Division Summary Memo for Regulatory Action and CDTL review

Date	
From	Patrick Archdeacon, MD Acting Associate Director for Therapeutics Division of Metabolism and Endocrinology Products
NDA # / Sequence #:	NDA 208751/S-010 and S-011
Applicant	Novo Nordisk
Date of Submission Receipt	February 21, 2018
PDUFA Goal Date	December 21, 2019
Proprietary Name / Established (USAN) names	Insulin aspart
Trade names	Fiasp
Dosage forms / Strength	Injection, 100 units/mL (U-100): 10 mL multiple-dose vial, 3 mL pen, 3 mL cartridges
Recommended Action	Approval
New Recommended Indication(s)/Populations(s)	To improve glycemic control in children with diabetes mellitus

1. Introduction

Fiasp ("faster insulin aspart"; NDA 208751) is an insulin aspart formulation approved in the United States on September 29, 2017 for subcutaneous (SC) and intravenous (IV) administration to improve glycemic control in adults with diabetes mellitus (DM). Novolog is another insulin aspart formulation [manufactured by the same Applicant (Novo Nordisk)]. The Fiasp formulation includes two additional excipients not present in NovoLog: nicotinamide (also known as niacinamide or vitamin B3) and L-arginine hydrochloride. (b) (4)

Administration of Fiasp via continuous subcutaneous insulin infusion (CSII, i.e., insulin pump) was added as a condition of use to the labeling for Fiasp on October 21, 2019, based on the review of sNDA 208751/S-008.

This document serves as the 'Summary Basis for Regulatory Action' memo for sNDA 208751/S-010 seeking to expand its indication for glycemic control to pediatric patients with diabetes mellitus and sNDA 208751/S-011 seeking to add continuous subcutaneous insulin infusion (CSII, i.e., insulin pump) as a condition of use to Fiasp in the pediatric population. The data submitted in sNDA 208751/S-010 include the results of Study 4101, conducted to fulfill PREA PMR 3253-1 (to "conduct a 26-week, randomized, controlled efficacy and safety study comparing Fiasp (insulin aspart) administered at mealtime and Fiasp (insulin aspart) administered postmeal to NovoLog administered at mealtime, in combination with insulin degludec, in pediatric patients with type 1 diabetes ages 1 to 17 years (inclusive)."

After review of the data contained in sNDA 208751/S-010 and sNDA 208751/S-011 and as detailed in this memo, I have concluded that the results suffice to expand the indication for glycemic control to pediatric patients with diabetes mellitus, including administration via CSII, given labeling that adequately conveys the benefits and risks. I have also concluded that the results of Study 4101 suffice to discharge PMR 3253-1.

This memo references the following documents/sources:

Subject	Author	Date
Clinical Review	Hyon Kwon	December 13, 2019
Clinical Pharmacology	Renu Singh	November 10, 2019
Statistics	Jennifer Clark	November 26, 2019
CDRH/ODE/GHDB	Rumi Young, Nikhil Thakur	November 18, 2019
CDRH/OHT-7/DCTD/DDDB	Jisun Yi	November 5, 2019
Office of Biotechnology Products	Anjali Shukla	November 12, 2019

Office of Prescription drug Promotion	Ankur Kalola	December 5, 2019
Patient Labeling Review	Sharon Williams, Ankur Kalola	December 4, 2019
Office of Scientific Investigations	Cynthia Kleppinger	October 30, 2019
DMEPA	Ariane Conrad	November 13, 2019

2. Background

Three PK/PD studies (Study 3888, Study 4371, and Study 4265) and one phase 3 efficacy and safety trial (Study 4101) were conducted to support expanding the indication of Fiasp for glycemic control to a pediatric population:

- Study 3888 evaluated both Fiasp and NovoLog PK/PD in children, adolescents, and adults with T1D. It was submitted under the original NDA. However, it provides supportive PD information only due to limitations with the insulin aspart assay used (it did not use a total insulin aspart assay).
- Study 4371 had the same design as Study 3888, except that it used both total and free insulin aspart ELISA assay.
- Study 4265 evaluated both Fiaps and NovoLog PK/PD in adults with T2D, using both total and free insulin aspart assays.
- Study 4101 was a 26 week randomized, three-armed parallel group trial comparing the efficacy and safety of mealtime Fiasp, postmeal Fiasp, and mealtime NovoLog.

As detailed in its agreed initial Pediatric Study Plan (iPSP), the scientific basis for expanding the indication of Fiasp for glycemic control to pediatric patients with diabetes mellitus (i.e., both T1D and T2D) is an extrapolation of efficacy based on 1) a comparative PK/PD euglycemic clamp study (Study 4265) in adults with type 2 diabetes (T2D) to show that the PK and PD differences between faster aspart and NovoLog observed in type 1 diabetes (T1D) are preserved in patients with T2D and 2) the efficacy results from a trial of intermittently dosed subcutaneous Fiasp in a pediatric population with T1D (Study 4101). The safety results of Study 4101 were also leveraged to support the extrapolation strategy. The results of Study 3888 and Study 4371 helped to inform the design and conduct of Study 4101, but were not part of the extrapolation plan.

The scientific basis for adding CSII as a condition of use to Fiasp in the pediatric population is an extrapolation of efficacy based on Study 3854 (the pump study in adults with T1D previously reviewed in sNDA 208751/S-008 to support CSII in adults), a single dose pump PK/PD study in adult subjects with T1DM (Study 4349, also previously reviewed in sNDA 208751/S-008 to support CSII in adults), and Study 4101 (described above). For details on Study 3854 and Study 4349, please see the relevant discipline reviews and the summary review for sNDA 209751/S-008.

The inspection for these efficacy supplements consisted of one domestic and two foreign clinical sites. Dr. Cynthia Kleppinger of the Office of Scientific Investigations concluded (and

I concur) that the inspectional findings support the validity of the data reported in these sNDAs.

3. CMC/Device

Dr. Anjali Shukla from the Office of Biotechnology Products in the Office of Pharmaceutical Quality reviewed the two efficacy supplements. Her reviews note that the submissions include no new CMC information and that the *in vitro* compatibility has previously been assessed by OBP and found acceptable. For that reason, she concludes (and I concur) that there are no CMC objections to sNDA 208751/S-010 and sNDA 208751/S-011.

The initial review of sNDA 208751/S-008 by Dr. Rumi Young from the Center for Devices and Radiologic Health, ODE/DAGRID/GHDB (now reorganized as OHT3/DHT3C/CDRH), supported approval of CSII in an adult population but indicated that the data submitted would not support approval of CSII in a pediatric population: (b) (4)

Dr. Jisun Yi from CDRH, Office of Health Technology 7 (OHT-7), Division of Chemistry and Toxicology Devices (DCTD), Diabetes Branch (DB) also reviewed sNDA 208751/S-010 and sNDA 208751/S-011 from the perspective of device specific clinical considerations around the pediatric pump indication. Based on the data submitted in the new efficacy supplements, Dr. Yi concluded (and I concur) that the information added to the labeling about insulin pump use with Fiasp after the review of sNDA 208751/S-008 applies to the pediatric population.

4. Nonclinical Pharmacology/Toxicology

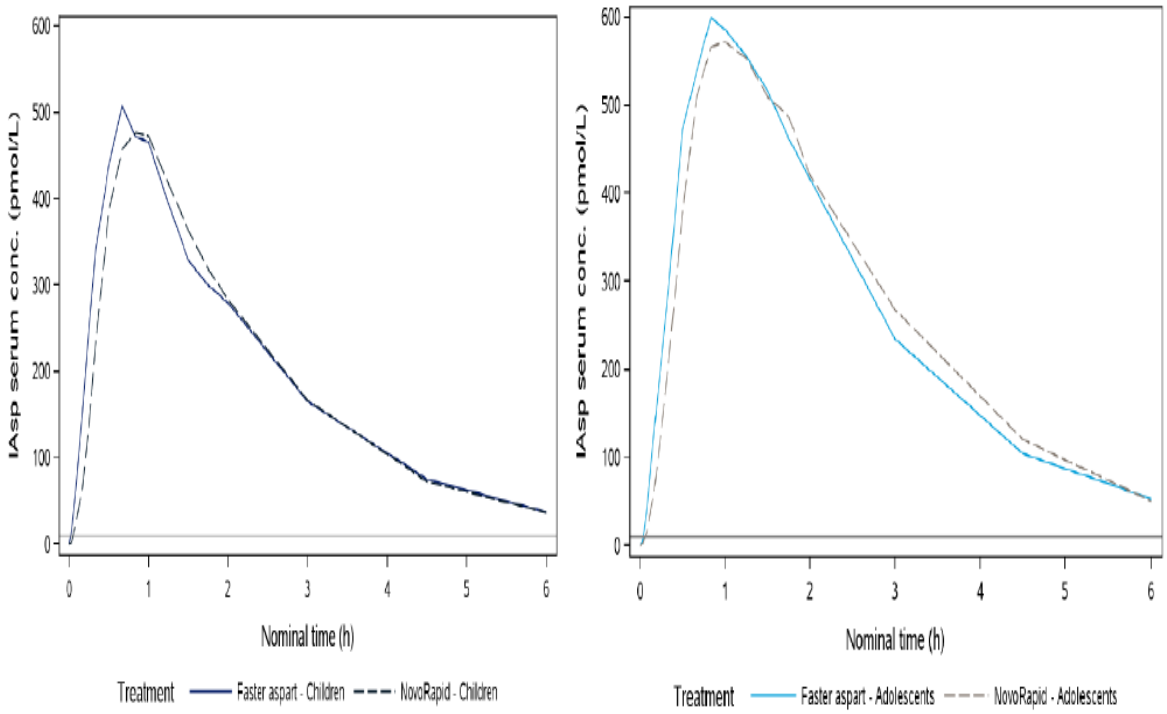
The submission does not contain new nonclinical pharmacology/toxicology data.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Renu Singh of the Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology 2 (DCP) reviewed the clinical pharmacology data for sNDAs 208751/S-010 and 208751/S-011. She concluded (and I concur) that the clinical pharmacology data is acceptable to support the use of Fiasp. Please see Dr. Singh's review for additional details.

Study 4371 (and, to a lesser degree, Study 3888) provided important support to the development of Fiasp for pediatric use. These were randomized, single-center, double-blind, single-dose of 0.2 U/kg, two-period cross-over studies that evaluated the PK of Fiasp and NovoLog in children (ages 6-11 years), adolescents (ages 12-17 years), and adults (ages 18- 64 years) with T1D. PD data were also evaluated using a meal test. In accordance with the objectives of the iPSP, the results demonstrated that the differences between Fiasp and NovoLog (administered as subcutaneous boluses) in PK and PD observed in adults with T1D were preserved in children and adolescents with T1D (see Figure 1).

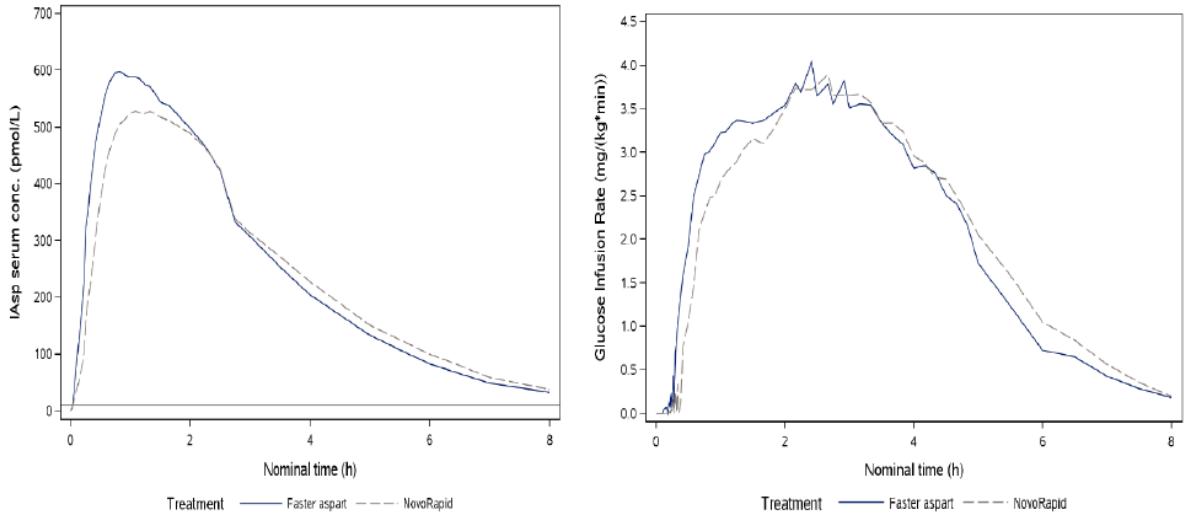
Figure 1: Mean PK in children and adolescents of Fiasp and NovoLog in Study 4371



Source: Module 2.7.2 Summary of Clinical Pharmacology Studies

As outlined in the iPSP, Study 4265 supported the extrapolation of the glycemic control indication to the pediatric T2D population: it was a randomized, single-center, double-blind, single-dose, two-period, cross-over, active-comparator study investigating the PK and PD of Fiasp in adults with T2D in the context of a euglycemic clamp. Fiasp demonstrated an earlier onset of exposure and greater early and maximum exposures compared with NovoLog, with a comparable total insulin exposure.

Figure 2: Mean PK (left) and mean GIR (right) profiles of Fiasp and NovoLog in Study 4265



Source: Module 2.7.2 Summary of Clinical Pharmacology Studies

Dr. Singh concluded that the overall unit dose-response of Fiasp and NovoLog were comparable, despite observed PK/PD profile differences. Dr. Singh concluded that the differences with regard to the PK/PD profiles of the two products that were initially observed in adults and in patients with T1D were preserved in children and adolescents and in patients with T2D. Dr. Singh deferred assessment of the efficacy, safety, and risk-benefit for Study 4101 to the Statistical and Clinical reviewers.

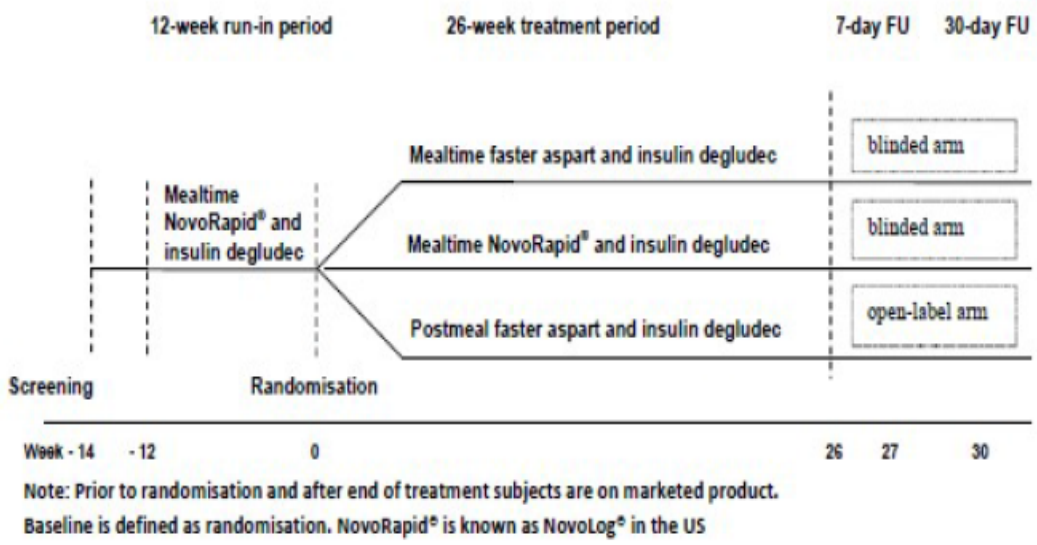
6. Clinical/Statistical- Efficacy

Dr. Jennifer Clark of the Office of Biostatistics (OB), Division of Biometrics II (DBII) and Hyon Kwon of the Office of New Drugs (OND), Division of Metabolism and Endocrinology Products reviewed the data from study 4101 (the clinical study submitted to support a finding of efficacy and safety of Fiasp in pediatric patients with T1D). Dr. Jennifer Clark concluded that the primary objective of study 4101 (to demonstrate the non-inferiority of Fiasp to NovoLog with regard to improved glycemic control) was achieved: the primary endpoint of difference in change in HbA1c for both mealtime Fiasp and postmeal Fiasp met the pre-specified non-inferiority margin of 0.4%. Dr. Clark also concluded that mealtime Fiasp demonstrated superiority over mealtime NovoLog for the primary endpoint of change in HbA1c.

Study 4101 was a 26-week, multicenter, partly double-blind, randomized, active-controlled, three-armed parallel trial to compare the efficacy and safety of mealtime Fiasp, postmeal Fiasp, and mealtime NovoLog (all in combination with insulin degludec) in children and adolescents (ages 1-17 years) with T1D. Due to the timing of the dose administration, the postmeal Fiasp arm was not blinded. However, the two meal-time study arms were blinded to treatment. Please see Dr. Clark's and Hyon Kwon's reviews for additional study details,

including those related to inclusion/exclusion criteria, the 12-week run-in period, and the methodologies of the statistical analyses.

Figure 3: Design of Study 4101



Source: Study 4101 Clinical Study Report

The study screened 933 patients, of which 777 were enrolled and randomized to treatment. Almost all the subjects completed the study (see Table 1). Baseline demographics were balanced across treatment arms (see Table 2).

Table 1: Patient disposition in Study 4101

	Meal Fiasp N (%)	Postmeal Fiasp N (%)	Meal NovoLog N (%)
Screened	933		
Screening failures	99		
Run-in failures	57		
Randomized	**260**	**259**	**258**
Premature discontinuation	**6 (2.3%)**	**9 (3.5%)**	**6 (2.3%)**
Adverse event	0	0	0
Hypoglycemia	0	0	0
Decision of subject	0	3 (1.2%)	3 (1.2%)
Decision of parent/guardian	3 (1.2%)	2 (0.8%)	0
Other	3 (1.2%)	4 (1.5%)	3 (1.2%)
Withdrawal from trial	**4 (1.5%)**	**8 (3.1%)**	**5 (1.9%)**
Adverse event	0	0	0
Lost to follow-up	0	0	0
Withdrawal by subject	0	1 (0.4%)	4 (1.6%)
Other	0	3 (1.2%)	0
Completed treatment period	254 (97.9%)	250 (96.5%)	252 (97.7%)
Completed trial period	**256 (98.5%)**	**251 (96.9%)**	**253 (98.1%)**

Source: FDA Clinical Review

Table 2: Baseline demographic characteristics in Study 4101

	Treatment Group			
Demographic Parameters	Meal Fiasp (N=260) n (%)	Postmeal Fiasp (N=259) n (%)	Meal NovoLog (N=258) n (%)	Total (N= 777) n (%)
Sex				
Male	134 (51.5)	137 (52.9)	148 (57.4)	419 (53.9)
Female	126 (48.5)	122 (47.1)	110 (42.6)	358 (46.1)
Age				
Mean years (SD)	11.72 (3.74)	11.62 (3.65)	11.70 (3.44)	11.68 (3.61)
Median (years)	12.00	12.00	12.00	12.00
Min; max (years)	2.0; 17.0	2.0; 17.0	4.0; 17.0	2.0; 17.0
Age Group				
1 to <6 years	16 (6.2)	16 (6.2)	14 (5.4)	46 (5.9)
1 to <3 years	2 (0.8)	2 (0.8)	0	4 (0.5)
3 to <6 years	14 (5.4)	14 (5.4)	14 (5.4)	42 (5.4)
6 to <12 years	100 (38.5)	100 (38.6)	101 (39.1)	301 (38.7)
12 to <18 years	144 (55.4)	143 (55.2)	143 (55.4)	430 (55.3)
Race				
White	206 (79.2)	217 (83.8)	209 (81.0)	632 (81.3)
Black or African American	6 (2.3)	4 (1.5)	5 (1.9)	15 (1.9)
Asian	46 (17.7)	37 (14.3)	43 (16.7)	126 (16.2)
American Indian or Alaska Native	0	1 (0.4)	1 (0.4)	2 (0.3)
Other	2 (0.8)	0	0	2 (0.3)
Ethnicity				
Hispanic or Latino	16 (6.2)	17 (6.6)	12 (4.7)	45 (5.8)
Not Hispanic or Latino	244 (93.8)	242 (93.4)	246 (95.3)	732 (94.2)
Region				
Europe	147 (56.5)	160 (61.8)	150 (58.1)	457 (58.8)
North America	67 (25.8)	62 (23.9)	66 (25.6)	195 (25.1)
Asia	46 (17.7)	37 (14.3)	42 (16.3)	125 (16.1)

N=number of subjects

Source: Study 4101 Clinical Study Report

The hypotheses tested in a stepwise hierarchical order to control type 1 error were:

- Non-inferiority of meal-time Fiasp compared to meal-time NovoLog in the change from baseline in HbA1c after 26 weeks of treatment;
- Non-inferiority of post-meal Fiasp compared to meal-time NovoLog in the change from baseline in HbA1c after 26 weeks of treatment;
- Superiority of meal-time Fiasp versus meal-time NovoLog in the change from baseline in HbA1c after 26 weeks of treatment.

These primary endpoints were analyzed according to a multiple imputation regression with a missing at random (MAR) assumption for all patients missing Week 26 HbA1c measurements. The analysis was run for 100 imputed datasets using an ANCOVA model with baseline HbA1c, treatment, age strata, and region. Subgroup analyses were done for age, race, sex, and geographic region.

Table 3: Efficacy results from Study 4101

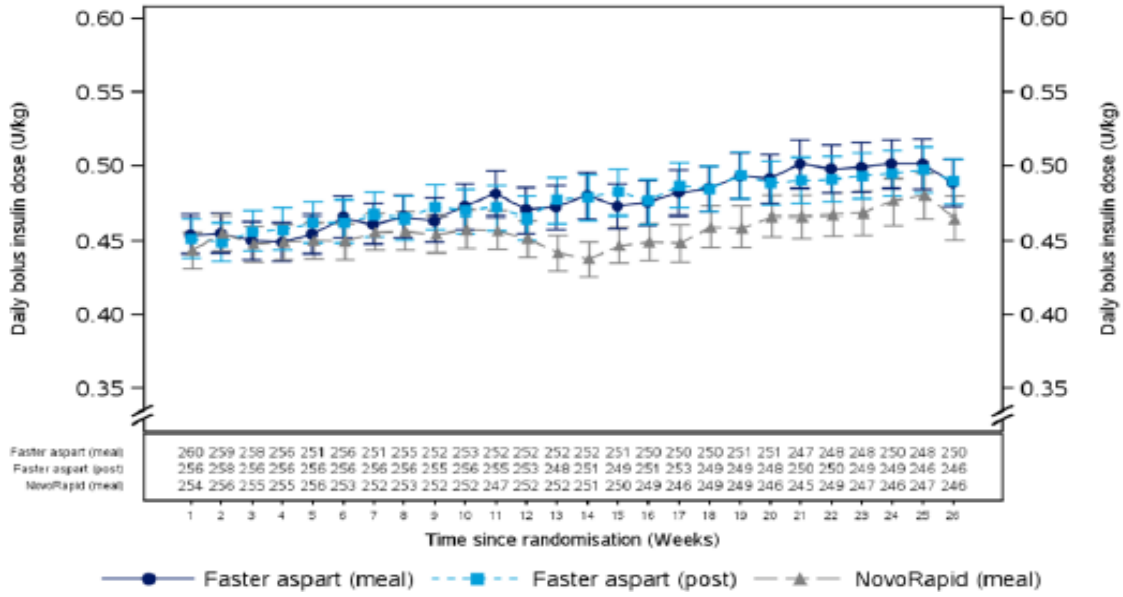
	Mealtime FIASP	Post-meal FIASP	NovoLog
N	260	259	258
Mean Baseline (Std. Dev.)	7.57 (0.80)	7.58 (0.84)	7.53 (0.83)
Week 26 Change from Baseline	0.06 (0.05)	0.35 (0.05)	0.22 (0.05)
Treatment Diff vs NovoLog (95% CI)	-0.17 (-0.3, -0.03)	0.13 (-0.01, 0.26)	.

Source: FDA Statistical Review

On their face, the analyses as confirmed by Dr. Clark support all three hypotheses tested in the hierarchical order (non-inferiority of meal-time Fiasp to meal-time NovoLog, non-inferiority of post-meal Fiasp to meal-time NovoLog, superiority of meal-time Fiasp to meal-time NovoLog). Dr. Clark's review also noted imbalances not favoring Fiasp for events of blood glucose (BG) confirmed hypoglycemia (less than 56 mg/dL) and a trend towards slightly higher median bolus doses for mealtime Fiasp compared to postmeal Fiasp and mealtime NovoLog. Overall, Dr. Clark concluded that statistical evidence of efficacy from this submission support approval for a pediatric indication for mealtime Fiasp and that "while evidence is less conclusive concerning post meal Fiasp, results from this arm should be included if this will be a viable option that patients may choose when prescribed this treatment."

Hyon Kwon's review also discussed insulin dose when interpreting the efficacy results. She concluded that the differences in the meal daily bolus insulin dose across treatment arms were small and appeared unlikely to have a large impact on the primary analysis (see Figure 4).

Figure 4: Mean Daily Bolus Insulin Dose in U/kg by Treatment Week in Study 4101



Source: Study 4101 Clinical Study Report

Hyon Kwon concurred with Dr. Clark that the statistical analyses of the primary endpoints meet pre-specified criteria for all three hypotheses. Based on the efficacy data in 4101 and also the clinical pharmacology studies and the clinical trials previously reviewed, she concluded that both mealtime Fiaps and postmeal Fiasp have efficacy with regards to glycemic control in pediatric patients with diabetes. While she did not believe differences in insulin doses across treatment arms were likely to have had a significant impact on the primary analysis, she (b) (4) , due to an accompanying observation of a numerical imbalance in blood glucose confirmed hypoglycemic events not favoring Fiasp. I concur with these conclusions.

7. Safety

Hyon Kwon also evaluated the clinical data from Study 4101 from the perspective of overall safety, in order to make a benefit-risk assessment regarding expanding the indication for Fiasp.

Deaths

One death was reported in the trial: a 12-year old drowned at sea during the second follow-up period. This death did not appear treatment related.

Serious Adverse Events (SAEs)

There were relatively few SAEs observed during the conduct of Study 4101. Of these, the majority related to infections and hypoglycemia.

Hypoglycemia

Events of hypoglycemia (both serious and non-serious) comprised the focus of the safety review of Study 4101. Serious events were infrequent: a total of 3 events were observed in the mealtime Fiasp arm, compared to 8 events in the postmeal Fiasp arm and 4 events in the mealtime NovoLog arm. Given the small number of events, Hyon Kwon did not arrive at any conclusions regarding whether these numeric differences suggest a true difference for the risk of severe hypoglycemic events across these treatment strategies. Events of symptomatic and asymptomatic hypoglycemia (defined as confirmed BG less than 56 mg/dL), on the other hand, were frequent in Study 4101 (see Table 4).

Table 4: Summary of BG Confirmed, Severe or BG Confirmed, and Severe Hypoglycemia in Study 4101

	Meal-time Fiasp			Post-meal Fiasp			Meal-time NovoLog		
Number of subjects	261			258			258		
Total exposure (yrs)	128.4			127.7			127.7		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
BG confirmed	**228 (87.4)**	**3580**	**2788**	**227 (88.0)**	**3586**	**2809**	**217 (84.1)**	**3272**	**2563**
Daytime	226 (86.6)	3184	2480	224 (86.8)	3112	2438	217 (84.1)	2960	2319
Nocturnal	112 (42.9)	396	308	125 (48.4)	474	371	104 (40.3)	312	244
Severe or BG confirmed*	**228 (87.4)**	**3583**	**2791**	**227 (88.0)**	**3594**	**2815**	**217 (84.1)**	**3276**	**2566**
Rate ratio vs NovoLog (95% CI)	1.11 (95% CI: 0.90, 1.37)			1.11 (95% CI: 0.90, 1.37)					
Daytime	226 (86.6)	3187	2482	224 (86.8)	3117	2442	217 (84.1)	2963	2321
Nocturnal	112 (42.9)	396	308	125 (48.4)	477	374	104 (40.3)	313	245
Severe or BG confirmed by age group									
1 to <6 years	15 (93.8)	243	3031	15 (93.8)	289	3616	12 (85.7)	163	2331
6 to <12 years	88 (87.1)	1540	3042	93 (93.9)	1490	3018	83 (82.2)	1472	2942
12 to <18 years	125 (86.8)	1800	2580	119 (83.2)	1815	2582	122 (85.3)	1641	2323
Severe	**3 (1.1)**	**3**	**2**	**8 (3.1)**	**8**	**6**	**4 (1.6)**	**4**	**3**
Rate ratio vs NovoLog (95% CI)	0.77 (0.17; 3.45)			2.11 (0.63; 7.02)					
Daytime	3 (1.1)	3	2	5 (1.9)	5	4	3 (1.2)	3	2
Nocturnal	0			3 (1.2)	3	2	1 (0.4)	1	1
Severe by age group									
6 to <12 years	2 (2.0)	2	4	4 (4.0)	4	8	3 (3.0)	3	6
12 to <18 years	1 (0.7)	1	1	4 (2.8)	4	6	1 (0.7)	1	1

N=number of subjects; E=number of events; R= event rate per 100 patient-years of exposure;
*Severe according to ISPAD 2014 classification and/or have a recorded plasma glucose <56 mg/dL;
Nocturnal is defined period between 23:00 and 07:00, both inclusive.

Source: Study 4101 Clinical Study Report

Hyon Kwon noted in her clinical review imbalances not favoring Fiasp with regard to BG confirmed hypoglycemia and BG confirmed nocturnal hypoglycemia for both the mealtime Fiasp arm and the postmeal Fiasp arm. While nominal statistical significance was met only for the safety endpoint of "severe or blood glucose confirmed nocturnal hypoglycemia", Study 4101 was not designed or powered to detect differences across treatment arms of the endpoint of BG confirmed hypoglycemia.

CDTL comment: Particularly in pediatric patients, events of blood glucose less than 56 mg/dL are considered clinically important. While the results of Study 4101 do not support a definitive conclusion that the Fiasp treatment strategies studied will result in higher rates of these events than the NovoLog-based treatment strategy, these data are concerning. While they do not preclude a finding of a favorable benefit-risk assessment for the use of Fiasp in pediatric patients, it should be communicated in the labeling that higher rates of BG confirmed events of hypoglycemia were observed with the Fiasp treatment arms than with the NovoLog treatment arm in Study 4101. This is particularly important to place into context the finding that mealtime Fiasp was statistically superior to mealtime NovoLog for the primary endpoint of change from baseline of HbA1c.

8. Advisory Committee Meeting

No new efficacy or safety issue rose to the level of requiring input from an advisory panel. Therefore, an advisory committee meeting was *not* convened for this NDA.

9. Pediatrics

The focus of these two efficacy supplements relate to pediatric studies and indications. On the basis of this review, the indication of Fiasp will be expanded to included pediatric patients with diabetes (both T1D and T2D). In addition, the existing labeling regarding use of CSII will be extended to pediatric patients. Finally, the data in these submissions has been deemed sufficient to discharge PREA PMR 3253-1.

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 the two efficacy supplements. Please see their respective reviews for details.

Based on input from OPDP and on internal deliberations regarding the interpretation of the efficacy data in the context of the observed imbalances in blood glucose confirmed hypoglycemic events not favoring Fiasp in the pivotal pediatric clinical study, I recommend the following approach to labeling:

Indication and Usage: expand indication to pediatric patients with diabetes mellitus

Dosage and Administration: no changes to CSII labeling; current labeling is applicable to the pediatric population

Adverse Reactions: Add adverse reactions data (including hypoglycemia data) observed with Fiasp from Study 4101; add statement that patients ins pediatric study reported a higher rate of BG confirmed hypoglycemia and nocturnal BG confirmed hypoglycemia with Fiasp than with NovoLog.

Pediatric Use (Section 8/4): Add statement that the safety and effectiveness of Fiasp has been established to improve glycemic control in pediatric patients with diabetes mellitus. Also include statement that Fiasp may cause hypoglycemia and to monitor closely.

Clinical Trials: Add Study 4101, including results of primary analysis of efficacy endpoints. Include estimands and 95% confidence intervals, but remove language (b) (4)

11. Recommendations

- Recommended Regulatory Action

Approval: I recommend approval of sNDA 208751/S-010 and sNDA 208751/S-011 to expand the indication of Fiasp to pediatric patients with diabetes. See Section 10 (Labeling) for details about labeling recommendations.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

Recommendation for other Postmarketing Requirements and Commitments

Recommend discharging PREA PMR 3253-1. No recommendation for new PMRs/PMCs.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PATRICK ARCHDEACON
12/15/2019 04:31:45 PM