CLINICAL REVIEW

Application Type	Efficacy supplement
Application Number(s)	sNDA 208751/S-10 and S-11
Priority or Standard	Standard
Submit Date(s)	February 21, 2019
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Division/Office	Division of Metabolism and Endocrinology Products (DMEP)
Reviewer Name(s)	Hyon Kwon, PharmD, MPH
Review Completion Date	
Established/Proper Name	Insulin aspart
(Proposed) Trade Name	Fiasp
Applicant	Novo Nordisk
Dosage Form(s)	Injection, 100 units/mL (U-100): 10 mL multiple-dose vial, 3 mL pen, 3 mL cartridges for use in a cartridge device
Applicant Proposed Dosing Regimen(s)	Individualized
Applicant Proposed Indication(s)/Population(s)	To improve glycemic control in children with diabetes mellitus
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Not applicable

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BG	Blood glucose
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
iPSP	initial Pediatric Study Plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PG	plasma glucose
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment

PMR	postmarketing requirement
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SMPG	Self-measured plasma glucose
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Fiasp is insulin aspart injection. Insulin aspart is an analogue of human insulin where the amino acid proline has been replaced with aspartic acid in position B28 and is produced by recombinant DNA technology using *Saccharomyces cerevisiae* (baker's yeast). Compared to NovoLog, another insulin aspart formulation which was used as an active control in clinical studies supporting the original FDA approval of Fiasp, Fiasp contains 2 additional excipients: nicotinamide (also known as niacinamide or vitamin B3) and L-arginine hydrochloride. (b) (4)

Fiasp was approved in the U.S. for subcutaneous (SQ) and intravenous (IV) administration to improve glycemic control in adults with diabetes mellitus on September 29, 2017. On October 21, 2019, Fiasp was approved for administration to adults with diabetes mellitus via continuous subcutaneous insulin infusion (CSII) in the U.S (sNDA 208761-008).

Supplement #10 intends to expand the indication to support the use of Fiasp in pediatric patients with diabetes mellitus.

Supplement #11 intends to support CSII use of Fiasp in insulin pump in pediatric patients with diabetes mellitus.

1.2. Conclusions on the Substantial Evidence of Effectiveness

I recommend approval of Supplement #10 and #11 submitted to NDA 208751. My recommendation is consistent with the recommendations of all review disciplines.

The efficacy of Fiasp in pediatric patients with type 1 diabetes mellitus (T1DM) was supported by the results from trial 4101. This trial evaluated the efficacy and safety of meal-time Fiasp and post-meal Fiasp compared to meal-time NovoLog, all in combination with insulin degludec as basal insulin, in pediatric patients 2-17 years of age with type 1 diabetes mellitus.

All subjects underwent 12 weeks of run-in period to titrate insulin degludec before randomization. During 26 weeks of treatment period, the bolus insulin doses were optimized individually in a treat-to-target fashion according to the pre-meals and bedtime glucose levels following standardized titration algorithms. After 26 weeks, meal-time Fiasp was shown to be statistically superior to meal-time NovoLog with treatment difference of -0.17% (95% CI: -0.30, -0.03), and post-meal Fiasp was shown to be not inferior to meal-time NovoLog with a non-

inferiority margin of 0.4% (Table 8).

In trial 4101, there were very few severe hypoglycemic episodes in each treatment group making treatment comparisons inconclusive; 3 events (2/100 person-year exposure [PYE]) with meal-time Fiasp, 8 events (6/100 PYE) with post-meal Fiasp, and 4 events (3/100 PYE) with NovoLog. The incidence of blood glucose (BG) hypoglycemia was numerically higher with meal-time Fiasp (2788/100 PYE) and post-meal Fiasp (2809/100 PYE) compared to NovoLog (2563/100 PYE).

The incidence of nocturnal 'severe or BG confirmed' hypoglycemia was numerically higher with meal-time Fiasp compared to NovoLog (rate ratio 1.29 [95% CI: 0.93, 1.79]) and was numerically and nominally statistically higher with post-meal Fiasp compared to NovoLog (rate ratio 1.5 [95%CI: 1.09, 2.08]). This was mainly driven by an imbalance in the nocturnal BG confirmed hypoglycemia since there were very few nocturnal severe hypoglycemic events.

Given this numerical imbalance in hypoglycemia not favoring Fiasp compared to NovoLog, (b) (4) Based on the observed imbalances in the overall and nocturnal BG confirmed hypoglycemia with Fiasp compared to NovoLog, more close blood glucose monitoring may be warranted in pediatric patients with diabetes when using Fiasp.

The Applicant submitted a comparative pharmacokinetics (PK)/pharmacodynamics (PD) clinical pharmacology study 4265 using euglycemic clamp procedure in adults with type 2 diabetes mellitus (T2DM). The results of trial 4265 showed that the PK and PD differences between Fiasp and NovoLog, as noted in T1DM, are preserved in T2DM patients. As outlined in August 11, 2015 Agreed Initial Pediatric Study Plan (iPSP; see Section 3.2 for details on agreement), based on the PK/PD results from trial 4265 in adults with T2DM combined with efficacy results from trial 4101 in pediatric patients with T1DM, the efficacy results from pediatric T1DM can be extrapolated to pediatric T2DM patients ages 10 and above. The safety results from trial NN4101 can also be leveraged to support this extrapolation.

In support of Supplement #11 for Fiasp use in insulin pump in pediatric patients with diabetes mellitus, the Applicant proposed extrapolation of the following efficacy results, as outlined in the Agreed iPSP:

- Efficacy data from Phase 3b pump efficacy and safety trial 3854 in adult patients with T1DM;
- Single dose pump PK/PD study 4349 in adults with T1DM; and
- Efficacy data from subcutaneous efficacy and safety trial 4101 in pediatric patients with T1DM.

Efficacy results of trial 3854 and clinical pharmacology study 4349 were reviewed under

Supplement #8 for Fiasp use in insulin pump in adult patients with diabetes, which was approved on October 21, 2019. The efficacy data from trial 4101 is discussed in this review under Supplement #10 to support the use of Fiasp in pediatric patients with diabetes. In addition, the Applicant is leveraging the safety and dosing information from trials 3854 and 4101 for Supplement #11. Extrapolation and leveraging adult pump data for use of pumps in the pediatric population is acceptable based on the results from trials 3854, 4349, and 4101.

Trial 4101 fulfills the Pediatric Research Equity Act (PREA) Postmarketing Requirement (PMR) 3253-1, which was 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).

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Diabetes is a chronic serious medical disease, and insulin therapy is critical for management of glycemic control in patients with type 1 diabetes as their pancreas do not make insulin.

To support the use of Fiasp in pediatric population the Applicant conducted trial 4101, which was a multicenter, multinational, randomized, partly double-blind, randomized, active-control, treat-to-target trial comparing the effect and safety of meal-time Fiasp, post-meal Fiasp, and meal-time NovoLog, all given with insulin degludec as basal-bolus regimen in pediatric subjects with T1DM. The primary objective was to show the non-inferiority of meal-time Fiasp compared to NovoLog, then non-inferiority of post-meal Fiasp compared to NovoLog, and finally superiority of meal-time Fiasp compared to NovoLog. Hierarchical testing was done to control for type 1 error.

After 26 weeks of treatment period, the mean change from baseline in HbA1c remained stable with meal-time Fiasp (0.06%) and increased with post-meal Fiasp (0.35%) and meal-time NovoLog (0.22%).

The estimated treatment difference between meal-time Fiasp and NovoLog was -0.17 (95% CI: -0.31, -0.04), establishing non-inferiority of meal-time Fiasp compared to meal-time NovoLog as the upper limit of 95% CI for the difference between meal-time Fiasp and NovoLog was <0.4% and met the non-inferiority margin. In addition, the superiority of meal-time Fiasp compared to meal-time NovoLog was confirmed as the upper bound of 95% CI was <0.

The estimated treatment difference between post-meal Fiasp and NovoLog was 0.13 (95% CI: -0.01, 0.26), establishing non-inferiority of post-meal Fiasp compared to meal-time NovoLog as the upper limit of 95% CI for the difference between post-meal FIasp and NovoLog was <0.4% and met the non-inferiority margin.

There were very few severe hypoglycemic episodes in each treatment group making it difficult to compare across treatment groups; 3 events (2/100 PYE) with meal-time Fiasp, 8 events (6/100 PYE) with post-meal Fiasp, and 4 events (3/100 PYE) with NovoLog. There was a numerical imbalance in the incidence of BG confirmed hypoglycemia not favoring meal-time Fiasp (2788/100 PYE) and post-meal Fiasp (2809/100 PYE) compared to NovoLog (2563/100 PYE). The incidence of nocturnal 'severe or BG confirmed' hypoglycemia was numerically higher with meal-time Fiasp (308/100 PYE) and post-meal Fiasp (374/100 PYE) compared to NovoLog (245/100 PYE). The estimated risk ratio for the endpoint of nocturnal 'severe or BG confirmed hypoglycemia' for meal-time Fiasp compared to NovoLog was 1.29 (95% CI: 0.93, 1.79) and for post-meal

Fiasp compared to NovoLog reached nominal statistical significance (1.50 [95% CI: 1.09, 2.08]). This imbalance was mainly driven by an imbalance in the nocturnal BG confirmed hypoglycemia since there were very few nocturnal severe hypoglycemic events.

The overall incidence of injection site reaction was numerically higher with post-meal Fiasp compared to NovoLog.

The overall incidence of lipodystrophy and allergic reactions were numerically higher with meal-time Fiasp compared to NovoLog.

In summary, the overall data from trial 4101 demonstrated that the meal-time Fiasp and post-meal Fiasp was not inferior (with margin of 0.4%) to meal-time NovoLog when used as basal-bolus regimen in pediatric patients with T1DM. The trial also showed statistical superiority in HbA1c reduction with meal-time Fiasp compared to NovoLog since the upper bound of 95% CI was <0. However, this small benefit in HbA1c reduction with meal-time Fiasp compared to NovoLog was offset by a numerical imbalance in BG confirmed hypoglycemia not favoring both meal-time and post-meal Fiasp compared to NovoLog. There was also an imbalance in nocturnal 'severe or BG confirmed' hypoglycemia with meal-time and post-meal Fiasp compared to NovoLog, which was mostly driven by nocturnal BG confirmed hypoglycemia.

Given this numerical imbalance in hypoglycemia not favoring Fiasp compared to NovoLog, (b) (4) . With adequate labeling of observed imbalance in hypoglycemia with Fiasp in pediatric patients and recommending more close monitoring of blood glucose in pediatric patients with Fiasp, I believe that the safety concerns are addressed and the overall benefit-risk for Fiasp use in pediatric patients with diabetes is favorable.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Diabetes is a chronic serious medical disease. Patients with type 1 diabetes do not make insulin which leads to hyperglycemia. Data from the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) showed that	Diabetes is a serious and life-threatening condition that if left untreated leads to an increased risk for morbidity and mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	improvement in long term glucose control through intensified insulin therapy can reduce the incidence of complications and delay progression of complications related to type 1 diabetes. Type 2 diabetes mellitus (T2DM) is a condition of chronic impaired glucose homeostasis leading to chronic hyperglycemia and an increased risk for microvascular (e.g., retinopathy, nephropathy, and neuropathy) and macrovascular (e.g., myocardial infarction, stroke) complications. The Center for Disease Control (CDC) estimates that there are nearly 30 million patients with T2DM in the United States.	
Current Treatment Options	• For Type 1 diabetes, insulin therapy is critical for treatment of hyperglycemia. Insulin can be given as subcutaneous injections in a basal-bolus regimen or as continuous subcutaneous insulin infusion in a pump setting. Types of available insulin include short-acting (regular) insulin, rapid-acting insulin analogs, intermediate-acting (NPH) insulin, and long-acting insulin analogs. Examples of short-acting (regular) insulin include Humulin R and Novolin R. Rapid-acting insulin analogs include insulin glulisine (Apidra), insulin lispro (Humalog), and insulin aspart (NovoLog). Long-acting insulin analogs include insulin glargine (Lantus, Toujeo Solostar), insulin detemir (Levemir), and insulin degludec (Tresiba). Intermediate-acting insulins include insulin NPH (Novolin N, Humulin N). • For Type 2 diabetes, there are currently 12 pharmacologic classes of antihyperglycemic medications (generally with multiple members within each class) approved to improve glycemic control in patients with T2DM. Many of these are also approved as fixed combination drug products (FCDP).	Insulin therapy is critical for glycemic control in patients with type 1 diabetes as their pancreas do not make insulin. Insulin can be given subcutaneously as basal-bolus regimen or as continuous subcutaneous insulin infusion in a pump setting to achieve strict blood glucose control. Despite many available treatment options for glycemic control, many patients with T2DM continue to have difficulty with achieving the desired degree of glycemic control. In addition, T2DM is a progressive disorder and patients typically need additional agents as the disease progresses over time.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The results from a 26-week, randomized, partly double-blind, active-control, treat-to-target trial 4101 in pediatric population demonstrated that the glycemic control with meal-time Fiasp was superior to meal-time NovoLog, both in combination with insulin degludec, with estimated treatment difference of -0.17% (95% CI: -0.31, -0.04). • Trial 4101 in pediatric population demonstrated that the glycemic control with post-meal Fiasp was non-inferior to meal-time NovoLog, both in combination with insulin degludec.	Study 4101 demonstrated that the meal-time Fiasp will lead to superior glycemic control compared to meal-time NovoLog when used in combination with insulin degludec after 26 weeks in pediatric patients with T1DM. In addition, post-meal Fiasp will lead to non-inferior glycemic control compared to meal-time NovoLog when used in combination with insulin degludec after 26 weeks in pediatric patients with T1DM.
Risk and Risk Management	• There were very few severe hypoglycemic episodes in each treatment group making treatment comparisons inconclusive; 3 events with meal-time Fiasp, 8 events with post-meal Fiasp, and 4 events with NovoLog. • The incidences of BG confirmed hypoglycemia were numerically higher with meal time and post-meal Fiasp compared to NovoLog. • The incidence of nocturnal 'severe or BG confirmed' hypoglycemia was numerically and nominally statistically higher with post-meal Fiasp compared to NovoLog (rate ratio 1.5 [95% CI: 1.09, 2.08]), while was numerically higher with meal-time Fiasp compared to NovoLog (rate ratio 1.29 [95% CI: 0.93, 1.79]); this was mainly driven by an imbalance in the nocturnal BG confirmed hypoglycemia since there were few nocturnal severe hypoglycemic events. • The incidence of injection site reaction was numerically higher with post-meal Fiasp compared to NovoLog. • The incidence of lipodystrophy and allergic reactions were numerically higher with meal-time Fiasp compared to NovoLog.	The adverse reactions and safety profile of Fiasp use in pediatric population will be added to labeling to communicate safety concerns.

1.4. Patient Experience Data

Not applicable. Patient experience data (e.g., information about patients' experience with a disease or condition, including the impact of such disease or condition, or a related therapy, on patients' lives; and patient preferences with respect to treatment of such disease or condition) were not submitted nor reviewed as part of this sNDA.

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia. There are two main types of diabetes mellitus: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM is an autoimmune disease characterized by an immune-mediated depletion of beta-cells that leads to lifelong dependence on exogenous insulin and is one of chronic diseases prevalent in pediatric patients. Improvement in long term glycemic control can reduce the incidence of complications and delay the progression of complications related to diabetes mellitus. T2DM is characterized by autoimmune destruction of pancreatic beta-cells leading to loss of insulin secretion with insulin resistance, with inadequate insulin production to maintain euglycemia.

The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommended an HbA1c range of <7.5%, and that each child should have their HbA1c target individualized with the goal of achieving HbA1c as normal as possible while avoiding severe hypoglycemia and frequent mild to moderate hypoglycemia[1]. American Diabetes Association (ADA) also recently recommended treatment HbA1c target of <7.5% for all pediatric age groups.[2]

2.2. Analysis of Current Treatment Options

For Type 1 diabetes, insulin therapy is needed for the treatment of hyperglycemia, and can be given as subcutaneous injection in basal-bolus regimen or continuous insulin infusion in a pump setting. The types of insulin include short-acting (regular) insulin, rapid-acting insulin, intermediate-acting (NPH) insulin, and long-acting insulin. Examples of short-acting (regular) insulin include Humulin R and Novolin R. Rapid-acting insulin include insulin glulisine (Apidra), insulin lispro (Humalog), and insulin aspart (NovoLog). Long-acting insulins include insulin glargine (Lantus, Toujeo Solostar), insulin detemir (Levemir), and insulin degludec (Tresiba). Intermediate-acting insulins include insulin NPH (Novolin N, Humulin N).

Type 2 diabetes mellitus can be treated with a combination of proper diet, exercise, and one or more of the drug products presented in Table 1. Fixed-combination drug products (FCDP) and injectable insulin plus non-insulin FCDPs are not shown.

[1] Rewers MJ, Pillay K, de Beaufort C et al. ISPAD Clinical Practice Consensus Guidelines 2014. Assessment and monitoring of glycemic control in children and adolescents with diabetes. Pediatric Diabetes 2014; 15:102-14.
[2] Chiang JL, Kirkman MS, Laffel LMB, Peters AL. Type 1 diabetes through the life span: A position Statement of the American Diabetes Association. Diabetes Care, 2014:37:2034-54.

Table 1: Approved Drug Products for the Management of Type 2 Diabetes Mellitus

Pharmacologic Class	Antihyperglycemic Drug Products*
ALPHA-GLUCOSIDASE INHIBITORS	Acarbose; Meglitol
AMYLIN MIMETICS	Pramlintide
BIGUANIDES	Metformin
BILE ACID SEQUESTRANTS	Colesevelam
DOPAMINE-2 AGONISTS	Bromocriptine
DPP-4 INHIBITORS	Alogliptin; Linagliptin; Saxagliptin; Sitagliptin
GLP-1 RECEPTOR AGONISTS	Albiglutide; Dulaglutide; Exenatide; Exenatide extended release; Liraglutide; Lixisenatide, Semaglutide
INSULINS AND INSULIN ANALOGUES	Inhaled insulin human; Insulin aspart: Insulin aspart protamine plus insulin aspart; Insulin degludec; Insulin degludec plus insulin aspart; Insulin detemir; Insulin glargine; Insulin glulisine; Insulin isophane (NPH); Insulin isophane plus regular; Insulin lispro; Insulin lispro protamine plus insulin lispro; Insulin regular (human); Premixed insulins (various)
MEGLITINIDES	Nateglinide; Repaglinide
SGLT2 INHIBITORS	Canagliflozin; Dapafliflozin; Empagliflozin, Ertugliflozin
SULFONYLUREAS	Chlorpropamide; Glimepiride; Glipizide; Glipizide extendedrelease; Glyburide; Tolazamide; Tolbutamide
THIAZOLIDINEDIONES	Pioglitazone; Rosiglitazone

Source: Drugs@FDA: FDA Approved Drug Products, available at: http://www.accessdata.fda.gov/scripts/cder/daf/.
Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; and SGLT2, sodium-glucose cotransporter 2.

Despite the armamentarium of pharmacologic therapies available for the treatment of T2DM, a substantial portion of patients either remain under poor glycemic control or experience deterioration of glycemic control after an initial period of successful treatment with an antidiabetic therapy. Progressive beta-cell dysfunction in patients with T2DM may lead to secondary treatment failures over time. In addition to diabetes disease progression, nonadherence to the prescribed antihyperglycemic regimen may influence the potential to achieve/maintain adequate glycemic control. Further, many pharmacologic classes may not be tolerated or have limited usefulness in certain populations. For example, metformin and SGLT2 inhibitors are contraindicated in patients with severe renal dysfunction, and DPP-4 inhibitors carry a class warning for severe/disabling arthralgia. As type 2 diabetes is a heterogenous disease in both pathogenesis and clinical manifestations, there remains a need for new antihyperglycemic treatment options.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Fiasp was approved by the U.S. FDA on September 29, 2017 for treatment of adults with diabetes mellitus, administered as subcutaneous injection and intravenous administration, and approved on October 21, 2019 for use in insulin pump administered as continuous subcutaneous insulin infusion (CSII).

3.2. Summary of Presubmission/Submission Regulatory Activity

At the time of Fiasp approval, the following PREA PMR was included in the approval letter:

> **3253-1:** 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).

On September 27, 2013, the Applicant submitted a Type C background package on the Pediatric Study Plan and we provided final written responses on December 11, 2013. The following agreements were made:

- Deferral for children 1-17 years of age in T1DM until efficacy and safety was established in adults;
- Partial waiver for Fiasp in children <1 year of age with T1DM;
- Partial waiver for Fiasp in children <10 years of age with T2DM;
- (b) (4)
- Agreement that antibody assessment would not be needed for Fiasp in pediatric trials unless data from adult trial indicate a potential immunogenicity issue with Fiasp;
- Comment that the extrapolation approach of efficacy and safety data for Fiasp in pediatric T1DM to children and adolescents age 10 and above with T2DM was reasonable, but need to be supported by demonstrating that the PK and PD differences between Fiasp and NovoLog are preserved in T2DM patients;
- Agreement with the proposed extrapolation strategy for pediatric pump use for age group 6-18 years, but noted lack of information for pump use in age <6 years;
- Agreement that no additional animal study was needed to assess the safety of two excipients (L-arginine and nicotinamide) in Fiasp formulation, and agreement that no juvenile animal study was needed;
- Request to submit the finalized protocol for trial NN1218-4101 to the FDA.

The Applicant submitted the finalized protocol for NN1218-4101 on December 1, 2014, and we provided the following comments and other recommendations about the protocol in a letter dated May 5, 2015:

- We commented that to support the pediatric indication for the full age range, the Applicant should ensure that there are sufficient number of subjects in each age strata of 1 to <6 years, 6 to <12 years, and 12 to <18 years. A minimum of 20 subjects in each age strata seems reasonable, but final determination of adequacy will be a review issue;
- We commented that the 8-point glucose profile based on self-measured plasma glucose is less reliable than centrally measured plasma glucose.

It should be noted that the Applicant did not propose to have a post-meal dosing arm in the original protocol for NN1218-4101.

On February 2, 2015, the Applicant submitted an initial Pediatric Study Plan (iPSP) and we sent a "No Agreement" letter on May 1, 2015 to this iPSP. We provided the following comments:

- We previously agreed in the December 11, 2013 Type C Written Responses that the efficacy and safety data on post-meal dosing from adult T1DM population can be extrapolated to pediatric T1DM population if supported by the results of PK/PD trial (NN1218-38). However, since the results of the PK/PD trial NN1218-3888 indicate that the PK/PD profiles of NN1218 are not similar between adults and pediatric are not similar between adults and pediatric subjects with T1DM, we do not agree that the efficacy and safety data on post-meal dosing can be extrapolated from adult T1DM to pediatric T1DM population. Therefore, a post-meal dosing arm with Fiasp may be needed in the pediatric efficacy and safety trial NN1218-4101 to assess the safety and efficacy of post-meal dosing in pediatric T1DM population;
- We recommended a comparative PK/PD study using euglycemic clamp procedure in adult T2DM to show that the PK and PD differences between Fiasp and NovoLog, as noted in T1DM, are preserved in T2DM patients, to support extrapolation of data from pediatric T1DM to pediatric T2DM patients;
- We agreed with partial waiver for T1DM under 1 year of age, and partial waiver for T2DM less than 10 years of age (b) (4) we recommended a deferral for pediatric patients between 10-18 years of age with T2DM with the possibility of extrapolation from pediatric T1DM to pediatric T2DM if supported by an appropriate PK/PD study.

(b) (4) extrapolation of adult pump efficacy and safety data to pediatric T1DM patients to allow an early pediatric CSII use with Fiasp. In response to this extrapolation strategy for pediatric pump indication, we commented as following in our May 1, 2015 letter:

- You may be able to extrapolate the adult pump efficacy and safety data to the pediatric

T1DM population if supported by an appropriate PK/PD study.

In response to our iPSP "No Agreement" Letter dated May 1, 2015 and our advice on study NN1218-4101 in May 5, 2015 letter, the Applicant submitted a revised PSP (b) (4) on June 30, 2015. A "No Agreement" letter was sent on July 28, 2015 with the following comments:

- A pediatric study without a post-meal dosing arm would not fulfill the PREA requirements for proposed dosing regimen, and strongly recommend that you include a post-meal dosing arm in the pediatric trial 4101;
- The plan to conduct a comparative PK/PD study using the euglycemic clamp procedure in adult T2DM to provide support for the proposed extrapolation from pediatric T1DM to pediatric T2DM is acceptable, provided that this study demonstrates that the PK and PD differences between Fiasp and NovoLog that are noted in T1DM are preserved in T2DM patients;
- (b) (4)

In response to our comments in the "iPSP No Agreement letter" dated July 28, 2015, the Applicant submitted an updated iPSP and revised trial design for pediatric T1DM trial NN1218-4101 on July 30, 2015. In this revision, trial NN1218-4101 was revised to add the post-meal dosing arm in the study rather than extrapolating post-meal dosing from adult T1DM to pediatric T1DM. In addition, based on our comments, the Applicant (b) (4), with plan to extrapolate pediatric pump indication from adult T1DM to pediatric T1DM based the planned Phase 3b pump efficacy and safety trial in adult subjects with T1DM (NN1218-3854), completed single dose pump PK/PD study in adult subjects with T1DM (b) (4)), and planned subcutaneous efficacy and safety trial in pediatric subjects with T1DM (NN1218-4101).

On August 10, 2015, we sent the following additional comments:

- Under PREA safety cannot be extrapolated. You should remove references to extrapolating safety and/or dosing throughout the document and instead use the term 'leverage';
- Given that at this time we believe you are not required under PREA to study the pump indication in pediatrics you should remove section 3.2 or state that you expect the Agency's determination of whether your strategy to leverage adult pump data for the use of pumps in the pediatric population is acceptable to be determined after review of the trials listed in section 3.2 (i.e., trials NN1218-3854, (b) (4), and NN1218-4101).

The Applicant revised iPSP on August 11, 2015 and we agreed to this iPSP. In this Agreed iPSP,

the following extrapolations strategies were agreed upon:

- **Extrapolation of efficacy from pediatric type 1 diabetes mellitus (T1DM) to pediatric type 2 diabetes mellitus (T2DM)**: extrapolation of efficacy results from pediatric T1DM subjects to pediatric T2DM patients age 10 and above, based on the following:
    1) A comparative PK/PD study using the euglycemic clamp procedure in adult T2DM to show that the PK and PD differences between Fiasp and NovoLog, as noted in T1DM, are preserved in T2DM patients;
    2) The efficacy results from a planned pediatric T1DM study, NN1218-4101;
    3) The Applicant also proposed to leverage the safety results from NN1218-4101 to support this extrapolation strategy.
- **Extrapolation strategy for pediatric pump indication:** extrapolation of efficacy results from the adult pump trial in T1DM to pediatric T1DM based on the following:
    1) Efficacy data from a planned Phase 3b pump efficacy and safety trial in adult subjects with T1DM (NN1218-3854);
    2) Single dose pump PK/PD study in adult subjects with T1DM (b) (4);
    3) Efficacy data from planned subcutaneous pediatric efficacy and safety trial in subjects with T1DM (NN1218-4101);
    4) The Applicant also proposed to leverage the safety and dosing information from trials NN1218-3854 and 4101.

3.3. Foreign Regulatory Actions and Marketing History

Canada approved Fiasp on January 6, 2017 and European Commission approved Fiasp on January 9, 2017. In both Canada and Europe, in addition to subcutaneous and intravenous use, Fiasp was approved for use as CSII via an insulin pump at the time of initial approval. Most recently, in March 2019, EMA approved use of Fiasp in adolescents and children aged one year and older.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Trial 4101 was a multinational, multicenter trial conducted at 150 sites in 17 countries, with 40 U.S. sites. Due to large number of subjects from Europe (~58%), the site inspection consisted of 2 European sites and one U.S. site, as recommended by Dr. Cynthia Kleppinger. The inspections of these three clinical sites supported the validity of data, see Dr. Kleppinger's review dated October 30, 2019.

4.2. Product Quality

The formulation of Fiasp used in the clinical trials for this supplement is the same as the Fiasp product used in the clinical development program supporting the NDA and is same as the marketed Fiasp product.

4.3. Clinical Microbiology

Not applicable for this supplement.

4.4. Nonclinical Pharmacology/Toxicology

Not applicable for this supplement.

4.5. Clinical Pharmacology

The results of clinical pharmacology trials 4371 and 4265 are briefly reviewed in this section; please see Dr. Renu Singh's review dated November 5, 2019 for complete details and discussion of these clinical pharmacology trials. Dr. Singh concluded that the results of clinical pharmacology studies support approval of Supplement #10 and #11.

To support Fiasp in pediatric patients with diabetes mellitus, a clinical pharmacology study in pediatric patients with T1DM (trial 4371) and a clinical pharmacology study in adults with T2DM (trial 4265) were conducted.

Trial 4371: A Trial Comparing the Pharmacokinetic Properties of Faster-acting Insulin Aspart between Children, Adolescents and Adults with Type 1 Diabetes

Trial 4371 was conducted with the same trial design as trial 3888 (trial 3888 was submitted and reviewed in the original NDA) but with the insulin aspart measurements based on the total insulin aspart ELISA assay instead of the free insulin aspart ELISA assay as the free serum insulin aspart assay was determined to be unreliable during the original NDA review and total serum insulin aspart measurements were used for PK evaluation. Therefore, only total serum insulin aspart levels were relied for PK conclusions in trial 4371.

Trial 4371 was a randomized, double-blind, single-dose, two-period cross-over study at a single site in Germany investigating the PK and PD properties of Fiasp and NovoLog in children (6-11 years), adolescents (12-17 years) and adults (18-64 years) with T1DM. Pharmacodynamic properties were evaluated using a meal test. A SQ dose of 0.2 Units/kg body weight was administered for both Fiasp and NovoLog. Serum insulin aspart levels were measured over 12 hours after administration of a single dose for PK assessment, and plasma glucose levels was collected for PD analysis for 6 hours after single dose.

In summary, in trial 4371, the mean profiles for total serum insulin aspart concentration with SQ administration of Fiasp were slightly shifted to the left compared to NovoLog in children and adolescents, suggesting earlier absorption and greater insulin exposure with Fiasp compared to NovoLog. A statistically significantly greater early total insulin aspart exposure was seen with Fiasp compared to NovoLog in both children and adolescents.

The duration of exposure for total insulin aspart was similar between Fiasp and NovoLog in children but about 12 minutes shorter for Fiasp compard to NovoLog in adolescents. The total exposure and maximum concentration of insulin aspart were comparable between Fiasp and NovoLog in both children and adolescents.
In conclusion, results of trial 4371 showed that initial absorption differences after SQ injection with Fiasp compared to NovoLog was preserved in children and adolescents, consistent with what was seen in adults. Other PK parameters such as onset, t_{max}, and duration of exposure were similar to adults.

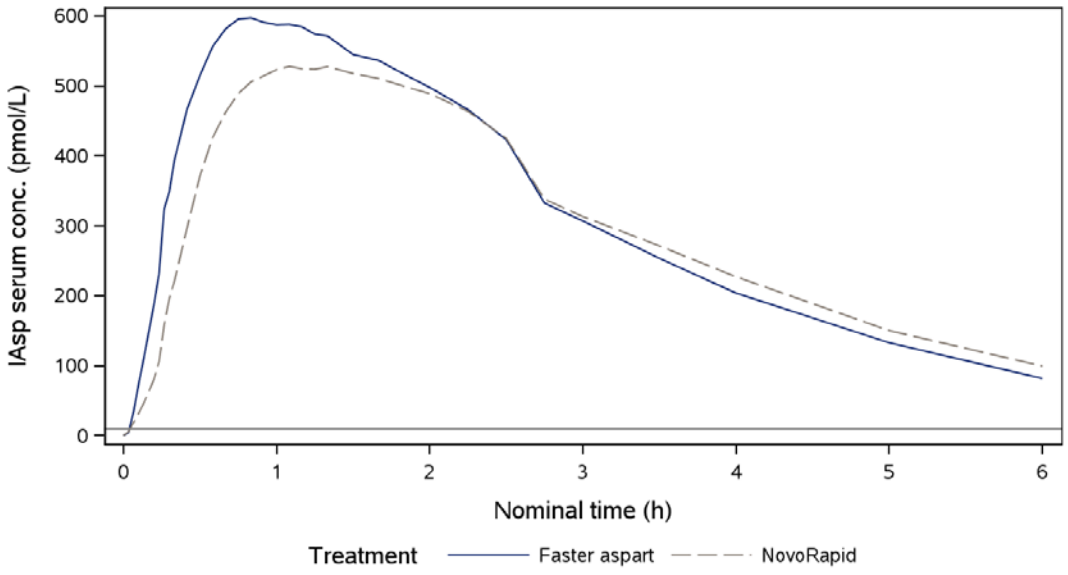
Trial 4265: A Trial Investigating the Pharmacokinetic and Pharmacodynamic Properties of Faster-acting Insulin Aspart in Subjects with Type 2 Diabetes Mellitus

To support the extrapolation of efficacy data supporting use of Fiasp in pediatric subjects with T1DM to pediatric subjects with T2DM, trial 4265 was conducted where the PK and PD of Fiasp and NovoLog were compared in adults with T2DM using a euglycemic clamp. This was a randomized, single-center, double-blind, single-dose, two-period, cross-over, active-comparator study investigating the PK and PD properties of Fiasp and NovoLog using a euglycemic clamp in adults (aged 18 to 77 years) with T2DM. Dose of 0.3 U/kg was used.

In adults with T2DM, Fiasp showed earlier onset of exposure, greater early and maximum exposure compared to NovoLog, as well as comparable total insulin exposure (Figure 1).

The mean GIR profiles were shifted left compared to NovoLog, showing a greater early glucose-lowering effect with Fiasp compared to NovoLog (Figure 2). Overall, Fiasp showed earlier onset and greater early of glucose-lowering effect compared to NovoLog, while maintaining a comparable total and maximum glucose-lowering effect.

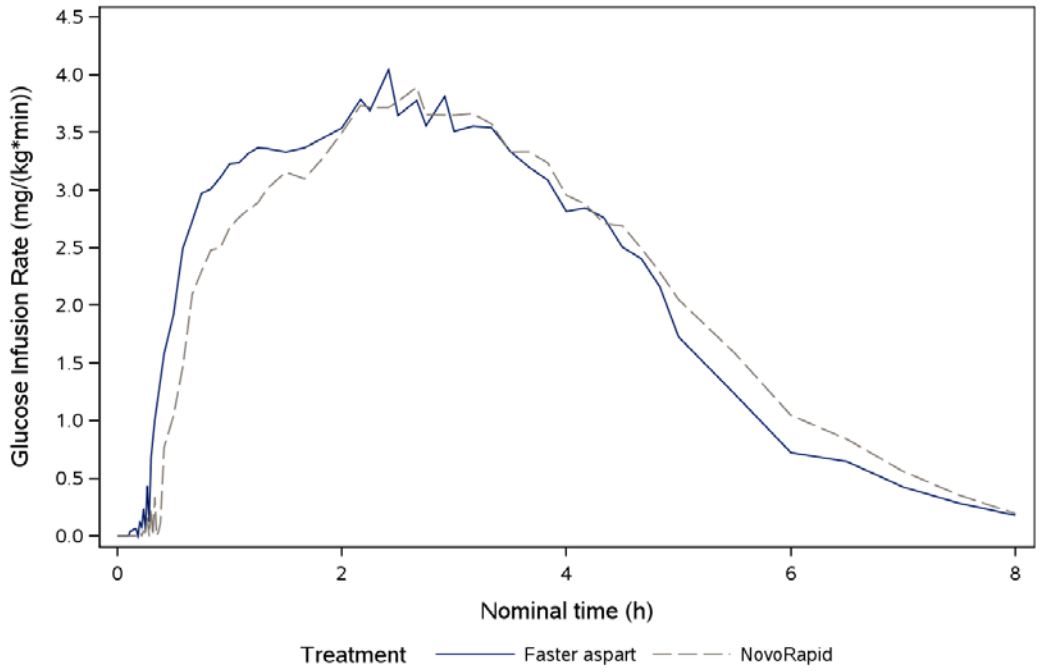
Figure 1: Mean Insulin Aspart Profile (0-6 hours) in Adults with T2DM in Trial 4265



IAsp serum conc.: Total insulin aspart serum concentration
Horizontal grey line at 10 pmol/L indicates the LLOQ

Source: Summary of Clinical Pharmacology, Figure 3-5

Figure 2: Mean GIR Profile (0-8 hours) in Adults with T2DM in Trial 4265



Source: Summary of Clinical Pharmacology, Figure 3-11

Reviewer's comment: *The results from trial 4265 showed that the PK and PD differences between Fiasp and NovoLog seen in T1DM are preserved in T2DM, allowing extrapolation of efficacy data from pediatric T1DM to pediatric T2DM in support of Fiasp use in pediatric patients with T2DM.*

4.6. Devices and Companion Diagnostic Issues

The labeling of at least one insulin pump should include Fiasp use in pediatric patients with Supplement #11 approval. (b) (4)

(b) (4)

4.7. Consumer Study Reviews

Not applicable for this submission. This efficacy supplement did not involve label comprehension, patient self-selection, or other human factor studies.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

In support of pediatric indication, two PK/PD studies (trial 4371 and 4265) and a safety and efficacy trial in pediatric patients with T1DM (trial 4101) were conducted.

See Section 4.5 for discussion of PK/PD studies.

Single efficacy and safety 26-week trial in pediatric patients with T1DM, trial 4101, is summarized in Table 1.

Table 2: Efficacy and Safety Clinical Trial Relevant for this sNDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Trial Number: 1218.4101 **Title:** Efficacy and Safety of Faster-acting Insulin Aspart compared to NovoRapid both in Combination with Insulin Degludec in Children and Adolescents with Type 1 Diabetes Mellitus	NCT02670915	Multicenter, multinational, randomized, partly double-blind, 3-arm, parallel-group, treat-to-target	Fiasp versus NovoLog, both given in a basal-bolus regimen in continuous subcutaneous insulin infusion	**Primary:** Change in HbA1c from baseline to Week 26	2-week screening period; 12-week run-in period; 26-week treatment period; 30-day follow-up period	Meal-time Fiasp: 236 Post-meal Fiasp: 259 NovoLog: 258	T1DM children and adolescents 2 to <18 years of age	150 sites; 17 countries

5.2. Review Strategy

The efficacy and safety of Fiasp in pediatric patient population was evaluated in one clinical efficacy and safety trial, Trial 4101, which is the focus of this review.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Trial NN1218-4101 – Efficacy and Safety of Faster-acting Insulin Aspart compared to NovoRapid both in Combination with Insulin Degludec in Children and Adolescents with Type 1 Diabetes

6.1.1. Study Design

Overview and Objective

Trial NN1218-4101 (referred to as trial 4101 throughout this review) was conducted to assess the efficacy and safety of Fiasp compared to NovoLog in children and adolescents with type 1 diabetes.

The primary objective was to confirm the non-inferiority in glycemic control of treatment with meal-time Fiasp by comparing it to meal-time NovoLog, both in combination with insulin degludec in children and adolescents with type 1 diabetes.

Two confirmatory secondary objectives:
- To confirm the non-inferiority in glycemic control of treatment with post-meal Fiasp by comparing it to meal-time NovoLog, both in combination with insulin degludec in children and adolescents with type 1 diabetes;
- To confirm the superiority in glycemic control of treatment with meal-time Fiasp by comparing it to meal-time NovoLog, both in combination with insulin degludec in children and adolescents with type 1 diabetes.

Other secondary objectives:
- To compare the effect and safety of treatment with meal-time Fiasp vs meal-time NovoLog, both in combination with insulin degludec in children and adolescents with type 1 diabetes;
- To compare the effect and safety of treatment with post-meal Fiasp vs meal-time NovoLog, both in combination with insulin degludec in children and adolescents with type 1 diabetes.

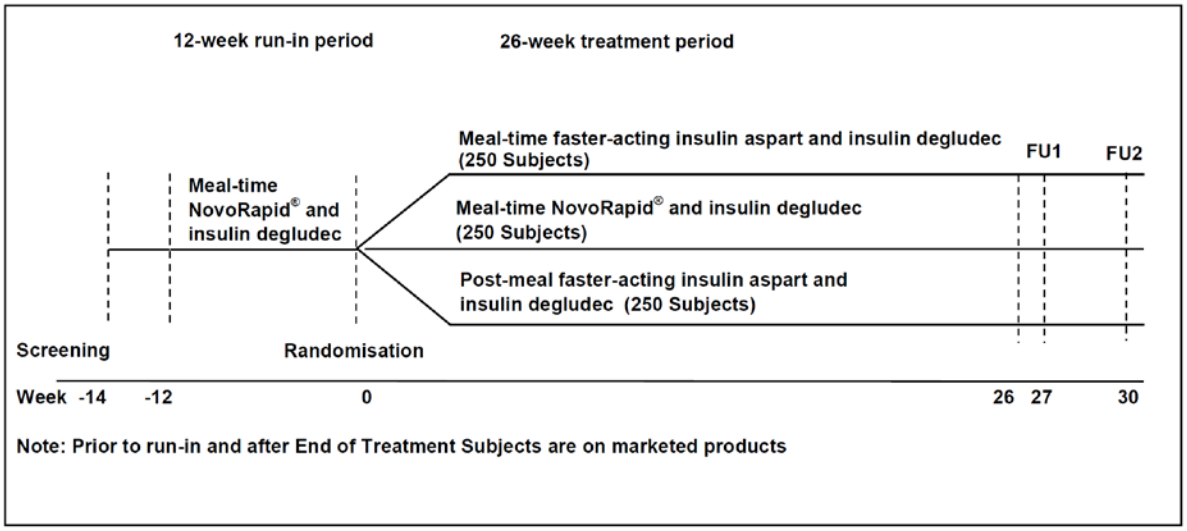
The non-inferiority margin was 0.4, which is one of the suggested margins in the FDA

Guidance[3].

Trial Design

Trial 4101 was a 26-week, randomized, partly double-blinded, active-controlled, treat-to-target, 3-arm, parallel group, multi-center and multi-national trial to compare the effect and safety of meal-time Fiasp versus meal-time NovoLog, both with insulin degludec once daily in a basal-bolus regimen in children and adolescents with T1DM who were 1 to less than 18 years of age[4]. Trial also included a 26-week open-label post-meal Fiasp arm in combination with insulin degludec. See Figure 3 for overview of study design.

Figure 3: Overview of Study 4101



Source: CSR 4101, Figure 9-1

The trial included up to 2 weeks for screening, a 12-week run-in period followed by a 26-week treatment period with a 7-day and a 30-day follow-up period.

Eligible subjects entered a 12-week run-in period and switched from their previous insulin treatment to insulin degludec once daily and mealtime NovoLog. During the run-in period, the basal insulin was optimized on a weekly basis to individual FPG targets.

After the run-in period, subjects with HbA1c ≤9.5% were randomized in a 1:1:1 ratio to receive either meal-time Fiasp, meal-time NovoLog, or post-meal Fiasp, all in combination with insulin degludec. Randomization was stratified by age groups to ensure comparable number of

[3] Guidance for Industry Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention Draft Guidance, February 2008.
[4] For Serbia only, 2 to less than 18 years of age were enrolled.

subjects in each stratum for each treatment group: age 1 to <3 years, 3 to <6 years, 6 to <12 years, and 12 to <18 years.

During the 12-week run-in period, the basal insulin was optimized, and during the 26-week treatment period, the bolus insulin was optimized to individual pre-meal targets per titration guideline (see Treatment below).

Inclusion Criteria:

- Male or female, age 1 to <18 years (for Serbia only, age 2 to <18 years) at randomization;
- Diagnosed with type 1 diabetes mellitus;
- Ongoing daily treatment with a basal-bolus insulin regimen using a basal insulin analogue or NPH insulin for at least 90 days;
- Able and willing to take at least 3 daily meal-time related bolus insulin injections, and adhere to protocol, including performing self-measured plasma glucose (SMPG) profiles;
- Total daily dose of insulin ≤2.0 U/kg;
- HbA1c ≤9.5%;
- Willing to not use real time CGM during the trial;
- Informed consent and child assent, as age-appropriate.

For subjects eligible for CGM and meal test subgroup:

- Male or female, age ≥8 years, weight ≥22.5 kg (49.5 lbs);
- Able and willing to use the principles of flexible bolus dosing based on carbohydrate counting.

Key Exclusion Criteria:

- Hypersensitivity to study products;
- Female who is pregnant, breast-feeding, or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (as required by local regulation or practice);
- Participation in another trial within 28 days;
- Anticipated initiation or change in concomitant medication in excess of 14 days known to affect weight or glucose metabolism (e.g., orlistat, thyroid hormones, corticosteroids);
- Diagnosis of malignant neoplasm past 5 years;
- Known hypoglycemic unawareness or recurrent severe hypoglycemic episodes;
- More than one episode of diabetic ketoacidosis requiring hospitalization past 90 days;
- Treatment with any medication for diabetes or obesity other than stated in the inclusion criteria for past 90 days.

Treatment:

All subjects were treated with insulin degludec once daily (QD) and meal related NovoLog/Fiasp in a basal-bolus regimen.

Insulin degludec was to be injected subcutaneously into thigh or upper arm (deltoid area), and bolus insulin (Fiasp, NovoLog) was to be injected into the abdominal wall. Rotation of injection sites within a given region was recommended. Insulin was titrated following a titration guideline based on the SMPG profiles, and no maximum or minimum insulin dose was specified.

Insulin degludec was to be given once daily at any time of the day, preferably at the same time every day. Meal-time Fiasp or NovoLog was to be given 0-2 minutes before meals, and post-meal Fiasp was to be given 20 minutes after start of a meal. Main meals were breakfast, lunch, and evening, with extra dosing allowed at the investigator's discretion.

Bolus insulin was double-blinded for meal-time Fiasp and NovoLog, and open-label for post-meal Fiasp group.

Basal insulin: At beginning of run-in period, all subjects were transferred from their previous basal insulin to insulin degludec QD. During 12 weeks of run-in period, basal insulin was titrated by the investigator every week to the pre-breakfast glycemic target of 71-145 mg/dL.

During the 26-week treatment period, adjustment of basal insulin dose was to be minimized unless needed at the investigator's discretion.

Bolus insulin: At the beginning of run-in period, all subjects were transferred from their pre-trial bolus insulin to NovoLog, but bolus insulin was not titrated during the run-in period unless needed for reasons of safety. At randomization, subjects were randomized to continue using meal-time NovoLog or to receive meal-time or post-meal Fiasp.

During the 26-week treatment period, bolus insulin was optimized weekly based on the 4-point SMPGs subjects performed on 3 days before weekly site visit/phone contact or using principles of flexible bolus doing based on the carbohydrate content of a meal.

The bolus insulin dose was titrated to pre-breakfast and pre-lunch target of 71-145 mg/dL and bedtime target of 120-180 mg/dL.

Administrative Structure:

A blinded, internal safety committee was established to conduct ongoing safety surveillance. Surveillance of insulin titration data was done centrally by the Applicant in a blinded manner.

Procedures and Schedule:

To optimize glycemic control, investigators were to maintain at least weekly contact with the subjects throughout the trial to adjust insulin doses. Subjects were provided with a diary to record the 4-point and 8-point SMBG profiles (per Table 3), insulin doses, and dates on 3 days before the site visit/phone contact, as well as all hypoglycemic episodes and hyperglycemic values.

Subjects were provided with a BG meter and no other BG meter was to be used to measure SMPG values.

Subjects were not allowed to wear their own real time CGM during the run-in or treatment period. At selected sites, a subgroup of subjects wore a blinded CGM device to assess their IG levels for at least 11 days and up to 13 days at Randomization/Visit 14 and Week 26/Visit 40 (Table 3).

About 150 subjects who were ≥8 years old at screening from selected sites were in CGM and meal-test subgroup. These subjects used a blinded CGM for 11 days over 13 days before randomization and at the end of 26-week treatment period. These subjects also had two standardized meal tests connected to these CGM periods at baseline and at the end of treatment period.

Table 3: Trial 4101 – Schedule of Events

NN1218-4101	Screening	12-week run-in period												Randomisation	26-week treatment period															Follow-up 1[c]	Follow-up 2[c]	Premature Discontinuation[c]
Visit (V) Phone contact (P)	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29	V30	P31 P32 P33	V34	P35 P36 P37	V38	P39	V40	V41	P42	V40A
Time of visit (week)	-14	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 22 23	24	25	26	+7 days after EoT	+30 days after EoT	
Visit window (days)[a]	+10	±3[b]	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5	
SUBJECT RELATED INFO/ASSESSMENTS																																	
Informed consent[a]	X																																
Informed assent	X																																
In/exclusion criteria	X	x																															
Randomisation criteria														x																			
Run-in failure criteria			x	x	x	x	x	x	x	x	x	x	x	x																			
Criteria for premature discontinuation of trial product															x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Demography	X													x[d]																			
Diagnosis of diabetes	X																																
Diabetes treatment history	X	x																												x	x	x	x
Concomitant illness/medical history	X																																
Concomitant medication	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CLINICAL ASSESSMENTS																																	
4-point profile (SMPG)			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[d]			x
8-point profile (SMPG)														x								x								x			x
Hypoglycaemic episodes[o]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Hyperglycaemic episodes[o]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Injection site reactions		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[f]	x
Technical complaints		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[d]			x
Height	x													x								x								x			x
Body weight	x													x								x								x			x
Vital signs	x													x								x								x			x
Physical examination	x													x								x								x			x
Pubertal status (Tanner staging)														x								x								x			x
CGM[g]												x	x	x															x	x	x[e]			x
Meal test[g]														x																x[d]			x
LABORATORY ASSESSMENTS																																	
Fasting plasma glucose[h]														x								x								x			x
HbA_{1c}	x											x		x								x								x			x

NN1218-4101	Screening	12-week run-in period												Randomisation	26-week treatment period																Follow-up 1[c]	Follow-up 2[c]	Premature Discontinuation[c]
Visit (V) Phone contact (P)	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29	V30	P31 P32 P33	V34	P35 P36 P37	V38	P39	V40	V41	P42	V40A
Time of visit (week)	-14	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 22 23	24	25	26	+7 days after EoT	+30 days after EoT	
Visit window (days)[a]	+10	±3[b]	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5	
1,5-anhydroglucitol														x								x								x			x
Biochemistry	x													x								x								x			x
Haematology	x													x								x								x			x
Antibodies														x								x								x			x
Lipids	x													x								x								x			x
Pregnancy test	x													x																x			x
TRIAL MATERIAL																																	
IV/WRS call	x	x				x				x				x				x		x		x		x		x		x		x[e]			x
Dispensing visit		x				x				x				x				x		x		x		x		x		x					
Dosing[f]		x												x																x			x
Doses of trial insulin on the 3 days before visit			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x
New doses of trial Insulin		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Drug accountability						x				x				x				x		x		x		x		x		x		x			x
REMINDERS																																	
Hand out ID Card	x																																
Training in diabetes and carbohydrate counting	x	x		x		x		x		x		x		x																			
Training in trial products and pen handling		x		x		x		x		x		x		x		x		x		x		x		x		x		x					
Handout direction for use		x																															
Handout and instruct in BG meter use		x																															
Supply and instruct in diary/collection of diary		x		x		x		x		x		x		x		x		x		x		x		x		x		x		x	x[j]		x
Handout FPG home blood sampling kit												x								x								x					x[k]
Instruct in safety precautions and hand out supplies		x																															
End of Treatment																														x			x
End of trial																														x[l]		x[m]	
Sign off case book																														x[l]		x[m]	

a) Visit windows before visit 14 is relative to visit 2. Visit windows after visit 14 are relative to visit 14, except for the follow-up visits which are relative to last day on trial product

b) Visit 2 can take place as soon as the subject has been found eligible and must take place no later than 17 days after the screening visit (visit 1). The results of all the screening assessments must be available (including central laboratory results) and must have been reviewed by the investigator before the subject can enter the run-in period

c) Subjects who prematurely discontinue trial product will be asked to attend the premature discontinuation visit and subsequently FU1 and FU2 according to section

d) For Germany only: The only demographic data to be collected at visit 14 is the subject's age at randomisation (to be used for stratification)

e) The assessment is not applicable for premature discontinued subjects

f) Injection site reactions must be captured on the AE form (no additional injection site reaction information needs to be completed)

g) Only applicable for a subgroup of subjects. In case of premature discontinuation please see Appendix B in protocol (Appendix 16.1.1)

h) Using the FPG home blood sampling kit

i) Start and stop date of trial product

j) Only collection of diary. For subjects who prematurely discontinue trial product a new diary will be handed out at this visit

k) Site staff should provide FPG home blood sample kits to the subject prior to the visit

l) Only for subjects prematurely discontinuing trial product

m) Only for subjects completed the full visit schedule. Subjects who prematurely discontinue trial product must have visit 40 planned

n) Informed consent for participation in the CGM and meal test subgroup can be obtained up to visit 12 (including visit 12)

o) Serious hypoglycaemic episodes and serious hyperglycaemic episodes must be reported from the first trial-related activity after the subject has signed the informed consent

Source: CSR, Table 9-3

Study Endpoints

The primary endpoint for trial 4101 was the change from baseline in HbA1c after 26 weeks of randomization for all randomized subjects, regardless of treatment discontinuation or use of ancillary therapies. As discussed in the 2008 FDA Draft Guidance for Industry for Developing

Drugs for Diabetes Mellitus[5], HbA1c is most widely accepted measure for evaluating overall long-term glycemic control in patients with diabetes for drug approval and labeling.

The primary endpoint addressed the primary objective and two confirmatory secondary objectives.

Supportive secondary efficacy endpoints include:

- Change from baseline in 8-point SMPG profile;
  - Mean PPG and PPG increment over all three meals;
  - Individual meal PPG and PPG increment;
  - Mean of 8-point profile;
  - Fluctuation in the 8-point profile;
- Change from baseline in FPG;
- Change from baseline in 1,5-anhydroglucitol;
- Percentage of subjects reaching HbA1c target of <7.5%;
- Percentage of subjects reaching HbA1c target of <7.5% without severe hypoglycemia;
- Insulin dose (U/day and U/kg/day).

Statistical Analysis Plan

The following analysis sets were used for endpoints:

- Full Analysis Set (FAS) included all randomized subjects, and subjects in the FAS will contribute to the evaluation 'as randomized';
- Per Protocol (PP) Analysis Set included all subjects in the FAS that comply with inclusion and exclusion criteria, 'as treated';
- Safety Analysis Set (SAS) included all subjects who received at least one dose of study drug, 'as treated'.

For endpoints evaluated as change from baseline, baseline was defined as collection at the randomization visit (Visit 14; see Table 3). When measurement was not available at randomization visit, the most recent measurement before randomization was used as baseline.

Two observation periods were:

- In-trial – the observation period from date of randomization until the last trial-related subject-site contact, including data collected after discontinuation of study drug;
- On-treatment – the observation period from date of first dose of study drug to no later than 7 days after the day of last dose of study drug, including data collected up to and including 7 days after discontinuation of study drug.

[5] Draft Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention, February 2008.

All primary and secondary efficacy endpoints used the FAS unless otherwise stated. Safety endpoints were summarized using the SAS and analyzed using FAS unless otherwise stated.

The primary and confirmatory secondary hypotheses were tested using a stepwise hierarchical testing procedure to control type 1 error, and tested study objectives in the following order using the two-sided 95% confidence interval approach until an insignificant result was found:

- *Step 1*: **Non-inferiority** of meal-time Fiasp compared to meal-time NovoLog, both in combination with insulin degludec, in the change from baseline in HbA1c after 26 weeks of treatment;
- *Step 2*: **Non-inferiority** of post-meal Fiasp compared to meal-time NovoLog, both in combination with insulin degludec, in the change from baseline in HbA1c after 26 weeks of treatment;
- *Step 3*: **Superiority** of meal-time Fiasp versus meal-time NovoLog, both in combination with insulin degludec, in the change from baseline in HbA1c after 26 weeks of treatment.

A sample size of 250 subjects per group, or 750 total subjects, were determined to have more than 93% power to show non-inferiority with limit of 0.4%, based on a t-statistic under the assumption of a one-sided test of 2.5% with zero mean treatment difference for the comparison between meal-time Fiasp and meal-time NovoLog. The sample size also ensured a power of 85% to show non-inferiority of post-meal Fiasp compared to meal-time NovoLog.

The primary analysis used a statistical model using multiple imputation where subjects without HbA1c value will have imputation from the available information from the treatment the subject was randomized to.

See Statistical Review for details of Statistical Analysis Plan.

Protocol Amendments

There were 4 amendments to the protocol, 3 of which were global and 1 specific for Serbia, which are summarized in the table below.

Amendment number	Issue date	Timing of change (before/after FPFV)	Countries affected	Key changes
1	16-Feb-2016	Before FPFV	Global	Added 'or equal to' in the definition of confirming of non-inferiority in trial protocol Section 17: General consideration.
2	30-Mar-2016	Before FPFV	Global	A mistake identified in the blood sampling volume at visit 14 and visit 40 for the subjects participating in the CGM and meal test subgroup. Consequently the required minimum weight for participation in the CGM and meal test subgroup was increased to ensure the blood volume collected at visit 14 and visit 40 did not exceed 1% of the subjects total blood volume.
3	29-Jul-2016	After FPFV	Serbia	Changes the inclusion criterion number 2 in order to include subjects from 2 years old and below 18 years old at the time of signing informed consent and below 18 years old at the time of randomisation.
4	13-Jan-2017	After FPFV	Global	An inaccuracy was identified in the layman language for reporting hypoglycaemic episodes. There was a need to clarify the run-in failure criteria, to provide more guidance on when to report a MESI, and that the FPG sample was to be collected using the FPG home sampling kit no matter if the FPG sample was taken at home or at site. The statistical section was updated to clarify the analyses made for the primary and secondary estimands, the supportive secondary CGM and meal test related efficacy endpoints. A clarification was made to which treatment emergent hypoglycaemic episodes should be included in the analyses. Appendix B was updated to reflect the changes that occurred due to the change in CGM supplier shortly before trial initiation.

CGM=continuous glucose monitoring; FPFV=first patient first visit; FPG=fasting plasma glucose; MESI=medical event of special interest
Source: CSR 4101, Table 9-10

These amendments are unlikely to have affected interpretation of results.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated that the trial 4101 was conducted in accordance with Declaration of Helsinki and International Conference on Harmonization (ICH) Good Clinical Practice (GCP). The trial was conducted in accordance with FDA 21 CFR 312.120, and the 21 Code of Federal Regulations, 312, 50, and 56 were followed.
The investigators were required to have been trained in GCP. The trial was monitored by the

Applicant by doing on-site visits, telephone calls, and regular inspection of paper CRFs and eCRFs. The Applicant conducted 33 internal audits.

OSI also conducted three clinical site inspections and did not find any major violations (see Section 4.1).

Financial Disclosure

In accordance with 21 CFR 54.4, the Applicant submitted the Form 3453 for Trial 3854, certifying that they had not entered into any financial arrangements with principal investigators/sub-investigators that could affect the outcome of the study as defined in 21 CFR 54.2.

There were 8 principal investigators in U.S. who held financial interests requiring disclosure, as following:

Site no.	Investigator	Disclosable financial Interests			Total Amount received	Number of patients randomized to site
		Explanation	Amount	Date		
(b) (6)		Honoraria	$37,800	(b) (6)	$37,800	(b) (6)
		Honoraria	$44,915		$44,915	
		Honoraria	$30,047		$30,047	
		Advisory Board (b) (6) Honoraria	$10,455 $14,520 $7,260		$32,235	
		Honoraria	$29,300		$29,300	
		Honoraria	$96,700		$96,700	
		Advisory Board Steering Committee Honoraria	$9,323 $14,233 $14,860		$38,416	
		Advisory Board (b) (6) Honoraria	$33,000 $6,300 $20,700 $163,335		$223,335	

Source: NDA submission, Module 1.3.4

The following are list of investigators from non-US sites with details about their disclosable financial interests:

Site no.	Investigator	Disclosable financial Interests			Total Amount received USD	Number of patients randomized to site
		Explanation	Amount USD	Date		
(b) (6)		Honorarium	63,165	(b) (6)	63,165	(b) (6)
		Donation to (b) (6) (b) (6)	69,769		69,769	
		Speaker Fees	4,703		7,471	
		Honorarium	2,237			
		Consultant Fees	531			
		Speaker Fees	5,958		11, 918	
		Honorarium	5,960			
		Honorarium	458		458	
		Donation to	49,385		49,385	

(b) (6)		(b) (6)		
(b) (6)	Speaker Fees	14,130	(b) (6)	(b) (6)
	Advisory Board	2,437	21,804	
	Results Meeting	1,062		
	Honorarium	4,175		
	Speaker Fees	319	319	
	Grant	52,444	52,444	
(b) (6)				

*** Site – The Principal investigator/s and sub-investigator reported on payments received in the form of donations to the specific site. Disclosable information is on behalf of the site and not on the individual investigator.

Source: NDA submission, Module 1.3.4

Given that Trial 4101 was a large, multi-center, multi-national trial conducted at 150 sites in 17 countries, and design of the study included randomization and blinding, the overall number of subjects recruited from these sites was relatively small and unlikely to have had a significant impact on the overall outcome of the trial.

Patient Disposition

Trial was conducted at 150 sites in 17 countries, and 40 sites were in the U.S.

See Table 4 for subject disposition of trial 4101. A total of 933 subjects were screened, of which 99 (~11%) were screen failures, mostly because they did not meet the HbA1c criterion (74 subjects). A total of 834 subjects entered the run-in period, and 57 (~7%) subjects were run-in failures due to failure to meet randomization criteria (31 subjects), withdrawal by

parent/guardian (10 subjects), withdrawal by subject (8 subjects), protocol violations of inclusion/exclusion criteria (4 subjects), adverse events (3 subjects), and other (1 subject).

Of 777 subjects randomized, majority of subjects completed the treatment period (756 [97.3%]) and completed the trial (760 [97.8%]). Numerically less proportion of subjects in the post-meal Fiasp group completed the treatment period and completed the trial (96.5% and 96.9% respectively), compared to subjects in the meal-time Fiasp (97.9% and 98.5% respectively) and NovoLog (97.7% and 98.1% respectively).

Of note, one subject (Subject (b) (6)) was randomized to the post-meal Fiasp group but was exposed to meal-time Fiasp during the treatment period. This subject was included in the meal-time Fiasp for the safety analysis set and per protocol analysis set, but not in the full analysis set. This is unlikely to have a large impact on results.

Table 4: Subject Disposition in Trial 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: Modified from Table 10-1, CSR 4101

A total of 21 subjects prematurely discontinued the study drug, and slightly more subjects in the post-meal Fiasp group prematurely discontinued the study drug (9 subjects; 3.5%) compared to meal-time Fiasp or NovoLog groups (6 subjects; 2.3% in both groups). The most common reason for premature discontinuation of study drug was due to 'other' in 10 subjects

(3 subjects in meal-time Fiasp and NovoLog groups, 4 subjects in post-meal Fiasp), followed by decision of subjects in 6 subjects and decision of parent/guardian in 5 subjects. The most common reason of 'other' was mainly due to personal reasons (long vacation, unable to come to site visits, busy academics, etc; see Table 10-2 in the CSR, not shown here). No subject discontinued the study drug due to an AE, hypoglycemia, protocol violation, or pregnancy.

A total of 17 subjects withdrew from the trial, and numerically more subjects in the post-meal Fiasp group withdrew from trial (8 subjects; 3.1%) compared to meal-time Fiasp (4 subjects; 1.5%) or NovoLog group (5 subjects; 1.9%). Withdrawal from trial was mostly due to parent/guardian (9 subjects) or due to subject withdrawal (5 subjects), with few 'other' (3 subjects; all related to not attending visits or completing assessments). No subject withdrew from the trial due to an AE.

Protocol Violations/Deviations

There were 94 site and 969 subject level protocol deviations (PD) that were considered important, as shown in Table 5. Important protocol deviations were considered those that could significantly impact the completeness, accuracy, and/or reliability of the trial data. Of 875 subject level deviations, 47 were during the screening/run-in failures, 275 subjects were in the meal-time Fiasp, 287 of subjects were in the post-meal Fiasp, and 287 of subjects were in the NovoLog group.

Table 5: Summary of Important Protocol Deviations at Subject Level

PD category	Site level (number of PDs)	Subject level (number of PDs)					Total
		Screen and run-in failures	Mealtime faster aspart	Post-meal time faster aspart	Mealtime NovoRapid®/ NovoLog®	Total no of subject level PDs	
Informed consent	5	24	36	24	38	122	127
Inclusion/exclusion/randomisation criteria	-	7	5	4	7	23	23
Trial product handling	7	2	24	19	24	69	76
Treatment compliance	1	1	17	27	13	58	59
Assessment deviations	8	3	131	127	148	409	417
Other	53	10	62	65	57	194	267
Total	**94**	**47**	**275**	**266**	**287**	**875**	**969**

Source: CSR 4101, Table 10-10
PD=protocol deviation

The most common protocol deviations were related to "Assessment deviations" with 409 subject level protocol deviations and 8 site level PDs. Twelve subjects missed the primary endpoint HbA1c assessment, and 40 other subjects missed other planned safety/efficacy laboratory assessments. About 20% subject level PDs were due to delayed handling of laboratory reports, 18% of subject level PDs were related to incorrect CGM assessments, 13% due to incorrect meal test assessments, 35 subjects due to missing or incorrect antibody samples, 18 subjects due to missing serum pregnancy test, 11 subjects due to canceling of FPG test, and 5 subjects due to missed randomization session and delayed dispending of trial product.

Reviewer's comment: *Given the size of this trial, it is unlikely that missing values in 12 subjects would impact the results of this trial. In addition, statistical analyses include sensitivity analyses to account for missing data.*

There were 73 important PDs a site 194 PDs at subject level categorized as 'other'. About 20% site level and 5 subject level PDs were due to trial task being done by incorrect site staff, 7 site and 40% subject level PDs due to diary handling issues, 21 subject level PDs related to late signing of AE or safety information by the investigator. About 55% site level PDs and 18 subject level PDs were due to monitoring and follow up visits not within the interval defined by the protocol. Seventeen subject level PDs were due to use of BG meter other than the one provided in the trial.

One site level PD related to treatment compliance was due to subject taking Humalog for 2 days because s/he forgot the study drug at school. About 44% of subject level PDs for treatment compliance was related to the use of commercially obtained study product not allowed per protocol, where 17 subjects took a commercial insulin product during the treatment period ranging from 1 dose to 10 days. About 36% of subject level PDs were due to subjects who administered wrong dose of study drug due to non-compliance or error; no medication error was reported, but 2 subjects reported hypoglycemia due to treatment non-compliance.

Reviewer's comment: *The short period of treatment with insulin product outside of trial in 17 subjects is unlikely to have any significant effect on the study results.*

Three site level PDs and about 57% of subject level PDs were related to incorrect storage of study drug being dispensed; however, the trial products were found suitable for use after evaluation. Other trial product handlings were also determined to be safe to use and no AEs were reported related to trial product handling PDs.

There were 6 PDs due to missing pregnancy test at Visit 1, and 5 PDs due to missing safety laboratory assessments at screening. Four PDs were related to violation of inclusion criteria, and all 4 were withdrawn from the trial. There were 8 PDs related to subjects being enrolled

before screening evaluation and documentation for inclusion/exclusion criteria, and site staff were re-trained to complete all evaluation and documentation before enrollment.

For all PDs concerning informed consent, the site personnel were retrained and missing or incorrect informed consent forms were corrected.

Table of Demographic Characteristics

The baseline demographic characteristics are summarized in Table 6. The study population included pediatric subjects with T1DM with mean age of 11.7 years (range 2 to 17 years), and more than half of pediatric subjects (55%) were adolescents (12 to 17 years of age). About 54% of subjects were males, the majority were Whites (81.3%) or Asian (16.2%), and of non-Hispanic or Latino (94.2%). The majority of subjects enrolled in Europe (58.8%) and North America (25.1%); the only North America site was in U.S.

Of 777 subjects randomized, 46 subjects (6%) were 1 to <6 years of age, 301 subjects (39%) were 6 to <12 years of age, and 430 subjects (55%) were 12 to <18 years of age.

A total of 4 subjects were <3 years old, 2 in the meal-time Fiasp and 2 in the post-meal Fiasp groups (Table 6). Due to few enrolled subjects who were 1 to <3 years of age, the Applicant changed planned analyses by combining lower group of age groups (i.e., 1 to <3 years, 3 to <6 years), and age group 1 to <6 years old are presented in the study results instead.

Table 6: Baseline Demographic Characteristics in Trial 4101 (FAS)

	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
*Includes the following countries with less than 5% of overall study population: Czech Republic, Estonia, Finland, Germany, Israel, Italy, Latvia, Lithuania, Poland, Serbia, Turkey.
Source: CSR 4101, Table 10-4

Reviewer's Comment: *Baseline demographic characteristics were balanced between treatment groups.*

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The baseline disease characteristics are summarized in Table 7. At baseline, the mean HbA1c was 7.56% (range 4.9 to 10.6%) and the mean duration of diabetes was 4.38 years (range 0.5 to 16.3 years). The mean body weight was 46.48 kg and the mean BMI was 19.66 kg/m^2.

About half of subjects were receiving insulin glargine (50.2%) as their basal insulin and insulin aspart (49.5%) as their bolus insulin at screening. No major imbalance was seen between three treatment groups with regard to types of insulin treatment at screening.

About 5.8% of study population reported history of diabetic complications.

Table 7: Baseline Diabetes Characteristics in Trial 4101 (FAS)

	Treatment Group			
Diabetes Characteristics	**Meal Fiasp** (N=260) n (%)	**Postmeal Fiasp** (N=259) n (%)	**Meal NovoLog** (N=258) n (%)	**Total** (N= 777) n (%)
HbA1c (%), mean (SD)	7.57 (0.80)	7.58 (0.84)	7.53 (0.83)	7.56 (0.82)
Min; max	4.9; 10.0	5.6; 9.6	5.3; 10.6	4.9; 10.6
FPG (mg/dL), mean (SD)	136.67 (64.22)	144.61 (60.31)	140.43 (62.67)	140.66 (62.35)
Duration of diabetes (years), mean (SD)	4.45 (3.50)	4.38 (3.15)	4.31 (3.14)	4.38 (3.26)
Min; max	0.5; 15.0	0.5; 15.3	0.5; 16.3	0.5; 16.3
BMI (kg/m^2), mean (SD)	19.69 (3.75)	19.66 (4.02)	19.64 (3.78)	19.66 (3.85)
Body weight (kg), mean (SD)	46.74 (18.17)	46.43 (18.96)	46.28 (17.18)	46.48 (18.10)
History of diabetic complications	19 (7.3)	13 (5.0)	13 (5.0)	45 (5.8)
Diabetic neuropathy	11 (4.2)	12 (4.6)	9 (3.5)	32 (4.1)
Diabetic nephropathy	6 (2.3)	0	5 (1.9)	11 (1.4)
Diabetic retinopathy	3 (1.2)	3 (1.2)	2 (0.8)	8 (1.0)
Diabetic ketoacidosis	5 (1.9)	5 (1.9)	3 (1.2)	13 (1.7)
Insulin treatment at screening				
Basal insulin				
Insulin glargine	137 (52.7)	128 (49.4)	125 (48.4)	390 (50.2)
Insulin detemir	59 (22.7)	64 (24.7)	69 (26.7)	192 (24.7)
Insulin degludec	31 (11.9)	33 (12.7)	37 (14.3)	101 (13.0)
NPH	33 (12.7)	33 (12.7)	27 (10.5)	93 (12.0)
Insulin lispro	0	1 (0.4)	0	1 (0.1)
Bolus insulin				
Insulin aspart (IAsp)	134 (51.5)	125 (48.3)	126 (48.8)	385 (49.5)
Insulin lispro (ILis)	74 (28.5)	71 (27.4)	74 (28.7)	219 (28.2)
Human insulin (HI)	32 (12.3)	46 (17.8)	46 (17.8)	124 (16.0)
Insulin glulisine (IGlu)	13 (5.0)	13 (5.0)	7 (2.7)	33 (4.2)
HI+IAsp	6 (2.3)	1 (0.4)	2 (0.8)	9 (1.2)
HI+ILis	1 (0.4)	2 (0.8)	2 (0.8)	5 (0.6)
IAsp+IGlu	0	1 (0.4)	1 (0.4)	2 (0.3)
Subjects doing carbohydrate counting, N	152 (58.5)	156 (60.2)	156 (60.5)	464 (59.7)

BMI=body mass index; FPG=fasting plasma glucose; SD=standard deviation;
Source: CSR 4101, modified from tables 10-5, 14.1.21, 14.1.22

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Protocol deviations related to treatment compliance were discussed above.

Aside from insulin treatment, there were no concomitant medications or rescue medications used for glycemic control in this trial.

Efficacy Results – Primary Endpoint

For FDA's analysis of efficacy, please see the Statistical Review by Dr. Jennifer Clark. This section will present a summarized review of the efficacy results presented by the Applicant.

The primary efficacy endpoint was the change from baseline in HbA1c after 26 weeks of treatment, using in-trial observation period. The use of HbA1c as the primary endpoint in this trial is in accordance with the 2008 Draft Guidance for Industry[6], as HbA1c is considered a well-validated surrogate endpoint for the complications of diabetes mellitus.

In addition to the change in HbA1c, HbA1c responders (subjects achieving HbA1c target of <7.5%) and insulin doses are also discussed in this section. Subgroup analyses for age groups for these endpoints are also discussed in relevant subsections here.

A small reduction in the mean HbA1c occurred in all treatment groups during 14 weeks before randomization (up to 2 weeks screening and 12-weeks of run-in period; from Week -14 to baseline). At baseline, the mean HbA1c was similar between treatment groups (Table 8).

After 26 weeks of treatment period, the observed mean HbA1c remained relatively stable in the meal-time Fiasp group (slight increase of 0.06%), while the observed mean HbA1c increased in the post-meal Fiasp (increase of 0.35%) and NovoLog groups (increase of 0.22%). See Figure 4 for display of mean HbA1c change by treatment week and Table 8 for summary of changes in HbA1c from baseline to Week 26 in each treatment group.

[6] Guidance for Industry Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention Draft Guidance, February 2008.

Table 8: Trial 4101 - Summary of Change in HbA1c (%) From Baseline to Week 26 (FAS)

	Mealtime Fiasp (N=260)	Post-meal Fiasp (N=259)	Meal-time NovoLog (N=258)
Week -14 (2 weeks of screening +12 weeks of run-in period before randomization), mean (SD)	7.76 (0.89)	7.71 (0.91)	7.67 (0.90)
Baseline (randomization; Week 0), mean (SD)	7.57 (0.80)	7.58 (0.84)	7.53 (0.83)
Week 26, LS mean (SD)	7.62 (0.89)	7.91 (0.97)	7.78 (1.05)
Adjusted mean change from baseline	0.06	0.35	0.22
Diff vs NovoLog (95% CI)	-0.17 (-0.30;-0.03)	0.13 (-0.01;0.26)	

SD=standard deviation; CI=confidence interval; N=number of subjects
Change from baseline in HbA1c is analyzed using an analysis of variance model after multiple imputation assuming treatment according to randomization. The model includes treatment, region and strata (age group) as factors, and baseline HbA1c as a covariate. Multiple imputation is used to sequentially impute missing values of change from baseline in HbA1c to Week 12 and 26 for each treatment group separately with region and strata (age group) as factors, and baseline HbA1c and earlier changes from baseline in HbA1c as covariates. Each imputed dataset is analyzed separately and estimates are combined using Rubin's rules.
Source: CSR 4101, Modified from Tables 14.2.88, 11-3

The estimated treatment difference between meal-time Fiasp and NovoLog was -0.17 (95% CI: -0.31, -0.04), establishing non-inferiority of meal-time Fiasp compared to meal-time NovoLog as the upper limit of 95% CI for the difference between meal-time Fiasp and NovoLog was <0.4% and met the non-inferiority margin.

The estimated treatment difference between post-meal Fiasp and NovoLog was 0.13 (95% CI: -0.01, 0.26), establishing non-inferiority of post-meal Fiasp compared to meal-time NovoLog as the upper limit of 95% CI for the difference between post-meal FIasp and NovoLog was <0.4% and met the non-inferiority margin.

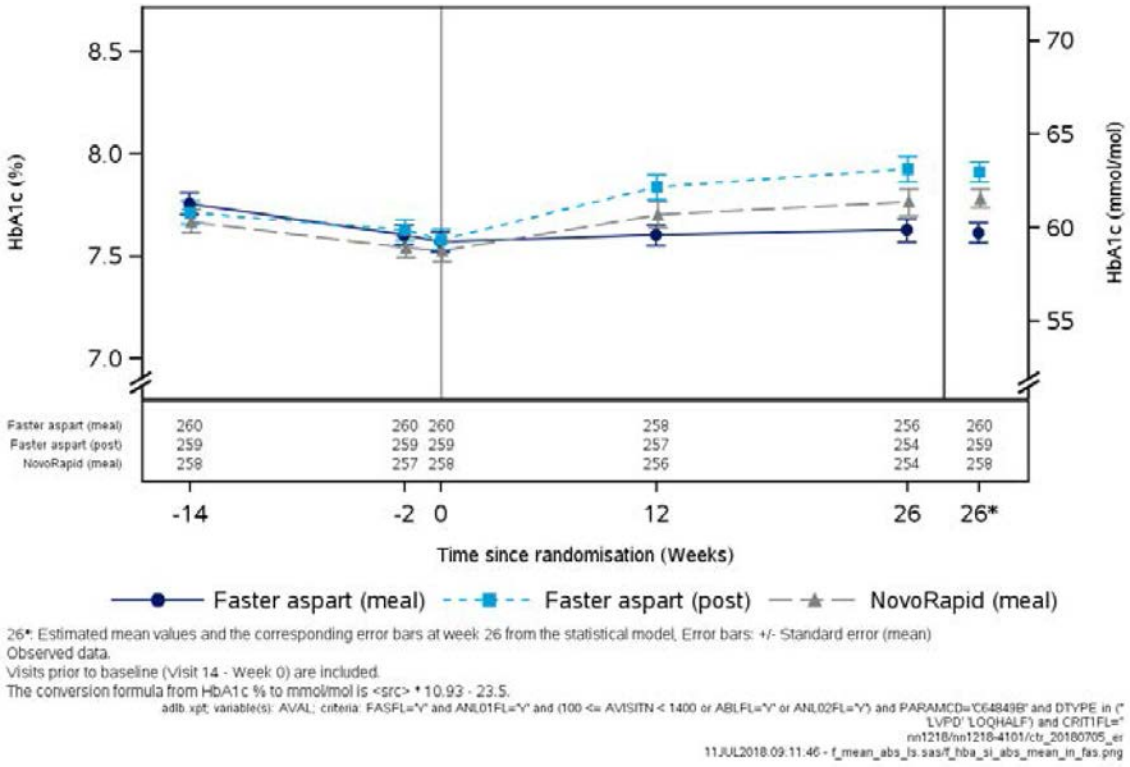
Reviewer's comment: *Although the post-meal Fiasp met the pre-specified non-inferiority margin, the average change from baseline in HbA1c for post-meal Fiasp is numerically worse than NovoLog; the treatment difference between post-meal Fiasp and NovoLog therefore favored NovoLog at 26 weeks.*

In addition, the superiority of meal-time Fiasp compared to meal-time NovoLog was confirmed as the upper bound of 95% CI was <0.

Sensitivity analyses using reduced model (reducing factors included) and assumption that missing data is missing at random showed similar results and supported the primary analysis (see Figure 11-3 in CSR; not shown here). The Applicant also conduced tipping point analyses, which supported the conclusion of the primary analysis (see Table 11-4; not shown here).

Evaluation of HbA1c by treatment week is shown in Figure 4

Figure 4: Trial 4101 - HbA1c by Treatment Week, Observed Mean and LS Mean Plot (FAS)



Source: CSR 4101, Figure 14.2.122

Reviewer's comment: *In a similarly designed study in adults with T1DM (Study 3852), there was a reduction of HbA1c across all treatment group after 26 weeks, all in combination with insulin detemir as basal insulin in a basal-bolus regimen. However, in pediatric subjects with T1DM, we see a relatively stable HbA1c with meal-time Fiasp (increase of 0.06%) and slight increase in HbA1c with post-meal Fiasp (increase of 0.35%) and meal-time NovoLog (increase of 0.22%) after 26 weeks of treatment (Figure 4).*

This treatment difference in glycemic change between adults and pediatric subjects is likely due to differences in glycemic target, both in HbA1c and difference in insulin titration goals, due to concerns about severe hypoglycemia in pediatric patients. For example, per standard of care, HbA1c target is <7% in adults compared to <7.5% in pediatric patients. In adult study 3852, bolus insulin dose was titrated to pre-prandial or bedtime SMPG target of 71-108 mg/dL and insulin titration was done twice weekly, whereas in this pediatric study, bolus insulin dose was titrated to a higher target (i.e., pre-prandial target of 71-145 mg/dL and bedtime target of 120-180 mg/dL) at weekly basis.

Overall, study 4101 showed that the meal-time Fiasp and post-meal Fiasp was not inferior to NovoLog in glycemic control when used as bolus insulin in pediatric subjects with T1DM.

Change in HbA1c in Age Groups:

During 14 weeks before randomization, the observed mean HbA1c did not decrease consistently in all age groups (Table 9). For example, in age group <6 years, while the HbA1c decreased from 7.61 to 7.33% in those that were later randomized to meal-time Fiasp, the HbA1c increased from 7.34 to 7.51% in subjects that were later randomized to post-meal Fiasp and from 7.25 to 7.39% in subjects that were later randomized to the meal-time NovoLog. However, the overall number of subjects in this age group was small (n=46) compared to other age groups and therefore likely to have been influenced by small data variations.

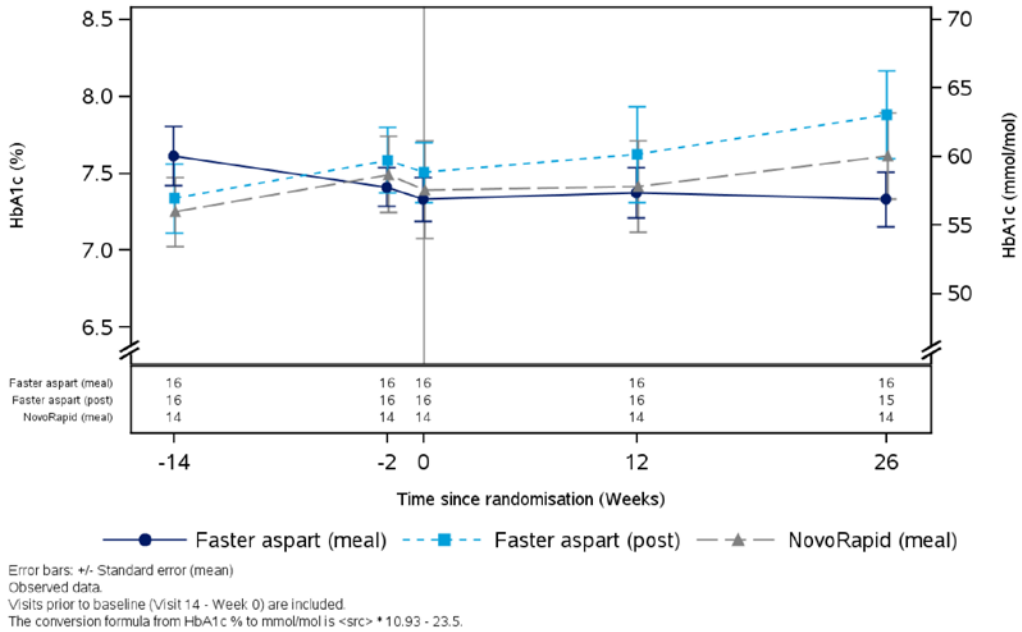
Table 9: Summary of Change in HbA1c (%) From Baseline to Week 26 per Age Group (FAS)

	Mealtime Fiasp (N=260)	Post-meal Fiasp (N=259)	Meal-time NovoLog (N=258)
Age < 6 years, N	**16**	**16**	**14**
Week -14 (2 weeks of screening +12 weeks of run-in period before randomization), mean (SD)	7.61 (0.77)	7.34 (0.91)	7.25 (0.84)
Baseline (randomization; Week 0), mean (SD)	7.33 (0.58)	7.51 (0.77)	7.39 (1.19)
Last in-trial, mean (SD)	7.33 (0.71)	7.81 (1.11)	7.61 (1.05)
Adjusted LS mean change from baseline	0	0.30	0.22
Age 6 to <12 years, N	**100**	**100**	**101**
Week -14 (2 weeks of screening +12 weeks of run-in period before randomization), mean (SD)	7.71 (0.94)	7.68 (0.89)	7.73 (0.85)
Baseline (randomization; Week 0), mean (SD)	7.55 (0.76)	7.60 (0.76)	7.63 (0.72)
Last in-trial, mean (SD)	7.58 (0.58)	7.75 (0.91)	7.68 (0.79)
Adjusted LS mean change from baseline	0.03	0.15	0.05
Age 12 to <18 years, N	**144**	**143**	**143**
Week -14 (2 weeks of screening +12 weeks of run-in period before randomization), mean (SD)	7.80 (0.88)	7.78 (0.92)	7.67 (0.94)
Baseline (randomization; Week 0), mean (SD)	7.61 (0.84)	7.58 (0.89)	7.46 (0.86)
Last in-trial, mean (SD)	7.69 (1.09)	8.04 (0.99)	7.83 (1.19)
Adjusted LS mean change from baseline	0.08	0.46	0.37

* p-values are from one-sided test for non-inferiority and superiority evaluated at 2.5% level.
**p-value is from one-sided test for non-inferiority evaluated at 2.5% level.
NOTE: In-trial population
Source: CSR 4101, Modified from Tables 14.2.89, 14.2.90, 14.2.91, 14.2.94, 14.2.95, 14.2.96

The change in HbA1c from baseline to Week 26 in age subgroups 1 to <6 years (Figure 5) and 12 to <18 years (Figure 7) demonstrated similar trend as the overall population; the HbA1c remained stable in the meal-time Fiasp group while increased in the post-meal Fiasp and NovoLog groups over 26 weeks of treatment. In the age group of 6 to <12 years, the HbA1c remained relatively stable in all three treatment groups (Figure 6). However, given that this is a subgroup analysis and not adjusted for multiplicity, the results are considered exploratory and inconclusive.

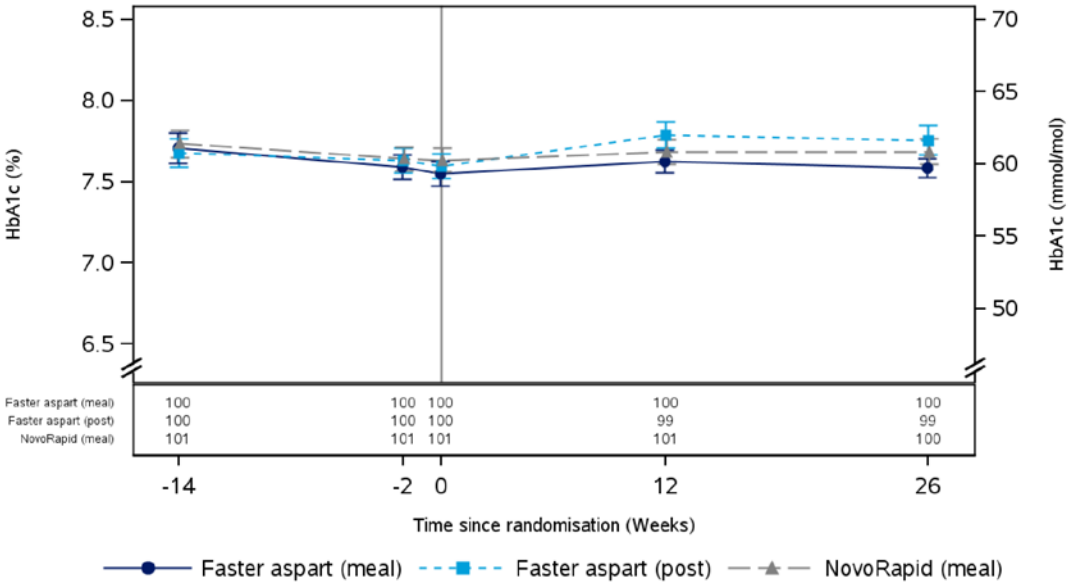
Figure 5: Mean Plot of HbA1c by Treatment Week in Children 1 to <6 years old (FAS)



Error bars: +/- Standard error (mean)
Observed data.
Visits prior to baseline (Visit 14 - Week 0) are included.
The conversion formula from HbA1c % to mmol/mol is <src> * 10.93 - 23.5.

Source: CSR 4101, Figure 14.2.123

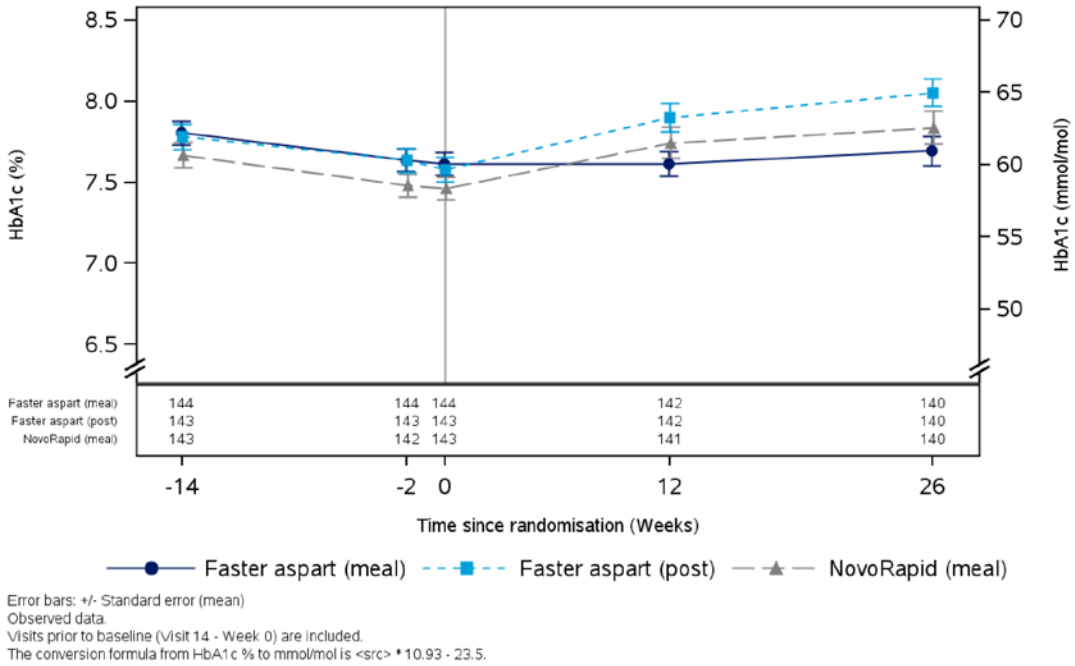
Figure 6: Mean Plot of HbA1c by Treatment Week in Children 6 to 12 years old (FAS)



Error bars: +/- Standard error (mean)
Observed data.
Visits prior to baseline (Visit 14 - Week 0) are included.
The conversion formula from HbA1c % to mmol/mol is <src> * 10.93 - 23.5.

Source: CSR 4101, Figure 14.2.124

Figure 7: Mean Plot of HbA1c by Treatment Week in Children 12 to <18 years old (FAS)



Source: CSR 4101, Figure 14.2.125

Reviewer's comment: *Overall, evaluation of change in HbA1c by age groups showed similar trends, where the HbA1c reduction after 26 weeks of treatment with meal-time Fiasp and post-meal Fiasp was not inferior compared to meal-time NovoLog.*

<u>Proportion of subjects reaching HbA1c target:</u>

See Table 10 for proportion of subjects achieving HbA1c target of <7.5%, with or without severe hypoglycemia.

Of note, more subjects had already reached HbA1c target of <7.5% at baseline compared to Week 26. Also, at baseline, numerically higher proportion subjects randomized to the NovoLog group had HbA1c target of <7.5% (50%) compared to meal-time Fiasp (44.6%) and post-meal Fiasp (43.6%). This imbalance at baseline is likely due to chance since subjects were randomized at baseline. However, given this slight imbalance at baseline between treatment groups, it would be more relevant to see the change in the proportion of subjects reaching HbA1c target from baseline to Week 26.

Table 10: Subjects [N (%)] Achieving HbA1c Targets by Treatment Week (FAS)

	Meal-time Fiasp (N=260)	Post-meal Fiasp (N=259)	NovoLog (N=258)
HbA1c <7.5%			
Baseline/Week 0	116 (44.6)	113 (43.6)	129 (50.0)
Week 12	107 (41.5)	94 (36.6)	107 (41.8)
Week 26	110 (42.3)	82 (31.7)	102 (39.5)
Change from baseline	*-2.3%*	*-11.9%*	*-10.5%*
Estimated odds of HbA1c <7.5%	0.67	0.33	0.50
Odds ratio vs NovoLog (95% CI)	1.33 (0.87, 2.01)	0.66 (0.43, 1.02)	
HbA1c <7.5% without severe hypoglycemia			
Week 26	109 (41.9)	80 (30.9)	99 (38.4)
Estimated odds of HbA1c <7.5% without severe hypoglycemia	0.67	0.33	0.50
Odds ratio vs NovoLog (95% CI)	1.37 (0.91, 2.08)	0.68 (0.44, 1.04)	

*Subjects achieving HbA1c target was analyzed using a logistic regression model with treatment, region and strata (age group) as factors, and baseline HbA1c as a covariate. Subjects without HbA1c measurement at Week 26 are considered not to have achieved HbA1c target.
Source: CSR 4104, Adapted from Table 14.2.141, 14.2.146; change from baseline calculated by the Reviewer by subtracting % at Week 26 from baseline %.

Overall, fewer subjects reached HbA1c target of 7.5% across all treatment groups after 26 weeks of treatment compared to baseline. From baseline to Week 26, there was a reduction of 2.3% of subjects with meal-time Fiasp and reduction of 11.9% with post-meal Fiasp compared to a reduction of 10.5% with NovoLog in the proportion of subjects achieving HbA1c target of 7.5%. Numerically, largest proportion of subjects reached HbA1c target of <7.5% without severe hypoglycemia with meal-time Fiasp (41.9%) compared to NovoLog (38.4%) and post-meal Fiasp (31.3%) at Week 26.

There was no statistically significant difference in the proportion of subjects achieving HbA1c target after 26 weeks of treatment, with or without severe hypoglycemia, between meal-time Fiasp and NovoLog or post-meal Fiasp and NovoLog (Table 10).

Insulin Dose:

In order to interpret the primary efficacy results, the mean daily insulin doses between treatment groups were evaluated to assess whether there was a difference between treatment groups in terms of insulin titration. The mean daily doses of bolus, basal, and total insulin doses in U and U/kg at baseline and last on-treatment are summarized in Table 11.

At the start of the run-in period (Week -11) and at baseline (Week 0), the mean basal insulin

dose was comparable across all treatment groups (Table 11). From the start of run-in period to baseline, all treatment groups had a slight increase in their daily basal insulin dose, most likely because basal insulin was being titrated to glycemic goal during the 12-week run-in period. During the 26-week treatment period, all treatment groups continued to have a slight increase in the daily basal insulin dose from baseline to Week 26 (i.e., Last on-treatment) even though the basal insulin was to be adjusted during the treatment period only if needed, but the magnitude of this daily increase was similar across all treatment groups.

During the run-in period, the mean daily bolus insulin doses were stable (Table 11). From baseline to Week 26, the mean daily bolus insulin dose increased in all three treatment groups. Based on U/kg basis, subjects in the post-meal Fiasp group had the largest overall increase in the bolus insulin dose (0.04 U/kg) compared to meal-time Fiasp (increase of 0.03 U/kg) or NovoLog (increase of 0.02 U/kg). The increase in the bolus insulin dose during the study appear to be mainly related to the mean daily bolus dose with lunch which appear to be similar across all treatment groups based on U/kg dose (i.e., 0.02 U/kg daily for all three treatment groups). Daily dose of 'other' insulin dose did not change notably in any of the three treatment groups.

The mean daily bolus dose at each treatment week in Units/kg is displayed in Figure 8, which appear to show that NovoLog group received slightly less daily bolus insulin dose from Weeks 12-19 compared to both meal-time and post-meal Fiasp group, but curves appear to converge by the end of treatment period.

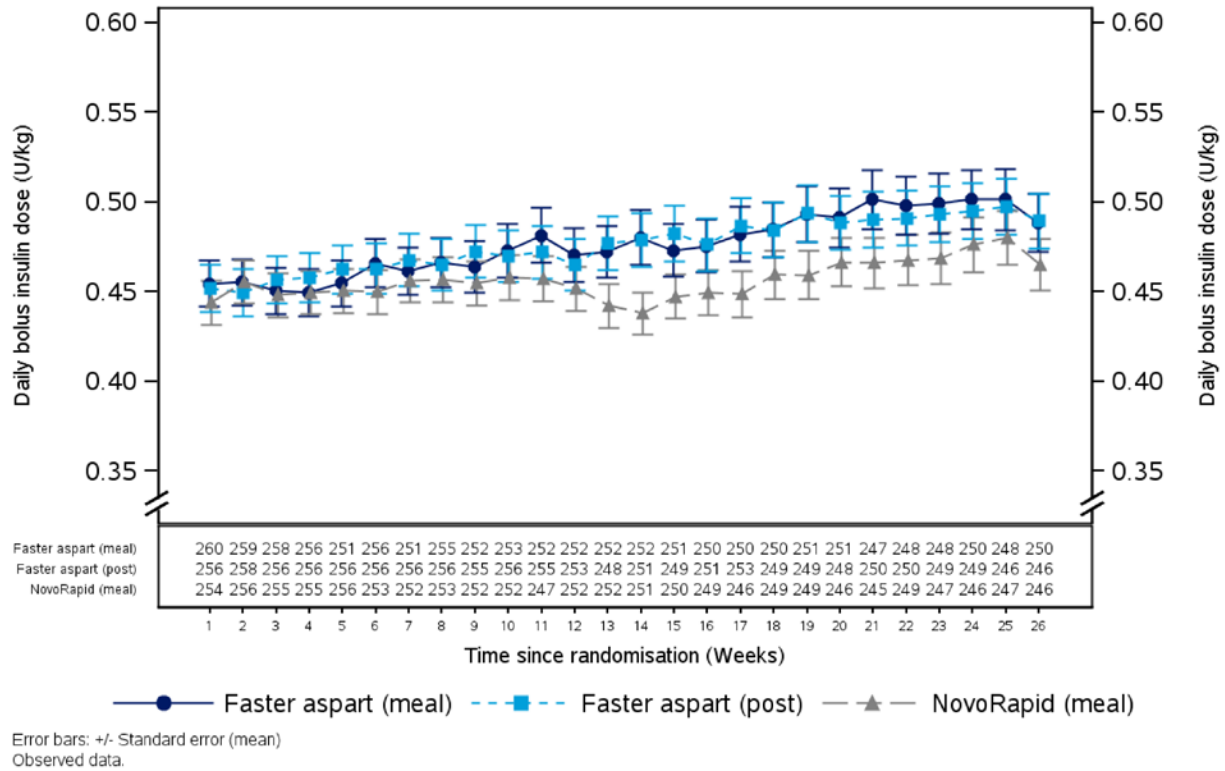
Overall, the total insulin dose increased from baseline to Week 26 in all three treatment groups, and this increase was reflective of both increases in daily basal and bolus insulin over 26 weeks.

Table 11: Change in Mean Daily Basal, Bolus, and Total Insulin Dose (SAS)

	Meal-time Fiasp (N=261)		Post-meal Fiasp (N=258)		NovoLog (N=258)	
Basal insulin dose	**U**	**U/kg**	**U**	**U/kg**	**U**	**U/kg**
Week -11	16.8	0.36	16.9	0.36	16.4	0.35
Week 0/Baseline	19.3	0.40	19.2	0.40	18.5	0.38
Last on-treatment	21.6	0.43	21.5	0.43	20.7	0.41
Change from baseline to last on-treatment	*2.3*	*0.03*	*2.3*	*0.03*	*2.2*	*0.03*
Bolus insulin dose	**U**	**U/kg**	**U**	**U/kg**	**U**	**U/kg**
Week -11	20.6	0.46	20.5	0.45	20.7	0.46
Week 0/Baseline	20.9	0.45	21.1	0.45	20.5	0.45
Last on-treatment	23.3	0.48	23.5	0.49	22.5	0.47
Change from baseline to last on-treatment	*2.4*	*0.03*	*2.4*	*0.04*	*2.0*	*0.02*
Total insulin dose	**U**	**U/kg**	**U**	**U/kg**	**U**	**U/kg**
Week 0/Baseline	40.2	0.85	40.2	0.85	39.0	0.83
Last on-treatment	44.8	0.92	45.0	0.92	43.2	0.88
Change from baseline to last on-treatment	*4.6*	*0.07*	*4.8*	*0.07*	*4.2*	*0.05*
Mean Daily Bolus Insulin Dose at Meals and Other						
Breakfast	**U**	**U/kg**	**U**	**U/kg**	**U**	**U/kg**
Week 1	6.5	0.14	6.5	0.14	6.4	0.14
Last on-treatment	7.3	0.15	7.1	0.15	6.8	0.14
Change from Week 1 to last on-treatment	*0.8*	*0.01*	*0.6*	*0.01*	*0.4*	*0*
Lunch						
Week 1	6.9	0.15	7.0	0.15	6.8	0.15
Last on-treatment	8.1	0.17	8.4	0.17	7.9	0.17
Change from Week 1 to last on-treatment	*1.2*	*0.02*	*1.4*	*0.02*	*1.1*	*0.02*
Dinner						
Week 1	7.4	0.16	7.4	0.16	7.3	0.16
Last on-treatment	8.1	0.16	8.0	0.17	7.7	0.16
Change from Week 1 to last on-treatment	*0.7*	*0*	*0.6*	*0.01*	*0.4*	*0*
Other						
Week 1	3.4	0.07	2.8	0.06	3.4	0.08
Last on-treatment	3.5	0.07	3.2	0.07	3.5	0.08
Change from Week 1 to last on-treatment	*0.1*	*0*	*0.4*	*0.01*	*0.1*	*0*

Last on-treatment value contains the last available measurement in the on-treatment period.
Source: CSR 4101, Adapted from Tables 11-11, 11-12, 11-13, 14.2.16, 14.2.17, 14.2.18, 14.2.22, 14.2.26, 14.2.34, 14.2.26, 14.2.30

Figure 8: Mean Plot of Daily Bolus Insulin Dose in Units/kg by Treatment Week – on-treatment, SAS



Error bars: +/- Standard error (mean)
Observed data.

Source: CSR 4101, Figure 14.2.50

Reviewer's comment: *The mean change in the total daily insulin dose from baseline to end of study, both in U and U/kg, was slightly larger with both meal-time Fiasp and post-meal Fiasp compared to NovoLog. This small mean increase in the total daily insulin dose with meal-time Fiasp and post-meal Fiasp groups appeared to be related to an increase in the mean daily bolus insulin dose, as the increase in the mean daily basal insulin dose appear to be similar across three treatment groups. This treatment difference in the mean daily bolus insulin dose during study appears to be small and unlikely to have a large impact on the primary efficacy endpoint (i.e., HbA1c). In addition, insulin titration was done in a blinded manner (except for open-label Fiasp group) with same glycemic target for both meal-time Fiasp and NovoLog treatment groups.*

Data Quality and Integrity

The initial submission had incomplete datasets, with the potential to lead to a refuse-to-file. However, Dr. Jennifer Clark, Statistical Reviewer, sent an Information Request to the Applicant on April 3, 2019 to have them fix the filing issues before the filing deadline, and the Applicant responded on April 5, 2019 with corrections that were adequate to address Dr. Clark's concerns

with data quality.

Efficacy Results – Secondary and other relevant endpoints

Other supportive secondary efficacy endpoints such as change from baseline in 8-point SMPG profiles and change from baseline in FPG are discussed here.

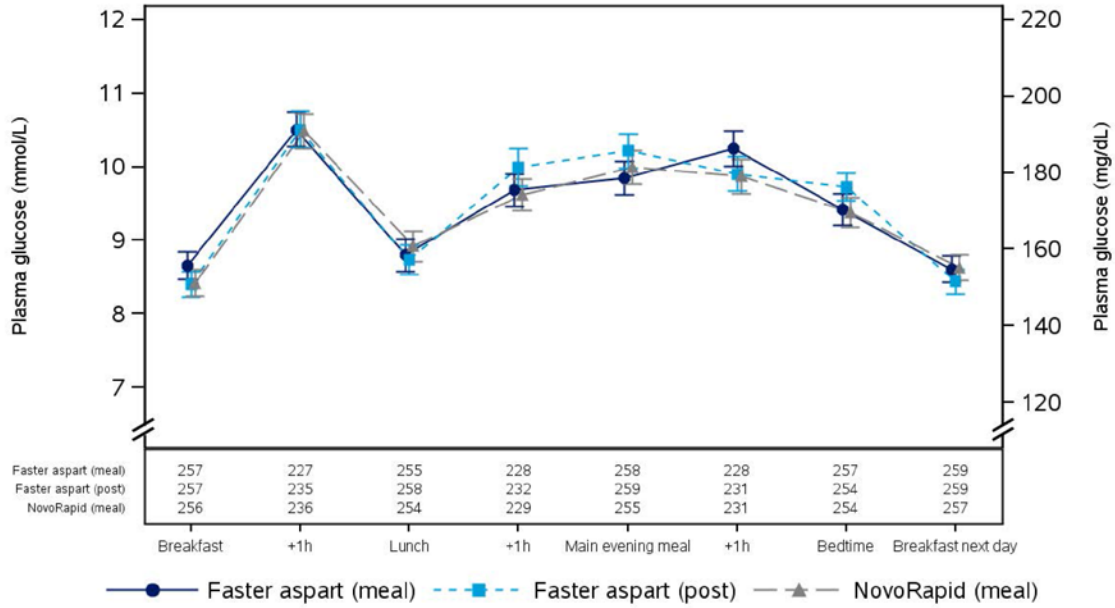
The Applicant evaluated the postprandial glucose and postprandial glucose increment using SMPG, which are not as reliable as lab-based, plasma glucose measurements and may be affected by non-standardized meals with different caloric composition, unlike standardized meal test. In addition, secondary efficacy endpoints with CGM were done only in subgroup of subjects at selected sites. Therefore, these secondary endpoints are not further discussed in this review.

Change from baseline in 8-pont SMPG profiles:

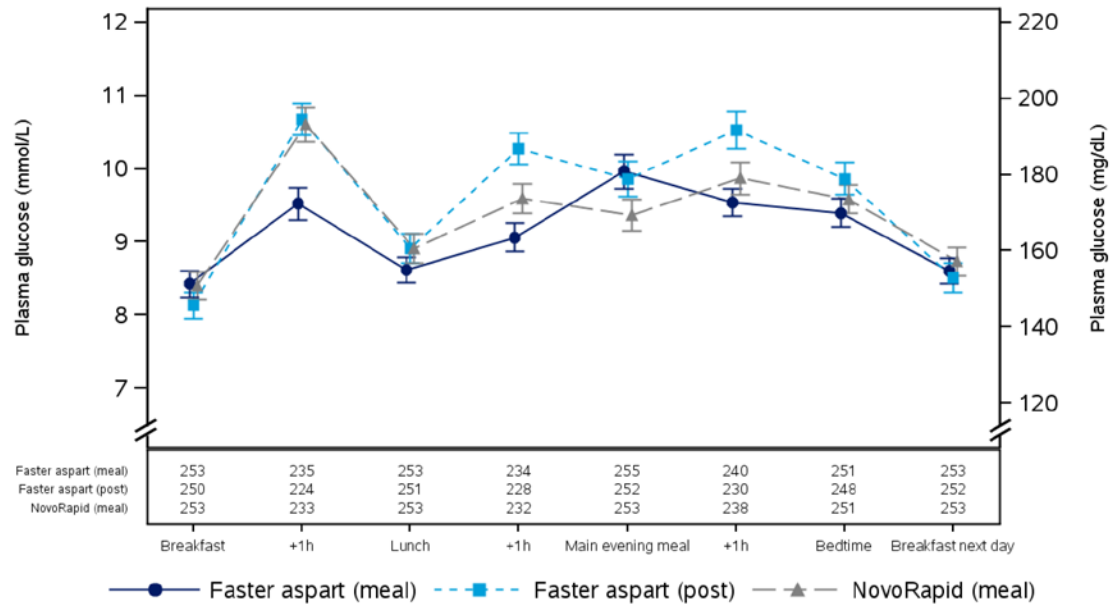
Subjects measured 8-point SMPGs on 2 consecutive days at baseline, Week 12 and Week 26. At baseline the 8-point SMPG profile appear similar between treatment groups (top Figure 9).

After 26 weeks, the mean SMPG was lower at 1-hour post breakfast, lunch, and main evening meal with meal-time Fiasp compared to NovoLog, whereas the mean SMPG was higher at 1-hour post lunch and main evening with post-meal Fiasp compared to NovoLog (bottom Figure 9). The mean SMPG before main evening meal appear to be higher with meal-time Fiasp compared to NovoLog group at Week 26 (bottom Figure 9).

Figure 9: Trial 4101 – Mean Plot of 8-point Self Measured Plasma Glucose Profile at Baseline (Top) and Week 26 (Bottom) - FAS



Error bars: +/- Standard error (mean)
The output is based on the mean of two 8-point profiles for each Subject.
Observed data.
The conversion factor from PG mmol/L to mg/dL is 18.02.
adsmpg.xpt; variable(s): AVAL; criteria: FASFL='Y' and ANL01FL='Y' and ABLFL='Y' and PARAMCD='C105585Y' and ATPT1='8-POINT PROFILE' and ATPT ne 'OTHER' and DTYPE='' and CRIT1FL=''
nn1218/nn1218-4101/ctr_20180705_er
11JUL2018:09:11:26 - f_mean_abs_8pp.sas/f_8pp_mean_w0_fas.png



Error bars: +/- Standard error (mean)
The output is based on the mean of two 8-point profiles for each Subject.
Observed data.
The conversion factor from PG mmol/L to mg/dL is 18.02.

Source: CSR 4101, Figure 11-4

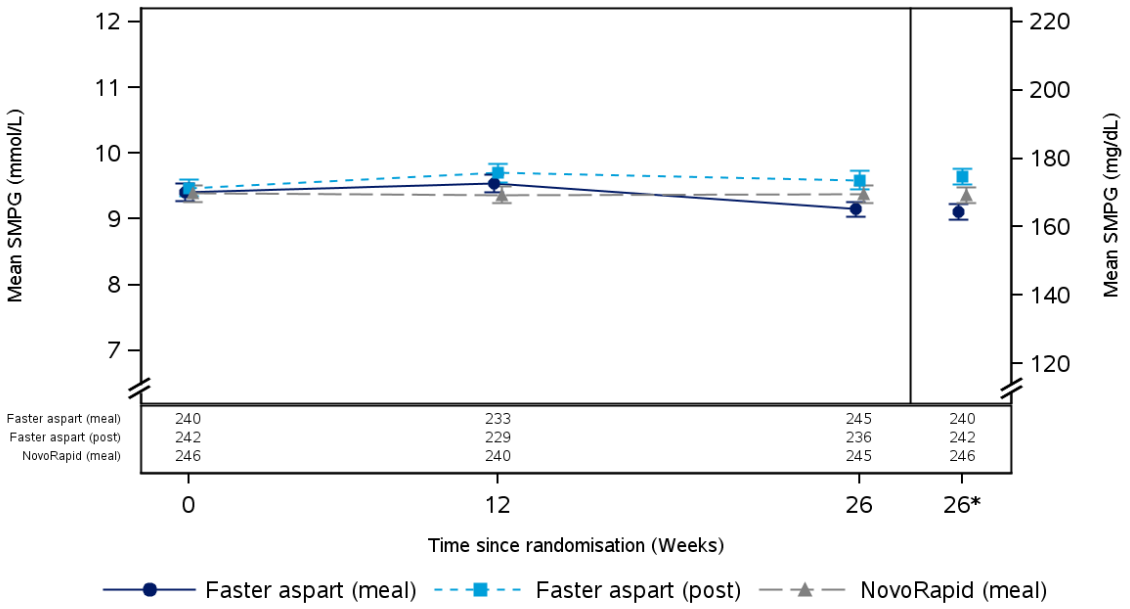
At baseline, the observed mean of the 8-point SMPG profiles were similar between treatment groups (Table 12). At the end of 26-week treatment period, the mean of the 8-point SMPG profile numerically decreased in the meal-time Fiasp (-5.59 mg/dL) and meal-time NovoLog (-1.05 mg/dL) groups and numerically increased in the post-meal Fiasp group (4.06 mg/dL). However, these numerical changes were small and there were no statistically significant differences in the estimated mean change from baseline in the 8-point SMPG profiles between meal-time Fiasp and NovoLog or between post-meal Fiasp and NovoLog (Table 12).

Table 12: Mean of 8-point SMPG Profiles (mg/dL; FAS)

	Mealtime Fiasp (N=260)	**Postmeal Fiasp (N=259)**	**NovoLog (N=258)**
Mean at baseline	169.53	170.74	169.22
At Week 26	164.24	173.88	168.78
Change from baseline at Week 26	-5.59	4.06	-1.05
Treatment Diff vs NovoLog (95% CI)	-4.55 (-10.45;1.36)	5.10 (-0.86, 11.06)	

FAS=full analysis set; CI=confidence interval; SMPG=self-measured plasma glucose;
Change from baseline in mean SMPG is analyzed using an analysis of variance model after multiple imputation assuming treatment according to randomization. The model includes treatment, region and strata (age groups) as factors, and baseline mean SMPG as a covariate. Multiple imputation is used to sequentially impute missing value of change from baseline in mean SMPG to Week 12 and 26 for each treatment group separately with region and strata (age group) as factors, and baseline mean SMPG and earlier changes from baseline in mean SMPG as covariates. Each imputed dataset is analyzed separately and estimates are combined using Rubin's rules.
Source: CSR, Adapted from Tables 14.2.257, 14.2.267

Figure 10: Mean and LSmean of 8-Point SMPG Profile by Treatment Week (FAS)



26*: Estimated mean values and the corresponding error bars at week 26 from the statistical model, Error bars: +/- Standard error (mean), SMPG: Self-measured plasma glucose
Observed data.
The conversion factor from PG mmol/L to mg/dL is 18.02.

Source: CSR 4101, Figure 14.2.269

Reviewer's comment: *There were no statistically or clinically significant changes in the mean of 8-point SMPG profile between treatment groups during the study.*

Change in Fasting Plasma Glucose (FPG):

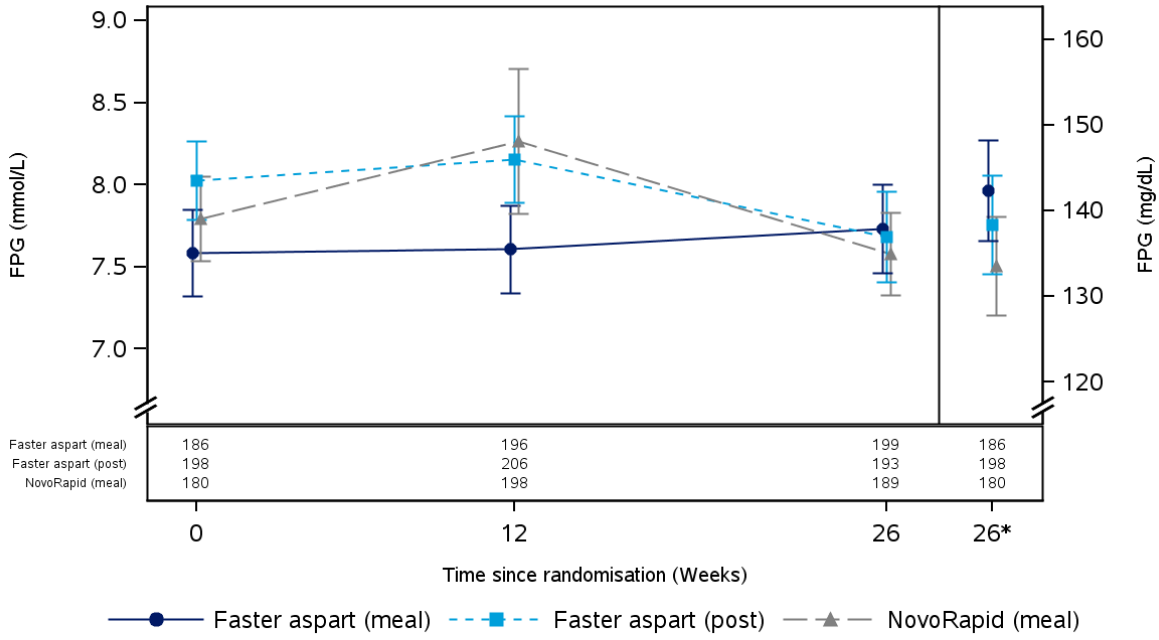
The changes in FPG for each treatment groups are summarized in Table 13. The mean FPG remained stable from baseline to Week 26 for all 3 treatment groups, without statistically significant difference between meal-time Fiasp and NovoLog or post-meal Fiasp and NovoLog for the change from baseline to Week 26 (Table 13 and Figure 11).

Table 13: Mean of Fasting Plasma Glucose (mg/dL) (FAS)

	Mealtime Fiasp (N=260)	Postmeal Fiasp (N=259)	NovoLog (N=258)
Mean at baseline	136.67	144.61	140.43
At Week 26	143.53	139.76	135.28
Change from baseline at Week 26	2.87	-0.90	-5.37
Treatment Diff vs NovoLog (95% CI)	8.25 (-6.86, 23.35)	4.48 (-10.47, 19.43)	

FAS=full analysis set; CI=confidence interval;
Change from baseline in fasting plasma glucose (FPG) is analyzed using an analysis of variance model after multiple imputation assuming treatment according to randomization. The model includes treatment, region and strata (age groups) as factors, and baseline FPG as a covariate. Multiple imputation is used to sequentially impute missing value of change from baseline in FPG to Week 12 and 26 for each treatment group separately with region and strata (age group) as factors, and baseline FPG and earlier changes from baseline in FPG as covariates. Each imputed dataset is analyzed separately and estimates are combined using Rubin's rules.
Source: CSR, Adapted from Tables 14.2.172, 11-9, 14.2.182

Figure 11: Mean and LS Mean of Fasting Plasma Glucose by Treatment Week (In trial, FAS)



26*: Estimated mean values and the corresponding error bars at week 26 from the statistical model, Error bars: +/- Standard error (mean), FPG: Fasting plasma glucose
Observed data.
The conversion factor from FPG mmol/L to mg/dL is 18.02.
adlb.xpt; variable(s): AVAL; criteria: FASFL='Y' and ANL01FL='Y' and (ABLFL='Y' or ANL02FL='Y') and PARAMCD='C105585P' and DTYPE=" and CRIT1FL="
nn1218/nn1218-4101/ctr_20180705_er
11JUL2018:09:12:11 - f_mean_abs_ls.sas/f_fpg_abs_mean_in_fas.png

Source: CSR 4101, Figure 14.2.184

Reviewer's comment: *There were no statistically or clinically significant changes in the mean of FPG between treatment groups during the study.*

Dose/Dose Response

Insulin dose was discussed above in the Efficacy Results – Primary Endpoints section.

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

None.

7. Integrated Review of Effectiveness

Since there was only one trial submitted for review, subsections not applicable to this submission have been deleted.[7]

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Trial 4101 evaluated the glycemic control of meal-time and post-meal Fiasp in combination with insulin degludec in pediatric patients with type 1 diabetes, with age range of 2 to 17 years old. About 25.6% of the overall study population was from U.S. Overall, the study population was reasonably representative of patients with T1DM and the U.S. population.

The trial population in Trial 4101 included a very small number of patients <3 years of age, as only 4 subjects were 2 to <3 years old, of which 2 subjects were randomized to meal-time Fiasp and 2 subjects were randomized to post-meal Fiasp group. There were no 1-year old pediatric patients enrolled in this study. In addition, about 5.4% of subjects randomized were 3 to <6 years of age, and the main pediatric age subgroup enrolled were 12 to <18 years (55.4%) and 6 to <12 years (39.1%). However, I have no reason to believe that the use of meal-time and post-meal Fiasp would not be effective for glycemic control in the younger pediatric patients.

[7] Deleted sections include: 7.1 Assessment of Efficacy Across Trials, 7.1.1 Primary Endpoints, 7.1.2 Secondary and Other Endpoints, 7.1.3 Subpopulations, 7.1.4 Dose and Dose-Response, 7.1.5 Onset, Duration, and Durability of Efficacy Effects

7.2.2. Other Relevant Benefits

Fiasp will provide another insulin option for management of diabetes in pediatric patients. One of the major benefits of Fiasp compared to NovoLog, the other insulin aspart product that is currently U.S. approved for use in pediatric patients with diabetes, is that Fiasp can be given after meal ingestion as well as before meals. NovoLog is currently approved to be administered 5-10 minutes before meals, whereas Fiasp can be administered at the start of a meal or within 20 minutes after starting a meal. Ability to administer meal time insulin dose after meal ingestion allows greater flexibility in dosing insulin around meals and better match carbohydrate intake, which would increase the convenience for pediatric patients and theoretically lead to better postprandial glucose control due to better match of insulin dose to meals. Although the overall HbA1c reduction was not better with post-meal Fiasp compared to NovoLog in trial 4101, this may be partly due to the fact that all post-meal Fiasp injection was to be given 20 minutes after a meal; it is likely that the optimal administration timing of bolus insulin may be patient-dependent, i.e., vary based on an individual, which can be done in clinical practice on an individual basis. Thus, there is a potential clinical benefit of having the flexibility of administering bolus insulin around the meals to optimize administration of insulin dose in an individual patient.

7.3. Integrated Assessment of Effectiveness

To support the use of Fiasp in pediatric patients with diabetes mellitus, the Applicant conducted a pediatric efficacy and safety trial 4101. This trial was conducted to satisfy PREA PMR 3253-1.

Trial 4101 was a randomized, partly double-blinded, active-control, treat-to-target trial comparing the effect and safety of meal-time Fiasp versus meal-time NovoLog and open-label post-meal Fiasp versus meal-time NovoLog, all in combination with insulin degludec one daily in a basal-bolus regimen in children and adolescents with T1DM who were 1 to less than 18 years of age. Insulin degludec was titrated during 12-week run-in period before randomization, and basal insulin dose was titrated during 26 weeks of treatment period based on pre-meal (71-145 mg/dL) and bedtime SMPG target (120-180 mg/dL) using standardized algorithm.

The mean age of randomized pediatric patients was 11.7 years, with age range of 2 to <17 years of age. There were no pediatric subjects 1 to <2 years of age, and only 4 subjects were 2 to <3 years of age out of 777 randomized subjects. About 25.6% of study population were from the United States, and the mean HbA1c was 7.6%.

After 26 weeks of treatment, the mean change from baseline in HbA1c remained stable with meal-time Fiasp (0.06%) and increased with post-meal Fiasp (0.35%) and meal-time NovoLog (0.22%).

The estimated treatment difference between meal-time Fiasp and NovoLog was -0.17 (95% CI: -

0.31, -0.04), establishing non-inferiority of meal-time Fiasp compared to meal-time NovoLog as the upper limit of 95% CI for the difference between meal-time Fiasp and NovoLog was <0.4% and met the non-inferiority margin. In addition, the superiority of meal-time Fiasp compared to meal-time NovoLog was confirmed as the upper bound of 95% CI was <0.

The estimated treatment difference between post-meal Fiasp and NovoLog was 0.13 (95% CI: -0.01, 0.26), establishing non-inferiority of post-meal Fiasp compared to meal-time NovoLog as the upper limit of 95% CI for the difference between post-meal FIasp and NovoLog was <0.4% and met the non-inferiority margin.

8. Review of Safety

8.1. Safety Review Approach

The safety evaluation for this supplement was based on the clinical safety data for the pediatric trial 4101. The safety evaluation in trial 4101 included collection and assessment of adverse events (including hypoglycemia, medication errors, infusion site reactions, and hyperglycemia; see Section 8.3.2), change from baseline in safety laboratory parameters, and vital signs. For evaluation of summary adverse event data, the Applicant's adverse event dataset was used to compare results to the Clinical Study Report. For evaluation of significant adverse event such as hypoglycemia, subject level data were reviewed. Narratives of all serious adverse events, adverse events leading to dropouts, and medical events of special events (i.e., medication error), other significant adverse events (i.e., severe hypoglycemia, injection site reactions) were reviewed.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Safety was evaluated using the 'on-treatment' period, unless otherwise noted. All subjects who were exposed to at least one dose of Fiasp or NovoLog were included in the safety analysis set (SAS), which included 261 subjects in the meal-time Fiasp, 258 subjects in the post-meal Fiasp, and 258 subjects in the NovoLog group.

During the run-in period, exposure was 60.3 subject-years for both meal-time and post-meal Fiasp groups and 59.9 subject-years for NovoLog group.

In the treatment period, the total exposure was 128.4 subject-years for meal-time Fiasp and 127.7 subject-years for both post-meal Fiasp and NovoLog. There were no notable differences in exposure between three treatment groups for each age group (Table 14).

The total observation time was 152.2 subject-years for meal-time Fiasp, 151.0 subject-years for post-meal Fiasp, and 150.9 subject-years for NovoLog.

Table 14: Exposure by Age Group (SAS)

	Meal-time Fiasp	Post-meal Fiasp	Meal-time NovoLog	Total
Number of subjects	261	258	258	777
Exposure, subject-years (%)				
Total	128.4 (100.0)	127.7 (100.0)	127.7 (100.0)	383.7 (100.0)
1 to <6 years	8.0 (6.2)	8.0 (6.3)	7.0 (5.5)	23.0 (6.0)
6 to <12 years	50.6 (39.4)	49.4 (38.7)	50.0 (39.2)	150.0 (39.1)
12 to <18 years	69.8 (54.3)	70.3 (55.1)	70.6 (55.3)	210.7 (54.9)

Source: CSR 4101, Table 14.2.12

The mean duration of exposure was 26 weeks (or 0.5 years) in all three treatment groups. The majority (97.5%) in all treatment groups were exposed to the study drug for ≥25 weeks (97.6%) and were observed for ≥27 weeks (97.7%).

Insulin dose was discussed in Section 6.1.2, Study Results (Table 11).

8.2.2. Relevant characteristics of the safety population:

This supplement only included a single trial 4101, and demographics of study populations were discussed in Section 6.1.2, Study Results (Table 6).

8.2.3. Adequacy of the safety database:

Overall, I believe that the size of the safety database, the duration of exposure to the study drug, patient demographics, and baseline disease characteristics with reference to the U.S. target population are acceptable. U.S. subjects comprised about 25.6% of the total study population in Trial 4101. The subjects had either study visit or phone contact with the site every week for insulin titration as well as assessment of adverse events and occurrence of hypoglycemia and hyperglycemia.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The submission quality was adequate for review overall, and no particular issues related to data quality or integrity that may affect the safety review were identified.

8.3.2. Categorization of Adverse Events

Adverse event (AE) was defined as any untoward medical occurrence in a subject administered

a product, and which does not necessarily have a causal relationship with this treatment. AE can therefore be any unfavorable and unintended sign, symptoms or disease temporarily associated with the use of a product, whether or not considered related to the product.

Treatment-emergent adverse events (TEAE) was defined as an event that has onset up to 7 days after last day of randomized treatment and excluded events occurring in the run-in period. All AEs discussed in this review are TEAE, unless otherwise noted.

A serious adverse event (SAE) was defined as events leading to:

- Death;
- A life-threatening experience;
- In-patient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability or incapacity;
- A congenital anomaly or birth defect;
- Important medical events based on medical judgement.

In addition, the following AEs were always reported as SAE using the important medical event criteria:

- Risk of liver injury defined as ALT or AST >3x upper limit normal (ULN) and total bilirubin >2x ULN without alternative etiology (Hy's law);
- Suspicion of transmission of infectious agents via the trial product.

Medication error was reported as a medical event of special interest (MESI):

- Administration of wrong drug;
- Wrong route of administration, such as intramuscular instead of subcutaneous;
- Administration of an overdose with the intention to cause harm (e.g., suicide attempt), misuse, or abuse of the study drug;
- Accidental administration of lower or higher dose than intended, irrespective of SAE criteria.

Subjects were to contact site in case of suspicion of an injection site reaction, and possible injection site reactions related to bolus and/or basal insulin were recorded on an injection site form.

All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. Medication errors, injection site reactions, lipodystrophy, and allergic reactions were identified based on a MedDRA search grouping using Preferred Terms (see listing in Appendix 16.2.7, Listing 16.2.7.14; not shown here).

Information on hypoglycemic episodes was collected and reported separately on the hypoglycemic episodes form and not the AE form (unless it fulfilled SAE criteria). Special forms

specific for each event were also used for medication errors, injection site reactions and hyperglycemic episodes.

Hypoglycemia:

Treatment emergent hypoglycemic episodes were defined as episodes occurring on or after the first day of study drug administration after randomization and no later than one day after the last day on study drug.

For each suspected hypoglycemic episode throughout the trial, plasma glucose (PG) was to be measured and recorded. All PG ≤70 mg/dL or >70 mg/dL occurring with hypoglycemic symptoms were required to be reported by the subject in the diary by completing hypoglycemic form and recommended to measure PG every 15 minutes until SMPG value is >70 mg/dL or symptoms had been resolved.

One hypoglycemic episode form in the diary covered up to 60 minutes of repeated SMPG measurements and symptoms. The lowest SMPG value was used as the value for hypoglycemic episode together with time for the first SMPG value and/or hypoglycemic symptoms. If a new low SMPG value was measured and/or symptoms did not disappear after 60 minutes after first reported low SMPG value, a new form was to be completed and this was considered a new hypoglycemic episode.

Nocturnal hypoglycemic episodes were those occurring between 23:00 and 07:00, inclusive.

Hypoglycemia was classified according to ISPAD's definition[8] of severe hypoglycemia, Novo Nordisk classification of hypoglycemia, and the ADA classification[9] of hypoglycemia.

Novo Nordisk definition of hypoglycemia in pediatrics (where BG confirmed hypoglycemia was defined as PG level below 56 mg/dL) as following:

- Severe hypoglycemia according to ISPAD: hypoglycemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose);
- Symptomatic BG confirmed hypoglycemia: an episode that is BG confirmed by PG <56 mg/dL with symptoms consistent with hypoglycemia;
- Asymptomatic BG confirmed hypoglycemia: an episode that is BG confirmed by PG <56 mg/dL without symptoms consistent with hypoglycemia;
- Severe or BG confirmed symptomatic hypoglycemia: an episode that is severe according to ISPAD classification or BG confirmed by PG <56 mg/dL with symptoms consistent with

[8] International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2014 Compendium. Pediatric Diabetes 2014;15 Suppl 20:1-290.
[9] Diabetes Care 2013;36:1384-95.

hypoglycemia;

- BG confirmed hypoglycemia: an episode that is BG confirmed by PG <56 mg/dL with or without symptoms consistent with hypoglycemia;
- Severe or BG confirmed hypoglycemia: an episode that is severe according to ISPAD classification or BG confirmed by PG <56 mg/dL with or without symptoms consistent with hypoglycemia.

ADA/ISPAD classification of hypoglycemia in pediatrics:

- Severe hypoglycemia according to ISPAD: hypoglycemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose);
- Asymptomatic hypoglycemia: An episode not accompanied by typical symptoms of hypoglycemia, but with a measured PG ≤70 mg/dL;
- Documented symptomatic hypoglycemia: An episode during which typical symptoms of hypoglycemia was accompanied by a measured PG level ≤70 mg/dL;
- Pseudo-hypoglycemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycemia with a measured PG level >70 mg/dL but approaching that level;
- Probably symptomatic hypoglycemia: An episode during which symptoms of hypoglycemia were not accompanied by a PG determination but that was presumably caused by a PG level ≤70 mg/dL.

Hyperglycemic episodes:

For each suspected hyperglycemic episode, SMPG was to be recorded. If SMPG was >250 mg/dL and the subject looked or felt ill, subject was to measure blood ketone levels using a BG meter or measure urine ketones using a urine stick.

A subject experiencing a hyperglycemic episode where s/he looked or felt ill and with either a SMPG >250 mg/dL and blood ketones >1.5 mmol/L or SMPG >250 mg/dL and urine ketones above 'moderate', the subject was to record this in the diary as a hyperglycemic episode, and to contact site for guidance on titration and treatment of symptoms.

One hyperglycemic episode form in the diary covered up to 24 hours of repeated SMPG measurements and symptoms. The highest value for SMPG and ketones were used as the values for the hyperglycemic episode. If SMPG value and blood or urine ketones and/or symptoms did not disappear after 24 hours, a new form was completed and was considered a new hyperglycemic episode.

8.3.3. Routine Clinical Tests

Clinical laboratory tests are listed in Table 15 and the frequency of all clinical tests was presented in Table 3. Except for urine pregnancy testing (done at site), ketone measurements (done at home), and antibody assessments (done by special laboratory), all laboratory tests were done by a central laboratory.

Table 15: Clinical Laboratory Tests

Haematology Erythrocytes Haemoglobin Haematocrit Leucocytes Thrombocytes	**Biochemistry** Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Bilirubin (total) Creatinine Potassium Sodium
Lipids Cholesterol (total) Low density lipoprotein (LDL) High density lipoprotein (HDL)	
Antibodies Insulin aspart antibodies (amount of antibodies specific for insulin aspart and cross-reacting with human insulin, and total of these)[1]	**Pregnancy** Human chorionic gonadotropin (hCG)[2]
	Urinalysis Ketones (dipstick)

[1]The subject was to be fasting and attend the visit without having taken any kind of insulin for at least 8 hours before blood sampling. Antibody samples could be retained until drug approval by U.S. Food and Drug Administration (FDA) and/or European Medicins Agency (EMA). The retained antibody samples could be used for further characterisation for antibody response towards drug if required by health authorities or for safety reasons as described in protocol Section 24.2 (Appendix 16.1.1).

[2]Only females of childbearing potential. A urine pregnancy test was performed locally and at site if menstrual period was missed, menarche occurred, deemed needed by the investigator or required by local law. A positive urine test was to be followed up by a confirmatory serum-hCG (central laboratory). The reporting of any pregnancy required in this trial is described in details in protocol Section 12.5 (Appendix 16.1.1).

[3]Only measured by a subject if experiencing a hyperglycaemic episode and could also be measured in the blood using a BG meter (Section 9.5.4.1).

Source: CSR 4101, Table 9-5

8.4. Safety Results

8.4.1. Deaths

One death was reported in the trial, which as not treatment related. A 12-year old boy drowned at sea during the second follow-up period, 11 days after the last dose of randomized treatment; he was randomized to NovoLog. An autopsy confirmed that the death was accidental drowning in natural water.

8.4.2. Serious Adverse Events

Thirty-five serious adverse events (SAEs) were reported by 27 subjects, with the highest incidence in the post-meal Fiasp group (5.0%, or 11.8/100 PYE) compared to meal-time Fiasp (1.9%, or 5.5/100 PYE) or NovoLog (3.5%, or 10.2 PYE) groups. SAEs are summarized in Table 16.

Table 16: Serious Adverse Events by Preferred Terms in Trial 4101 (SAS)

	Meal-time Fiasp			Post-meal Fiasp			Meal-time NovoLog		
Total subjects	261			258			258		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Total events	**5 (1.9)**	**7**	**5.5**	**13 (5.0)**	**15**	**11.8**	**9 (3.5)**	**13**	**10.2**
SOC and PT									
Infections and infestations SOC	***3 (1.1)***	***4***	***3.1***	***1 (0.4)***	***1***	***0.8***	***5 (1.9)***	***5***	***(3.9)***
Gastroenteritis	0			0			3 (1.2)	3	2.3
Appendicitis	2 (0.8)	2	1.6	0			0		
Gastrointestinal viral infection	1 (0.4)	1	0.8	0			0		
Influenza	0			1 (0.4)	1	0.8	0		
Osteomyelitis	0			0			1 (0.4)	1	0.8
Pneumonia	1 (0.4)	1	0.8	0			0		
Tonsillitis	0			0			1 (0.4)	1	0.8
Metabolism and nutrition disorders SOC	***1 (0.4)***	***1***	***0.8***	***4 (1.6)***	***4***	***3.1***	***4 (1.6)***	***5***	***3.9***
Diabetic ketoacidosis	0			2 (0.8)	2	1.6	2 (0.8)	2	1.6
Hypoglycemia	1 (0.4)	1	0.8	2 (0.8)	2	1.6	1 (0.4)	1	0.8
Diabetes mellitus inadequate control	0			0			1 (0.4)	1	0.8
Hyperglycemia	0			0			1 (0.4)	1	0.8
Gastrointestinal disorders SOC	***0***			***0***			***2 (0.8)***	***3***	***2.3***
Gastritis	0			0			1 (0.4)	2	1.6
Abdominal pain	0			0			1 (0.4)	1	0.8
Injury, poisoning and procedural complications SOC	***1 (0.4)***	***1***	***0.8***	***2 (0.8)***	***2***	***1.6***	***0***		
Accidental overdose	1 (0.4)	1	0.8	2 (0.8)	2	1.6	0		
Nervous system disorders SOC	***1 (0.4)***	***1***	***0.8***	***2 (0.8)***	***2***	***1.6***	***0***		
Hypoglycemic unconsciousness	0			2 (0.8)	2	1.6	0		
Indiopathic partial epilepsy	1 (0.4)	1	0.8	0			0		
Renal and urinary disorders SOC	***0***			***2 (0.8)***	***2***		***0***		
Nephrotic syndrome	0			1 (0.4)	1		0		
Renal colic	0			1 (0.4)	1		0		
Cardiac disorders SOC	***0***			***1 (0.4)***	***1***	***0.8***	***0***		
Palpitations	0			1 (0.4)	1		0		
Musculoskeletal and connective tissue SOC	***0***			***1 (0.4)***	***1***	***0.8***	***0***		
Epiphysiolysis	0			1 (0.4)	1		0		
Psychiatric disorders SOC	***0***			***1 (0.4)***	***1***	***0.8***	***0***		
Adjustment disorder with mixed disturbance of emotion and conduct	0			1 (0.4)	1		0		
Surgical and medical procedures SOC	***0***			***1 (0.4)***	***1***	***0.8***	***0***		
Diabetes mellitus management	0			1 (0.4)	1		0		

SOC=system organ class; PT=preferred terms
Source: CSR 4101, Table 14.3.1.20

The majority of SAEs were in the 'Infections and Infestations' and 'Metabolism and Nutrition

Disorders' System Organ Class, but the incidences of individual events were infrequent and did not show consistent trends with Fiasp treatment.

Hypoglycemia-related SAEs occurred with 2 events in the meal-time Fiasp group (one each of accidental overdose and hypoglycemia), 4 events in the post-meal Fiasp group (2 events each of accidental overdose and hypoglycemic unconsciousness), and one event with NovoLog (hypoglycemia). However, one subject with 'accidental overdose' also reported 'hypoglycemia' with meal-time Fiasp at the same day, and two subjects with 'accidental overdose' reported 'hypoglycemic unconsciousness' at the same day with post-meal Fiasp.

One events of 'diabetic ketoacidosis' with post-meal Fiasp were related to decreased appetite and not eating and drinking water for several days, and the other event occurred in a 7-year old who had repeated vomited due to 'toxic food infection' before the DKA event. Both events of 'diabetic ketoacidosis' (DKA) with meal-time NovoLog occurred in subjects with other acute disease before the episode: one subject had gastroenteritis and developed vomiting, and the other subject had also vomited before the DKA event.

The majority of SAEs resolved, except for two SAEs where recovery/resolution occurred with sequelae: 'adjustment disorder with mixed disturbance of emotion and conduct' with post-meal Fiasp and 'gastritis' with NovoLog. The event of 'adjustment disorder with mixed disturbance of emotion and conduct' with post-meal Fiasp occurred in a 12-year old female having an altercation with her mother due to cell phone privileges being revoked and did not appear to be related to Fiasp treatment.

The event of 'idiopathic partial epilepsy' with meal-time Fiasp and 'nephrotic syndrome' with post-meal Fiasp did not recover/did not resolve; however, review of narratives did not show causal relationship with Fiasp and it is unlikely that these events were related to Fiasp.

Reviewer's comment: *Review of narratives and comparison of incidences of all SAEs did not identify any new safety issues related to Fiasp use in pediatric population. Hypoglycemia is a potential labeled event with all insulins and Fiasp is also labeled for the risk of hypoglycemia.*

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No subject withdrew from the trial 4101 due to an adverse event. No subject prematurely discontinued the study drug due to an adverse event.

8.4.4. Significant Adverse Events - Hypoglycemia

Hypoglycemia is a significant adverse event that occurs with all insulins. Differences in the incidence of hypoglycemia across treatment groups are discussed in this section. Definitions of hypoglycemia were provided in Section 8.3.2.

Reviewer's comment: *My review here will focus on significant adverse events defined as 'severe hypoglycemia' and 'severe or blood glucose-confirmed hypoglycemia' (as defined by the Applicant) because they are most specific, have clinical relevance, and have precedence for labeling.*

Of note, trial 4101 excluded patients with known hypoglycemic unawareness or recurrent severe hypoglycemic episodes, and more than one episode of diabetic ketoacidosis requiring hospitalization within past 90 days before screening.

Run-in period:

During the 12-week run-in period, 96.9% of the overall study population reported non-treatment hypoglycemic episodes. The proportion of subjects reporting non-treatment hypoglycemic episodes was similar in subjects later randomized to meal-time Fiasp (96.9%; 8847 episodes per 100 PYE), post-meal Fiasp (96.5%; 8477 episodes per 100 PYE), and NovoLog (97.3%; 8477 episodes per 100 PYE). Severe hypoglycemic episodes were reported in 2.3% (10 per 100 PYE) of subjects later randomized to meal-time Fiasp, 1.6% (8 per 100 PYE) of subjects later randomized to post-meal Fiasp, and 1.6% (8 per 100 PYE) of subjects later randomized to NovoLog.

Treatment-Emergent Hypoglycemia:

Table 17 provides a summary of all treatment-emergent hypoglycemic events by classification.

Table 17: Treatment-Emergent Hypoglycemic Episodes by Classification (SAS)

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	261				258				258			
Total exposure (yrs)	128.4				127.7				127.7			
Total events	251	(96.2)	9701	7556	250	(96.9)	9550	7481	249	(96.5)	8902	6973
BG confirmed	228	(87.4)	3580	2788	227	(88.0)	3586	2809	217	(84.1)	3272	2563
Severe or BG confirmed symptomatic	192	(73.6)	2242	1746	194	(75.2)	2427	1901	185	(71.7)	2194	1719
Severe or BG confirmed	228	(87.4)	3583	2791	227	(88.0)	3594	2815	217	(84.1)	3276	2566
NN unclassifiable	251	(96.2)	6118	4765	244	(94.6)	5956	4666	245	(95.0)	5626	4407
ADA/ISPAD												
Severe (ISPAD 2014)	3	(1.1)	3	2	8	(3.1)	8	6	4	(1.6)	4	3
Documented symptomatic	210	(80.5)	5391	4199	213	(82.6)	5712	4475	207	(80.2)	5170	4050
Asymptomatic	215	(82.4)	4255	3314	214	(82.9)	3781	2962	211	(81.8)	3656	2864
Probable symptomatic	8	(3.1)	12	9	6	(2.3)	10	8	9	(3.5)	24	19
Pseudo-hypoglycaemia	19	(7.3)	35	27	9	(3.5)	37	29	13	(5.0)	47	37
ADA unclassifiable	5	(1.9)	5	4	1	(0.4)	2	2	1	(0.4)	1	1

ADA=American Diabetes Association; ISPAD=International Society of Pediatric and Adolescent Diabetes; BG=blood glucose; E=number of events; N=number of subjects; PG=plasma glucose; R=event rate per 100 patient years of exposure;
Treatment emergent is defined as event with onset of up to 1 day after last day of randomized treatment and exclude events during the run-in period.
Severe or BG confirmed=severe according to the ISPAD 2014 classification and/or have a recorded PG <56 mg/dL;
NN unclassifiable=includes non-severe episodes (ISPAD 2014) that are not BG confirmed (PG <56 mg/dL) and non-severe episodes that cannot be classified due to missing data.
Source: CSR 4101, Table 12-16

Table 18 provides an overall summary of severe, BG confirmed, and severe or PG confirmed hypoglycemia.

Severe Hypoglycemia:

The incidence of severe hypoglycemic episode was numerically higher in the post-meal Fiasp group (3.1% or 6 /100 PYE) compared to NovoLog group (1.6% or 3/100 PYE). The estimated rate ratio did not reach statistical significance and the confidence interval was very large (2.11 [95% CI: 0.63; 7.02]).

The incidence of severe hypoglycemic episode was numerically lower in the meal-time Fiasp group (1.1% or 2/100 PYE) compared to NovoLog group (1.6% or 3/100 PYE), but the estimated rate ratio did not reach statistically significance and the confidence interval was again large (0.77 [95% CI: 0.17; 3.45]).

Reviewer's comment: *Given the small number of severe hypoglycemic episodes, it is difficult to conclude whether the treatment differences in the incidence of severe hypoglycemia with post-meal Fiasp (6/100 PYE; 8 events) or meal-time Fiasp (2/100 PYE; 3 events) compared to NovoLog (3/100 PYE; 4 events) are real differences for the risk of severe hypoglycemia. Therefore, this*

data is inconclusive. It is reassuring that a similar 26-week basal-bolus study with Fiasp in adults with T1DM (trial 3852), which reported higher incidences of severe hypoglycemia compared to trial 4101, did not show treatment differences in the incidence of severe hypoglycemia with post-meal Fiasp (26/100 PYE; 47 events) or meal-time Fiasp (25/100 PYE; 46 events) compared to NovoLog (27/100 PYE; 51 events).

The majority of severe hypoglycemic episodes occurred during daytime, and the post-meal group reported the largest number of nocturnal severe hypoglycemia. However, the number of events was small; 3 events of nocturnal severe hypoglycemia were reported with post-meal Fiasp, none with meal-time Fiasp, and 1 event of nocturnal severe hypoglycemia was reported with NovoLog.

There was no particular pattern seen for severe hypoglycemia with relation to a meal (see CSR Table 14.3.1.63; not shown here).

No severe hypoglycemia was reported in subjects <6 years of age.

Table 18: Summary of BG Confirmed, Severe or BG Confirmed, and Severe Hypoglycemia (SAS)

	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: CSR 4101, Tables 12-17, 14.3.1.54, 14.3.1.55, 14.3.1.56, 14.3.1.61, 12-18, 12-20

Severe or BG Confirmed Hypoglycemia:

About 87.4% of subjects (2791 per 100 PYE) in the meal-time Fiasp group, 88.0% of subjects (2815 per 100 PYE) in the post-meal Fiasp group, and 84.1% of subjects (2566 per 100 PYE) in the meal-time NovoLog group reported severe or BG confirmed hypoglycemia (PG <56 mg/dL). The rate of severe or BG confirmed hypoglycemia was not statistically different between meal-time Flasp and NovoLog (estimated rate ratio of 1.11 [95% CI: 0.90, 1.37]) or between post-meal Fiasp and NovoLog (estimated rate ratio of 1.11 [95% CI: 0.90, 1.37]).

The rate of severe or BG confirmed hypoglycemia was numerically higher with meal-time and post-meal Fiasp groups compared to NovoLog in the age groups 1 to <6 years and 6 to <12 years. Given the small number of subjects in these age subgroups, this finding is considered exploratory and it is difficult to draw any conclusion.

Reviewer's comment: *It should be noted that the combined hypoglycemic episodes of 'severe or BG confirmed' were mainly driven by BG confirmed hypoglycemia given that the overall number of severe hypoglycemia events was small, as discussed in the preceding subsection 'Severe Hypoglycemia'. Therefore, the slight increased rate ratio (rate ratio 1.1) of 'severe or BG confirmed' hypoglycemia with meal-time and post-meal Fiasp compared to NovoLog was mainly due to 'BG confirmed' hypoglycemia. The clinical significance of this is unclear, but more close monitoring of blood glucose with Fiasp may be warranted in pediatric patients.*

Most severe or BG confirmed hypoglycemia were daytime episodes, and a minor number of episodes (1186 of 10453 all episodes) were nocturnal. However, a higher proportion of subjects in the post-meal Fiasp group (48.4%) reported nocturnal severe or BG confirmed hypoglycemia compared to meal-time Fiasp (42.9%) or NovoLog (40.3%), as well as higher event rate (Table 18).

The estimated rate ratio for nocturnal severe or BG confirmed hypoglycemia for post-meal Fiasp compared to NovoLog was 1.50 and was nominally statistically significant (95% CI: 1.09, 2.08). The estimated rate ratio for nocturnal severe or BG confirmed hypoglycemia for meal-time Fiasp compared to NovoLog was 1.29 and not nominally statistically significant (95% CI: 0.93, 1.73).

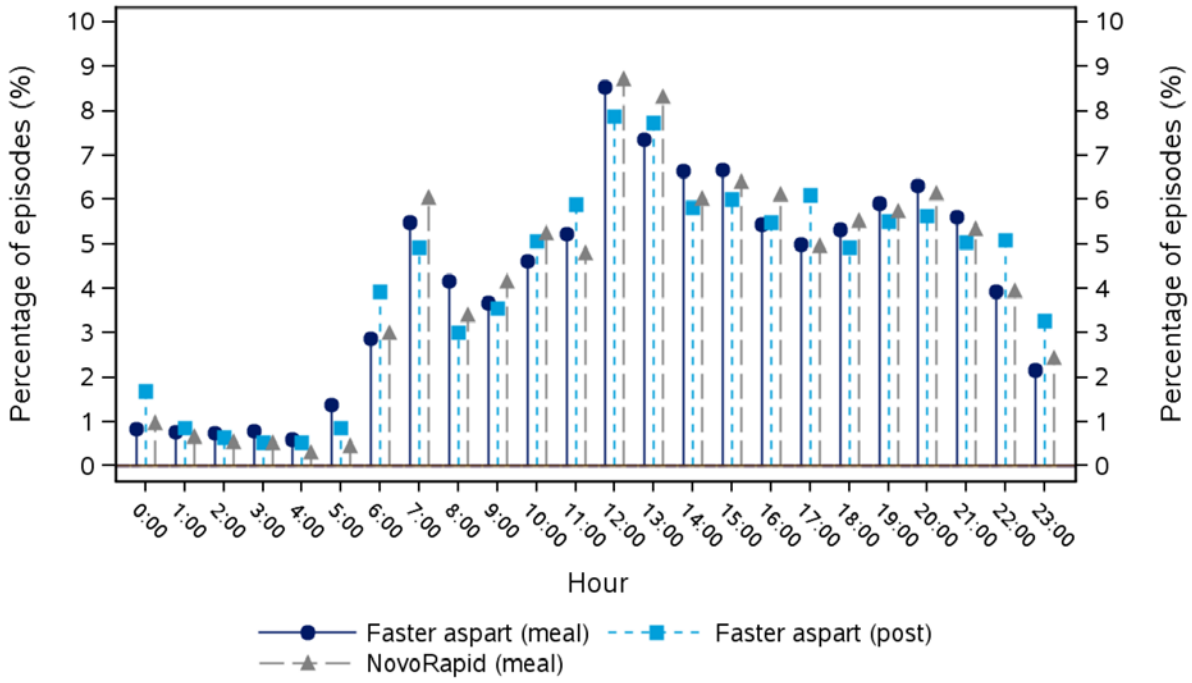
Reviewer's comment: *Again, the imbalance in the nocturnal 'severe or BG confirmed' hypoglycemia was mainly driven by BG confirmed hypoglycemia. Although the majority of BG confirmed hypoglycemia occurred during daytime (9256 events out of 10438 events), this imbalance in nocturnal hypoglycemia not favoring both meal-time and post-meal Fiasp groups compared to NovoLog can be of clinical concern in pediatric patients. Therefore, pediatric patients may need more close glucose monitoring to prevent BG confirmed hypoglycemia, particularly to prevent nocturnal period.*

This observed imbalance in BG confirmed hypoglycemia including nocturnal hypoglycemia with Fiasp can be described in the Hypoglycemia under Adverse Reactions section 6 and Pediatric Use section 8.4, with recommendation to more closely monitor blood glucose levels in pediatric patients with Fiasp.

These higher incidence of nocturnal episodes of severe or blood glucose confirmed hypoglycemic episodes with post-meal Fiasp mainly occurred during late evening 22:00 to 1:00

and at 6:00 am in the morning (Figure 12).

Figure 12: Episodes of Severe or Blood Glucose Confirmed Hypoglycemic Episodes Over Day (SAS)



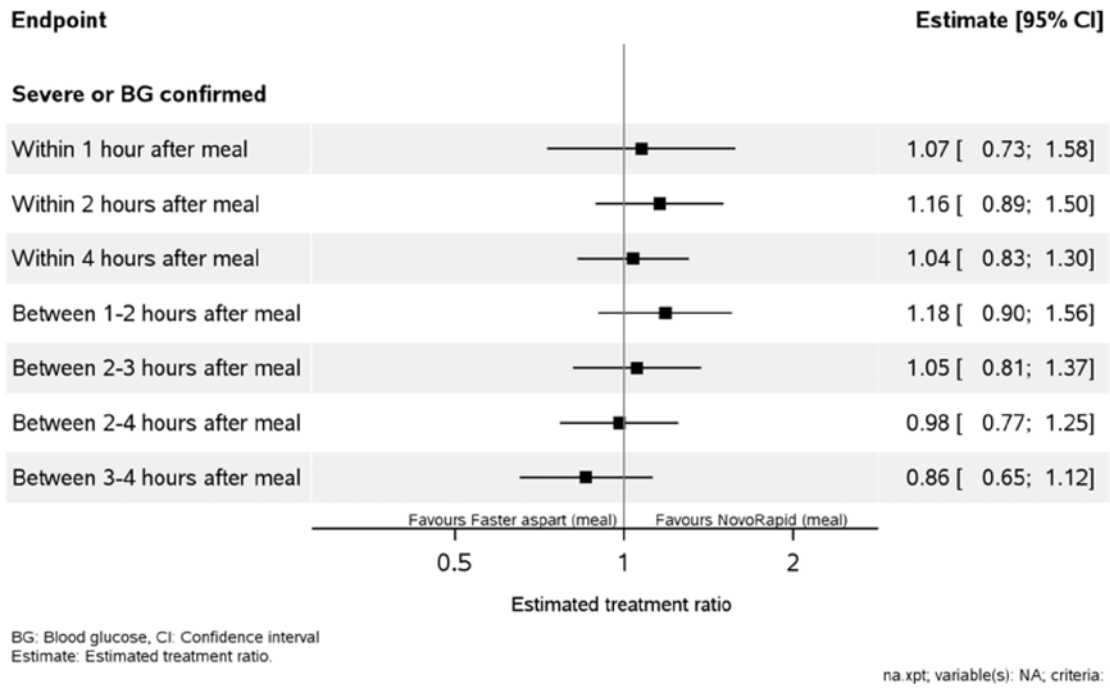
Hour x:00 [x:00; x:59].
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Episodes with missing time stamps are excluded.

Source: CSR 4101, Figure 12-3

<u>Severe or BG confirmed hypoglycemia related to a meal:</u>

There was no statistically significant difference between meal-time Fiasp and NovoLog in the rate of severe or BG confirmed hypoglycemia in relation to a meal, as shown in Figure 13.

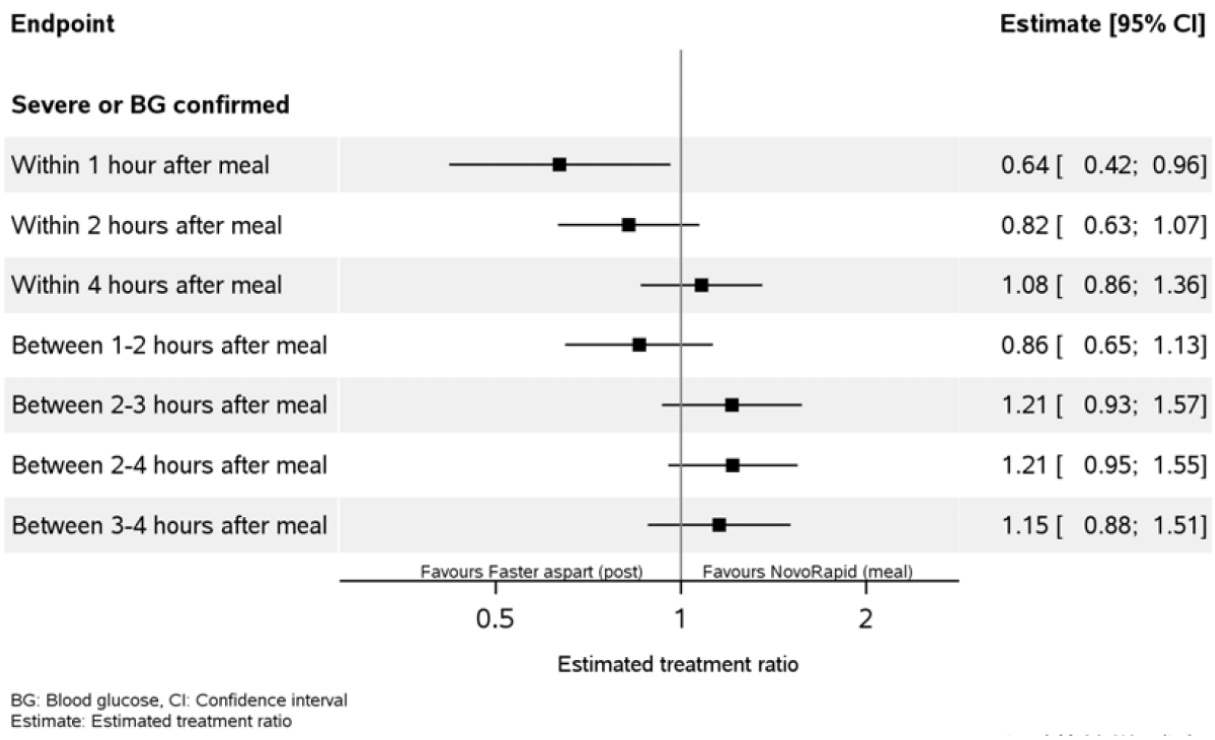
Figure 13: Forest Plot of Meal-time Fiasp versus NovoLog - Severe or Blood Glucose Confirmed Hypoglycemia Related to a Meal (FAS)



Source: CSR 4101, Figure 12-7

However, the rate of severe or BG confirmed hypoglycemia within 1 hour after starting a meal was nominally statistically significantly lower in the post-meal Fiasp group compared to NovoLog (Figure 14), with the estimated treatment ratio of 0.64 (95% CI: 0.42, 0.96). There were no other nominally statistically significant differences between post-meal Fiasp and NovoLog.

Figure 14: Forest Plot of Post-time Fiasp versus NovoLog - Severe or Blood Glucose Confirmed Hypoglycemia Related to a Meal (FAS)



BG: Blood glucose, CI: Confidence interval
Estimate: Estimated treatment ratio
Source: CSR 4101, Figure 12-8

Reviewer's comment: *Although the post-meal Fiasp group nominally showed statistically significantly lower rate of severe or BG confirmed hypoglycemia within 1 hour after meals compared to NovoLog, this was not surprising given that post-meal Fiasp group was instructed to administer their dose 20 minutes after a meal while meal-time Fiasp and NovoLog were to administer their bolus insulin dose 0-2 minutes before meal.*

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The proportion of subjects with an AE was numerically higher with post-meal Fiasp and NovoLog compared to meal-time Fiasp: 73.9% with meal-time Fiasp, 77.1% with post-meal Fiasp, and 78.7% with meal-time NovoLog. The overall AE rate per 100 person-year exposure (PYE) was numerically higher with post-meal Fiasp: 448.6 PYE with meal-time Fiasp, 531.1 PYE with post-meal Fiasp, and 464.5 with meal-time NovoLog.

Medication Errors:

During the run-in period, 7 medication errors were reported by 7 subjects; 5 were reported as

'wrong drug administered' and 2 were reported as 'accidental overdose'. All subjects recovered from these events. One 'wrong dose administered' was classified as serious and occurred in a 17-year old female who was later randomized to meal-time Fiasp.

During the treatment period, 6 medication errors were reported in 6 subjects, 3 events in 3 subjects in the meal-time Fiasp, 2 events in 2 subjects in the post-meal Fiasp, and 1 event in a subject in the NovoLog group.

Five medication errors were 'accidental overdose', two with meal-time Fiasp, two with post-meal Fiasp, and one with NovoLog group. One remaining error was 'incorrect dose administered' in the meal-time Fiasp group. Four 'accidental overdose' was associated with hypoglycemia. Three 'accidental overdose' were serious medication errors and are discussed in Section 8.4.2.

8.4.6. Laboratory Findings

Biochemistry and hematology assessments done during the trial are listed in Table 15 and were obtained at baseline, Week 12, and Week 26 or at premature discontinuation.

A clinical laboratory abnormality that was considered to be clinically significant by the investigator was to be recoded as an adverse event, under the 'Investigations' System Organ Class (data not shown; Table 14.3.1.16 of CSR). There were no clinically concerning differences across treatment groups with regard to these PTs and none were serious or led to study drug discontinuations.

The mean values for biochemistry and hematology tests remained stable during the trial without treatment differences in the mean or change in the mean values during the trial (not shown here; see Tables 14.3.5.1 to 14.3.5.3 for biochemistry and Tables 14.3.5.21 to 14.3.5.23 for hematology in CSR 4101). The majority of subjects also had normal biochemistry and hematology values throughout the trial (see Tables 14.3.5.4 and 14.3.5.24 in CSR 4101; not shown here). Evaluation of shift tables for 'low', 'normal', and 'high' values for laboratory findings also did not show any particular trend.

Reviewer's comment: *Overall there were no evident safety concerns from results of routine laboratory testing for Fiasp in pediatric patients.*

8.4.7. Vital Signs

The mean blood pressure (systolic and diastolic) and pulse remained stable across three treatment groups with small changes from baseline to end of trial that are not considered clinically significant differences (Table 19).

Table 19: Summary of Vital Signs in Trial 4101 (SAS)

	Meal-time Fiasp		Post-meal Fiasp		Meal-time NovoLog	
	SBP/DBP (mmHg)	Pulse (beats/min)	SBP/DBP (mmHg)	Pulse (beats/min)	SBP/DBP (mmHg)	Pulse (beats/min)
Mean at baseline	106.4/65.4	80.6	107.0/65.7	80.5	106.8/65.4	79.4
Mean at end of trial	107.1/66.6	80.1	108.5/67.1	80.9	107.9/66.8	80.1
Mean change from baseline to end of trial	0.8/1.2	-0.6	1.5/1.4	0.3	1.1/1.4	0.7

SBP=systolic blood pressure; DBP=diastolic blood pressure; End of trial=last on-treatment value
Source: CSR 4101, Table 12-23

The mean observed change in body weight from baseline to last on-treatment value increased in all treatment groups but was not clinically or statistically different between treatment groups: +2.22 kg in the meal-time Fiasp group, +1.92 kg in the post-meal Fiasp group, and +2.16 kg in the NovoLog group.

Reviewer's comment: *There was no safety signal for Fiasp with regard to vital signs. At the end of the trial, all treatment groups had similar weight increase of about 2 kg.*

8.4.8. Electrocardiograms (ECGs)

ECGs were not done in trial 4101.

8.4.9. QT

ECGs were not done in trial 4101. There were no AEs reported related to QT changes.

8.4.10. Immunogenicity

Not applicable with this supplement. Immunogenicity with Fiasp was reviewed during the original NDA approval.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Injection Site Reactions

The reported injection site reactions using a pre-defined list of MedDRA Preferred Terms (see Appendix 16.2.7.14 for list; not included here) are summarized in Table 20. The overall incidence was highest in the post-meal Fiasp group where 31 events (24.3 PYE) were reported in 14 subjects (5.4%), compared to 11 events (8.6 PYE) in 8 subjects (3.1%) with meal-time Fiasp and 17 events (13.3 PYE) in 11 subjects (4.3%) with NovoLog. None of these were SAEs.

Injection site hemorrhage was the most frequently reported term with 26 events in 6 subjects and was also the most frequently reported term in the post-meal Fiasp group compared to

other treatment groups. Of these, 25 events were reported by 5 subjects enrolled at one site (Site 603 in Turkey) where 3 subjects randomized to post-meal Fiasp reported 19 injection site hemorrhage events, one subjects randomized to meal-time Fiasp reported 4 injection site hemorrhage events, and one subjects randomized to NovoLog reported 2 injection site hemorrhage events. The verbatim reported term for these events that were 'ecchymosis on abdomen, leg, or arm due to injection technique'. None of these were considered possibly or probably related to the study drug.

Table 20: Injection Site Reactions in Trial 4101 (SAS)

	Meal-time Fiasp			**Post-meal Fiasp**			**Meal-time NovoLog**		
Number of subjects	261			258			259		
Total exposure	128.4			127.7			127.7		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Injection site reactions	**8 (3.1)**	**11**	**8.6**	**14 (5.4)**	**31**	**24.3**	**11 (4.3)**	**17**	**13.3**
Preferred Terms reported									
Injection site hemorrhage	1 (0.4)	4	3.1	4 (1.6)	20	15.7	1 (0.4)	2	1.6
Injection site bruising	0			3 (1.2)	4	3.1	2 (0.8)	2	1.6
Injection site pain	3 (1.1)	3	2.3	0			2 (0.8)	3	2.3
Injection site reaction	0			5 (1.9)	5	3.9	1 (0.4)	1	0.8
Injection site hematomata	1 (0.4)	1	0.8	0			2 (0.8)	4	3.1
Injection site hypertrophy	0			1 (0.4)	1	0.8	2 (0.8)	2	1.6
Injection site swelling	1 (0.4)	1	0.8	0			1 (0.4)	1	0.8
Injection site discoloration	1 (0.4)	1	0.8	0			0		
Injection site erythema	0			0			1 (0.4)	1	0.8
Injection site mass	0			0			1 (0.4)	1	0.8
Injection site nodule	0			1 (0.4)	1	0.8	0		
Injection site edema	1 (0.4)	1	0.8	0			0		

N=number of subjects; E=number of events; R=event rate per 100 patient-years of exposure
Source: CSR 4101, Table 14.3.1.42

Investigator had also reported injection site reactions on a specific AE form during the study. Some injection site reactions reported by the investigator were not all captured by the MedDRA search, and some AEs captured as injection site reactions by using MedDRA search were not all reported by the investigator as injection site reactions.

Thirty-three injection site reactions summarized in Table 20 that were captured by MedDRA search were not reported as an injection site reaction by the investigator on the specific from.

There were 15 injection site reaction reported by the investigator on a specific form that were not captured by the MedDRA search. Nine of these were 'lipohypertrophy' reported in 4 subjects with meal-time Fiasp, 1 subject with post-meal Fiasp and 4 subjects with NovoLog group; four were 'hypertrophy' reported in 1 subject each in meal-time and post-meal Fiasp

and 2 subjects in the NovoLog group; one 'contusion' in the post-meal Fiasp group and one 'hematoma' in the post-meal Fiasp group. See Section 8.5.2 for discussion of 'lipohypertrophy'.

Reviewer's comment: *The incidence of injection site reactions from trial 4101 should be added to the Adverse Reactions section of the labeling.*

8.5.2. Lipodystrophy

Seventeen events of lipodystrophy were reported in 15 subjects; 8 events in 7 subjects (2.7%) with meal-time Fiasp, 5 events in 4 (1.6%) subjects with post-meal Fiasp, and 4 events in 4 subjects (1.6%) with NovoLog. The overall AE rate was 6.2 PYE with meal-time Fiasp, 3.9 PYE with post-meal Fiasp, and 3.1 PYE with NovoLog. Fifteen of 17 events were reported as 'lipohypertrophy' while 2 were reported as 'lipodystrophy acquired' with post-meal Fiasp. These events occurred in subjects who were 6 to 17 years of age (mean 12 years of age).

All lipodystrophy events were non-serious. All events were mild in severity except for one event that was of moderate severity with meal-time Fiasp.

Of 8 events of lipodystrophy with meal-time Fiasp, 3 events occurred in the abdomen area, 2 events occurred on arm/legs, 1 event occurred on thigh and abdomen, and 2 events did not specify the location.

Of 5 events of lipodystrophy with post-meal Fiasp, 2 were 'lipodystrophy acquired' where one was due to technique on abdomen and one was due to technique on leg, one event was in the abdomen, one event was in the arm, and one did not specify the location.

Of 4 events of lipodystrophy with NovoLog, one was in the abdomen, one was in abdomen and arms, one was on the leg, and one did not specify the location.

Reviewer's comment: *Insulin degludec was to be injected into thigh or upper arm area while bolus insulin was to be injected into the abdominal area. Some lipodystrophy events did not specify the location and some lipodystrophy occurred on leg or arms which are likely related to insulin degludec administration. Four events (in 3 subjects) with meal-time Fiasp, 2 events (in 2 subjects) with post-meal Fiasp, and 2 events (in 2 subjects) with meal-time NovoLog reported lipodystrophy in the abdomen area likely due to bolus insulin injection. The incidence of lipodystrophy from trial 4101 should be added to the Adverse Reactions section of the labeling.*

8.5.3. Allergic Reaction

Allergic reactions were identified based on a search using a list of pre-defined MedDRA Preferred Terms (see Appendix 16.2.7.14 for list; not included here) and are summarized in Table 21. Numerically, slightly higher proportion of subjects in the meal-time Fiasp group

(5.0%) reported overall allergic reaction compared to post-meal Fiasp and NovoLog groups (3.1% and 3.5% respectively). None of these allergic reactions were serious. The most frequently reported allergic reactions were 'rash' and 'rhinitis allergic'.

Table 21: Allergic Reactions in Trial 4101 (SAS)

	Meal-time Fiasp			**Post-meal Fiasp**			**Meal-time NovoLog**		
Number of subjects	261			258			259		
Total exposure	128.4			127.7			127.7		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Allergic reactions	**13 (5.0)**	**17**	**13.2**	**8 (3.1)**	**8**	**6.3**	**9 (3.5)**	**13**	**10.2**
Preferred Terms reported									
Rash	4 (1.5)	4	3.1	1 (0.4)	1	0.8	2 (0.8)	2	1.6
Rhinitis allergic	2 (0.8)	5	3.9	0			4 (1.6)	4	3.1
Eczema	2 (0.8)	2	1.6	1 (0.4)	1	0.8	1 (0.4)	1	0.8
Dermatitis	1 (0.4)	1	0.8	1 (0.4)	1	0.8	1 (0.4)	2	1.6
Urticaria	1 (0.4)	2	1.6	1 (0.4)	1	0.8	1 (0.4)	1	0.8
Allergic dermatitis	1 (0.4)	1	0.8	1 (0.4)	1	0.8	0		
Allergic conjunctivitis	1 (0.4)	1	0.8	0			1 (0.4)	1	0.8
Hypersensitivity	1 (0.4)	1	0.8	0			0		
Rash macular	0			1 (0.4)	1	0.8	0		
Lip swelling	0			1 (0.4)	1	0.8	0		
Dermatitis infected	0			1 (0.4)	1	0.8	0		
Swelling face	0			0			1 (0.4)	1	0.8
Allergic cough	0			0			1 (0.4)	1	0.8

N=number of subjects; E=number of events; R=event rate per 100 patient-years of exposure
Source: CSR 4101, Table 14.3.1.47

Reviewer's comment: *The incidence of allergic reactions from trial 4101 should be added to the Adverse Reactions section of the labeling.*

8.6. Safety Analyses by Demographic Subgroups

This single trial was not adequately powered to reach meaningful conclusions about safety among demographic subgroups.

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not applicable.

8.8.2. Human Reproduction and Pregnancy

Women who were pregnant, breast-feeding, or intend to become pregnant or was of child-bearing potential and not using adequate contraceptive methods were excluded from participation in the trial.

No pregnancies were reported during the trial.

8.8.3. Pediatrics and Assessment of Effects on Growth

Pubertal status was assessed as part of safety assessment in this pediatric study population by recording Tanner Staging in accordance with stages 1-4[10] at baseline, Week 12, and at Week 26.

Tanner staging at baseline and at Week 26 in males are summarized in Table 22. The majority of male subjects were classified to Level 1 according to 'public hair development' and 'penis development' both at baseline and at Week 26. During the study, the proportion of male subjects classified to Level 1 decreased and proportion of male subjects classified to Level 5 increased, and these changes appear to be similar across treatment groups.

Tanner staging at baseline and at Week 26 in females are summarized in Table 23. The majority of female subjects were classified to Level 1 or Level 5 according to 'public hair development' and 'breast development' both at baseline and at Week 26. During the study, the proportion of female subjects classified to Level 1 decreased and proportion of female subjects classified to Level 5 increased, and these changes appear to be consistent across treatment groups.

[10] Tanner JM. Normal growth and techniques of growth assessment. Clinics in endocrinology and metabolism 1986;15(3):411-451.

Table 22: Summary of Tanner Score [N (%)] at Baseline and Week 26 in Trial 4101 in Males (SAS)

	Meal-time Fiasp	Post-meal Fiasp	Meal-time NovoLog	Total
Male, N	**135**	**136**	**148**	**419**
Public Hair Development				
Baseline, N	135	136	146	414
Level 1	56 (42.4)	47 (34.6)	58 (39.7)	161 (38.9)
Level 2	12 (9.1)	19 (14.0)	16 (11.0)	47 (11.4)
Level 3	15 (11.4)	22 (16.2)	25 (17.1)	62 (15.0)
Level 4	24 (18.2)	27 (19.9)	27 (18.5)	78 (18.8)
Level 5	25 (18.9)	21 (15.4)	20 (13.7)	66 (15.9)
Week 26, N	127	128	144	399
Level 1	41 (32.3)	38 (29.7)	50 (34.7)	129 (32.3)
Level 2	21 (16.5)	19 (14.8)	14 (9.7)	54 (13.5)
Level 3	11 (8.7)	16 (12.5)	14 (9.7)	41 (10.3)
Level 4	21 (16.5)	22 (17.2)	35 (24.3)	78 (19.5)
Level 5	33 (26.0)	33 (25.8)	31 (21.5)	97 (24.3)
Penis Development				
Baseline, N	132	136	146	414
Level 1	51 (38.6)	44 (32.4)	54 (37.0)	149 (36.0)
Level 2	17 (12.9)	19 (14.0)	17 (11.6)	53 (12.8)
Level 3	15 (11.4)	23 (16.9)	26 (17.8)	64 (15.5)
Level 4	25 (18.9)	26 (19.1)	28 (19.2)	79 (19.1)
Level 5	24 (18.2)	24 (17.6)	21 (14.4)	69 (16.7)
Week 26, N	126	131	144	401
Level 1	40 (31.7)	38 (29.0)	49 (34.0)	127 (31.7)
Level 2	21 (16.7)	15 (11.5)	16 (11.1)	52 (13.0)
Level 3	14 (11.0)	20 (15.3)	13 (9.0)	47 (11.7)
Level 4	20 (15.9)	24 (18.3)	34 (23.6)	78 (19.5)
Level 5	31 (24.6)	34 (26.0)	32 (22.2)	97 (24.2)

N=number of subjects
Source: CSR 4101, Tables 14.3.6.3

Table 23: Summary of Tanner Score [N (%)] at Baseline and Week 26 in Trial 4101 in Females (SAS)

	Meal-time Fiasp	Post-meal Fiasp	Meal-time NovoLog	Total
Female, N	**126**	**122**	**110**	**358**
Public Hair Development				
Baseline, N	124	121	106	351
Level 1	37 (29.8)	43 (35.5)	36 (34.0)	116 (33.0)
Level 2	17 (13.7)	18 (14.9)	9 (8.5)	44 (12.5)
Level 3	14 (11.3)	11 (9.1)	16 (15.1)	41 (11.7)
Level 4	19 (15.3)	24 (19.8)	13 (12.3)	56 (16.0)
Level 5	37 (29.8)	25 (20.7)	32 (30.2)	94 (26.8)
Week 26, N	125	119	107	351
Level 1	33 (26.4)	36 (30.3)	30 (28.0)	99 (28.2)
Level 2	14 (11.2)	18 (15.1)	10 (9.3)	42 (12.0)
Level 3	18 (14.4)	10 (8.4)	10 (9.3)	38 (10.8)
Level 4	19 (5.2)	20 (16.8)	21 (19.6)	60 (17.1)
Level 5	41 (32.8)	35 (29.4)	36 (33.6)	112 (31.9)
Breast Development				
Baseline, N	124	121	107	352
Level 1	37 (29.8)	41 (33.9)	37 (34.6)	115 (32.7)
Level 2	15 (12.1)	19 (15.7)	11 (10.3)	45 (12.8)
Level 3	13 (10.5)	13 (10.7)	13 (12.1)	39 (11.1)
Level 4	21 (16.9)	20 (16.5)	16 (15.0)	57 (16.2)
Level 5	38 (30.6)	28 (23.1)	30 (28.0)	96 (27.3)
Week 26, N	125	120	106	351
Level 1	31 (24.8)	35 (29.2)	30 (28.3)	96 (27.4)
Level 2	12 (9.6)	19 (15.8)	12 (11.3)	43 (12.3)
Level 3	20 (16.0)	11 (9.2)	7 (6.6)	38 (10.8)
Level 4	20 (16.0)	18 (15.0)	21 (19.8)	59 (16.8)
Level 5	42 (33.6)	37 (30.8)	36 (34.0)	115 (32.8)

N=number of subjects
Source: CSR 4101, Tables 14.3.6.4

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Accidental overdose related to medication errors are discussed in Section 8.4.5.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Fiasp was approved in the U.S. on September 29, 2017, and no safety concerns have been identified through postmarketing experience.

8.9.2. Expectations on Safety in the Postmarket Setting

The approval of this supplement will allow pediatric patients with diabetes mellitus to use Fiasp as bolus insulin and in insulin pumps for management of their diabetes. I expect that the safety of Fiasp in postmarketing setting will remain similar with the approval of these supplements, and that individual patient can safety use Fiasp with individual titration.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified by the other review disciplines.

8.10. Integrated Assessment of Safety

The safety findings in trial 4101 in pediatric population are generally consistent with previous findings of safety for Fiasp in adult population.

There were no deaths in the trial. Few SAEs were reported and did not appear to be causally related to Fiasp except for some cases of hypoglycemia due to accidental overdoses.

Hypoglycemia is always a safety concern with any insulin product. In trial 4101, there was a slight imbalance in the incidence of severe hypoglycemia not favoring post-meal Fiasp (6/100 PYE; 8 events) compared to NovoLog (3/100 PYE; 4 events). However, given the small number of severe hypoglycemic episodes, this data is inconclusive. It is reassuring that an imbalance in severe hypoglycemia was not seen with Fiasp compared to NovoLog in a similar 26-week basal-bolus study with Fiasp in adults with T1DM (trial 3852).

A numerically increased incidences of BG confirmed hypoglycemia was seen with meal-time Fiasp and post-meal Fiasp compared to NovoLog. Although the majority of BG confirmed hypoglycemia occurred during daytime (9256 of 10438 episodes), there was an imbalance in nocturnal BG confirmed hypoglycemia not favoring meal-time Fiasp (308/100 PYE) and post-meal Fiasp (371/100 PYE) compared to NovoLog (244/100 PYE). The clinical significance of this imbalance is not clear, but more close monitoring of blood glucose may be warranted in pediatric patients with Fiasp.

The overall incidence of injection site reaction was numerically higher with post-meal Fiasp compared to NovoLog.

The overall incidence of lipodystrophy and allergic reactions were numerically higher with meal-time Fiasp compared to NovoLog.

9. Advisory Committee Meeting and Other External Consultations

Not applicable for this submission. No Advisory Committee meeting was held for this supplement.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Content and Format of Labeling for Human Prescription Drug and Biological Products" released on January 24, 2006, available at: https://www.fda.gov/ohrms/dockets/98fr/06-545.pdf.

The relevant labeling revisions proposed by the Applicant that are the subject of this review include:

- Indication section: Adding 'pediatric patients' for indication of use given that we are extrapolating pediatric indication to include pediatric patients with type 2 diabetes;
- Adding severe hypoglycemia information from Trial 4101 in Section 6.1, Hypoglycemia, as well as describing the imbalance in blood glucose (BG) confirmed hypoglycemia, particularly nocturnal BG confirmed hypoglycemia, with meal-time Fiasp and post-meal Fiasp compared to NovoLog;
- Recommend adding the incidence of injection site reactions, lipodystrophy, and allergic reactions from Trial 4101 in Section 6.1;
- Revising Section 8.4, Pediatric Use based on the results of Trial 4101;
- Adding the results of Trial 4101 in Section 14, Clinical Studies. I agree with including the results of Trial 4101 with the final language to be negotiated with the Applicant. (b) (4) [redacted]

I've also made labeling recommendations throughout the document.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Given the favorable safety profile of this drug, there are no additional risk management strategies required beyond the recommended labeling.

12. Postmarketing Requirements and Commitments

No postmarketing requirements (PMRs) or postmarketing commitments (PMCs) are recommended.

13. Appendices

13.1. References

References are cited throughout the document in footnotes.

13.2. Financial Disclosure

Trial 4101 was a covered trial. The Applicant had adequately disclosed financial arrangements with clinical investigators as recommended in the Guidance for Industry Financial Disclosure by Clinical Investigators.

Covered Clinical Study (Name and/or Number): Trial 4101

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 579		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 24		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: 0 Significant payments of other sorts: 17 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

APPEARS THIS WAY ON ORIGINAL

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/

HYON J KWON
12/13/2019 01:26:48 PM

PATRICK ARCHDEACON
12/13/2019 01:54:05 PM