 17 years (inclusive) with T2D.

No new PMRS are recommended.

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/s/

PATRICK ARCHDEACON
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