

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

208751Orig1s011

Trade Name: **FIASP**
Generic or Proper Name: insulin aspart

Sponsor: **Novo Nordisk Inc.**

Approval Date: December 19,2019

Indication: FIASP is a rapid-acting human insulin analog indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus (1).

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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APPROVAL LETTER



NDA 208751/S-010
NDA 208751/S-011

**SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING
REQUIREMENT**

Novo Nordisk Inc.
Attention: Helen Chen, MSc, RAC
Associate Director, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Ms. Chen:

Please refer to your supplemental new drug applications (sNDAs) dated and received February 21, 2019 (S-010) and February 25, 2019 (S-011), and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fiasp (insulin aspart injection).

These Prior Approval supplemental new drug applications provide for:

S-010: addition of a pediatric indication

S-011: addition of continuous subcutaneous insulin infusion (CSII) use in pediatrics

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, and Instructions for Use), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

FULFILLMENT OF POSTMARKETING REQUIREMENT

This supplemental application (S-010) contained the final report for the following postmarketing requirement listed in the September 29, 2017, 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).

We have reviewed your submission and conclude that the above requirement was fulfilled.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

This completes all of your postmarketing requirements acknowledged in our September 29, 2017, letter.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.³

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵ For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.⁶

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

³ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁶ <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
 - Patient Package Insert
 - Flex Touch Instructions for Use (previously approved October 21, 2019)
 - PenFill Instructions for Use (previously approved October 21, 2019)
 - Vial Instructions for Use (previously approved October 21, 2019)

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/

LISA B YANOFF
12/19/2019 03:30:12 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208751Orig1s011

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FIASP safely and effectively. See full prescribing information for FIASP.

FIASP® (insulin aspart injection) for subcutaneous or intravenous use
Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

Indications and Usage (1) -----12/2019
Dosage and Administration (2.2, 2.3) -----10/2019
Warnings and Precautions (5.2, 5.8) -----10/2019

INDICATIONS AND USAGE

- FIASP is a rapid-acting human insulin analog indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus (1).

DOSAGE AND ADMINISTRATION

- Individualize and adjust the dosage of FIASP based on route of administration, individual's metabolic needs, blood glucose monitoring results and glycemic control goal (2.2).
- Dosage adjustments may be needed when switching from another insulin, with changes in physical activity, changes in concomitant medications, changes in meal patterns, changes in renal or hepatic function or during acute illness (2.2).
- **Subcutaneous injection (2.2)**
 - Inject at the start of a meal or within 20 minutes after starting a meal into the abdomen, upper arm, or thigh.
 - Rotate injection sites within the same region to reduce the risk of lipodystrophy and localized cutaneous amyloidosis.
 - Should generally be used in regimens with an intermediate- or long-acting insulin.
- **Continuous Subcutaneous Infusion (Insulin Pump) (2.2)**
 - Refer to the insulin infusion pump user manual to see if FIASP can be used. Use in accordance with the insulin pumps' instructions for use.
 - Administer by continuous subcutaneous infusion using an insulin pump in a region recommended in the instructions from the pump manufacturer. Rotate infusion sites within the same region to reduce the risk of lipodystrophy and localized cutaneous amyloidosis.
- **Intravenous Infusion:** Administer only under medical supervision after diluting to concentrations from 0.5 to 1 unit/mL insulin aspart in infusion systems using polypropylene infusion bags (2.2).

DOSAGE FORMS AND STRENGTHS

Injection: 100 units/mL (U-100):

- 10 mL multiple-dose vial (3)
- 3 mL single-patient-use FIASP FlexTouch® pen (3)
- 3 mL single-patient-use PenFill® cartridges for use in a PenFill cartridge device (3)

CONTRAINDICATIONS

- During episodes of hypoglycemia (4).
- Hypersensitivity to insulin aspart or one of the excipients in FIASP (4).

WARNINGS AND PRECAUTIONS

- *Never share* a FIASP FlexTouch pen, PenFill cartridge or PenFill cartridge device between patients, even if the needle is changed (5.1).
- **Hyperglycemia or hypoglycemia with changes in insulin regimen:** Make changes to a patient's insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) under close medical supervision with increased frequency of blood glucose monitoring (5.2).
- **Hypoglycemia:** May be life-threatening. Increase frequency of glucose monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal impairment or hepatic impairment or hypoglycemia unawareness (5.3).
- **Hypoglycemia due to medication errors:** Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection (5.4).
- **Hypokalemia:** May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated (5.5).
- **Hypersensitivity reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue FIASP, monitor and treat if indicated (5.6).
- **Fluid retention and heart failure with concomitant use of thiazolidinediones (TZDs):** Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs (5.7).
- **Hyperglycemia and Ketoacidosis Due to Insulin Pump Device Malfunction** Monitor glucose and administer FIASP by subcutaneous injection if pump malfunction occurs (5.8).

ADVERSE REACTIONS

Adverse reactions observed with FIASP include: hypoglycemia, allergic reactions, hypersensitivity, injection/infusion site reactions, lipodystrophy, and weight gain (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-800-727-6500 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Drugs that Increase Hypoglycemia Risk or Increase or Decrease Blood Glucose Lowering Effect** Adjustment of dosage may be needed; closely monitor blood glucose (7).
- **Drugs that Blunt Hypoglycemia Signs and Symptoms (e.g., beta-blockers, clonidine, guanethidine, and reserpine):** Increased frequency of glucose monitoring may be required (7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FIASP is indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Always check insulin label before administration [see *Warnings and Precautions (5.4)*].
- Inspect FIASP visually before use. It should appear clear and colorless. Do not use FIASP if particulate matter or coloration is seen.
- Do not mix FIASP with any other insulin.

2.2 Route of Administration Instructions

Subcutaneous Injection:

- Inject FIASP at the start of a meal or within 20 minutes after starting a meal subcutaneously into the abdomen, upper arm, or thigh.
- Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis [see *Adverse Reactions (6.1, 6.3)*].
- FIASP given by subcutaneous injection should generally be used in regimens with intermediate or long-acting insulin [see *Warnings and Precautions (5.2)*].
- Instruct patients on basal-bolus treatment who forget a mealtime dose to monitor their blood glucose level to decide if an insulin dose is needed, and to resume their usual dosing schedule at the next meal.
- The FIASP FlexTouch pen dials in 1 unit increments.
- Use FIASP FlexTouch pen with caution in patients with visual impairment that may rely on audible clicks to dial their dose.

Continuous Subcutaneous Infusion (Insulin Pump):

- Refer to the continuous subcutaneous insulin infusion pump user manual to see if FIASP can be used with the insulin pump. Use FIASP in accordance with the insulin pump system's instructions for use.
- Administer FIASP by continuous subcutaneous infusion in a region recommended in the instructions from the pump manufacturer. Rotate infusion sites within the same region to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis [see *Adverse Reactions (6.1)*].
- Train patients using continuous subcutaneous insulin infusion therapy to administer insulin by injection and have alternate insulin therapy available in case of insulin pump failure [see *Warnings and Precautions (5.8)*].
- Change FIASP in the pump reservoir at least every 6 days, or according to the pump user manual, whichever is shorter. Follow the FIASP-specific information for in-use time because FIASP-specific information may differ from general insulin pump user manual instructions.

- Change the infusion sets and the infusion set insertion site according to the manufacturers user manual.
- Do not mix with other insulins or diluents in the insulin pump .
- Do not expose FIASP in the pump reservoir to temperatures greater than 98.6°F (37°C).

Intravenous Administration:

- Administer FIASP intravenously only under medical supervision with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia [*see Warnings and Precautions (5.3, 5.5)*].
- Dilute FIASP to concentrations from 0.5 unit/mL to 1 unit/mL insulin aspart in infusion systems using polypropylene infusion bags.
- FIASP is stable at room temperature for 24 hours in 0.9% sodium chloride or 5% dextrose infusion fluids [*see How Supplied/Storage and Handling (16.2)*]

2.3 Dosage Information

- Individualize the dosage of FIASP based on the patient’s metabolic needs, blood glucose monitoring results, and glycemic control goal.
- If converting from another mealtime insulin to FIASP, the initial change can be done on a unit-to-unit basis.
- Dose adjustments may be needed when switching from another insulin, with changes in physical activity, changes in concomitant medications, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness to minimize the risk of hypoglycemia or hyperglycemia [*see Warnings and Precautions (5.2, 5.3) and Drug Interactions (7)*].
- Closely monitor blood glucose when converting insulins used in insulin pumps as individualization of insulin pump parameters may be necessary to minimize the risk of hypoglycemia and hyperglycemia [*see Warnings and Precautions (5.2, 5.3) and Adverse Reactions (6.1)*]
- During changes to a patient’s insulin regimen, increase the frequency of blood glucose monitoring [*see Warnings and Precautions (5.2)*].
- Dosage adjustment may be needed when FIASP is coadministered with certain drugs [*see Drug Interactions (7)*].

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 units of insulin aspart per mL (U-100) is available as a clear and colorless solution in:

- 10 mL multiple-dose vial
- 3 mL single-patient-use FIASP FlexTouch pen
- 3 mL single-patient-use PenFill cartridges for use in a PenFill cartridge delivery device

4 CONTRAINDICATIONS

FIASP is contraindicated

- During episodes of hypoglycemia [*see Warnings and Precautions (5.3)*].
- In patients with known hypersensitivity to insulin aspart or one of the excipients in FIASP [*see Warnings and Precautions (5.6)*].

5 WARNINGS AND PRECAUTIONS

5.1 Never Share a FIASP FlexTouch Pen, PenFill Cartridge or PenFill Cartridge Device Between Patients

FIASP FlexTouch disposable pen, PenFill cartridge and PenFill cartridge devices should never be shared between patients, even if the needle is changed. Patients using FIASP vials should never share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in an insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) may affect glycemic control and predispose to hypoglycemia [*see Warnings and Precautions (5.3)*] or hyperglycemia. Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia; and a sudden change in the injection site (to an unaffected area) has been reported to result in hypoglycemia [*see Adverse Reactions (6.1, 6.3)*].

Make any changes to a patient's insulin regimen under close medical supervision with increased frequency of blood glucose monitoring. Advise patients who have repeatedly injected into areas of lipodystrophy or localized cutaneous amyloidosis to change the injection site to unaffected areas and closely monitor for hypoglycemia. For patients with type 2 diabetes, dosage adjustments in concomitant anti-diabetic treatment may be needed.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction of all insulin therapies, including FIASP [*see Adverse Reactions (6.1)*]. Severe hypoglycemia can cause seizures, may lead to unconsciousness, may be life-threatening, or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g. driving or operating other machinery). FIASP, or any insulin, should not be used during episodes of hypoglycemia [*see Contraindications (4)*].

Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) [*see Drug Interactions (7)*], or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia

The risk of hypoglycemia after an injection is related to the duration of action of the insulin and, in general, is highest when the glucose lowering effect of the insulin is maximal. The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulation. As with all insulin preparations, the glucose lowering effect time course of FIASP may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature [*see Use in Specific Populations (8.4), Clinical Pharmacology (12.2)*].

Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication [see *Drug Interactions (7)*]. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [see *Use in Specific Populations (8.6, 8.7)*].

Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

5.4 Hypoglycemia Due to Medication Errors

Accidental mix-ups between insulin products have been reported. To avoid medication errors between FIASP and other insulins, instruct patients to always check the insulin label before each injection.

5.5 Hypokalemia

All insulin products, including FIASP, can cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to potassium concentrations).

5.6 Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including FIASP [see *Adverse Reactions (6.1)*]. If hypersensitivity reactions occur, discontinue FIASP; treat per standard of care and monitor until symptoms and signs resolve. FIASP is contraindicated in patients who have had hypersensitivity reactions to insulin aspart, or one of the excipients in FIASP [see *Contraindications (4)*].

5.7 Fluid Retention and Heart Failure with Concomitant Use of PPAR-Gamma Agonists

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including FIASP, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

5.8 Hyperglycemia and Ketoacidosis Due to Insulin Pump Device Malfunction

Pump or infusion set malfunctions can lead to a rapid onset of hyperglycemia and ketoacidosis. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection of FIASP may be required. Patients using

continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure [see *Dosage and Administration (2.2)*, *How Supplied/Storage and Handling (16.2)*, and *Patient Counseling Information (17)*].

6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere:

- Hypoglycemia [see *Warnings and Precautions (5.3)*]
- Hypokalemia [see *Warnings and Precautions (5.5)*]
- Hypersensitivity and allergic reactions [see *Warnings and Precautions (5.6)*]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates actually observed in clinical practice.

The data in Table 1 reflect the exposure of 763 adult patients with type 1 diabetes to FIASP in one clinical trial with a mean exposure duration of 25 weeks [see *Clinical Studies (14.2)*]. The mean age was 44.4 years and the mean duration of diabetes was 19.9 years. 59% were male, 93% were Caucasian, 2% were Black or African American and 7% were Hispanic. The mean BMI was 26.7 kg/m² and the mean HbA_{1c} at baseline was 7.6%.

The data in Table 2 reflect the exposure of 341 adult patients with type 2 diabetes to FIASP in one clinical trial with a mean exposure duration of 24 weeks [see *Clinical Studies (14)*]. The mean age was 59.6 years and the mean duration of diabetes was 13.2 years. 47% were male, 80% were Caucasian, 6% were Black or African American and 8% were Hispanic. The mean BMI was 31.5 kg/m² and the mean HbA_{1c} at baseline was 8.0%.

The data in Table 3 reflect the exposure of 519 pediatric patients with type 1 diabetes to FIASP in one clinical trial with a mean exposure duration of 26 weeks [see *Clinical Studies (14.3)*]. The mean age was 11.7 years and the mean duration of diabetes was 4.4 years. 54% were male, 81% were Caucasian, 16% were Asian and 2% were Black or African American. The mean BMI was 19.7 kg/m² and the mean HbA_{1c} at baseline was 7.6%.

Common adverse reactions, excluding hypoglycemia, were defined as events occurring in ≥5% and occurring at the same rate or greater for FIASP-treated subjects than comparator-treated subjects.

Table 1. Adverse Reactions (%*) in Adult Patients with Type 1 Diabetes

	Mealtime FIASP + Insulin detemir (N=386)	Postmeal FIASP + Insulin detemir (N=377)
Nasopharyngitis	20.2	23.9
Upper respiratory tract infection	9.1	7.4
Nausea	4.9	5.0
Diarrhea	5.4	3.2
Back pain	5.2	4.0

*Incidence $\geq 5\%$ and occurring at the same rate or greater with FIASP than comparator

Table 2. Adverse Reactions (%*) in Adult Patients with Type 2 Diabetes

	FIASP + Insulin glargine (N=341)
Urinary tract infection	5.9

*Incidence $\geq 5\%$ and occurring at the same rate or greater with FIASP than comparator

Table 3: Adverse Reactions (%*) in Pediatric Patients with Type 1 Diabetes

	Mealttime FIASP + Insulin degludec (N=261)	Postmeal FIASP + Insulin degludec (N=258)
Viral upper respiratory tract infection	23.0	20.5
Upper respiratory tract infection	8.4	12.4
Influenza	7.7	5.8
Rhinitis	3.8	6.2
Headache	6.1	10.1
Pyrexia	8.4	6.2
Vomiting	3.4	8.1

*Incidence $\geq 5\%$ and occurring at the same rate or greater with FIASP than comparator

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including FIASP. The rates of reported hypoglycemia depend on the definition of hypoglycemia used, diabetes type, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia in clinical trials for FIASP with the incidence of hypoglycemia for other products may be misleading and also, may not be representative of hypoglycemia rates that occur in clinical practice.

Incidence rates for severe hypoglycemia in adults with type 1 and type 2 diabetes mellitus and pediatric patients with type 1 diabetes treated with FIASP in clinical trials are shown in Table 4 [see *Clinical Studies (14)*].

Table 4. Proportion (%) of Patients with Type 1 Diabetes and Type 2 Diabetes Experiencing at Least One Episode of Severe Hypoglycemia in Adult and Pediatric Clinical Trials

	Study A (Type 1) Adults		Study B (Type 2) Adults	Study E (Type 1) Pediatric		Study D (Type 1 CSII)
	Mealttime FIASP + Insulin detemir (N=386)	Postmeal FIASP + Insulin detemir (N=377)	FIASP + Insulin glargine (N=341)	Mealttime FIASP + Insulin degludec (N=261)	Postmeal FIASP + Insulin degludec (N=258)	FIASP (N=236)
Severe hypoglycemia*	6.7	8.0	3.2	1.1	3.1	4.7

*Severe hypoglycemia: an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions

Blood glucose confirmed hypoglycemia was defined as a self-measured glucose calibrated to plasma of less than 56 mg/dL.

In Study D, adult patients with type 1 diabetes treated with FIASP in a pump reported a higher rate of blood glucose confirmed hypoglycemic episodes within the first hour after a meal compared to patients treated with NovoLog [see *Clinical Trials (14.5)*].

In Study E, pediatric patients with type 1 diabetes treated with mealtime and postmeal FIASP reported a higher rate of blood glucose confirmed hypoglycemic episodes compared to patients treated with NovoLog; the imbalance was greater during the nocturnal period [see *Use in Specific Populations (8.4), Clinical Trials (14.3)*].

Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including FIASP, and may be life threatening. In the clinical program, generalized hypersensitivity reactions (manifested by generalized skin rash and facial edema) were reported in 0.4% of adult patients treated with FIASP. Allergic skin manifestations reported with FIASP in 1.7% of adult patients from the clinical program include eczema, rash, rash pruritic, urticaria and dermatitis. In Study D, allergic reactions were reported in 4.2% of adult patients with type 1 diabetes treated with FIASP. In Study E, allergic reactions were reported in 4% of pediatric patients with type 1 diabetes treated with Fiasp.

Lipodystrophy

Administration of insulin, including FIASP, has resulted in lipohypertrophy (enlargement or thickening of tissue) and lipoatrophy (depression in the skin). In the clinical program, lipodystrophy was reported in 0.4% of adult patients and 2.1% of pediatric patients treated with FIASP [see *Dosage and Administration (2.2)*].

Injection/Infusion Site Reactions

As with other insulin therapy, patients may experience rash, redness, inflammation, pain, bruising or itching at the site of FIASP injection or infusion. These reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of FIASP. In the clinical program, injection site reactions occurred in 1.6% of adult patients treated with FIASP. In Study A, adult patients with type 1 diabetes treated with FIASP reported 2.2% injection site reactions. In Study D, infusion site reactions were reported in 10.2% of adult patients with type 1 diabetes treated with FIASP. In Study E, injection site reactions were reported in 4.2% of pediatric patients with type 1 diabetes treated with FIASP.

Weight Gain

Weight gain can occur with insulin therapy, including FIASP, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria. In Study A, adult patients with type 1 diabetes treated with FIASP gained an average of 0.7 kg and in Study B, adult patients with type 2 diabetes treated with FIASP gained an average of 2.7 kg.

Peripheral Edema

Insulin, including FIASP, may cause sodium retention and edema, particularly if previous poor metabolic control is improved by intensified insulin therapy. In the clinical program, peripheral edema occurred in 0.8% of adult patients treated with FIASP.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other insulin products may be misleading.

In a 26-week study in adult subjects with type 1 diabetes (Study A [*see Clinical Studies (14.2)*]), among the 763 subjects who received FIASP, 97.2% were positive for cross-reacting anti-insulin antibodies (AIA) at least once during the study, including 90.3% that were positive at baseline. A total of 24.8% of patients who received FIASP were positive for anti-drug (insulin aspart) antibodies (ADA) at least once during the study, including 17.3% that were positive at baseline.

In a 26-week study in pediatric subjects with type 1 diabetes (Study E [*see Clinical Studies (14.3)*]), among the 519 subjects who received FIASP, 97.1% were positive for cross-reacting anti-insulin antibodies (AIA) at least once during the study, including 94.6% that were positive at baseline. A total of 19.1% of patients who received FIASP were positive for anti-drug (insulin aspart) antibodies (ADA) at least once during the study, including 16.0% that were positive at baseline.

6.3 Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of insulin aspart. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Localized cutaneous amyloidosis at the injection site has occurred. Hyperglycemia has been reported with repeated insulin injections into areas of localized cutaneous amyloidosis; hypoglycemia has been reported with a sudden change to an unaffected injection site.

7 DRUG INTERACTIONS

Table 5 includes clinically significant drug interactions with FIASP.

Table 5. Clinically Significant Drug Interactions with FIASP

Drugs That May Increase the Risk of Hypoglycemia	
<i>Drugs:</i>	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics.
<i>Intervention:</i>	Dose reductions and increased frequency of glucose monitoring may be required when FIASP is co-administered with these

	drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of FIASP	
<i>Drugs:</i>	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
<i>Intervention:</i>	Dose increases and increased frequency of glucose monitoring may be required when FIASP is co-administered with these drugs.
Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of FIASP	
<i>Drugs:</i>	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
<i>Intervention:</i>	Dose adjustment and increased frequency of glucose monitoring may be required when FIASP is co-administered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia	
<i>Drugs:</i>	Beta-blockers, clonidine, guanethidine, and reserpine.
<i>Intervention:</i>	Increased frequency of glucose monitoring may be required when FIASP is co-administered with these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with FIASP in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. Available information from published randomized controlled trials with insulin aspart use during the second trimester of pregnancy have not reported an association with insulin aspart and major birth defects or adverse maternal or fetal outcomes [see Data]. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see Clinical Considerations].

In animal reproduction studies, administration of subcutaneous insulin aspart to pregnant rats and rabbits during the period of organogenesis did not cause adverse developmental effects at exposures 8- times and equal to the human subcutaneous dose of 1.0 unit/kg/day, respectively. Pre- and post-implantation losses and visceral/skeletal abnormalities were seen at higher exposures, which are considered secondary to maternal hypoglycemia. These effects were similar to those observed in rats administered regular human insulin [see Data].

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA_{1c} >7% and has been reported to be as high as 20-25% in women with a HbA_{1c} >10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human Data

Published data from 5 randomized controlled trials of 441 pregnant women with diabetes mellitus treated with insulin aspart starting during the late 2nd trimester of pregnancy did not identify an association of insulin aspart with major birth defects or adverse maternal or fetal outcomes. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including a variable duration of treatment and small size of the majority of the trials.

Animal Data

Fertility, embryo-fetal and pre- and postnatal development studies have been performed with insulin aspart and regular human insulin in rats and rabbits. In a combined fertility and embryo-fetal development study in rats, insulin aspart was administered before mating, during mating, and throughout pregnancy. Further, in a pre- and postnatal development study insulin aspart was given throughout pregnancy and during lactation to rats. In an embryo-fetal development study insulin aspart was given to female rabbits during organogenesis. The effects of insulin aspart did not differ from those observed with subcutaneous regular human insulin. Insulin aspart, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 units/kg/day (approximately 32 times the human subcutaneous dose of 1.0 unit/kg/day, based on human exposure equivalents) and in rabbits at a dose of 10 units/kg/day (approximately three times the human subcutaneous dose of 1.0 unit/kg/day, based on human exposure equivalents). No significant effects were observed in rats at a dose of 50 units/kg/day and in rabbits at a dose of 3 units/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 unit/kg/day for rats and equal to the human subcutaneous dose of 1.0 unit/kg/day for rabbits, based on human exposure equivalents. The effects are considered secondary to maternal hypoglycemia.

8.2 Lactation

Risk Summary

There are no data on the presence of FIASP in human milk, the effects on the breastfed infant, or the effect on milk production. One small published study reported that exogenous insulin, including insulin aspart, was present in human milk. However, there is insufficient information to determine the effects of insulin aspart on the breastfed infant and no available information on the effects of insulin aspart on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for insulin, any potential adverse effects on the breastfed child from FIASP or insulin aspart or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of FIASP have been established to improve glycemic control in pediatric patients with diabetes mellitus. Use of FIASP for this indication is supported by evidence from an adequate and well-controlled study in 777 pediatric patients with type 1 diabetes mellitus aged 2 to 17 years, and from studies in adults with diabetes mellitus [see *Clinical Pharmacology (12.3) and Clinical Studies (14)*].

Pediatric patients with type 1 diabetes treated with mealtime and postmeal FIASP reported a higher rate of blood glucose confirmed hypoglycemic episodes compared to patients treated with NovoLog; the imbalance was greater during the nocturnal period. Monitor blood glucose levels closely in pediatric patients [see *Warnings and Precautions (5.3), Clinical Trial Experience (6.1)*].

8.5 Geriatric Use

In the three controlled clinical studies, 192 of 1219 (16%) FIASP treated patients with type 1 or type 2 diabetes were ≥ 65 years of age and 24 of 1219 (2%) were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between these elderly patients and younger adult patients.

Nevertheless, caution should be exercised when FIASP is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia [see *Warnings and Precautions (5.3), Adverse Reactions (6.1) and Clinical Studies (14)*].

Pharmacokinetic/pharmacodynamic study to assess the effect of age on the onset of FIASP action has been performed [see *Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

Patients with renal impairment may be at increased risk of hypoglycemia and may require more frequent FIASP dose adjustment and more frequent blood glucose monitoring [see *Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

Patients with hepatic impairment may be at increased risk of hypoglycemia and may require more frequent FIASP dose adjustment and more frequent blood glucose monitoring [see *Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia [see *Warnings and Precautions (5.3, 5.5)*]. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes with coma, seizure or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

11 DESCRIPTION

FIASP (insulin aspart injection) is a rapid-acting insulin analog for subcutaneous or intravenous administration used to lower blood glucose. Insulin aspart is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae*. Insulin aspart has the empirical formula $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8 daltons.

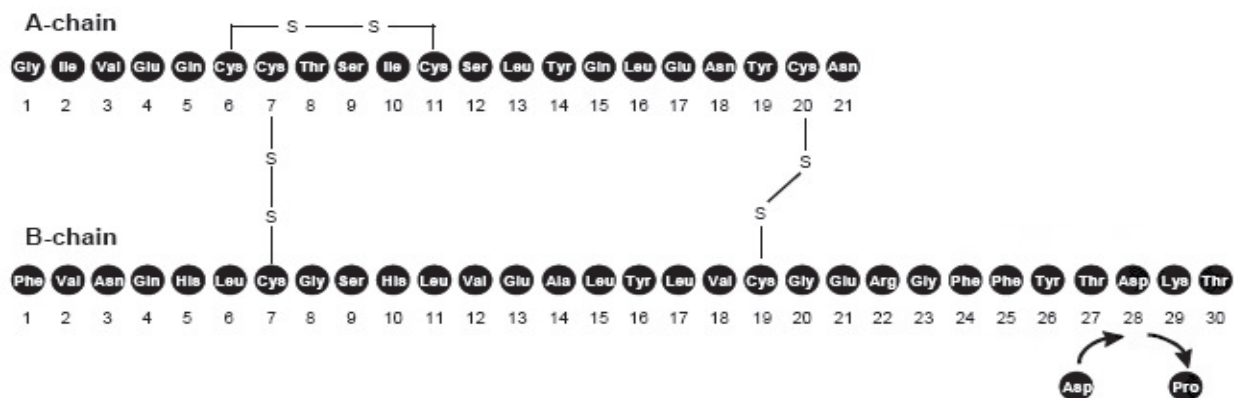


Figure 1. Structural Formula of Insulin Aspart

FIASP (insulin aspart injection) is an aqueous, sterile, clear and colorless solution. Each mL contains 100 units of insulin aspart and the inactive ingredients: arginine (as L-arginine hydrochloride), USP (3.48 mg); disodium phosphate dihydrate, USP (0.53 mg); glycerol, USP (3.3 mg); metacresol, USP (1.72 mg); niacinamide, USP (20.8 mg); phenol, USP (1.50 mg); zinc (as zinc acetate), USP (19.6 mcg) and water for injection, USP. FIASP has a pH of 7.1. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The primary activity of FIASP is the regulation of glucose metabolism. Insulins, including insulin aspart, the active ingredient in FIASP, exert their specific action through binding to insulin receptors. Receptor-bound insulin lowers blood glucose by facilitating cellular uptake of glucose into skeletal muscle and adipose tissue and by inhibiting the output of glucose from the liver. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

12.2 Pharmacodynamics

The time course of insulin action (i.e., glucose lowering) may vary considerably in different individuals or within the same individual. The average pharmacodynamic profile [i.e., glucose lowering effect measured as glucose infusion rate (GIR) in a euglycemic clamp study] for subcutaneous administration of 0.1, 0.2, and 0.4 unit/kg of FIASP in 46 patients with Type 1 diabetes is shown in Figure 2 and key characteristics of the timing of the effect are described in Table 6 below.

Table 6. Timing of insulin effect (i.e., mean pharmacodynamic effect) after subcutaneous administration of 0.1, 0.2 and 0.4 unit/kg of FIASP in patients (N=46) with Type 1 Diabetes and corresponding to the data shown in Figure 2

Parameter for Insulin Effect	FIASP 0.1 unit/kg	FIASP 0.2 unit/kg	FIASP 0.4 unit/kg
Time to first measurable effect	~20 minutes	~17 minutes	~16 minutes
Time to peak effect	~91 minutes	~122 minutes	~133 minutes
Time for effect to return to baseline	~5 hours	~6 hours	~7 hours

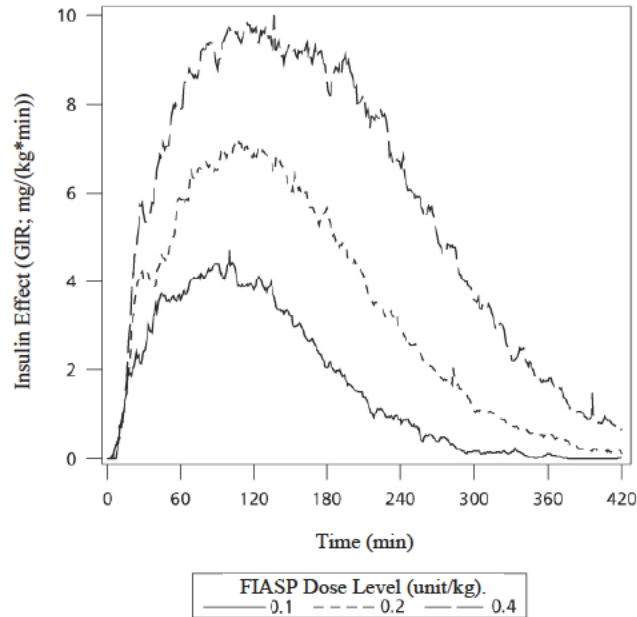


Figure 2. Mean insulin effect (i.e., mean pharmacodynamic effect) over time after subcutaneous administration of 0.1, 0.2 and 0.4 unit/kg of FIASP in patients (N=46) with Type 1 diabetes

On average, the pharmacodynamic effects of FIASP, measured as area under the glucose infusion rate-time curve (AUC_{GIR}), was 697 mg/kg, 1406 mg/kg, and 2427 mg/kg following administration of 0.1, 0.2, and 0.4 unit/kg of FIASP.

The day-to-day variability in glucose-lowering-effect of FIASP within patients was ~18% for total glucose lowering ($AUC_{GIR, 0-12h}$) and ~19% for maximum glucose lowering effect (GIR_{max}).

12.3 Pharmacokinetics

Absorption

Pharmacokinetic results from a euglycemic clamp study in adult patients with type 1 diabetes (N=51) showed that insulin aspart appeared in the circulation ~2.5 minutes after administration of FIASP (Figure 3). Time to maximum insulin concentrations was achieved ~63 minutes after administration of FIASP.

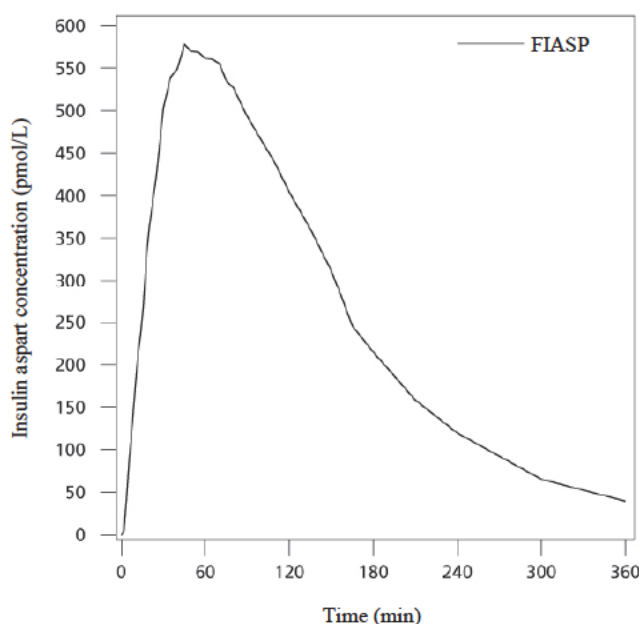


Figure 3. Mean Insulin Aspart Serum Concentration Profile in Adult Subjects with Type 1 Diabetes (N=51) following a single 0.2 unit/kg dose (subcutaneous) of FIASP

Total insulin exposure and maximum insulin concentration increase proportionally with increasing subcutaneous dose of FIASP within the therapeutic dose range.

Distribution

Insulin aspart has a low binding affinity to plasma proteins (<10%), similar to that seen with regular human insulin.

Elimination

The apparent terminal half-life after subcutaneous administration of FIASP is about 1.1 hours.

Specific Populations

Age, gender, BMI, and race did not meaningfully affect the pharmacokinetics and pharmacodynamics of FIASP.

Patients with Renal and Hepatic Impairment

Based on studies conducted with insulin aspart, renal and hepatic impairment is not known to impact the pharmacokinetics of insulin aspart.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with insulin aspart at 10, 50, and 200 units/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0

units/kg/day, based on units/body surface area, respectively). At a dose of 200 units/kg/day, insulin aspart increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors for insulin aspart was not significantly different than for regular human insulin. The relevance of these findings to humans is not known.

Insulin aspart was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, *in vivo* micronucleus test in mice, and in *ex vivo* UDS test in rat liver hepatocytes.

In fertility studies in male and female rats, at subcutaneous doses up to 200 units/kg/day (approximately 32 times the human subcutaneous dose, based on units/body surface area), no direct adverse effects on male and female fertility, or general reproductive performance of animals was observed.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

The efficacy of FIASP was evaluated in 3 randomized, active-controlled trials of 18 to 26 weeks duration in adults and one randomized, active-controlled, treat-to-target trial of 26 weeks duration in pediatric patients.

In total 1224 adult subjects (N=763 with type 1 diabetes; N=461 with type 2 diabetes) and 519 pediatric subjects with type 1 diabetes were randomized to FIASP. In adult and pediatric patients with type 1 diabetes, mealtime FIASP and postmeal FIASP led to non-inferior glycemic control compared to mealtime NovoLog, both in combination with basal insulin. In adult patients with type 2 diabetes, mealtime FIASP provided non-inferior glycemic control compared to mealtime NovoLog, both in combination with metformin. In addition, mealtime FIASP in a basal-bolus regimen with metformin also provided statistically significant improvement in the overall glycemic control compared to basal insulin therapy alone with metformin in adult patients with type 2 diabetes.

In adults with type 1 diabetes (N=472), FIASP led to non-inferior glycemic control compared to NovoLog when both were administered by continuous subcutaneous insulin infusion (CSII) pump.

14.2 Type 1 Diabetes - Adults

Study A (NCT01831765): FIASP added to insulin detemir in adult patients with Type 1 DM inadequately controlled at baseline.

The efficacy of FIASP was evaluated in a 26-week, randomized, active controlled, treat-to-target, multicenter trial in 1143 adult patients with type 1 diabetes inadequately controlled at baseline. Patients were randomized to either blinded mealtime FIASP (N=381), blinded mealtime NovoLog (N=380), or open-label postmeal FIASP (N=382), all in combination with once or twice daily insulin detemir. At randomization, patients were switched to FIASP on a unit to unit basis. Mealtime FIASP or NovoLog was injected 0-2 minutes before the meal, and postmeal FIASP was injected 20 minutes after the start of the meal.

The mean age of the randomized subjects was 44.4 years and mean duration of diabetes was 19.9 years. 59% were male, 93% were White, 2% were Black or African American, and 7% were Hispanic. The mean BMI was 26.7 kg/m².

After 26 weeks of treatment, treatment difference in HbA_{1c} reduction from baseline between mealtime FIASP compared to mealtime NovoLog, and the treatment difference between postmeal FIASP compared to mealtime NovoLog met the pre-specified non-inferiority margin (0.4%). See Table 7. Insulin doses were similar among study arms at baseline and at the end of the trial.

Table 7. Results from Study A: 26-Week Trial of Mealtime FIASP and Postmeal FIASP compared to Mealtime NovoLog Used in Combination with Insulin Detemir in Adults with Type 1 Diabetes

	Mealtime FIASP + insulin detemir	Postmeal FIASP + insulin detemir	Mealtime NovoLog + insulin detemir
Number of subjects randomized (N)	381	382	380
HbA_{1c} (%)			
Baseline (mean)	7.6	7.6	7.6
Adjusted mean change from baseline	-0.32	-0.13	-0.17
Estimated treatment difference vs. mealtime NovoLog [95% CI]*	-0.15 [-0.23;-0.07]	0.04 [-0.04;0.12]	

Baseline is based on the mean of the observed last available values prior to randomization.

*Tested for non-inferiority

Estimated treatment difference was calculated using mixed model for repeated measurements (MMRM).

7.6% of subjects on the Mealtime FIASP arm, 7.6% of subjects on the Postmeal FIASP arm, and 5.3% of subjects on the Mealtime NovoLog arm were missing the final HbA_{1c} assessment.

14.3 Type 1 Diabetes - Pediatric Patients

Study E (NCT02670915): FIASP added to insulin degludec in pediatric patients with Type 1 DM.

The efficacy of FIASP was evaluated in a 26-week, randomised, multinational, active controlled, treat-to-target, 3-armed parallel-group trial in 777 pediatric patients with type 1 diabetes. Patients were randomized to either blinded mealtime FIASP (N=260), blinded mealtime NovoLog (N=258), or open-label postmeal FIASP (N=259), all in combination with once daily insulin degludec. Mealtime FIASP or NovoLog was injected 0-2 minutes before the meal, and postmeal FIASP was injected 20 minutes after the start of the meal.

The mean age of the subjects at baseline was 11.7 years (range 2 to 17 years) and the mean duration of diabetes was 4.4 years. 54% were male, 81% were Caucasian, 16% were Asian and 2% were Black or African American. The mean BMI was 19.7 kg/m².

After 26 weeks of treatment, the treatment difference for change in HbA_{1c} from baseline between mealtime FIASP compared to mealtime NovoLog, and the treatment difference between postmeal FIASP compared to mealtime NovoLog met the pre-specified non-inferiority margin (0.4%). See Table 8. Insulin doses were similar among study arms at baseline and at the end of the trial.

Table 8. Results from Study E: 26-Week Trial of Mealtime FIASP and Postmeal FIASP compared to Mealtime NovoLog Used in Combination with Insulin Degludec in Pediatrics with Type 1 Diabetes

	Mealtime FIASP + insulin degludec	Postmeal FIASP + insulin degludec	Mealtime NovoLog + insulin degludec
Number of subjects randomized (N)	260	259	258
HbA_{1c} (%)			
Baseline (mean)	7.57	7.58	7.53
Adjusted mean change from baseline	0.06	0.35	0.22
Estimated treatment difference vs. mealtime NovoLog [95% CI]*	-0.17 [-0.30; -0.03]	0.13 [-0.01; 0.26]	

Baseline is based on the mean of the observed last available values prior to randomization.

*Tested for non-inferiority

Estimated treatment difference was calculated using ANCOVA. Week 26, change in HbA_{1c} was missing for 1.5%, 1.9%, and 1.6% of subjects in mealtime FIASP, post-meal FIASP, and NovoLog respectively. Missing values were imputed with a missing at random assumption.

14.4 Type 2 Diabetes - Adults

Study B (NCT01819129): FIASP added to basal insulin and oral antidiabetics in patients with Type 2 DM inadequately controlled at baseline on basal insulin and oral antidiabetics

The efficacy of FIASP was evaluated in a 26-week randomized, double-blind, active controlled, treat-to-target, multicenter, multinational, parallel group trial in 689 adult patients with type 2 diabetes who were inadequately controlled at baseline on basal insulin and oral antidiabetic therapy and had been on these therapies for at least 6 months. Patients were randomized to either mealtime FIASP or to mealtime NovoLog, both in combination with insulin glargine and metformin in a basal-bolus regimen. Mealtime FIASP or mealtime NovoLog was injected 0-2 minutes before the meal.

The mean age of the randomized subjects was 59.5 years and the mean duration of diabetes was 12.7 years. 49% were male, 81% were White, 6% were Black or African American, and 6% were Hispanic. The mean BMI was 31.2 kg/m².

After 26 weeks of treatment, the treatment difference in HbA_{1c} reduction from baseline between mealtime FIASP and mealtime NovoLog, both in combination with insulin glargine and metformin, met the pre-specified non-inferiority margin (0.4%). See Table 9. Insulin doses were similar among study arms at the end of the trial.

Table 9. Results from Study B: 26-Week Trial of Mealtime FIASP Compared to Mealtime NovoLog, Both used in Combination with Insulin Glargine and Metformin, in Adults with Type 2 Diabetes

	Mealtime FIASP +insulin glargine +metformin	Mealtime NovoLog +insulin glargine +metformin
Number of subjects randomized (N)	345	344
HbA_{1c} (%)		
Baseline	8.0	7.9
Adjusted change from baseline	-1.38	-1.36
Estimated treatment difference vs. NovoLog [95%CI]*	-0.02 [-0.15;0.10]	

Baseline is based on the mean of the observed last available values prior to randomization.

*Tested for non-inferiority

Estimated treatment difference was calculated using mixed model for repeated measurements (MMRM).

11.9% of subjects on the Mealtime FIASP arm and 10.2% of subjects on the Mealtime NovoLog arm were missing the final HbA_{1c} assessment.

Study C (NCT01850615): FIASP added to basal insulin and metformin in patients with Type 2 DM inadequately controlled at baseline on basal insulin and metformin

The efficacy of FIASP was evaluated in an 18-week randomized, open-label, parallel group trial in 236 adult patients with type 2 diabetes who were inadequately controlled on basal insulin and metformin therapy, either with or without other oral antidiabetic therapy, for at least 3 months. Patients were randomized to either mealtime FIASP in addition to basal insulin and metformin or to continuing basal insulin and metformin therapy without FIASP. The basal insulins used in both treatment arms were insulin glargine, insulin detemir or NPH. All patients were also required to be on ≥ 1000 mg metformin treatment at baseline.

The mean age of the trial population was 57.4 years and the mean duration of diabetes was 11.3 years. 48% were male, 70% were White, 4% were Black or African American, and 37% were Hispanic. The mean BMI was 30.8 kg/m².

After 18 weeks of treatment, addition of FIASP to basal insulin and metformin statistically significantly reduced HbA_{1c} compared to continuing basal insulin and metformin therapy without addition of FIASP (Table 10).

Table 10. Results from Study C: 18-Week Trial of Mealtime FIASP in Adults with Type 2 Diabetes Inadequately Controlled at Baseline on Basal Insulin and Metformin

	FIASP + basal insulin + metformin	Basal insulin + metformin
Number of subjects randomized (N)	116	120
HbA_{1c} (%)		
Baseline	7.9	7.9
Adjusted change from baseline	-1.16	-0.22
Estimated treatment difference vs. basal insulin+metformin [95%CI]	-0.94 [-1.17; -0.72]*	
Proportion of patients Achieving HbA_{1c} < 7% at Trial End	60.3%	18.3%

Baseline is based on the mean of the observed last available values prior to randomization.

*p<0.0001, 1-sided p-value evaluated at 2.5% level for superiority.

Estimated treatment difference was calculated using mixed model for repeated measurements (MMRM).

6.0% of subjects on the mealtime FIASP arm and 3.3% of subjects on the placebo arm were missing the final HbA_{1c} assessment.

14.5 Type 1 Diabetes – Adult Continuous Subcutaneous Insulin Infusion (CSII)

Study D (NCT02825251): FIASP in Continuous Subcutaneous Insulin Infusion (CSII) in Adults with Type 1 DM

The efficacy and safety of FIASP vs. NovoLog in CSII in adult subjects with T1DM (N=472) was evaluated in a randomized, multicenter, multinational, active controlled, treat-to-target, parallel group trial with a 4-week run-in and a 16-week treatment period. Meal-time bolus insulin infusion was initiated 0-2 minutes before a meal.

The mean age of the randomized subjects was 43 years and the mean duration of diabetes was 24 years. 43% were male. 89% were Caucasian, 1% were Black or African American, 1% were Asian, and 3% were Hispanic. The mean BMI was 26.3 kg/m².

After 16 weeks of treatment, the treatment difference in HbA_{1c} reduction from baseline between FIASP and NovoLog was 0.10 with 95%CI [0.02, 0.18] (Table 11).

Table 11. Results from Study D: 16-Week Trial FIASP in Adults with Type 1 Diabetes

	FIASP	NovoLog
Number of subjects randomized (N)	236	236
HbA_{1c} (%)		
Baseline	7.5	7.5
Adjusted change from baseline	-0.04	-0.14
Estimated treatment difference FIASP vs. NovoLog [95%CI]*	0.10 [0.02; 0.18]	
Proportion of patients Achieving HbA_{1c} < 7% at Trial End	20.3%	23.3%

Baseline is based on the mean of the observed last available values prior to randomization.

*Tested for non-inferiority using a margin of 0.4%.

Estimated treatment difference was calculated using ANCOVA.

2.1% of subjects on the FIASP arm and 2.5% of subjects on the NovoLog arm were missing the final HbA_{1c} assessment. Missing values were imputed using multiple imputation with a mean equal to the baseline value of the corresponding patient.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FIASP (insulin aspart injection) 100 units of insulin aspart per mL (U-100) is available as a clear and colorless solution in the following presentations and packaging configurations:

Carton of one 10 mL multiple-dose vials	NDC 0169-3201-11
Carton of five 3 mL single-patient use FIASP FlexTouch pens	NDC 0169-3204-15
Carton of five 3 mL single-patient-use PenFill cartridges *	NDC 0169-3205-15

The FIASP FlexTouch pen dials in 1 unit increments.

* FIASP PenFill cartridges are designed for use with Novo Nordisk insulin delivery devices.

16.2 Recommended Storage

Dispense in the original sealed carton with the enclosed Instructions for Use.

Unused FIASP vials should be stored between 2° to 8°C (36° to 46°F) in a refrigerator, but not in or near a freezing compartment. FIASP should not be exposed to excessive heat or light and must never be frozen. Do not use FIASP if it has been frozen. FIASP should not be drawn into a syringe and stored for later use.

Keep the cap on the pen in order to protect from light. Remove the needle from the FIASP FlexTouch pen after each injection and store without a needle attached. Use a new needle for each injection. Keep unused vials, FIASP FlexTouch and PenFill Cartridges in the carton so they will stay clean and protected from light.

The storage conditions for vials, FIASP FlexTouch pens, and 3 mL PenFill cartridges are summarized in Table 12:

Table 12. Storage Conditions for Vial, FIASP FlexTouch, and PenFill Cartridges

FIASP presentation	Not in-use (unopened)		In-use (opened)	
	Room Temperature (below 30°C)	Refrigerated (2°C to 8°C)	Room Temperature (below 30°C)	Refrigerated (2°C to 8°C)
10 mL multiple-dose vial	28 days	Until expiration date	28 days*	28 days*
3 mL single-patient-use FIASP FlexTouch pen	28 days	Until expiration date	28 days	28 days
3 mL single-patient-use PenFill cartridges	28 days	Until expiration date	28 days	Do not refrigerate

*For insulin pump use, the total in-use time is 28 days, including 6 days pump in-use time

Storage of FIASP in Insulin Pump:

FIASP in the pump reservoir should be replaced at least every 6 days, or according to the pump user manual, whichever is shorter, to avoid insulin degradation or after exposure to temperatures that exceed 37°C (98.6°F). The infusion set and infusion set insertion sites should be changed according to the manufacturers’ user manual.

Storage of FIASP in Intravenous Infusion Fluids:

Infusion bags prepared as indicated under *Dosage and Administration (2.2)* are stable at room temperature for 24 hours.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-Approved Patient Labeling (Patient Information and Instructions for Use).

Never Share a FIASP FlexTouch Pen Device, PenFill Cartridge or PenFill Cartridge Device Between Patients

Advise patients that they should never share a FIASP FlexTouch pen device, PenFill cartridge or PenFill cartridge devices with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens. Advise patients using FIASP vials not

to share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens [see *Warnings and Precautions (5.1)*].

Hyperglycemia or Hypoglycemia

Inform patients that hypoglycemia is the most common adverse reaction with insulin. Instruct patients on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia, especially at initiation of FIASP therapy. Instruct patients on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals. Instruct patients on the management of hypoglycemia [see *Warnings and Precautions (5.3)*].

Inform patients that their ability to concentrate and react may be impaired as a result of hypoglycemia. Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery.

Advise patients that changes in insulin regimen can predispose to hyperglycemia or hypoglycemia and that changes in insulin regimen should be made under close medical supervision [see *Warnings and Precautions (5.2)*].

Hypersensitivity Reactions

Advise patients that hypersensitivity reactions have occurred with FIASP. Inform patients on the symptoms of hypersensitivity reactions [see *Warnings and Precautions (5.6)*].

Hypoglycemia due to Medication Errors

Instruct patients to always check the insulin label before each injection to avoid mix-ups between insulin products.

Patients Using Continuous Subcutaneous Insulin Pumps

- Train patients in intensive insulin therapy with multiple injections and in the function of their pump and pump accessories.
- Instruct patients to follow healthcare provider recommendations when setting basal and meal time infusion rate.
- Refer to the continuous subcutaneous infusion pump user manual to see if FIASP can be used with the pump. See recommended reservoir and infusion sets in the insulin pump user manual.
- Instruct patients to replace insulin in the reservoir at least every 6 days, or according to the pump user manual, whichever is shorter; infusion sets and infusion set insertion sites should be changed in accordance with the manufacturers' user manual. By following this schedule, patients avoid insulin degradation, infusion set occlusion, and loss of the insulin preservative.
- Instruct patients to discard insulin exposed to temperatures higher than 37°C (98.6°F).
- Instruct patients to inform physician and select a new site for infusion if infusion site becomes erythematous, pruritic, or thickened.
- Instruct patients on the risk of rapid hyperglycemia and ketosis due to pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and degraded insulin. Instruct

patients on the risk of hypoglycemia from pump malfunction. If these problems cannot be promptly corrected, instruct patients to resume therapy with subcutaneous insulin injection and contact their physician [*see Warnings and Precautions (5) and How Supplied/Storage and Handling (16.2)*].

Date of Issue: 12/2019

Version: 5

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PATENT Information: <http://novonordisk-us.com/patients/products/product-patents.html>

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Manufactured by:

Novo Nordisk A/S

DK-2880 Bagsvaerd, Denmark

For information about FIASP contact:

Novo Nordisk Inc.

800 Scudders Mill Road

Plainsboro, New Jersey 08536

1-800-727-6500

www.novonordisk-us.com

Patient Information
FIASP® (fee' asp)
(insulin aspart injection)
for subcutaneous or intravenous use

Do not share your FIASP with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

What is FIASP?

- FIASP is a man-made insulin that is used to control high blood sugar in adults and children with diabetes mellitus.

Who should not take FIASP?

Do not take FIASP if you:

- are having an episode of low blood sugar (hypoglycemia).
- have an allergy to insulin aspart or any of the ingredients in FIASP.

Before taking FIASP, tell your healthcare provider about all your medical conditions including, if you:

- have kidney problems.
- have liver problems.
- are pregnant or plan to become pregnant. Talk with your healthcare provider about the best way to control your blood sugar if you plan to become pregnant or while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if FIASP passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby while using FIASP.
- are taking new prescription or over-the-counter medicines, vitamins, or herbal supplements.

Before you start taking FIASP, talk to your healthcare provider about low blood sugar and how to manage it.

How should I take FIASP?

- **Read the Instructions for Use** that come with your FIASP.
- Take FIASP exactly as your healthcare provider tells you to.
- **FIASP starts acting fast.** You should take your dose of FIASP at the beginning of the meal or within 20 minutes after starting a meal.
- Know the type and strength of insulin you take. **Do not** change the type of insulin you take unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you take different types of insulin.
- If you miss a dose of FIASP, monitor your blood sugar levels to decide if an insulin dose is needed. Continue with your regular dosing schedule at the next meal.
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.
- **Do not reuse or share needles with other people. You may give other people a serious infection or get a serious infection from them.**
- FIASP can be injected under the skin (subcutaneously) of your stomach area, upper legs, or upper arms, or by continuous infusion under the skin (subcutaneously) through an insulin pump into an area of your body recommended in the instructions that come with your insulin pump.
- **Change (rotate) your injection sites within the area you choose with each dose** to reduce your risk of getting pits in skin or thickened skin (lipodystrophy) and skin with lumps (localized cutaneous amyloidosis) at the injection sites.
 - o **Do not** use the exact same spot for each injection.
 - o **Do not** inject where the skin has pits, is thickened, or has lumps.
 - o **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.

What should I avoid while taking FIASP?

While taking FIASP do not:

- Drive or operate heavy machinery until you know how FIASP affects you.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

What are the possible side effects of FIASP?

FIASP may cause serious side effects that can lead to death, including:

- **low blood sugar (hypoglycemia).** Signs and symptoms that may indicate low blood sugar include:

- dizziness or light-headedness
- sweating
- confusion
- headache
- blurred vision
- slurred speech
- shakiness
- fast heart beat
- anxiety, irritability, or mood changes
- hunger

- **low potassium in your blood (hypokalemia).**
- **serious allergic reactions (whole body reactions).** Get emergency medical help right away, if you have any of these signs or symptoms of a severe allergic reaction:
 - a rash over your whole body, trouble breathing, a fast heartbeat, swelling of your face, tongue or throat, sweating, extreme drowsiness, dizziness, confusion.
- **heart failure.** Taking certain diabetes pills called TZDs (thiazolidinediones) with FIASP may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure it may get worse while you take TZDs with FIASP. Your healthcare provider should monitor you closely while you are taking TZDs with FIASP. Tell your healthcare provider if you have any new or worse symptoms of heart failure including shortness of breath, swelling of your ankles or feet, sudden weight gain. Treatment with TZDs and FIASP may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.

Your insulin dose may need to change because of:

- change in level of physical activity or exercise
- weight gain or loss
- increased stress
- illness
- change in diet

Common side effects of FIASP may include:

- skin problems such as eczema, rash, itching, redness and swelling of your skin (dermatitis)
- reactions at the injection site such as itching, rash
- skin thickening or pits at the injection site (lipodystrophy)
- weight gain

These are not all the possible side effects of FIASP. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of FIASP.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about FIASP that is written for health professionals. Do not use FIASP for a condition for which it was not prescribed. Do not give FIASP to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in FIASP?

Active Ingredient: insulin aspart

Inactive Ingredients: glycerol, phenol, metacresol, zinc, disodium phosphate dihydrate, arginine hydrochloride, niacinamide and water for injections

Manufactured by: Novo Nordisk A/S DK-2880 Bagsvaerd, Denmark

For more information, go to www.novonordisk-us.com or call 1-800-727-6500.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised:12/2019

Instructions for Use
FIASP® (fee' asp) FlexTouch® Pen
(insulin aspart injection)

- **Do not** share your FIASP FlexTouch Pen with other people, even if the needle is changed. You may give other people a serious infection, or get a serious infection from them.
- **FIASP FlexTouch Pen ("Pen") is a prefilled disposable, single-patient-use pen** containing 300 units of U-100 FIASP (insulin aspart injection). You can inject from 1 to 80 units in a single injection. The units can be increased by 1 unit at a time.
- People who are blind or have vision problems should not use the Pen without help from a person trained to use the Pen.
- **Do not** use a syringe to remove FIASP from the FlexTouch Pen.

Supplies you will need to give your FIASP injection:

- FIASP FlexTouch Pen
- a new NovoFine, NovoFine Plus or NovoTwist needle
- alcohol swab
- a sharps container for throwing away used Pens and needles. **See "After your injection" at the end of these instructions.**

Preparing your FIASP FlexTouch Pen:

Wash your hands with soap and water.

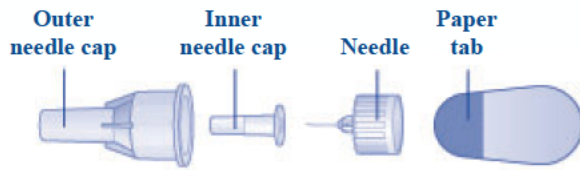
Before you start to prepare your injection, check the FIASP FlexTouch Pen label to make sure you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin.

FIASP should look clear and colorless. **Do not** use FIASP if it is thick, cloudy, or is colored.

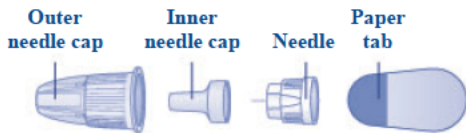
Do not use FIASP past the expiration date printed on the label or 28 days after you start using the Pen.

Always use a new needle for each injection to help ensure sterility and prevent blocked needles. **Do not** reuse or share needles with another person. You may give other people a serious infection, or get a serious infection from them.

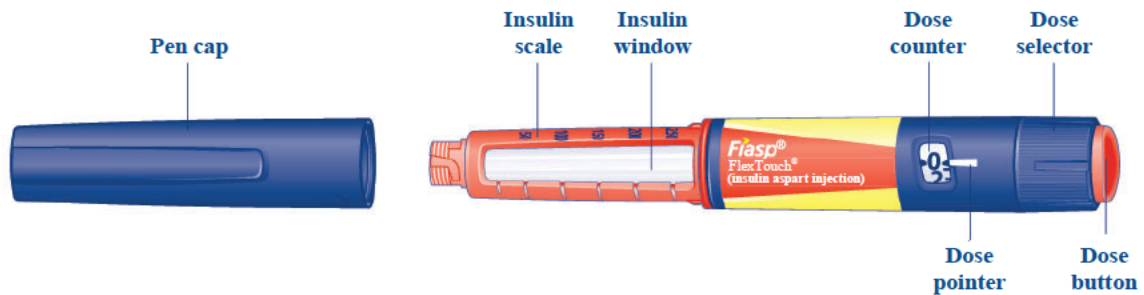
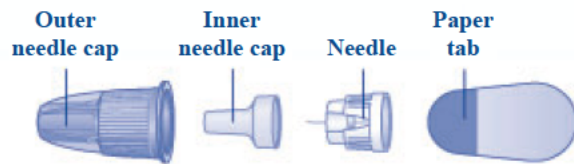
NovoFine®



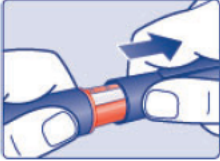
NovoFine® Plus

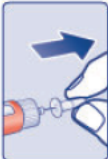


NovoTwist®



(Figure A)

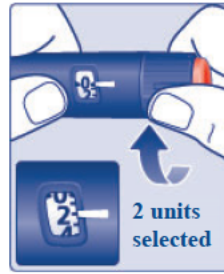
Step 1: Pull Pen cap straight off (See Figure B).	 (Figure B)
Step 2: • Check the liquid in the Pen (See Figure C). FIASP should look clear	 (Figure C)

and colorless. Do not use it if it looks cloudy or colored.	
Step 3: • Select a new needle. • Pull off the paper tab from the outer needle cap (See Figure D).	NovoFine® NovoFine® Plus  NovoTwist®  (Figure D)
Step 4: Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).	NovoFine® NovoFine® Plus  NovoTwist®  (Figure E)
Step 5: Pull off the outer needle cap. Do not throw it away (See Figure F).	NovoFine® NovoFine® Plus  NovoTwist®  (Figure F)
Step 6: Pull off the inner needle cap and throw it away (See Figure G).	NovoFine® NovoFine® Plus  NovoTwist®  (Figure G)

Priming your FIASP FlexTouch Pen:

Step 7:

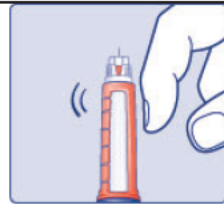
Turn the dose selector to **select 2 units** (See Figure H).



(Figure H)

Step 8:

Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).



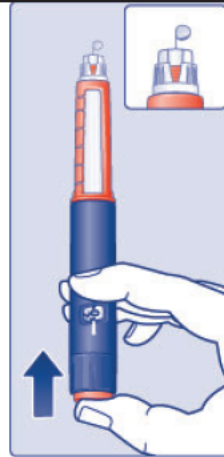
(Figure I)

Step 9:

Hold the Pen with the needle pointing up. Press and hold in the dose button until the dose counter shows "0". The "0" must line up with the dose pointer.

A drop of insulin should be seen at the needle tip (See Figure J).

- If you **do not** see a drop of insulin, repeat steps 7 to 9, no more than 6 times.
- If you **still do not** see a drop of insulin, change the needle and repeat steps 7 to 9.



(Figure J)

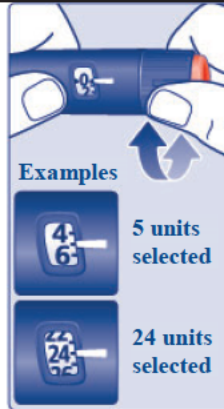
Selecting your dose:

Step 10:

Check to make sure the dose selector is set at 0.

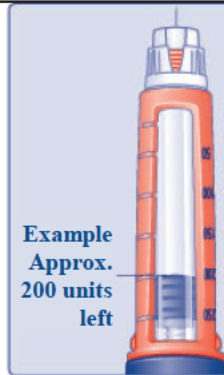
Turn the dose selector to select the number of units you need to inject. The dose pointer should line up with your dose (See Figure K).

- If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
- The **even** numbers are printed on the dial.
- The **odd** numbers are shown as lines.



(Figure K)

The FIASP FlexTouch Pen insulin scale will show you how much insulin is left in your Pen (See Figure L).



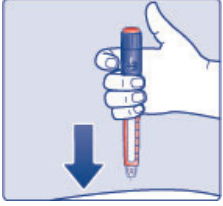
(Figure L)

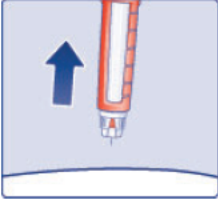
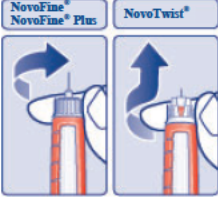
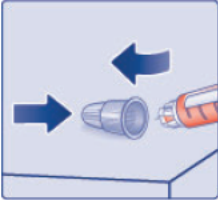
To see how much insulin is left in your FIASP FlexTouch Pen:

- Turn the dose selector until it stops. The dose counter will line up with the number of units of insulin that is left in your Pen. If the dose counter shows 80, there are **at least 80** units left in your Pen.
- If the dose counter shows **less than 80**, the number shown in the dose counter is the number of units left in your Pen.

Giving your injection:

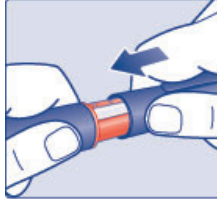
- Inject your FIASP exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
- You should take your dose of FIASP at the start of a meal or within 20 minutes after starting a meal.
- FIASP can be injected under the skin (subcutaneously) of your stomach area (abdomen), upper legs (thighs) or upper arms. **Do not** inject FIASP into your muscle.
- Change (rotate) your injection sites within the area you choose for each dose to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites. **Do not** use the same injection site for each injection. **Do not** inject where the skin has pits, is thickened, or has lumps. **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.

Step 11: • Choose your injection site and wipe the skin with an alcohol swab. Let the injection site dry before you inject your dose (See Figure M).	 (Figure M)
Step 12: • Insert the needle into your skin (See Figure N). ○ Make sure you can see the dose counter. Do not cover it with your fingers; this can stop your injection.	 (Figure N)
Step 13: • Press and hold down the dose button until the dose counter shows "0" (See Figure O). ○ The "0" must line up with the dose pointer. You may then hear or feel a click. • Keep the needle in your skin after the dose counter has returned to "0" and slowly count to 6 (See Figure P). ○ When the dose counter returns to "0", you will not	 (Figure O)

get your full dose until 6 seconds later. ○ If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip. ○ If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.	Count slowly:  (Figure P)
Step 14: • Pull the needle out of your skin (See Figure Q). ○ If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. Do not rub the area.	 (Figure Q)
Step 15: • Carefully remove the needle from the Pen and throw it away (See Figure R). ○ Do not recap the needle. Recapping the needle can lead to needle stick injury. • If you do not have a sharps container, carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can. ○ Do not store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.	 (Figure R)  (Figure S)

Step 16:

- Replace the Pen cap by pushing it straight on (See Figure T).



(Figure T)

After your injection:

- Put your used FIASP FlexTouch Pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and Pens in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
 - upright and stable during use
 - leak-resistant
 - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share needles or syringes with another person. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

How should I store my FIASP FlexTouch Pen?**Before use:**

- Store unused FIASP FlexTouch Pens in the refrigerator at 36°F to 46°F (2°C to 8°C) or at room temperature below 86°F (30°C).
- **Do not** freeze FIASP. **Do not** use FIASP if it has been frozen.
- Unused Pens may be used until the expiration date printed on the label, if kept in the refrigerator.

- If FIASP FlexTouch Pens are stored at room temperature prior to first use, it should be used or thrown away within 28 days.

Pen in use:

- Store the Pen you are currently using without the needle attached at room temperature below 86°F (30°C) or in the refrigerator at 36°F to 46°F (2°C to 8°C) for up to 28 days.
- Keep FIASP away from excessive heat or light.
- The FIASP FlexTouch Pen you are using is to be thrown away after 28 days, even if it still has insulin left in it and the expiration date has not passed.

General Information about the safe and effective use of FIASP:

- **Keep FIASP FlexTouch Pens and needles out of the reach of children.**
- **Always** use a new needle for each injection.
- **Do not** share FIASP FlexTouch Pens or needles with other people. You may give other people a serious infection, or get a serious infection from them.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Novo Nordisk A/S

DK-2880 Bagsvaerd, Denmark

Revised: 10/2019



For more information go to
www.FIASPflextouch.com

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208751Orig1s011

SUMMARY REVIEW

Division Summary Memo for Regulatory Action and CDTL review

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

1. Introduction

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

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

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

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

This memo references the following documents/sources:

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

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

2. Background

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

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

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

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

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

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

3. CMC/Device

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

The initial review of sNDA 208751/S-008 by Dr. Rumi Young from the Center for Devices and Radiologic Health, ODE/DAGRID/GHDB (now reorganized as OHT3/DHT3C/CDRH), supported approval of CSII in an adult population but indicated that the data submitted would not support approval of CSII in a pediatric population: the review noted that at least one CSII pump would need approval for use of Fiasp in a pediatric population prior to approval of this supplement, but indicated that there was not enough data available to support safe use of Omnipod (the pump labeled for use with Fiasp in the adult population) in the pediatric population. Nikhil Thakur from OHT3/DHT3C/CDRH amended the initial review, noting that while CDRH continues to work with Insulet (the Medical Device Sponsor of Omnipod) regarding at-large issues related to Omnipod, to clarify that there are no outstanding issues specific to the delivery of Fiasp and that none of the identified general issues should affect the approvability of NDA 208751/S-011. The Master File (MAF) for the Omnipod DASH system has been updated to approve use of Fiasp in a pediatric population.

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

4. Nonclinical Pharmacology/Toxicology

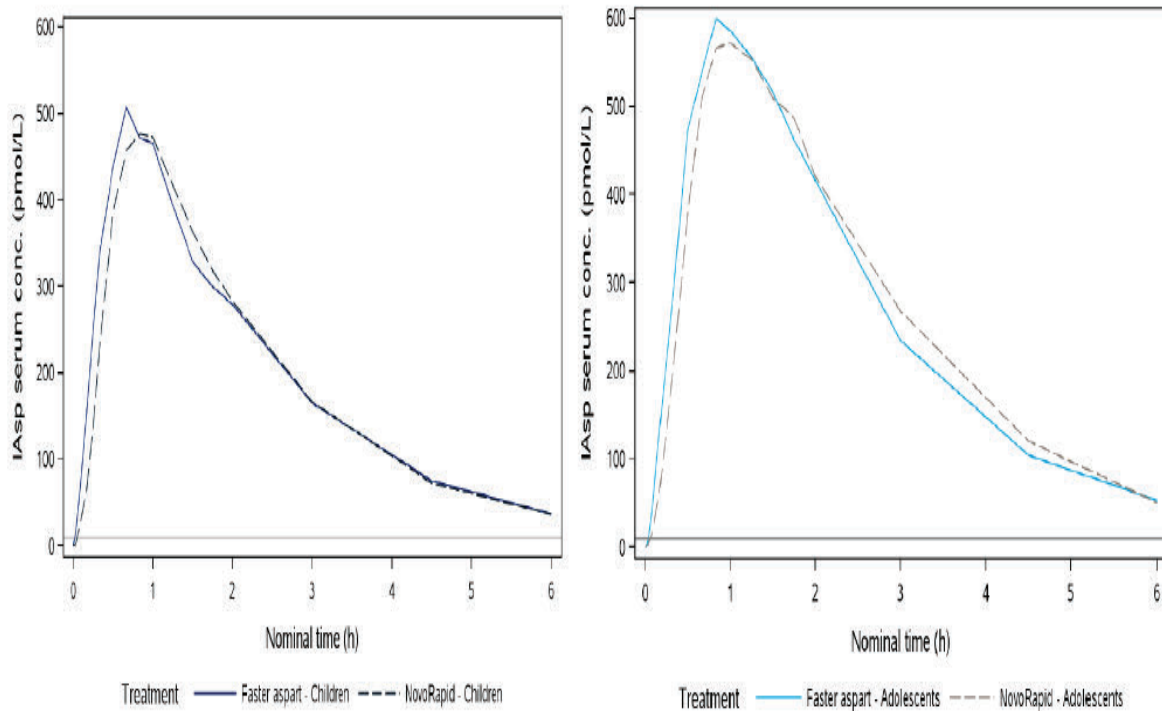
The submission does not contain new nonclinical pharmacology/toxicology data.

5. Clinical Pharmacology/Biopharmaceutics

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

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

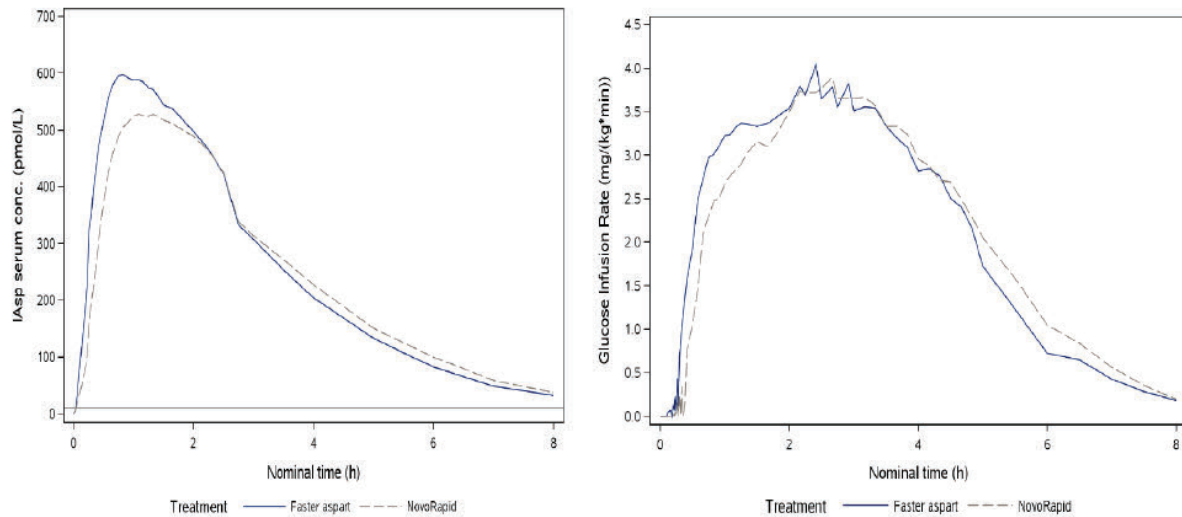
Figure 1: Mean PK in children and adolescents of Fiasp and NovoLog in Study 4371



Source: Module 2.7.2 Summary of Clinical Pharmacology Studies

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

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



Source: Module 2.7.2 Summary of Clinical Pharmacology Studies

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

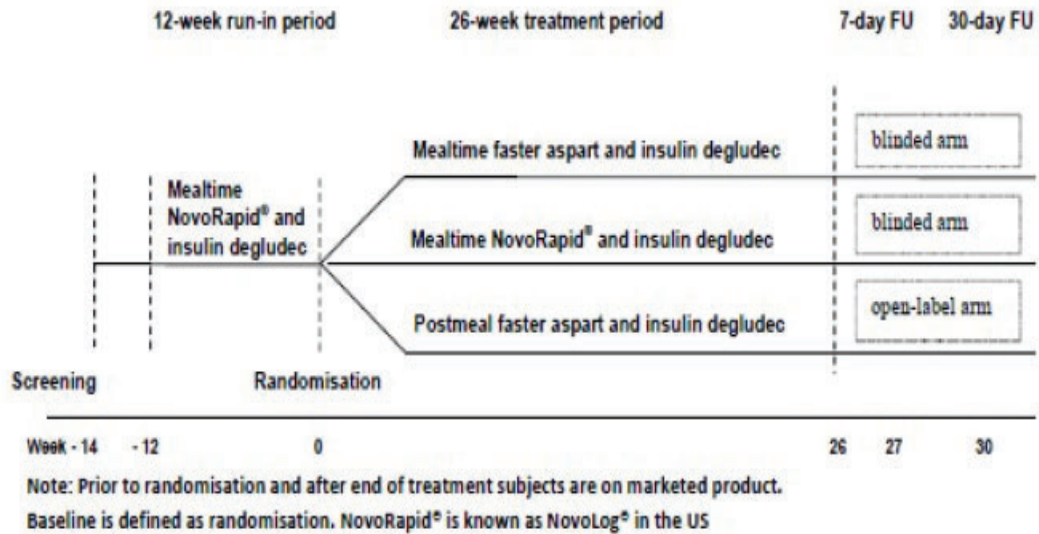
6. Clinical/Statistical- Efficacy

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

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

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

Figure 3: Design of Study 4101



Source: Study 4101 Clinical Study Report

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

Table 1: Patient disposition in Study 4101

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

Source: FDA Clinical Review

Table 2: Baseline demographic characteristics in Study 4101

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

N=number of subjects

Source: Study 4101 Clinical Study Report

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

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

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

Table 3: Efficacy results from Study 4101

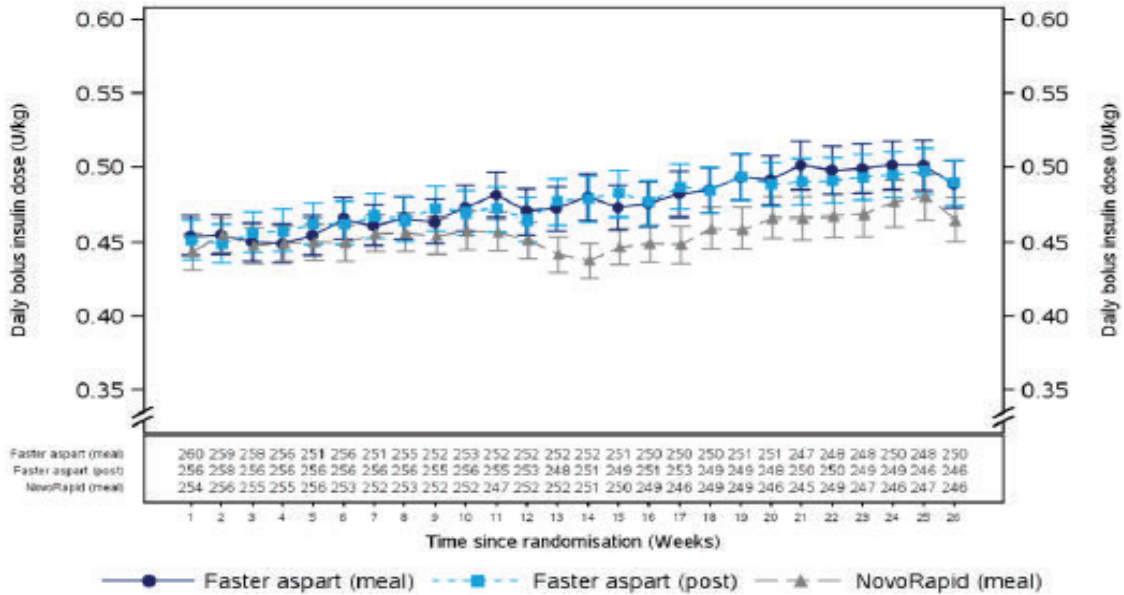
	Mealtime FIASP	Post-meal FIASP	NovoLog
N	260	259	258
Mean Baseline (Std. Dev.)	7.57 (0.80)	7.58 (0.84)	7.53 (0.83)
Week 26 Change from Baseline	0.06 (0.05)	0.35 (0.05)	0.22 (0.05)
Treatment Diff vs NovoLog (95% CI)	-0.17 (-0.3, -0.03)	0.13 (-0.01, 0.26)	.

Source: FDA Statistical Review

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

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

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



Source: Study 4101 Clinical Study Report

Hyon Kwon concurred with Dr. Clark that the statistical analyses of the primary endpoints meet pre-specified criteria for all three hypotheses. Based on the efficacy data in 4101 and also the clinical pharmacology studies and the clinical trials previously reviewed, she concluded that both mealtime Fiasp and postmeal Fiasp have efficacy with regards to glycemic control in pediatric patients with diabetes. While she did not believe differences in insulin doses across treatment arms were likely to have had a significant impact on the primary analysis, she recommended against labeling language that would convey (b) (4)

I concur with these conclusions.

APPEARS THIS WAY ON ORIGINAL

7. Safety

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

Deaths

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

Serious Adverse Events (SAEs)

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

Hypoglycemia

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

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

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

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

Source: Study 4101 Clinical Study Report

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

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

8. Advisory Committee Meeting

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

9. Pediatrics

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

10. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA), the Patient Labeling Team in the Division of Medical Policy Programs (DMPP), and the Office of Prescription Drug Promotion (OPDP) all reviewed the two efficacy supplements. Please see their respective reviews for details.

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

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

Division Summary Memo
NDA 208751/S-010 and S-011
Fiasp (insulin aspart)

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

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

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

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

11. Recommendations

- Recommended Regulatory Action

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

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

Recommendation for other Postmarketing Requirements and Commitments

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

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

/s/

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

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208751Orig1s011
CLINICAL REVIEW(S)

Clinical Review
 Hyon Kwon, PharmD, MPH
 sNDA 208751/S-010 and S-011
 Fiasp (insulin aspart)

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
Received Date(s)	February 21, 2019
PDUFA Goal Date	December 21, 2019
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

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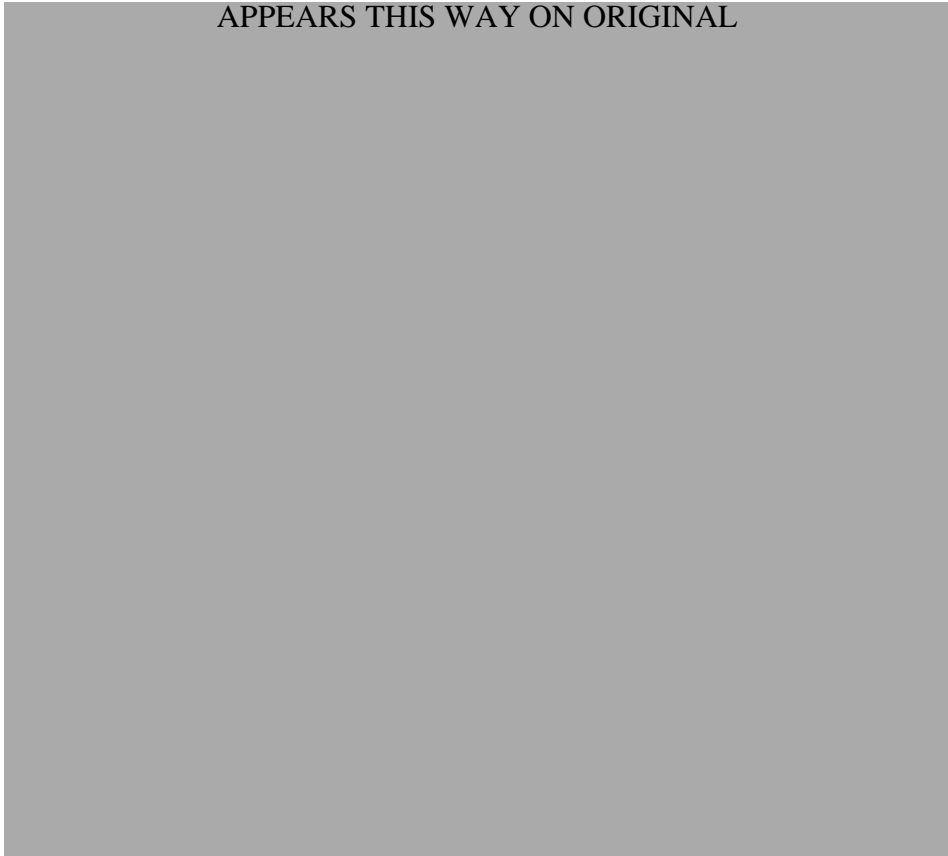
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PMR	postmarketing requirement
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis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

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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.

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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-

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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.

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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

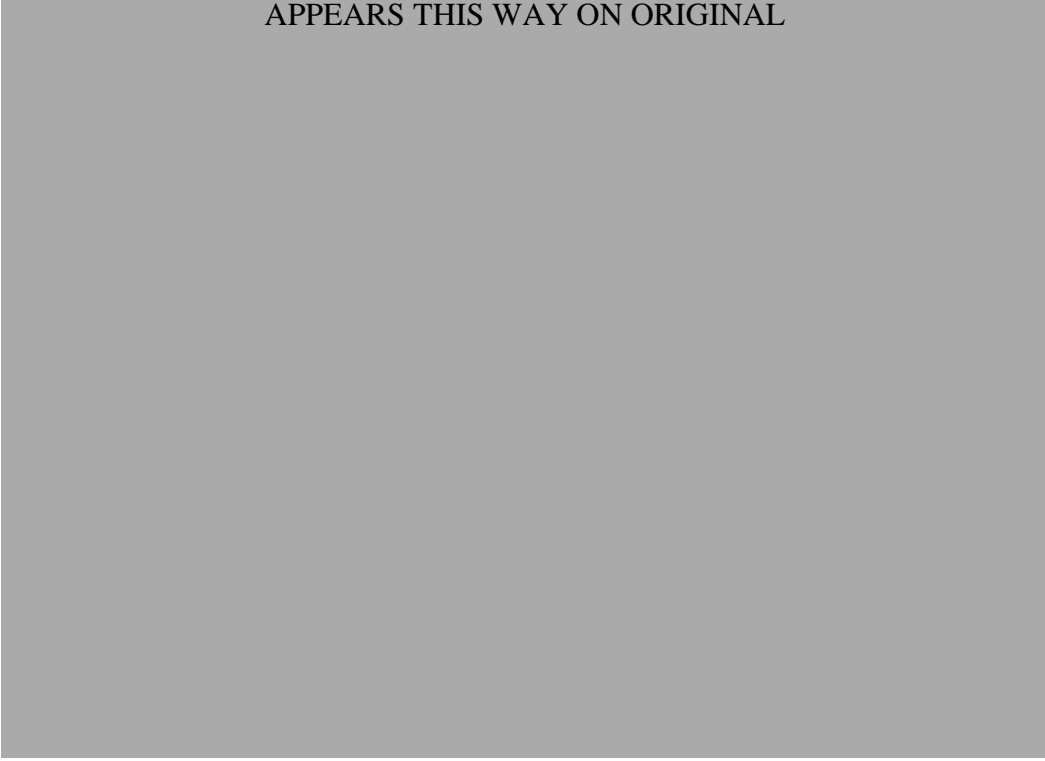
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Supplement #8 for Fiasp use in insulin pump in adult patients with diabetes, which was approved on October 21, 2019. The efficacy data from trial 4101 is discussed in this review under Supplement #10 to support the use of Fiasp in pediatric patients 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**

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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

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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.

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(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.

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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)	
☒	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 hypoglycemia¹. 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.

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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 extended release; 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;
- Partial waiver for Fiasp in children and adolescents between 10 to 18 years of age with T2DM;
- 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.

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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 but did not agree with partial waiver for pediatric patients 10-18 years of age with T2DM; 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.

It should be noted that in this February 2, 2015 iPSP submission, the Applicant was considering

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(b) (4) 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

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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 and revised protocol (b) (4). 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;
- At this time, we believe that under PREA you would not be required to conduct a pediatric pump study because NovoLog is qualified for use in insulin pumps, and therefore, Fiasp’s use in pumps would not be considered a new dosing regimen or route of administration. Note that final determination will occur at the time of NDA approval.

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 removed (b) (4) (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 (NN1218-3890), 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 (b) (4). You should remove (b) (4) (b) (4) 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, NN1218-3890, and NN1218-4101).

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

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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 (NN1218-3890);
 - 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.

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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.

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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 compared 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

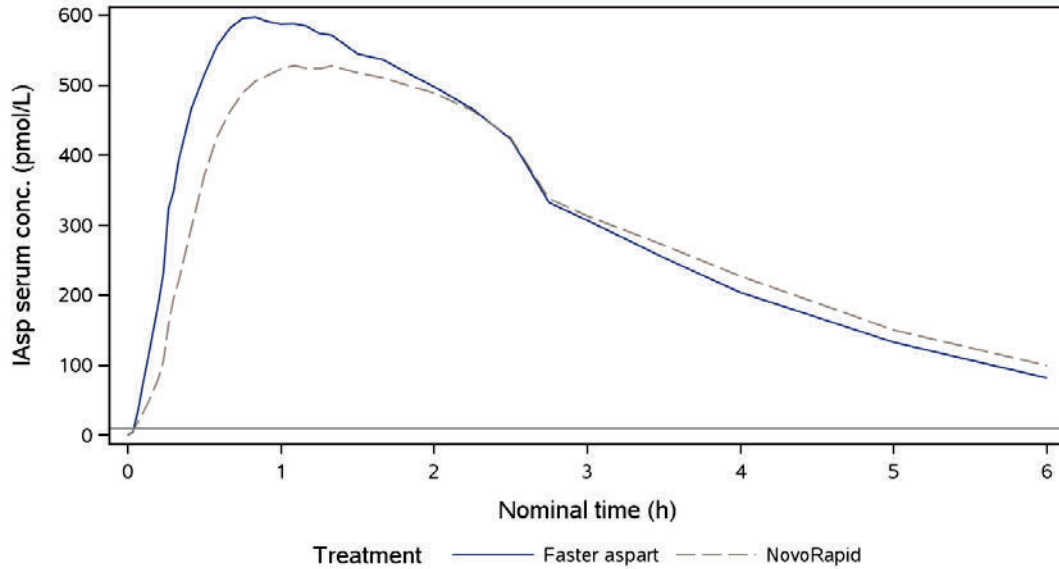
To support the extrapolation of efficacy data supporting use of Fiasp in pediatric subjects with T1DM to pediatric subjects with T2DM, trial 4265 was conducted where the PK and PD of Fiasp and NovoLog were compared in adults with T2DM using a euglycemic clamp. This was a randomized, single-center, double-blind, 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.

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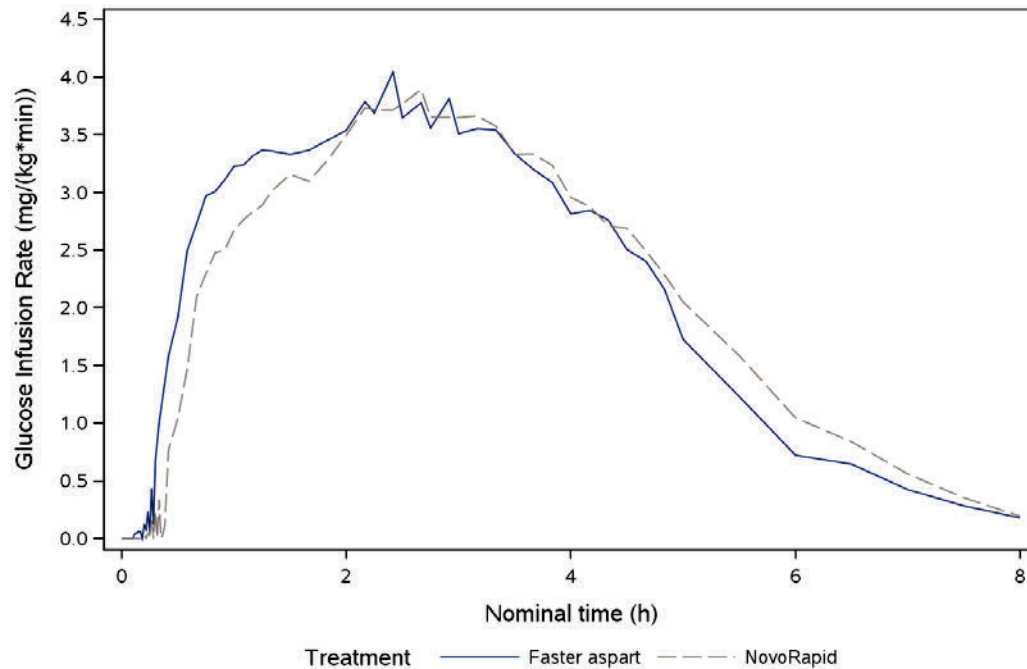
Figure 1: Mean Insulin Aspart Profile (0-6 hours) in Adults with T2DM in Trial 4265



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

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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. CDRH was consulted to provide recommendation for pump use in pediatrics. Nikhil Thakur from CDRH recommended approvable (see his final review dated November 25, 2019).

The Applicant intends to use Omnipod DASH Insulin Management System (cleared by CDRH on October 21, 2019 [K192659]) which was recently cleared when sNDA 208751/S-008 was approved for Fiasp use in insulin pump in adult patients. At that time, Insulet Corporation, who owns the Omnipod DASH and holds Medical Device Master File associated with Omnipod DASH (MAF (b) (4)) updated the labeling to include the statement that "FIASP has a faster initial absorption than other rapid-acting U-100 insulins and is only approved for use in adults". CDRH discussed with Insulet Corporation about updating the MAF to align the Omnipod DASH labeling with Fiasp labeling with approval of Supplement #11 by removing the phrase "...is only approved for use in adults". CDRH stated that Insulet Corporation is committed to updating the Omnipod DASH labeling before the approval of Supplement #11. See Nikhil Thakur's review dated November 25, 2019 for full discussion of details.

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.

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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

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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

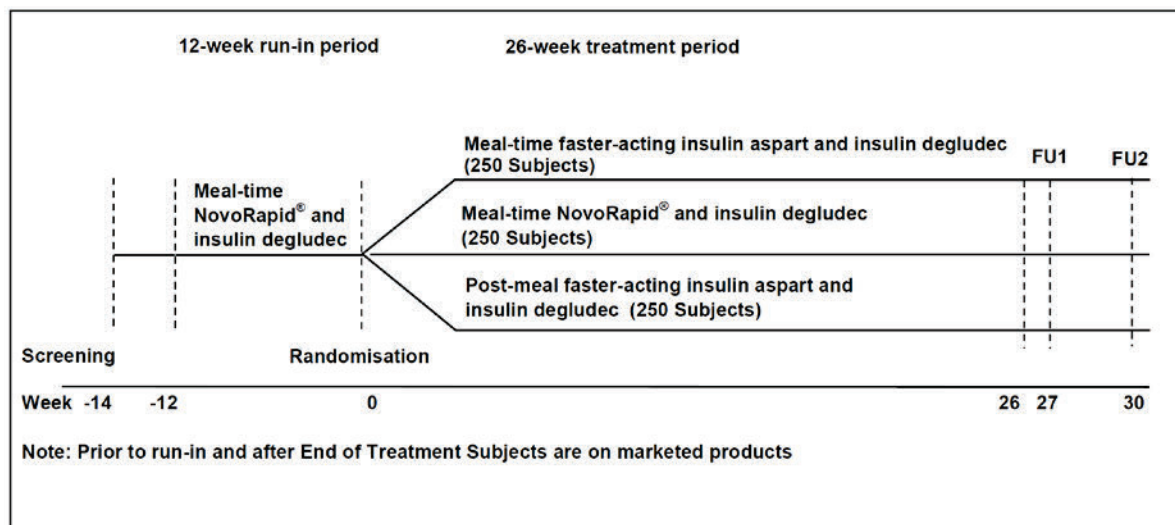
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Guidance³.

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 age⁴. 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 $\leq 9.5\%$ 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.

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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 $\leq 9.5\%$;
- 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.

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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 dosing 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.

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Procedures and Schedule:

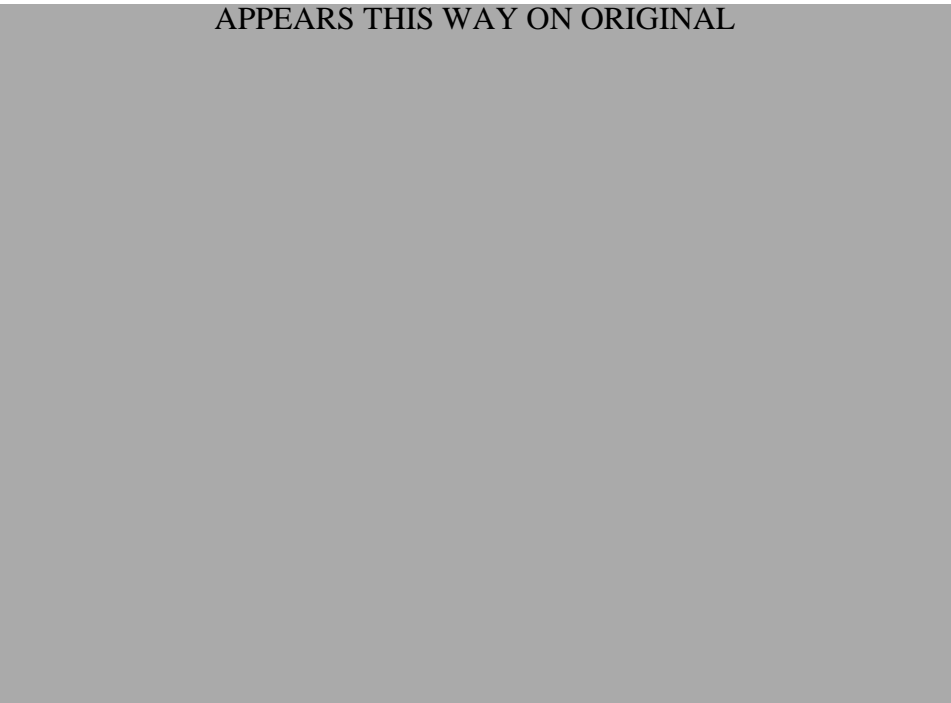
To optimize glycemic control, investigators were to maintain at least weekly contact with the subjects throughout the trial to adjust insulin doses. Subjects were provided with a diary to record the 4-point and 8-point SMBG profiles (per Table 3), insulin doses, and dates on 3 days before the site visit/phone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

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Drugs for Diabetes Mellitus⁵, 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.

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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.

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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

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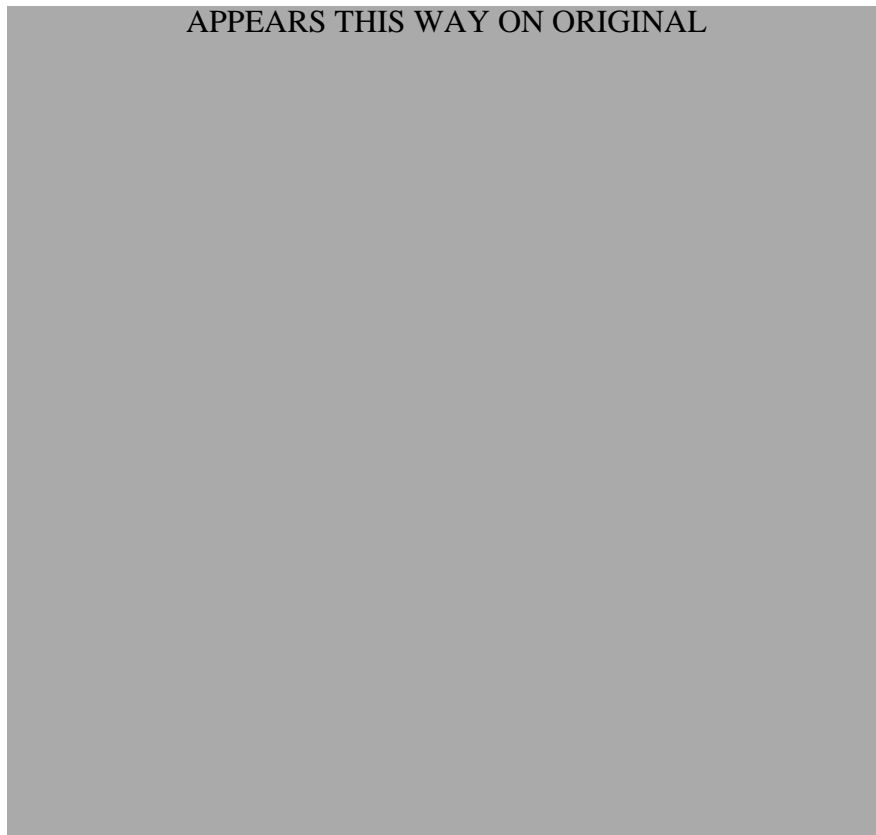
Applicant by doing on-site visits, telephone calls, and regular inspection of paper CRFs and eCRFs. The Applicant conducted 33 internal audits.

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:



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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)
	(b) (6)	Honoraria	\$44,915	(b) (6)	\$44,915	(b) (6)
	(b) (6)	Honoraria	\$30,047	(b) (6)	\$30,047	(b) (6)
	(b) (6)	Advisory Board	\$10,455	(b) (6)	\$32,235	(b) (6)
	(b) (6)		\$14,520	(b) (6)		
	(b) (6)	Honoraria	\$7,260	(b) (6)		
	(b) (6)	Honoraria	\$29,300	(b) (6)	\$29,300	(b) (6)
	(b) (6)	Honoraria	\$96,700	(b) (6)	\$96,700	(b) (6)
	(b) (6)	Advisory Board	\$9,323	(b) (6)	\$38,416	(b) (6)
	(b) (6)	Steering Committee	\$14,233	(b) (6)		
	(b) (6)	Honoraria	\$14,860	(b) (6)		
	(b) (6)	Advisory Board	\$33,000	(b) (6)	\$223,335	(b) (6)
	(b) (6)		\$6,300	(b) (6)		
	(b) (6)		\$20,700	(b) (6)		
	(b) (6)	Honoraria	\$163,335	(b) (6)		

Source: NDA submission, Module 1.3.4

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

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Site no.	Investigator	Disclosable financial Interests			Total Amount received USD	Number of patients randomized to site
		Explanation	Amount USD	Date		
(b) (6)	(b) (6)	Honorarium	63,165	(b) (6)	63,165	(b) (6)
		Donation to (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		458	
		Honorarium	458			
		Donation to	49,385		49,385	

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

*** Site (b) (6) and (b) (6) – 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

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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 (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

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(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

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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 dispensing 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

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

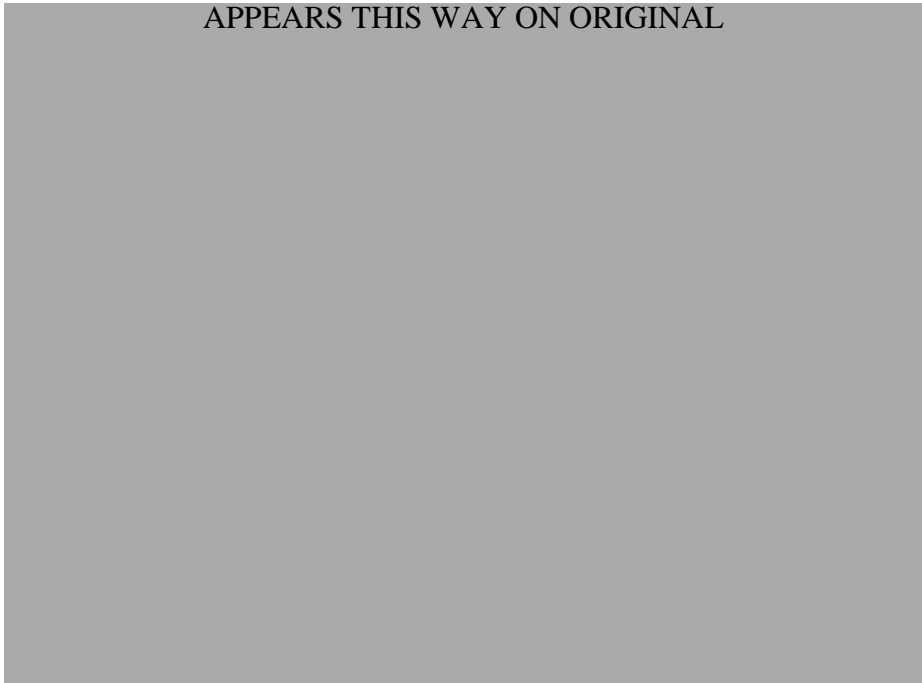
For all PDs concerning informed consent, the site personnel were retrained and missing or incorrect informed consent forms were corrected.

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.



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

Demographic Parameters	Treatment Group			
	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.

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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/m².

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.

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

Diabetes Characteristics	Treatment Group			
	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/m²), 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.

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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 Industry⁶, 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.

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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.*

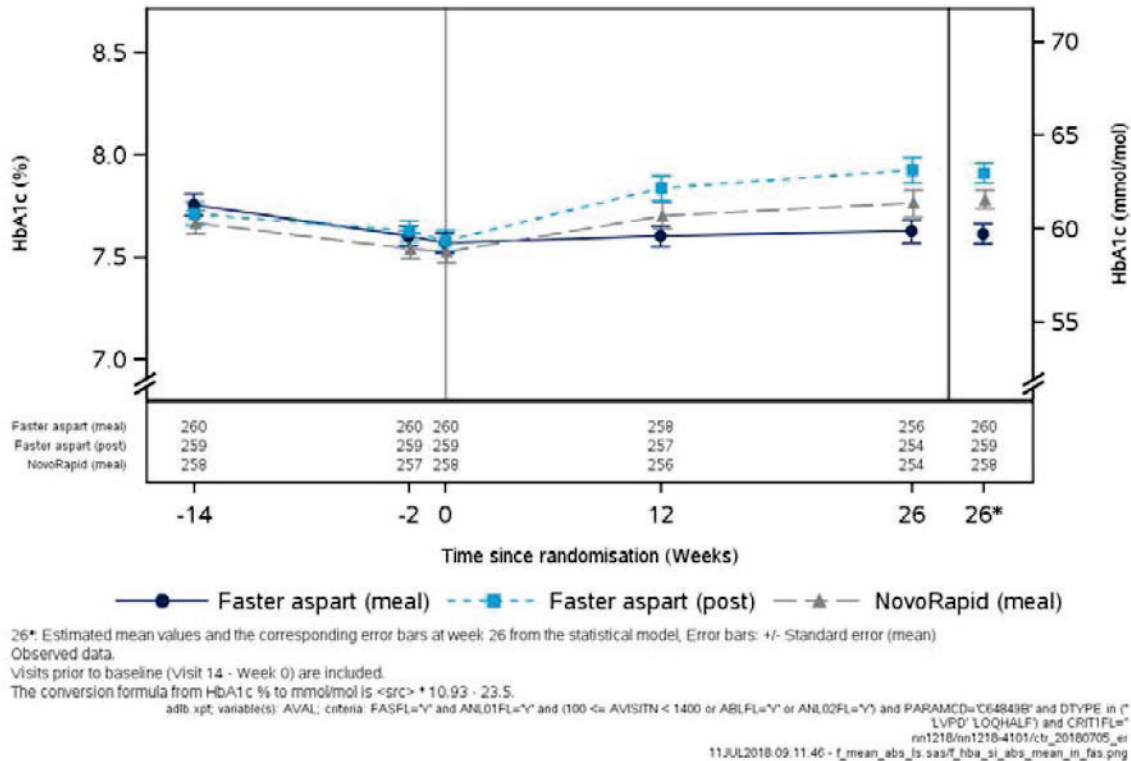
In addition, the superiority of meal-time Fiasp compared to meal-time NovoLog was confirmed as the upper bound of 95% CI was <0.

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 conducted tipping point analyses, which supported the conclusion of the primary analysis (see Table 11-4; not shown here).

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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.

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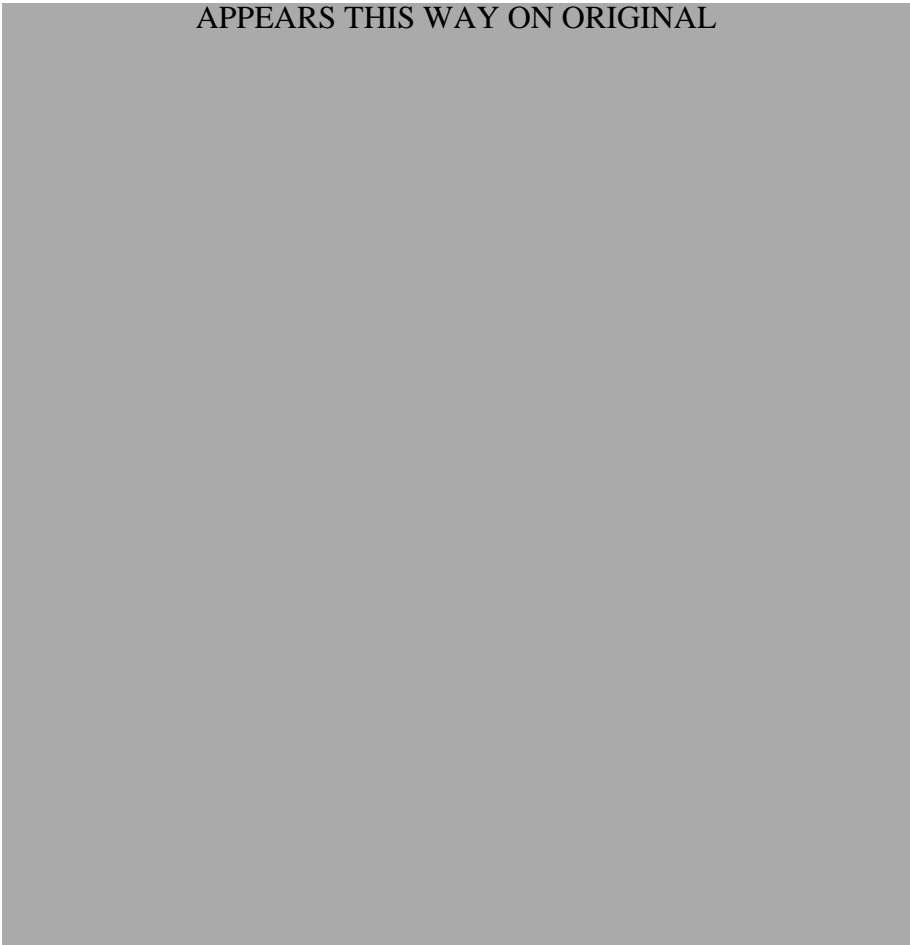
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Overall, study 4101 showed that the meal-time Fiasp and post-meal Fiasp was not inferior to NovoLog in glycemic control when used as bolus insulin in pediatric subjects with T1DM.

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.

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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.

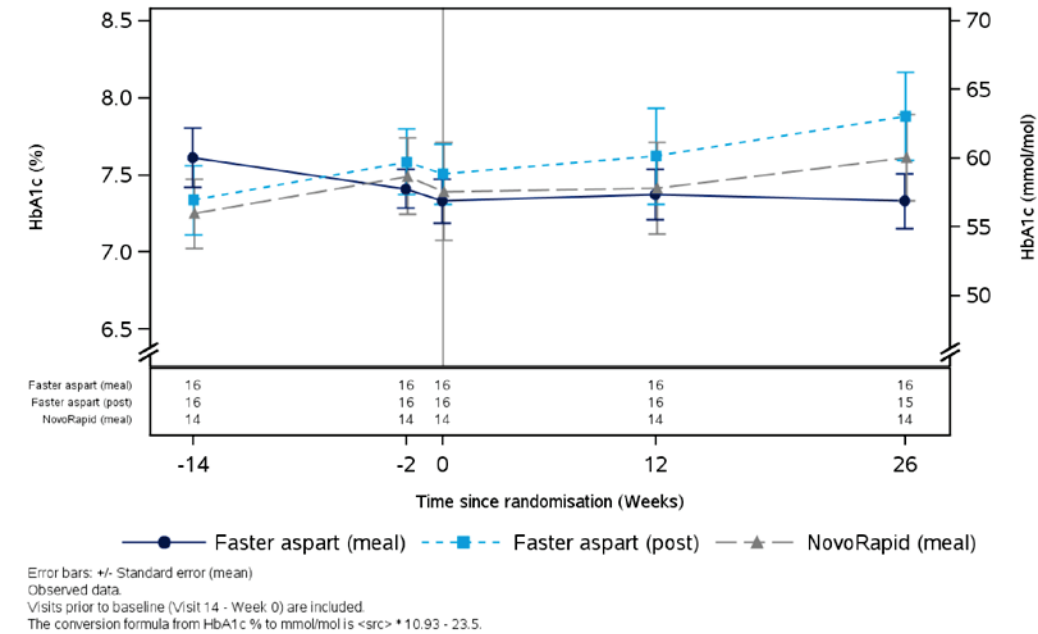
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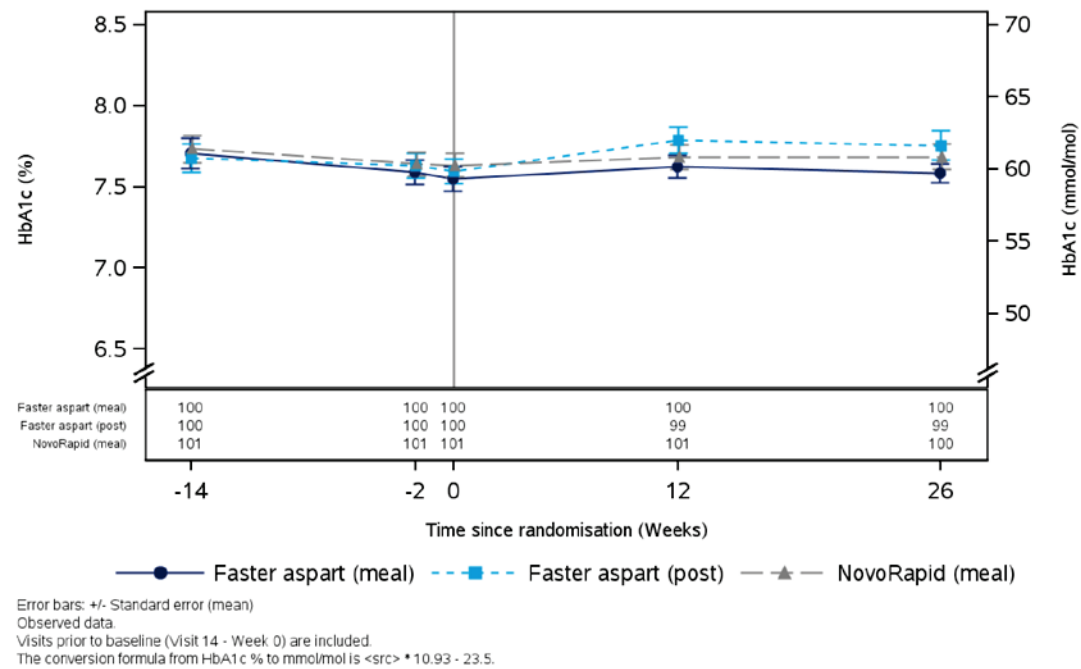
Fiasp (insulin aspart)

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



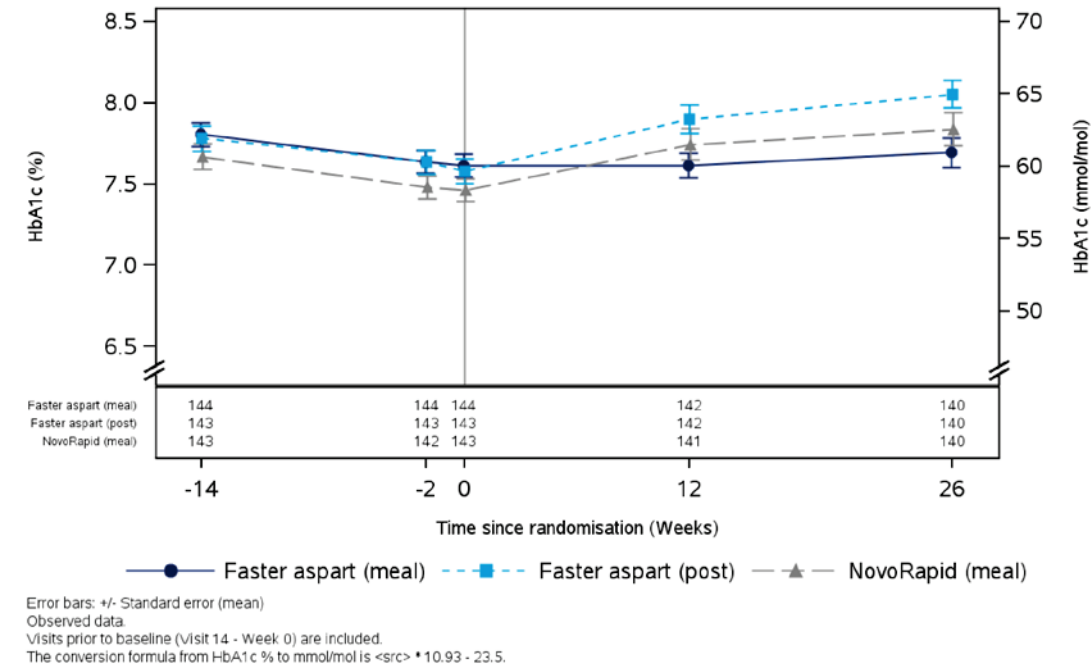
Source: CSR 4101, Figure 14.2.123

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



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.

Proportion of subjects reaching HbA1c target:

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.

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Fiasp (insulin aspart)

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)
<i>Change from baseline</i>	<i>-2.3%</i>	<i>-11.9%</i>	<i>-10.5%</i>
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

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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.

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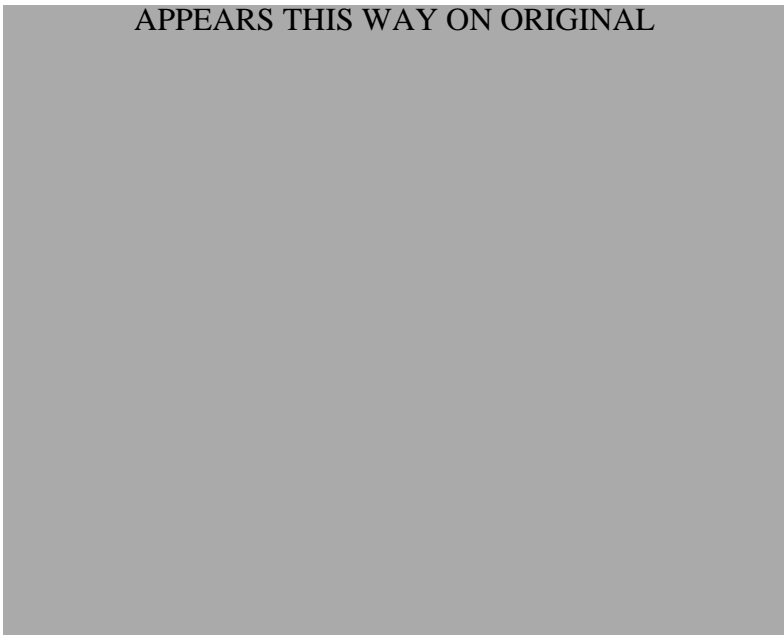


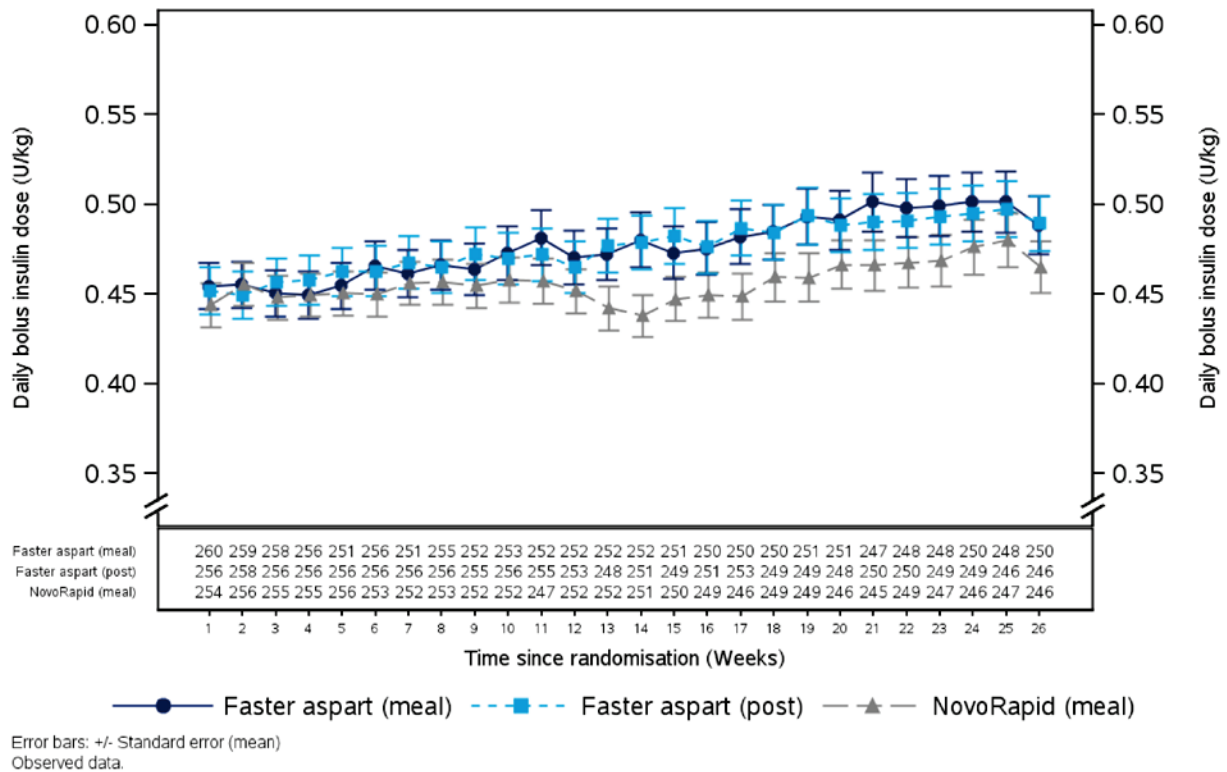
Table 11: Change in Mean Daily Basal, Bolus, and Total Insulin Dose (SAS)

	Meal-time Fiasp (N=261)		Post-meal Fiasp (N=258)		NovoLog (N=258)	
	U	U/kg	U	U/kg	U	U/kg
Basal insulin dose						
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
<i>Change from baseline to last on-treatment</i>	<i>2.3</i>	<i>0.03</i>	<i>2.3</i>	<i>0.03</i>	<i>2.2</i>	<i>0.03</i>
Bolus insulin dose						
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
<i>Change from baseline to last on-treatment</i>	<i>2.4</i>	<i>0.03</i>	<i>2.4</i>	<i>0.04</i>	<i>2.0</i>	<i>0.02</i>
Total insulin dose						
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
<i>Change from baseline to last on-treatment</i>	<i>4.6</i>	<i>0.07</i>	<i>4.8</i>	<i>0.07</i>	<i>4.2</i>	<i>0.05</i>
Mean Daily Bolus Insulin Dose at Meals and Other						
Breakfast						
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
<i>Change from Week 1 to last on-treatment</i>	<i>0.8</i>	<i>0.01</i>	<i>0.6</i>	<i>0.01</i>	<i>0.4</i>	<i>0</i>
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
<i>Change from Week 1 to last on-treatment</i>	<i>1.2</i>	<i>0.02</i>	<i>1.4</i>	<i>0.02</i>	<i>1.1</i>	<i>0.02</i>
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
<i>Change from Week 1 to last on-treatment</i>	<i>0.7</i>	<i>0</i>	<i>0.6</i>	<i>0.01</i>	<i>0.4</i>	<i>0</i>
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
<i>Change from Week 1 to last on-treatment</i>	<i>0.1</i>	<i>0</i>	<i>0.4</i>	<i>0.01</i>	<i>0.1</i>	<i>0</i>

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



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

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with data quality.

Efficacy Results – Secondary and other relevant endpoints

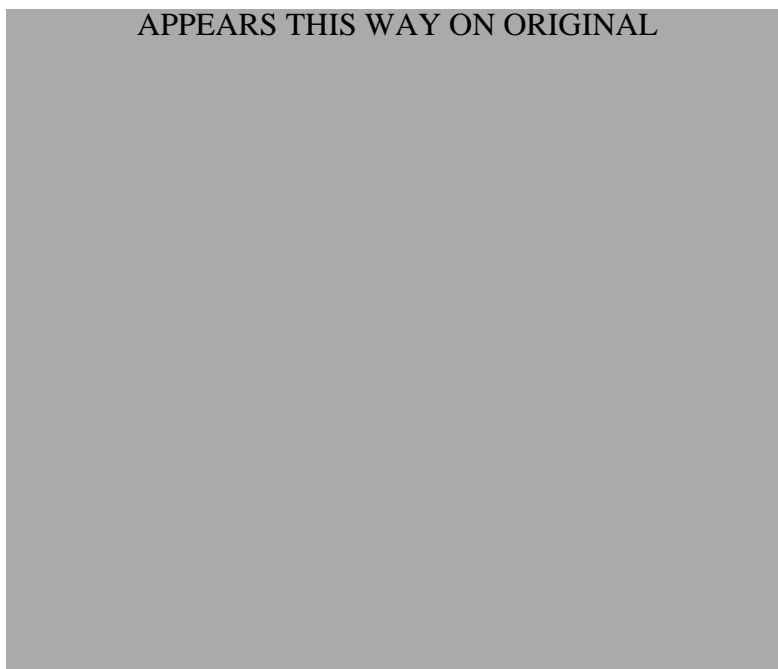
Other supportive secondary efficacy endpoints such as change from baseline in 8-point SMPG profiles and change from baseline in FPG are discussed here.

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-point 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).



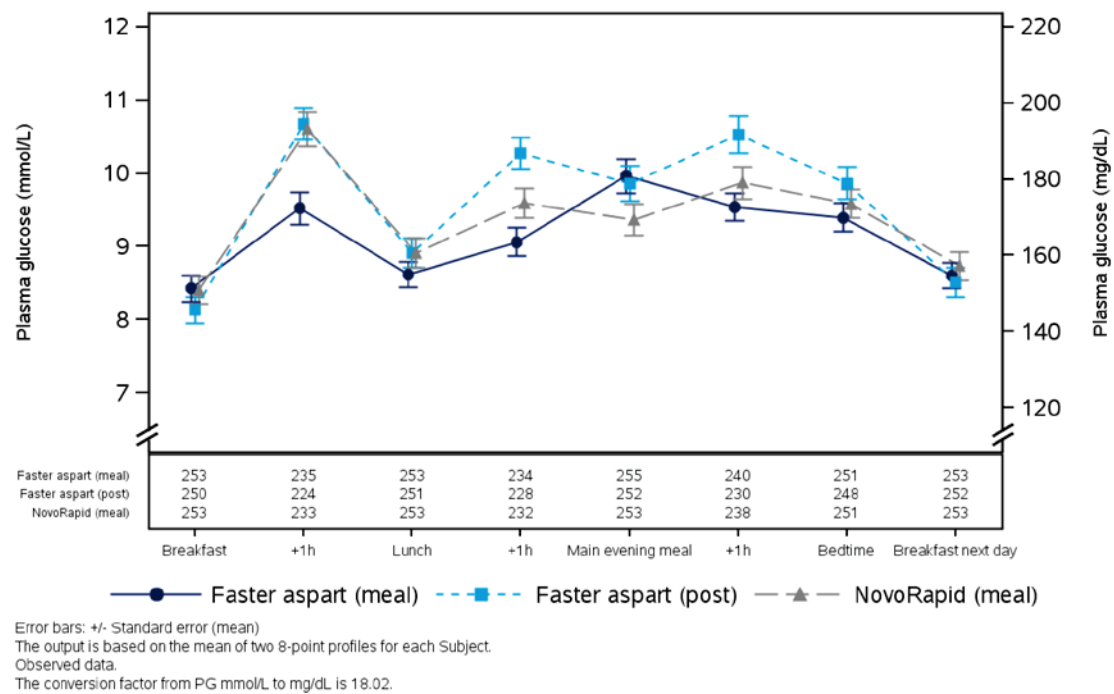
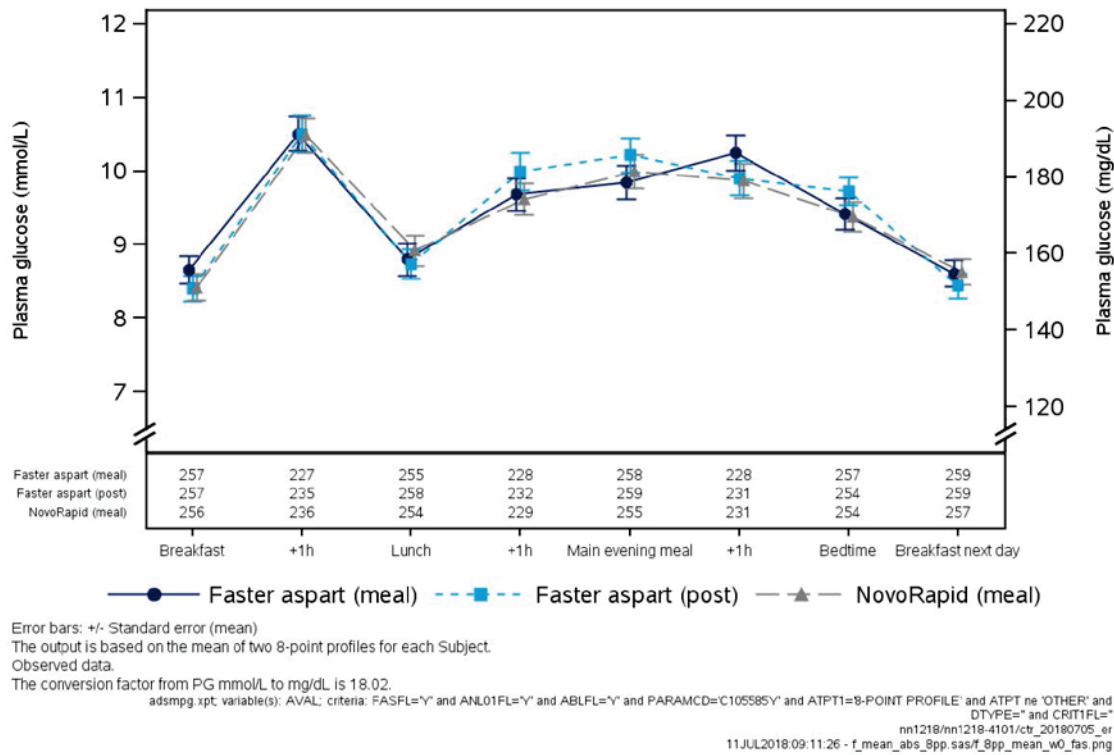
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Figure 9: Trial 4101 – Mean Plot of 8-point Self Measured Plasma Glucose Profile at Baseline (Top) and Week 26 (Bottom) - FAS



Source: CSR 4101, Figure 11-4

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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).

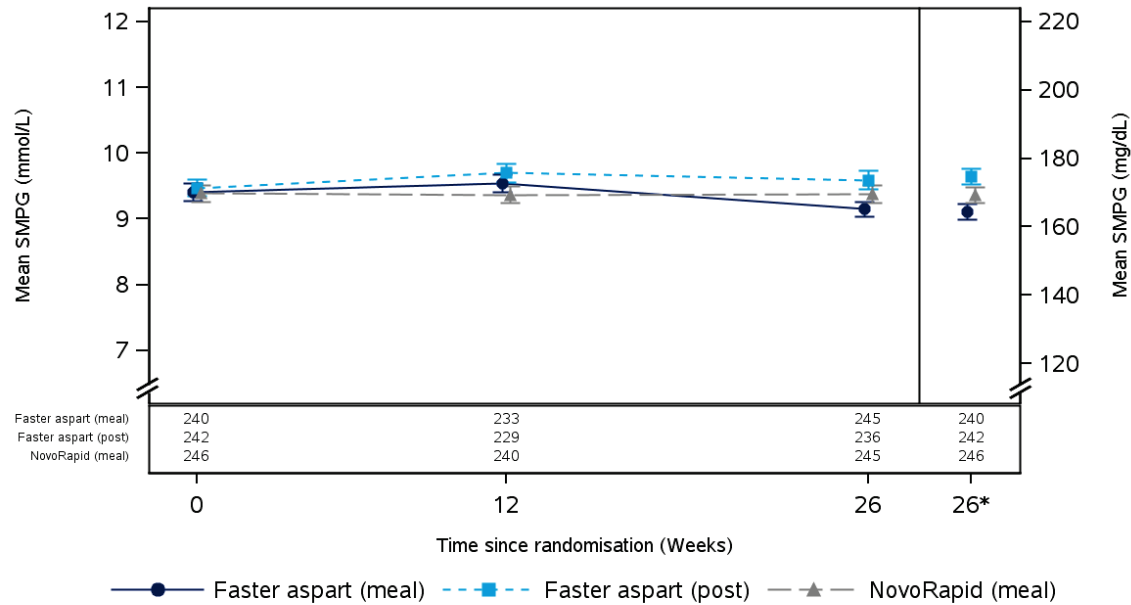
Table 12: Mean of 8-point SMPG Profiles (mg/dL; FAS)

	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)

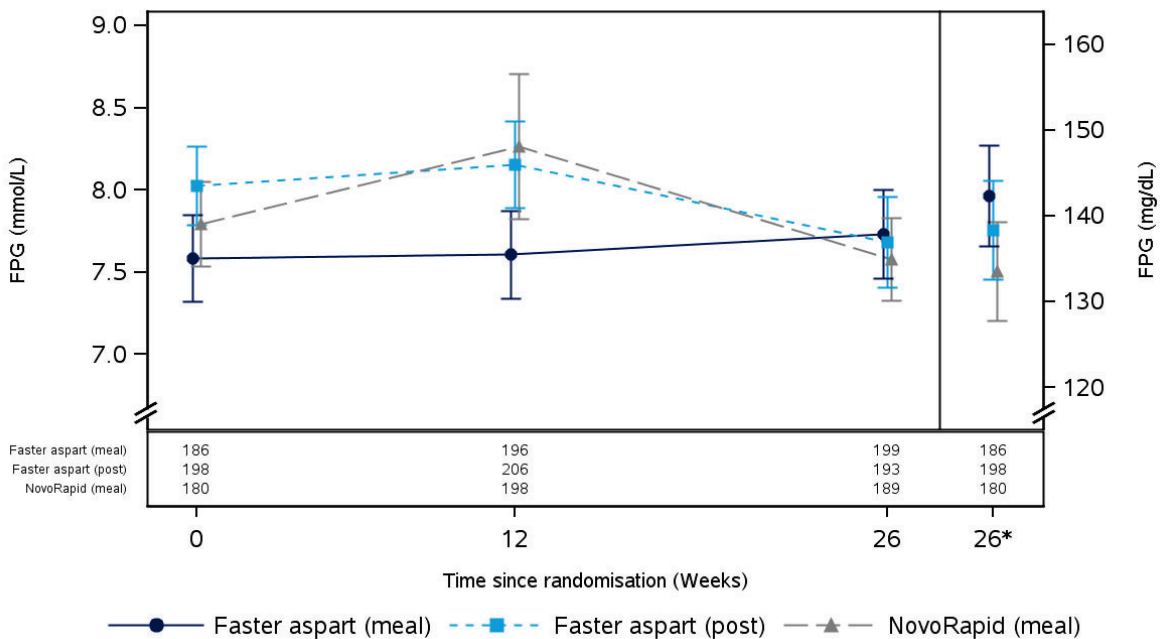
	Mealtime Fiasp (N=260)	Postmeal Fiasp (N=259)	NovoLog (N=258)
Mean at baseline	136.67	144.61	140.43
At Week 26	143.53	139.76	135.28
Change from baseline at Week 26	2.87	-0.90	-5.37
Treatment Diff vs NovoLog (95% CI)	8.25 (-6.86, 23.35)	4.48 (-10.47, 19.43)	

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=""
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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.

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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

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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: -

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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).

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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

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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

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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 definition⁸ of severe hypoglycemia, Novo Nordisk classification of hypoglycemia, and the ADA classification⁹ 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.

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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

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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)

¹The 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 Medicines 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).

²Only 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).

³Only 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 was 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.

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

	Meal-time Fiasp			Post-meal Fiasp			Meal-time NovoLog		
	261			258			258		
Total subjects	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		
Idiopathic 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

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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.

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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.

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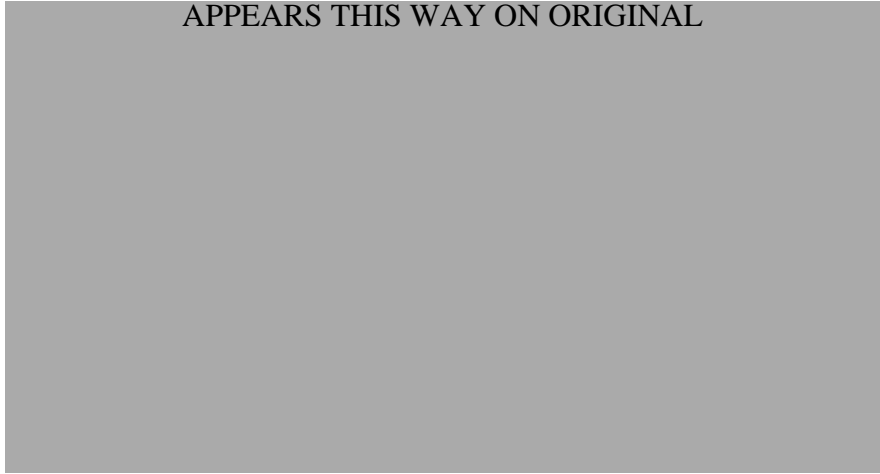


Table 17: Treatment-Emergent Hypoglycemic Episodes by Classification (SAS)

	Faster aspart (meal)				Faster aspart (post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	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*

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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.

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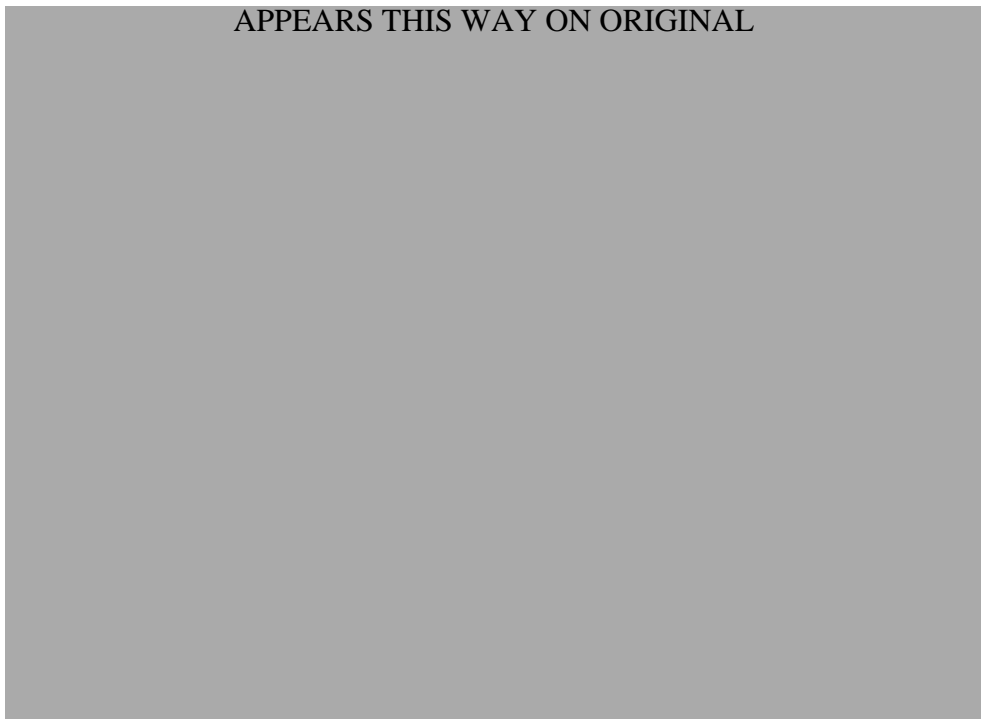


Table 18: Summary of BG Confirmed, Severe or BG Confirmed, and Severe Hypoglycemia (SAS)

	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 Fiasp 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]).

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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.*

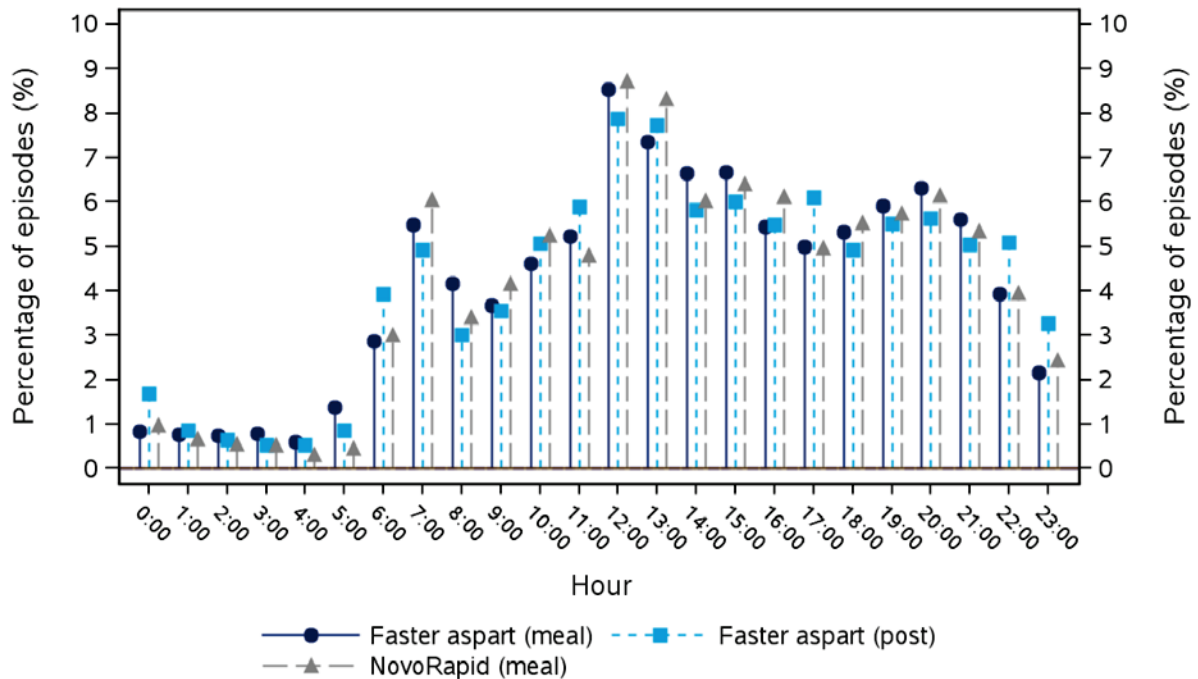
This observed imbalance in BG confirmed hypoglycemia including nocturnal hypoglycemia with Fiasp can be described in the Hypoglycemia under Adverse Reactions section 6 and Pediatric Use section 8.4, with recommendation to more closely monitor blood glucose levels in pediatric patients with Fiasp.

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

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

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



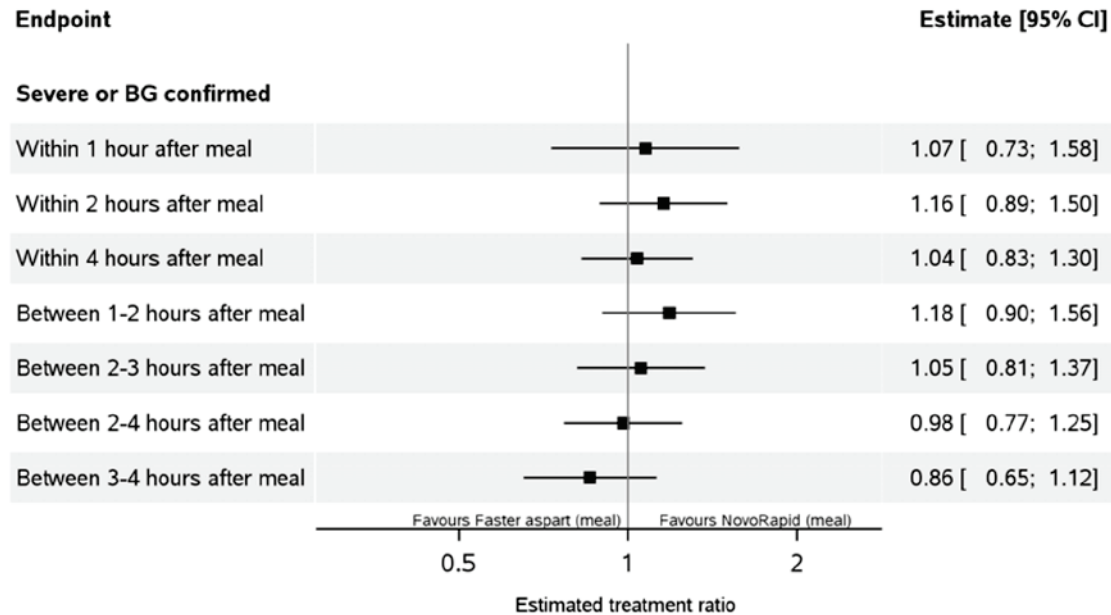
Hour x:00 [x:00; x:59].
 Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
 Episodes with missing time stamps are excluded.
 Source: CSR 4101, Figure 12-3

Severe or BG confirmed hypoglycemia related to a meal:

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.

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



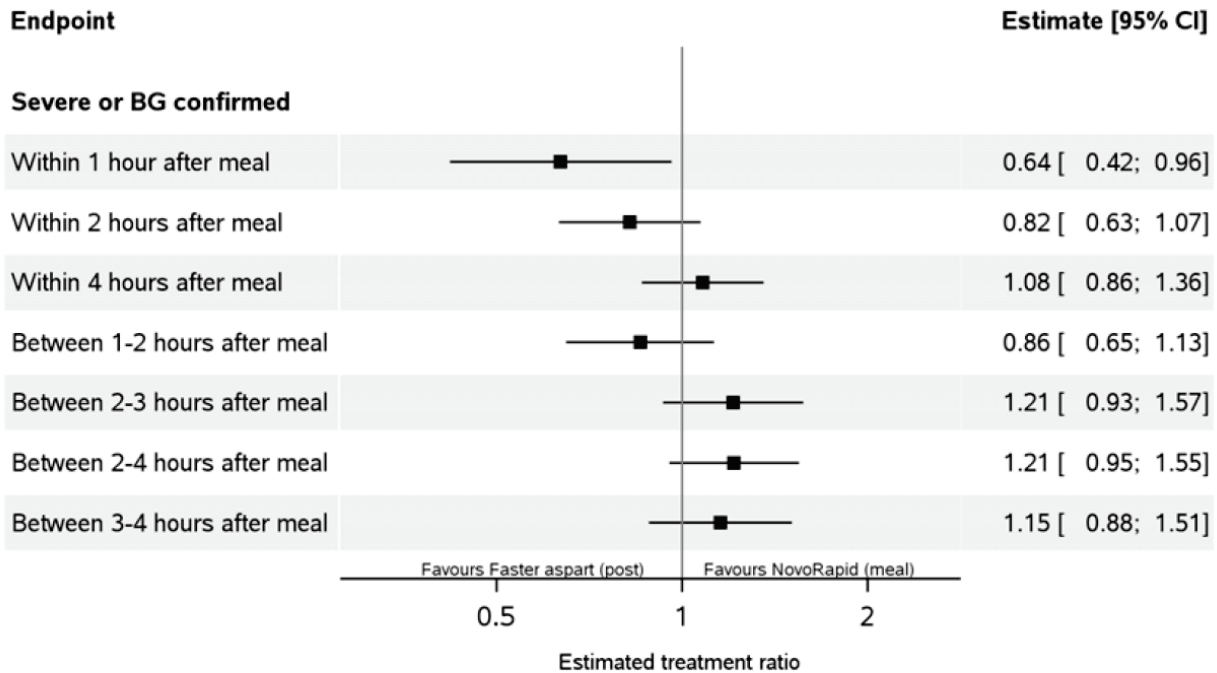
BG: Blood glucose, CI: Confidence interval
 Estimate: Estimated treatment ratio.

na.xpt; variable(s): NA; criteria:

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

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‘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).

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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

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other treatment groups. Of these, 25 events were reported by 5 subjects enrolled at one site (b) (6) 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 hematoma	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 form.

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

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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

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(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

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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 1-4¹⁰ 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.

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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

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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

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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 safely 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 incidence 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.

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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.

I’ve also made labeling recommendations throughout the document.

10.2. Nonprescription Drug Labeling

Not applicable.

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Fiasp (insulin aspart)

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: <u>579</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>24</u>		
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		

Clinical Review

Hyon Kwon, PharmD, MPH

sNDA 208751/S-010 and S-011

Fiasp (insulin aspart)

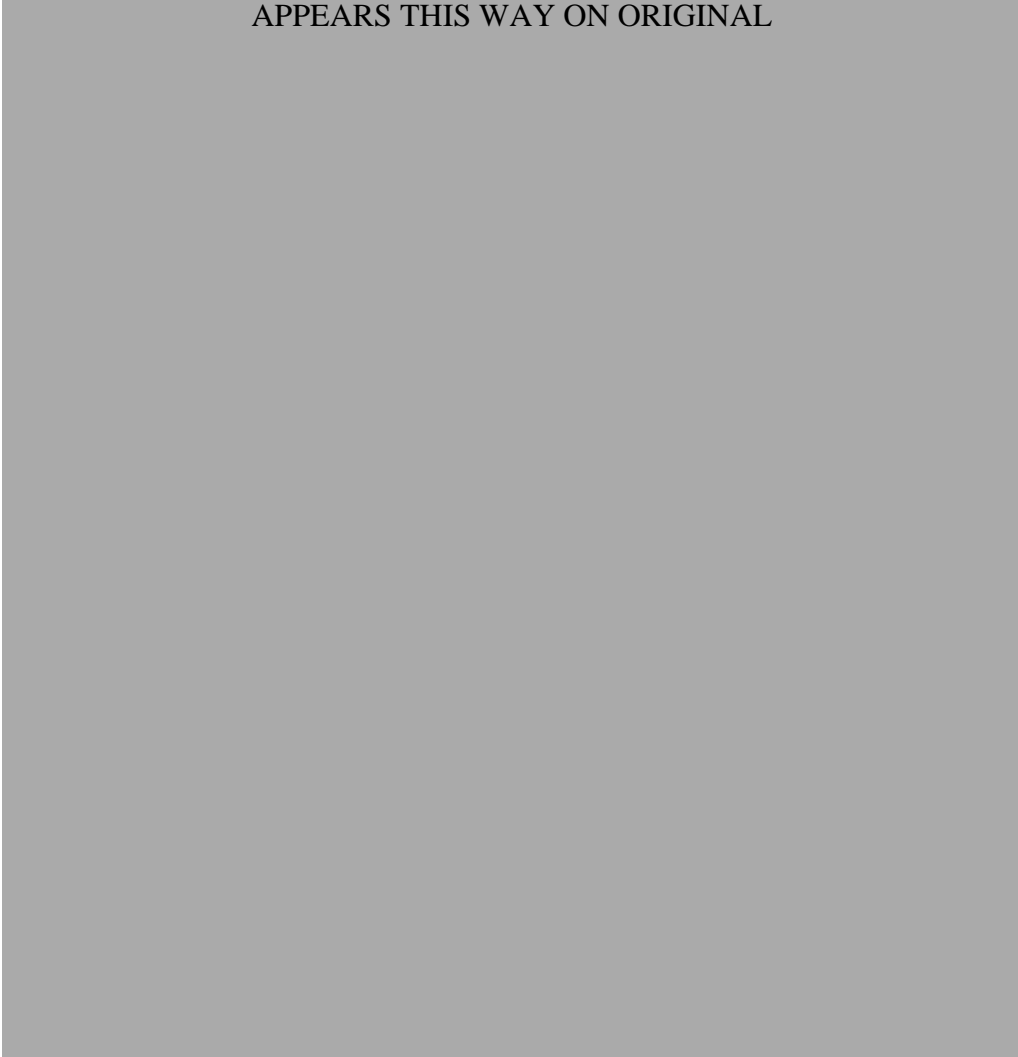
influenced by the outcome of the study: <u>0</u>		
Significant payments of other sorts: <u>17</u>		
Proprietary interest in the product tested held by investigator: <u>0</u>		
Significant equity interest held by investigator: <u>0</u>		
Sponsor of covered study: <u>0</u>		
Is an attachment provided with 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)

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Clinical Review
Hyon Kwon, PharmD, MPH
sNDA 208751/S-010 and S-011
Fiasp (insulin aspart)

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PATRICK ARCHDEACON
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208751Orig1s011

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #: 208751

Supplement #: S-10 and S-11

Drug Name: FIASP (insulin aspart injection)

Indication(s): Pediatric patients with diabetes mellitus

Applicant: Novo Nordisk

Date(s): Submission Date: February 27, 2019
Primary Review Due Date: November 12, 2019
PDUFA Goal Date: December 21, 2019

Review Priority: Standard

Biometrics Division: DB2

Statistical Reviewer: Jennifer Clark, PhD

Concurring Reviewers: Yun Wang (Team Lead), PhD
Mark Rothmann (Division Director), PhD

Medical Division: DMEP

Clinical Team: Hyon Kwon, M.D.

Project Manager: Callie CappelLynch

Keywords: Pediatric Study, non-inferiority

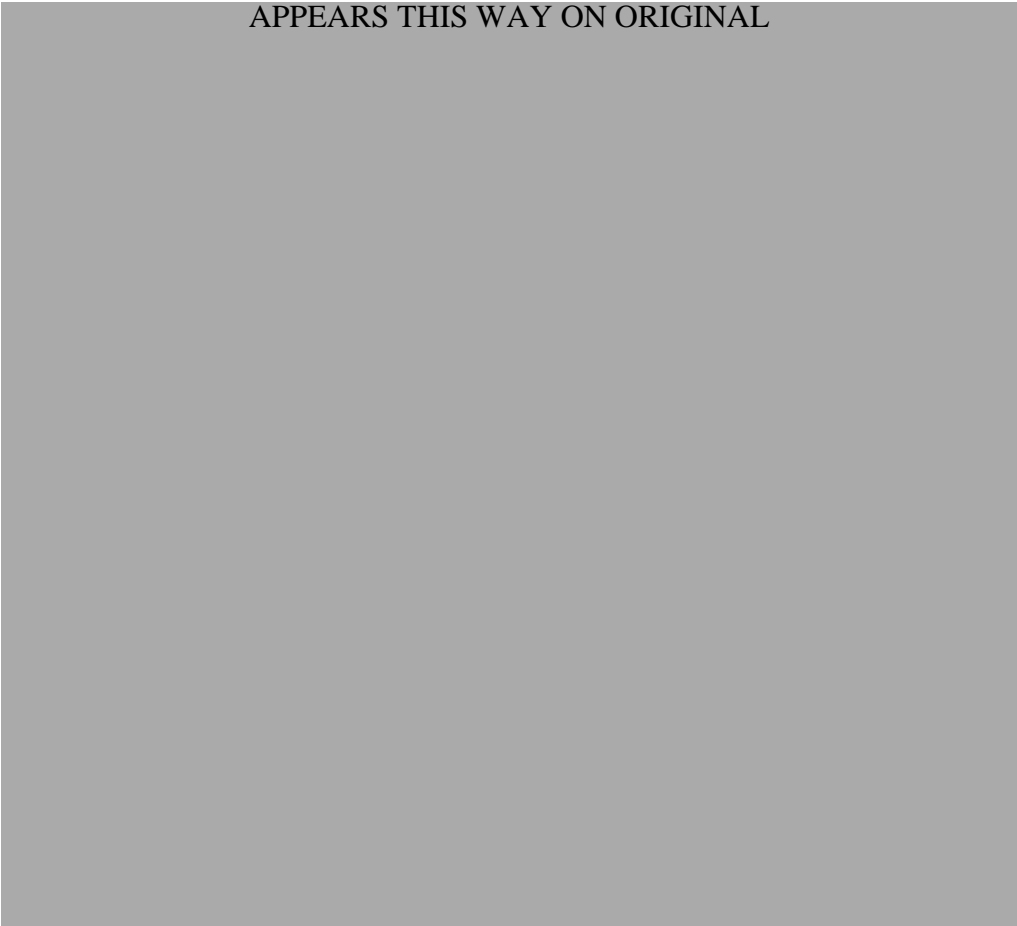
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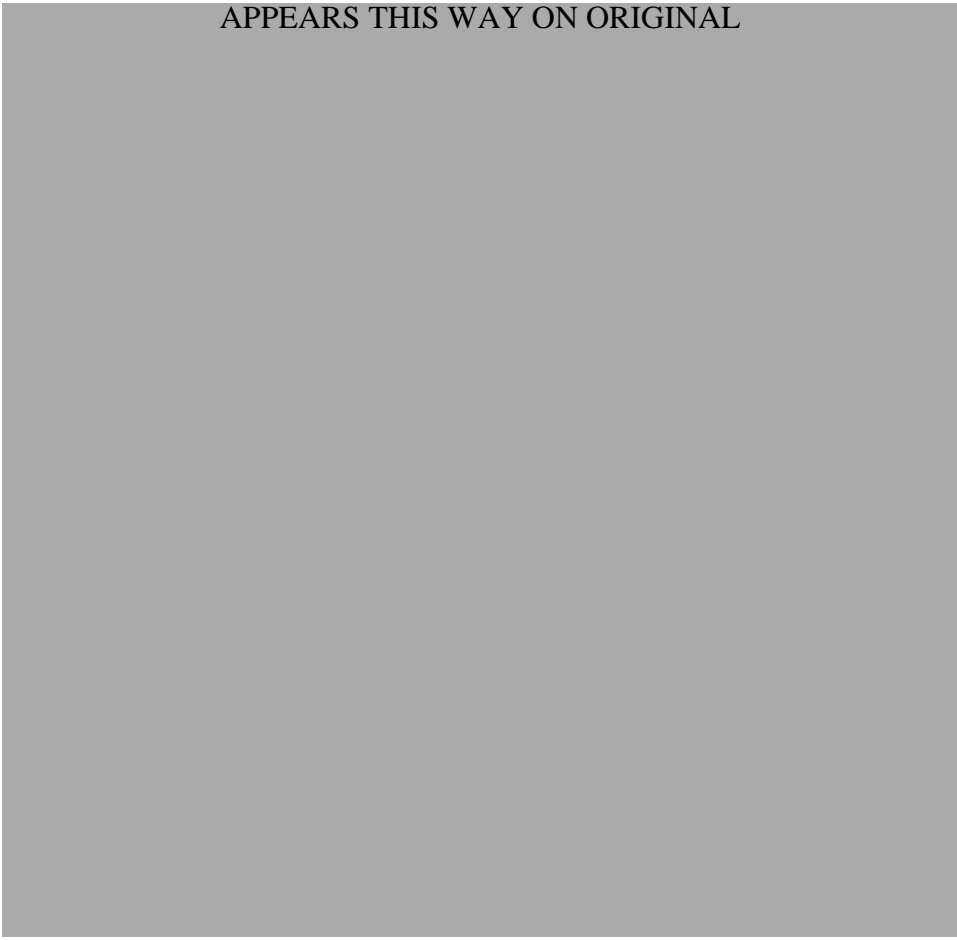
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EXECUTIVE SUMMARY

The current submission is a supplemental new drug application (sNDA, supplement 10) to support expanding an indication of faster aspart (FIASP) for improved glycemic control to children with diabetes mellitus. Data from a single pediatric study which was a post-marketing requirement required under the Pediatric Research Equity Act was included in the submission. A total of 777 pediatric patients, ages ranging from 2 to 17, with type 1 diabetes mellitus (T1DM) were randomized to either mealtime FIASP, post-meal FIASP, or a NovoLog/NovoRapid control. The study met all its prespecified primary and secondary objectives of demonstrating non-inferiority of both mealtime FIASP and post-meal FIASP to control arm with a non-inferiority margin of 0.4 and superiority of mealtime FIASP over the control arm in HbA1c.

	Mealtime FIASP	Post-meal FIASP	NovoLog/NovoRapid
N	260	259	258
Week 26 Change (Week 26 – Baseline)	0.06 (0.05)	0.35 (0.05)	0.22 (0.05)
Trt vs NovoLog (95% CI)	-0.17 (-0.3, -0.03)	0.13 (-0.01, 0.26)	.

In a separate supplement (supplement 11), the applicant requested results from this pediatric study along with results from an adult device study in different supplement (supplement 8) be used to extrapolate use of the device in the pediatric population without a separate pediatric device study.

Statistical Issues and Findings

Issues from this submission include:

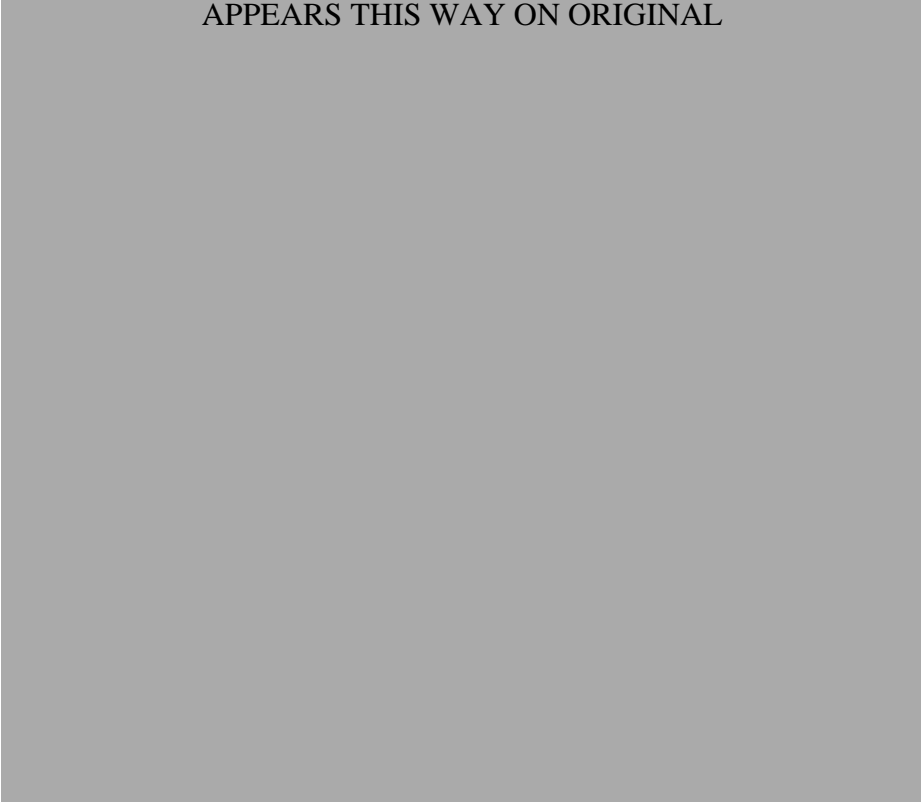
- Baseline measurements were taken after randomization for some patients (section 3.2.3)
- HbA1c increased from baseline at Week 26 (section 3.3.6)
- There was a slightly higher dosing of mealtime FIASP when compared to NovoLog/NovoRapid (Figure 10)
- Some patients experienced a much higher number of hypoglycemic events in the mealtime FIASP arm (Figure 12)
- There were some differences between the comparable adult and pediatric studies (section 3.3.8). Whether we can extrapolate results from this study and adult device study to support use of Fiasp in device for pediatric patients (Section 5.2)

Overall, the study did show a benefit in HbA1c for pediatric patients on mealtime FIASP when compared to NovoLog/NovoRapid. Most major issues were resolved upon further analysis with the benefit-risk assessment indicating that the large number of hypoglycemic events that a few patients experienced in the mealtime FIASP arm could outweigh the glycemic benefits they receive. This small group of patients may be better served with a different treatment (section 3.5). Patients in the NovoLog/NovoRapid arm, on average, had lower HbA1c at baseline which is likely why they also tended to have lower basal insulin doses throughout the study. It is possible that this could be due to unblinded randomization which would nullify any results seen in this study; however, it is more likely due to chance randomization. Generally, results from

this study do appear adequate to support expansion of labeling to include children in the indication.

The adult device study (Supplement 8) was reviewed by Dr. Kiya Hamilton. The Agency approved FIASP for use in insulin infusion pump for adults with Type 1 and 2 diabetes on October 22, 2019, based on this adult device study. There were some differences between the comparable adult and pediatric studies. However, results from this pediatric study do not preclude extrapolation of efficacy benefits in the device for the pediatric population, as long as the numeric treatment effect found in adults is not extrapolated to the pediatric population.

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1 INTRODUCTION

The applicant, Novo Nordisk, submitted supplement 10, a Prior Approval Efficacy Supplement (sNDA), on 21 February 2019 to support the use of faster insulin aspart (FIASP) in pediatric patients with diabetes mellitus. FIASP was originally approved to improve glycemic control in adults with diabetes mellitus on 29 September 2017. The submitted phase 3b confirmatory efficacy and safety trial in T1DM pediatric subjects (NN1218-4101) was required under the Pediatric Research Equity Act (PREA) and a Post-Marketing Requirement (PMR) study described in the original approval. The initial Pediatric Study Plan (iPSP) for study NN1218-4101, an efficacy and safety study of faster-acting insulin aspart compared to NovoLog both in combination with insulin degludec in children and adolescents with type 1 diabetes, was agreed on 28 August 2015. Proposed labeling changes for section 1 include (b) (4)

(b) (4) to the current indication (*italics have been added to the changes*) to become, (b) (4)

(b) (4) Additionally, study results are proposed to be added to sections 6 and 14 of the label. (b) (4)

Currently, the active comparator insulin aspart is a fast-acting insulin analogue which is marketed as NovoRapid (NovoLog in the US) and indicated for the treatment of diabetes and approved for children as young as 1. FIASP is insulin aspart in a different formulation which can lead to greater early glucose-lowering effects when compared to NovoLog. Currently, the pediatric program for FIASP consists of 2 clinical pharmacology trials and one therapeutic confirmatory trial in pediatric subjects with T1DM. Only the confirmatory trial will be considered in this statistical review.

The applicant also concurrently submitted supplement 11 for this same NDA. This submission is meant to extrapolate efficacy results from the adult pump trial in T1DM to pediatric T1DM based on study NN1218-3854, a Phase 3b pump study currently under review in the Agency, study NN1218-4349, a completed adult single dose pump PK/PD study, and Study NN1218-4101, the current study that is reviewed here. Considerations regarding extrapolation of the adult study to the pediatric population based on results from study 4101 and the comparable adult study 3852 for supplement 11 will be included in this review. Please see the review by Dr. Kiya Hamilton for further discussions regarding extrapolation using analyses from study 3854, the adult pump study.

2 Overview

Study 4101 was a therapeutic confirmatory, 26-week, multicenter, partly double-blind, randomized, active controlled, treat-to-target, 3-armed parallel trial to compare the efficacy and safety of faster aspart with NovoRapid/NovoLog, both in combination with insulin degludec, in children and adolescents ages 1 to <18 with T1DM. The overall aim of the trial was to confirm the treatment effect and compare safety of mealtime FIASP with mealtime NovoLog in a basal-bolus regimen. A post-meal dosing arm was also included to confirm that post-meal administration of FIASP could be effective in achieving glucose control and could therefore

offer a clinically acceptable treatment option. Due to the timing of when the dose was administered, this arm was not blinded while the other two meal-time arms were blinded.

Two other studies under this NDA which have been or are currently under review are included in Table 1. References will be made in this review to study 3852 for discussions regarding extrapolation and results from the completed statistical review by Dr. Alex Cambon; analysis results cited in the statistical review signed on 2 September 2016 are used here and no new analyses were performed. Any discussions regarding extrapolation for study 3854, currently under review by Dr. Hamilton, will be included in the completed statistical review for supplement 8 under this NDA.

Table 1: Studies Referenced in this Review

Study	Design*	Treatment Arms	Study Population	Endpoint/Analysis	Supp	Statistical Reviewer	Stamp Date
4101	MC, R, PDB, AC trial (26 wks)	Mealtime FIASP/ N=260 NovoLog/ N=259 Post-meal FIASP/ N=258	Children and adolescent (1-17 yrs) with T1DM	Primary Endpoint: Change in HbA1c from baseline to week 26	10 and 11	Clark	CUR*
3854	R, MC, DB, AC, treat-to-target, PG trial (26 wks)	FIASP / N=236 NovoLog / N=236	Adults with T1DM	Primary Endpoint: Change in HbA1c from baseline to week 16	8 and 11	Hamilton	CUR*
3852	R, DB, MC, AC trial (26 wks)	Mealtime FIASP/ N=381 NovoLog / N=380 Post-meal FIASP/ N=380	Adults with T1DM	Primary Endpoint: Change in HbA1c from baseline to week 26	Orig	Cambon	9/2/2016

*CUR: currently under review, MC: multi-center, R: randomized, PDB: partially double-blind, PG: parallel group, AC: active controlled, DB: double blind

2.1 History of the Submission

The original approval for FIASP included three safety and efficacy trials, one of which had an adult T1DM population (Trial 3852) and is similar to the current pediatric study. Table 6 includes results for this adult study as given in the current label. Although not explicitly stated in the label, looking at the statistical review of this study, it seems like these adult study results are taken from the pre-specified mixed model repeated measures (MMRM) analysis and not the statistical reviewer recommendation of using results from the sensitivity analysis. Methods used to derive study results should be included in the label in order to facilitate appropriate interpretation and comparability with results from similar treatments.

During the IND phase of the pediatric study, the applicant submitted the protocol and revisions three different times for which they received statistical comments for each submission. One comment which was sent for the protocol review dated 24 July 2015 requested that the applicant justify the proposed non-inferiority margin (NIM) of 0.4%. Previous studies for this product, including the adult studies, used the same NIM without appropriate justification; comments regarding this, including a request that they justify the margin, were included in the statistical review of the adult studies.

3 STATISTICAL EVALUATION

3.1 Data Sources

Material for this statistical review, including the data and clinical study report (CSR) were submitted electronically under the network path location [<\\CDSESUB1\evsprod\NDA208751\0072>](#). The information necessary for this review was contained in Module 1 (Cover Letters, Previous Meeting Minutes, Labeling) and Module 5 (Clinical Study Report, Protocol, Amendments, Statistical Analysis Plan, Data, and Data Dictionary). Independent coding for the statistical analyses and plots was run for this review.

3.2 Data and Analysis Quality

3.2.1 Filing Issues

The initial submission had incomplete datasets wherein analysis results could not be reproduced with the incomplete data. The poor quality of the initial data submission had the potential to lead to a refuse-to-file. However, the following IR was sent to the applicant on 3 April 2019 to have them fix the filing issues before the filing deadline:

There seems to be a problem with your “adlb.xpt” dataset for Trial 4101, all data starting on row 29741 appears to be missing or set to 0. Please resend this dataset, along with any others that may have this same affliction, with all the data ASAP. If a dataset is too big to be properly submitted within one data file, you may consider split it into several files. Failure to have all the relevant data for the study endpoints and label outcomes could result in us being unable to file this submission.

The applicant response sent on 5 April 2019, included corrections to 13 datasets for Trial 4101, as well as corrections to datasets in Trials 4371 and 4265, also presumably affected by this error. Corrections to the datasets before the filing deadline meant the submission could be filed from a statistical perspective.

3.2.2 Stratification Age Groups

There were 21 instances where the age variable did not match the calculated age at baseline. In fourteen of these cases, the differences change the stratification group for the patient. All fourteen cases had an analysis age of 11 (strata group 6-11) and descriptive age as 12 (strata

group would be 12-18). All analyses run by the applicant appear to use the calculated age. As calculated age is typically more reliable, this was used in the FDA analyses.

3.2.3 Baseline Measurements

One subject in the post-meal FIASP arm had HbA1c measurements taken two weeks before randomization and at randomization. The applicant used the two-week measurement (HbA1c = 7.8) for baseline, all FDA analyses used the randomization measurement (HbA1c = 8.1) for baseline. This difference does not numerically change any analysis results.

Some subjects did not have measurements at randomization, so baseline was set as the measurements taken at visits closest to randomization; these ranged anywhere from one to nineteen days after randomization. This could potentially lead to problems if there are many patients with baseline measurements taken post study treatment exposure; however, since everyone was exposed to NovoLog in the run-in phase, it may not impact results in this study. There were eight patients in the NovoLog arm, three in the mealtime FIASP arm, and none in the post-meal FIASP arm with HbA1c baseline measurements taken after randomization. These measurements were in line with other baseline measurements taken at randomization. Sensitivity analyses pertaining to this issue indicated that these subjects were not influential in changing the results for this study.

3.2.4 Visit Windows

Visits were supposed to occur within ± 3 days of the specified visit week. While most were within this range, there were some that were taken well beyond this window for the primary Week 26 visit. There were 14 subjects that were more than 2 weeks outside of the target day (± 2 weeks is approximately a 1-month window). Given that HbA1c tended to increase over time after randomization, it could be that these subjects may show bigger increases in HbA1c. Sensitivity analyses looking at the 14 subjects indicated that they were not highly influential on the treatment effect.

Table 2: Number of Days Outside Visit Target Day

	Within ± 3 Days	± 3 to 7 Days	± 7 to 14 Days	± 14 to 21 Days	± 21 Days or more
FIASP (meal)	196 (76.6%)	41 (16.0%)	15 (5.9%)	2 (0.8%)	2 (0.8%)
FIASP (post)	185 (72.8%)	51 (20.1%)	12 (4.7%)	3 (1.2%)	3 (1.2%)
NovoLog (meal)	202 (79.5%)	31 (12.2%)	17 (6.7%)	3 (1.2%)	1 (0.4%)

Source: Statistical reviewer's analysis

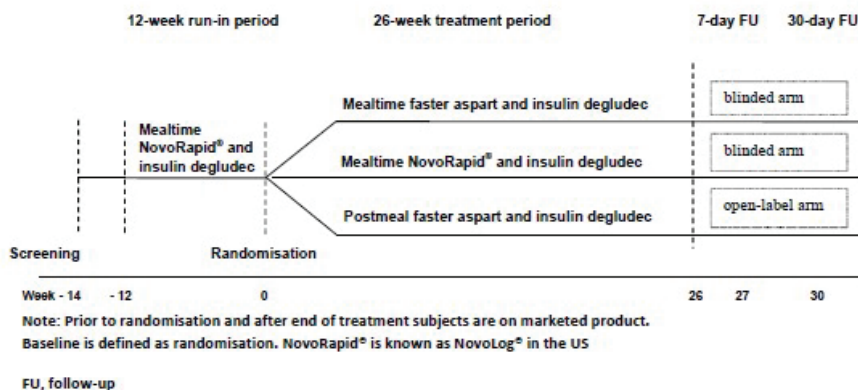
3.3 Evaluation of Efficacy

3.3.1 Study Design and Endpoints

Trial 4101 was a 26 week, randomized, partly double-blind, multicenter, multinational, active controlled, treat-to-target, 3-armed parallel-group trial with a 12-week run-in period. Treatment arms included mealtime FIASP, post-meal FIASP, and NovoLog in combination with insulin

degludec once daily in a basal-bolus regimen. The total trial duration was approximately 45 weeks with a 2-week screening period, 12-week run-in to optimize the insulin degludec dose, a 26-week treatment period, and a 7-day and 30-day follow-up period. Subjects were given NovoRapid/NovoLog during the run-in period and then switched to mealtime or post-meal FIASP or continued with NovoRapid/NovoLog in a 1:1:1 randomization. An applicant created schematic is shown in Figure 1 below. Both mealtime arms were blinded, and the post-meal arm was open-label due to the difference in timing for taking the study treatment.

Figure 1: Applicant Created Study Schematic



Source: CSR Page 55

During the 12-week run-in period, patients switched from their previous insulin treatment to insulin degludec once daily, titrated by investigators weekly to the fasting plasma glucose (FPG) pre-breakfast glycaemic target, and mealtime NovoLog. This period was focused on optimizing the basal insulin dose on a weekly basis to individual FPG targets. Much of change from week -12 to baseline, which tended to show an improvement in HbA1c (Figure 5), may be attributable to this. Patients with HbA1c at or below 9.5% who had shown ability and willingness to adhere to the trial protocol (investigator’s judgement) were randomized at week 0. This entry criteria ensures that most subjects will be more likely to adhere to the study treatment during the 26-week treatment period. Adjustment of the basal insulin dose could be made if needed after randomization, but the focus after randomization was on titrating the bolus insulin. All three arms used insulin degludec in combination with the randomized study treatment. Titration during each phase was conducted using a treat-to-target principle with the target varying depending on which part of the trial the subject was in. The run-in period titrated the basal insulin towards a pre-breakfast self-measured plasma glucose (SMPG) glyceimic target of 71-145 mg/dL. After randomization, bolus insulin had a pre-breakfast and pre-lunch target of 71-145 mg/dL, and a pre-dinner target of 120-180 mg/dL.

Mealtime dosing was defined as injecting 0-2 minutes before the meal; post-meal dosing was defined as injecting 20 minutes after the start of the meal. The study bolus insulin was administered for each of the 3 main meals (i.e., breakfast, lunch, and main evening meal) with additional bolus dosing allowed at the discretion of the investigator. Titration was based on the SMPG profiles recorded by the patients.

During the treatment period, adjustment of basal insulin dose was minimized, but could be adjusted if needed based on the investigator's discretion. The bolus insulin was titrated in a treat-to-target fashion to reach glycaemic pre-meal and bedtime targets. There was a high frequency of contacts in order to ensure optimal titration of FIASP and NovoLog.

Randomization was done 1:1:1 to each of the three arms after the 12-week run-in period. Randomization was stratified by age group based on the subject's age at randomization ($1 \leq \text{age} < 3$, $3 \leq \text{age} < 6$, $6 \leq \text{age} < 12$, $12 \leq \text{age} < 18$). Mealtime FIASP and NovoLog treatment groups were blinded, and the post-meal FIASP group was open-label due to the timing of the treatment administration.

3.3.2 Estimands

The primary estimand for this study was defined as the treatment difference between subjects randomized to FIASP and NovoRapid/NovoLog both in combination with insulin degludec assessed by change from baseline in HbA1c at week 26 of the study for all randomized subjects, regardless of treatment discontinuation or use of ancillary therapies. A secondary estimand was also defined for a hypothetical treatment effect assuming all subjects adhered to treatment.

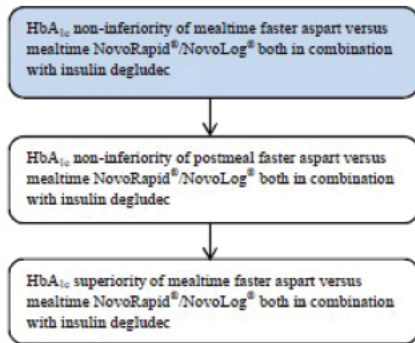
3.3.3 Statistical Methodologies

The applicant's pre-specified primary analysis used a multiple imputation (MI) regression with a missing at random (MAR) assumption for all patients missing Week 26 HbA1c measurements. The analysis was run for 100 imputed datasets using an ANCOVA model with baseline HbA1c, treatment, age strata, and region. The imputation regression used a model similar to the primary endpoint but also included week 12 HbA1c measurements within each treatment arm.

The MAR assumption with the MI analysis makes strong assumptions that those who are not followed-up at Week 26 have outcomes similar to those in the same treatment arm who are measured. Since HbA1c increased in each of the treatment arms after baseline, typically conservative sensitivity analyses such as return to baseline become anti-conservative. However, since missing data were minimal in this study (Table 4), it had little impact on their results. A sensitivity analysis applying a penalty equivalent to the NIM was run comparing mealtime FIASP to NovoLog.

Multiplicity for primary and secondary endpoints was controlled using a stepwise hierarchical testing procedure for the primary estimand. The primary non-inferiority hypothesis using a NIM of 0.4% was first in the sequence, followed by non-inferiority for post-meal FIASP vs. NovoLog, the last hypothesis in the hierarchy was for superiority of mealtime FIASP vs. NovoLog. Figure 2 shows an applicant created schematic of the hierarchy.

Figure 2: Applicant created schematic of the testing hierarchy



Source: Clinical Summary p.18

The sponsor provided a post-hoc rationale for the choice of the NIM in the study report. The sponsor cites an FDA guidance document for the NIM of 0.4%. The justification for this comes from a previous study in an adult T2DM population where the treatment effect of NovoLog vs. placebo is somewhere around -0.94% (-1.17, -0.72). The lower bound is typically used when looking to preserve treatment effect, using this lower bound of -0.72, we could expect a preserved treatment effect closer to -0.32 assuming that the T1DM treatment effect is similar to what is seen with the T2DM population.

3.3.4 Patient Disposition, Demographic and Baseline Characteristics

Baseline characteristics were generally well-balanced between the three treatment arms. Patients in Europe made up a majority of the study population, and nearly one quarter of the population from North America.

Table 3: Demographics and Baseline Characteristics

Characteristic	Category	Faster aspart (meal) N=260	Faster aspart (post) N=259	NovoLog(meal) N=258
Age	N	260	259	258
	Mean (SD)	11.7 (3.8)	11.7 (3.6)	11.7 (3.4)
	Median (Min, Max)	12.0 (2.0, 17.0)	12.0 (2.0, 17.0)	12.0 (4.0, 17.0)
Race	White	206 (79.2%)	217 (83.8%)	209 (81.0%)
	Asian	46 (17.7%)	37 (14.3%)	43 (16.7%)
	Black	6 (2.3%)	4 (1.5%)	5 (1.9%)
	Am Indian or Alaska	0 (0.0%)	1 (0.4%)	1 (0.4%)
	Other	2 (0.8%)	0 (0.0%)	0 (0.0%)
Ethnicity	Not Hispanic or Latino	244 (93.8%)	242 (93.4%)	246 (95.3%)

	Hispanic or Latino	16 (6.2%)	17 (6.6%)	12 (4.7%)
Sex	Male	134 (51.5%)	137 (52.9%)	148 (57.4%)
	Female	126 (48.5%)	122 (47.1%)	110 (42.6%)
Country	USA	67 (25.8%)	62 (23.9%)	66 (25.6%)
	Russia	32 (12.3%)	35 (13.5%)	37 (14.3%)
	Japan	24 (9.2%)	19 (7.3%)	23 (8.9%)
	Ukraine	20 (7.7%)	20 (7.7%)	20 (7.8%)
	India	22 (8.5%)	18 (6.9%)	19 (7.4%)
	Bulgaria	15 (5.8%)	15 (5.8%)	18 (7.0%)
	Czech Republic	6 (2.3%)	15 (5.8%)	15 (5.8%)
	Turkey	13 (5.0%)	15 (5.8%)	8 (3.1%)
	Israel	11 (4.2%)	9 (3.5%)	11 (4.3%)
	Italy	9 (3.5%)	10 (3.9%)	10 (3.9%)
	Poland	7 (2.7%)	9 (3.5%)	6 (2.3%)
	Serbia	5 (1.9%)	9 (3.5%)	6 (2.3%)
	Germany	8 (3.1%)	8 (3.1%)	2 (0.8%)
	Estonia	8 (3.1%)	5 (1.9%)	4 (1.6%)
	Latvia	6 (2.3%)	2 (0.8%)	5 (1.9%)
	Finland	5 (1.9%)	4 (1.5%)	4 (1.6%)
	Lithuania	2 (0.8%)	4 (1.5%)	4 (1.6%)
Region	Europe	147 (56.5%)	160 (61.8%)	150 (58.1%)
	North America	67 (25.8%)	62 (23.9%)	66 (25.6%)
	Asia (not Japan)	22 (8.5%)	18 (6.9%)	19 (7.4%)
	Japan	24 (9.2%)	19 (7.3%)	23 (8.9%)
HbA1c	N	260	259	258
	Mean (SD)	7.6 (0.8)	7.6 (0.8)	7.5 (0.8)
	Median (Min, Max)	7.6 (4.9, 10.0)	7.6 (5.6, 9.6)	7.5 (5.3, 10.6)
BMI	N	260	259	258
	Mean (SD)	19.7 (3.8)	19.7 (4.0)	19.6 (3.8)
	Median (Min, Max)	18.9 (11.8, 32.7)	18.5 (12.9, 33.5)	18.9 (12.9, 31.6)
Duration Diabetes	N	260	259	258
	Mean (SD)	4.5 (3.5)	4.4 (3.2)	4.3 (3.1)
	Median (Min, Max)	3.3 (0.5, 15.0)	3.8 (0.5, 15.3)	3.4 (0.5, 16.3)

Source: Statistical reviewer's analysis

Patient disposition, as done by the sponsor, was based on meeting certain milestone marker dates relative to the randomization date. Follow-up and treatment status, shown in Table 4, is based on when the actual week 26 visit occurred and whether the patient was on treatment at least 30 days before the primary week 26 measurement occurred.

Table 4: Treatment and HbA1c at Week 26 Status

	On Treatment	Off Treatment	Missing HbA1c
FIASP (meal)	252 (96.9%)	2 (0.8%)	6 (2.3%)
FIASP (post)	250 (96.5%)	1 (0.4%)	8 (3.1%)
NovoLog	253 (98.1%)	1 (0.4%)	4 (1.6%)

Source: Statistical reviewer's analysis

There are some differences between disposition and follow-up due to the differing criteria using dates relative to randomization vs. dates based on when the actual week 26 visit occurred.

Two patients which the applicant classified as completed the study on treatment had their week 26 HbA1c measurements taken more than 30 days after the target week 26 day, so these are considered missing in the table above but were classified by the sponsor as part of the week 26 assessment; data were not imputed in the applicant's primary analysis for these two patients. Both also had their last exposure to study treatment more than 30 days before their week 26 assessment.

One patient who completed the study on treatment did not have a week 26 HbA1c measurement, so they are also considered missing in the table even though they are also classified as someone who completed on treatment for disposition; imputation was used for this subject in the primary analysis.

Of the eighteen patients who are missing a week 26 measurement in Table 4, four had an end of study treatment date that was within 30 days of the week 26 goal date, so they could be considered missing on treatment. The MAR assumption for missing data would be more applicable for these patients than for the other patients missing a week 26 HbA1c measurement.

Two patients who were considered early discontinuers of both the study and study treatment were discontinued less than 30 days before the week 26 primary endpoint target day, so these measurements were still counted as part of the primary endpoint. Even though these patients are classified as prematurely discontinuing for the sponsor disposition, they are considered observed on treatment in Table 4; measurements for these subjects were used in the primary analysis and no imputation was done.

Three patients which are considered early discontinuers and missing for both sponsor disposition and Table 4 had measurements taken between 42 and 82 days before the week 26 primary endpoint which were used in the primary endpoint analysis. No imputation was used for these three subjects (all in post-meal FIASP) in the applicant's primary analysis. No imputation was run for the two subjects who had week 26 measurements taken more than 30 days after the week 26 target day (both in mealtime FIASP).

So, of the 18 patients considered missing in Table 4, 13 were imputed for the applicant’s primary endpoint analysis. A sensitivity analysis imputing for all 18 patients in Table 4 was run for the primary analysis.

3.3.5 Results and Conclusions

The study results using the same ANCOVA model as the sponsor with a MAR MI on the 13 subjects discussed in section 3.3.4 were the same as was described in the study report. Table 5 shows the average baseline HbA1c for each arm, which was similar, as well as model results for change from baseline in each arm and the treatment effect comparing both FIASP arms to NovoLog.

Table 5: HbA1c Results

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

Source: Statistical reviewer’s analysis

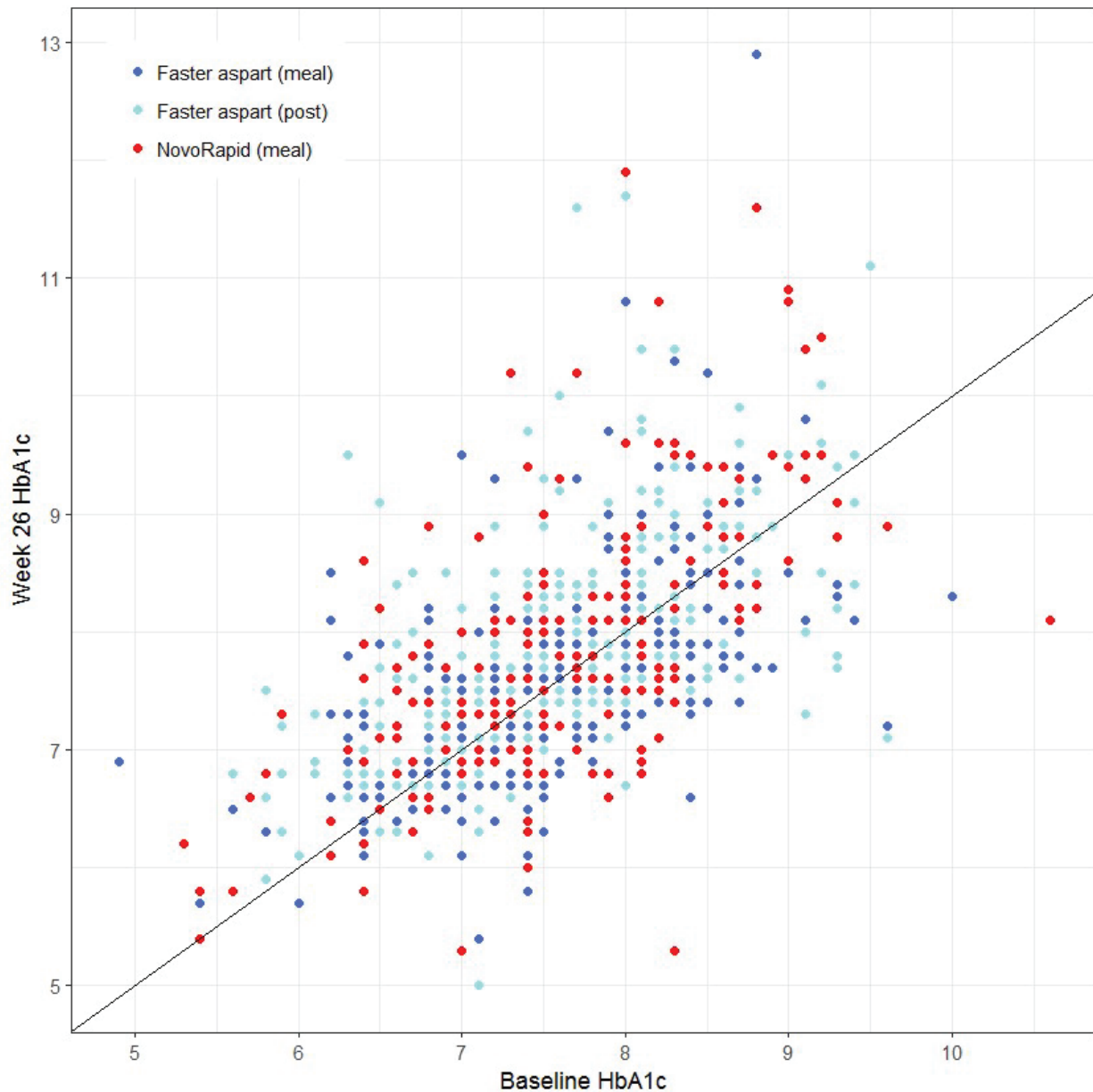
It is worth noting that change from baseline in all three treatment arms increased with higher HbA1c at week 26 than was seen at baseline. To better understand these results, further analyses were run looking at HbA1c and insulin doses over the run-in and treatment periods of the study.

Missing data were not an issue in the primary endpoint analysis. Sensitivity analysis results imputing for all 18 subjects specified in Table 4 did not change results seen in Table 5. More conservative sensitivity analyses applying a NIM penalty of 0.4% to the FIASP arms were also relatively robust with an overall treatment effect for mealtime FIASP vs. NovoLog of -0.16 (-0.3, -0.2) and post-meal FIASP vs. NovoLog as 0.14 (0.005, 0.27). Overall conclusions on non-inferiority and superiority remain the same, and nominal significance on whether post meal FIASP is worse than NovoLog remains something that should be investigated further if a unambiguous interpretation is needed.

3.3.6 HbA1c

The scatter plot below shows patients’ baseline HbA1c measurements plotted against their Week 26 measurements. The diagonal line shows where baseline measurements are equal to Week 26. Patients plotted above the line have HbA1c measurements that worsened at Week 26. There does seem to be slightly more patients with measurements showing a worse HbA1c at Week 26 when compared to baseline, although they are generally scattered around the line.

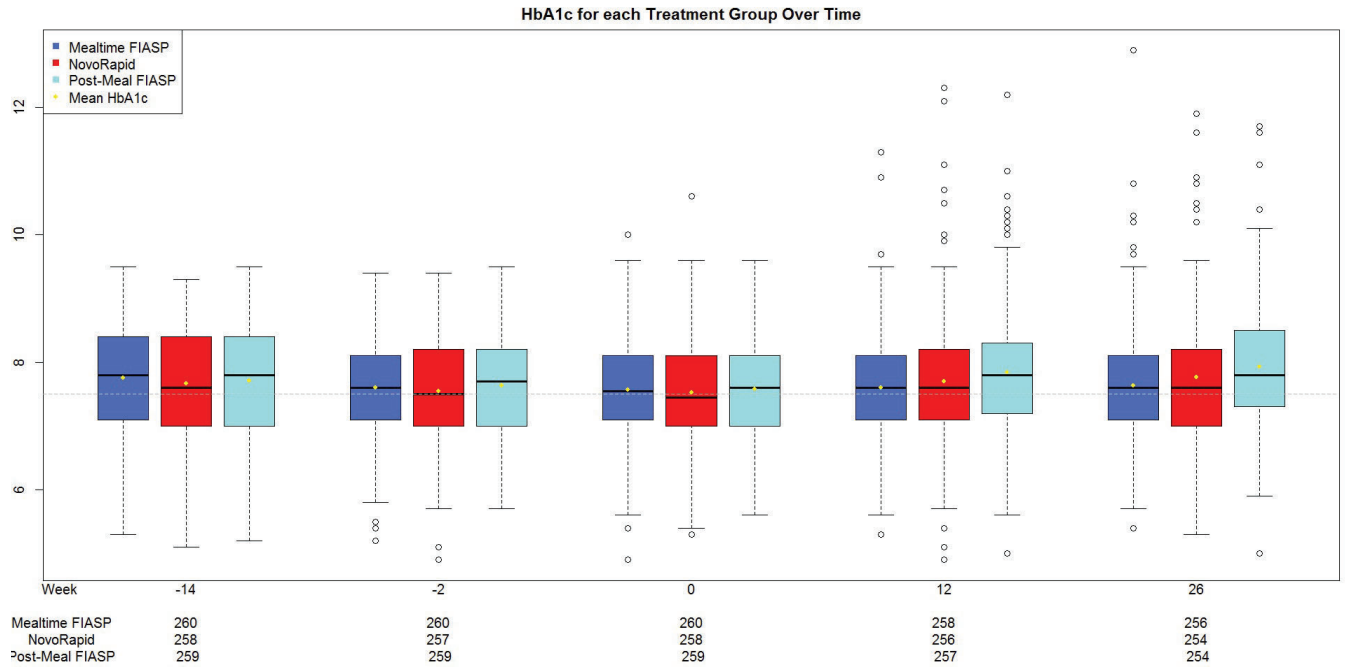
Figure 3: Baseline by Week 26 HbA1c



Source: Statistical reviewer's analysis

To better understand why these measurements are bigger after randomization we first examined the distribution of HbA1c measurements throughout the study periods. The boxplots in Figure 4 show HbA1c results for each treatment arm along with the average HbA1c and a line drawn at the target HbA1c of 7.5%. As we would expect, the distribution of HbA1c appears fairly comparable for all three arms up through baseline (week 0). Variability of HbA1c measurements seems to increase within each of the treatment arms after randomization with some increase in the mean for the post-meal FIASP and NovoLog arms. While the mealtime FIASP seems to have the least amount of increase, it also seems to have an increased variability seen in all three treatment arms.

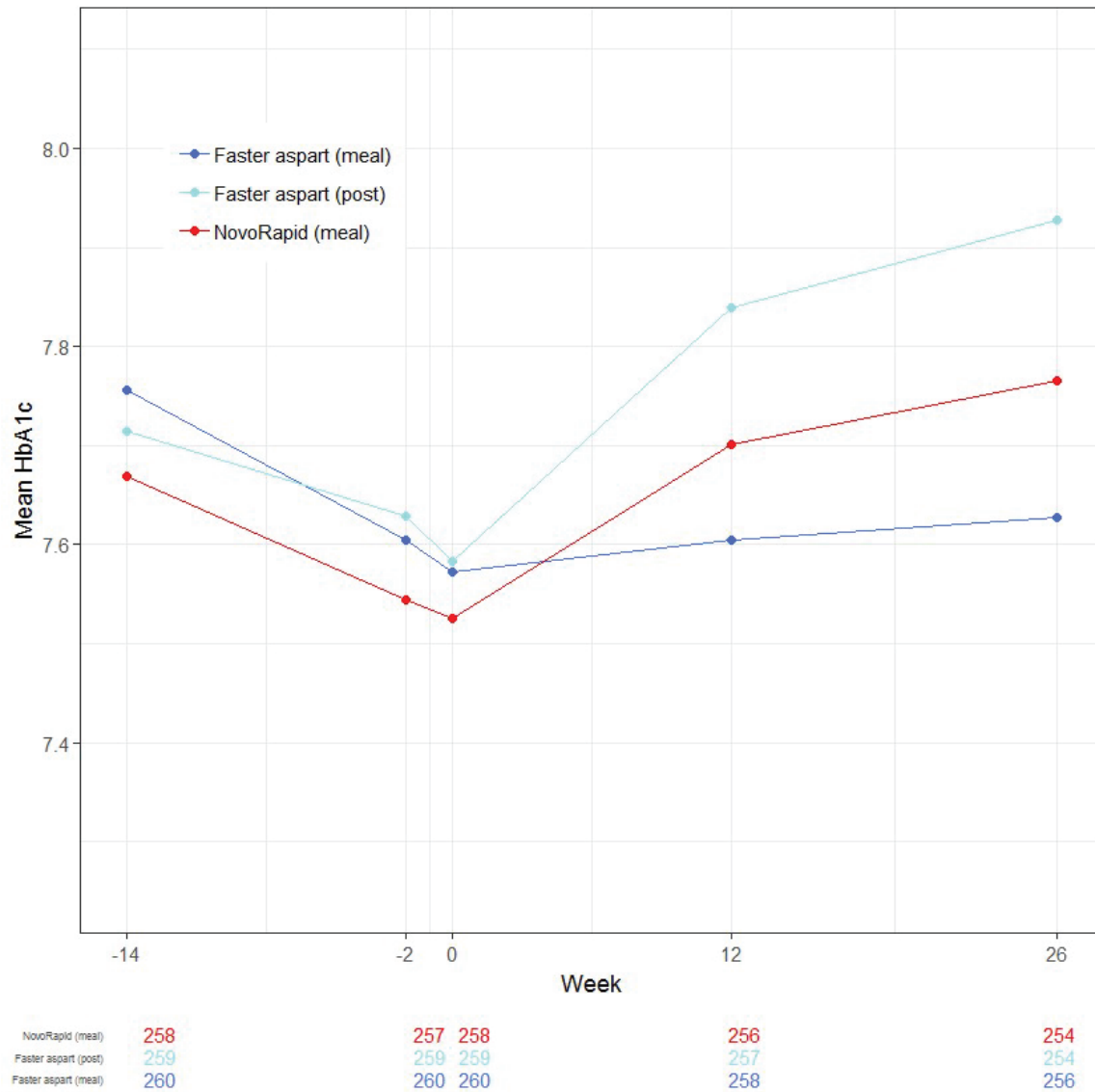
Figure 4: HbA1c over Time



Source: Statistical reviewer’s analysis

The trend of HbA1c over time can more easily be seen in Figure 5 with the mean HbA1c at each visit. HbA1c was lowest at randomization. Post-randomization mealtime FIASP had the least amount of increase while post-meal FIASP had the greatest increase. The increase in NovoLog is surprising as this was what was used during the run-in period for all patients up to randomization at Week 0. Such an increase from baseline was not seen in similar adult studies for T1DM and could be indicative of a lack in adherence to treatment in the juvenile population or a consequence of the different treatment targets. This issue appears to be an issue in all three treatment arms, so it is likely not due to any specific study treatment.

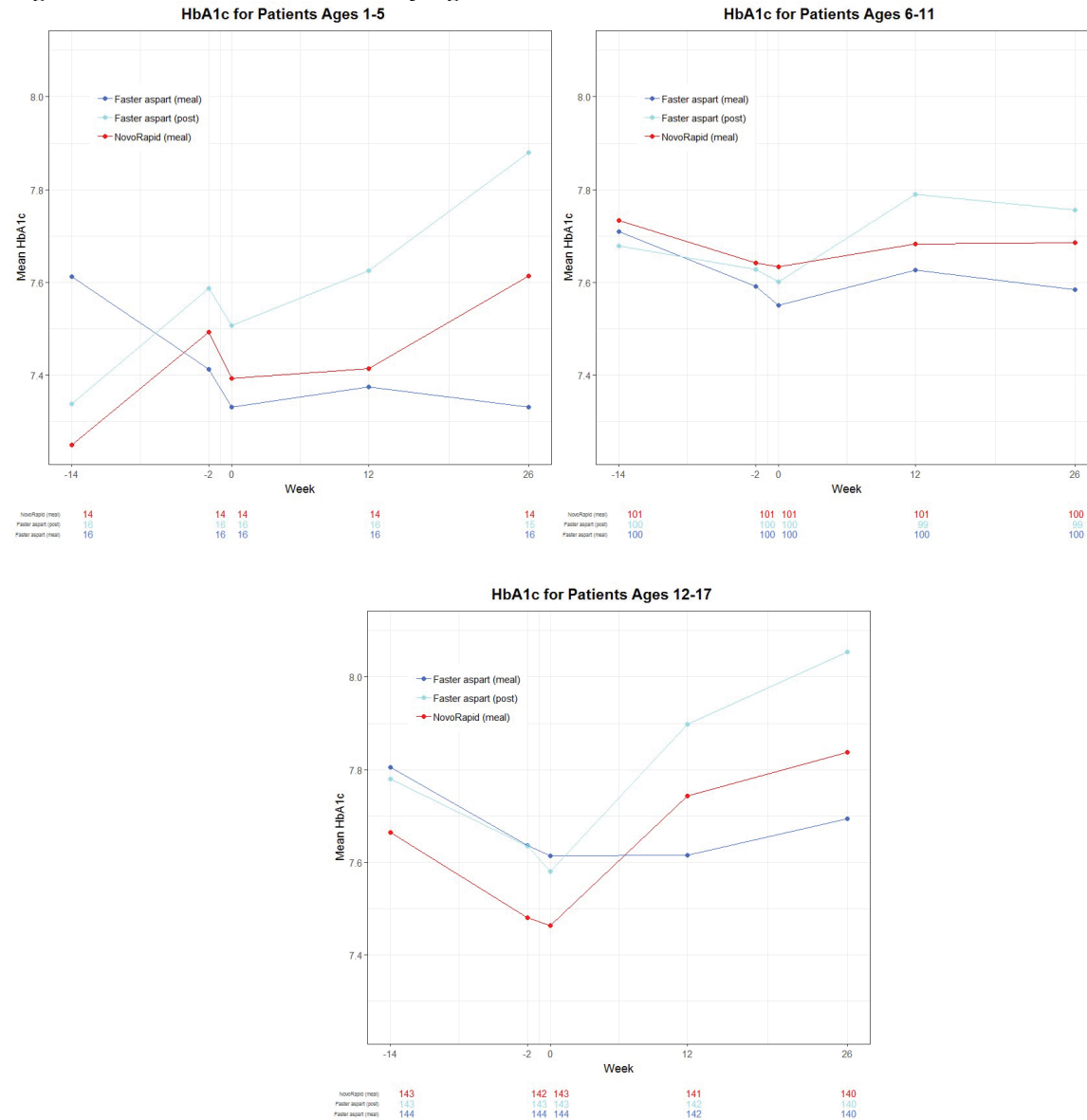
Figure 5: Mean HbA1c Over Time



Source: Statistical reviewer's analysis

Figure 6 shows mean HbA1c for each age stratification group. The patterns of HbA1c post-randomization remains similar between each of the groups with mealtime FIASP showing the smallest amount of increase and post-meal FIASP showing the greatest increase amongst the treatment arms. The biggest increases from baseline, no matter what the treatment, tend to be in the oldest age group. Interpretation for the youngest age group should be done with great caution due to the small sample size.

Figure 6: Mean HbA1c Over Time by Age Stratification



Source: Statistical reviewer’s analysis

3.3.7 Study Dosing and Titration Targets

The pediatric protocol for this study specified a treat-to-target principle wherein doses were adjusted for each subject to achieve prespecified glycaemic targets. Basal insulin was titrated towards a pre-breakfast self-measured plasma glucose (SMPG) target of 4.0-8.0 mmol/L (71-145 mg/dL) during the 12 week run-in period. After randomization, titration focused on bolus insulin using the treat-to-target principle, with adjustments to basal insulin dose made if needed. The bolus insulin was titrated to a pre-breakfast and pre-lunch target of 4.0-8.0 mmol/L (71-145 mg/dL), and a pre-dinner target of 6.7-10.0 mmol/L (120-180 mg/dL).

Daily Bolus Doses

Split violin plots in Figure 7 and Figure 8 below show the distribution of daily bolus doses taken throughout the study. A kernel density estimation is used to show the distribution shape of the data. Wider sections of the plot indicate a higher probability of that particular dose. A line is drawn at the median dose for each distribution. The distribution for mealtime FIASP is shown in darker blue, post-meal FIASP in lighter blue, and NovoLog in red. Doses comparing mealtime and post-meal FIASP to NovoLog seem well matched throughout the study.

Figure 7: Bolus Dose Over Time, Mealtime FIASP and NovoLog

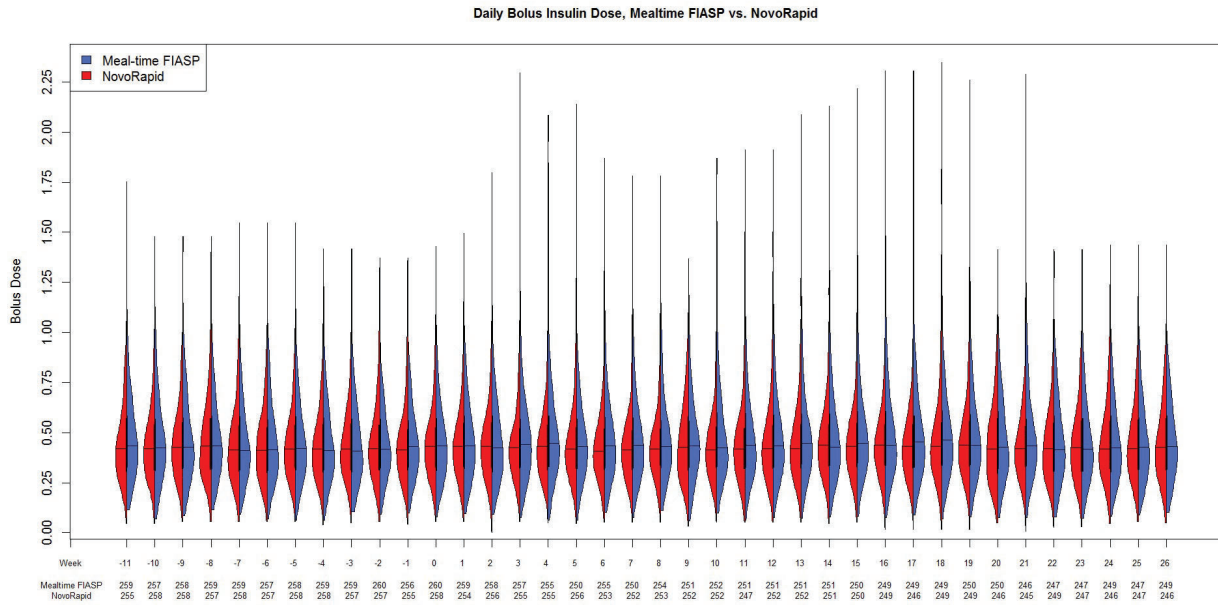
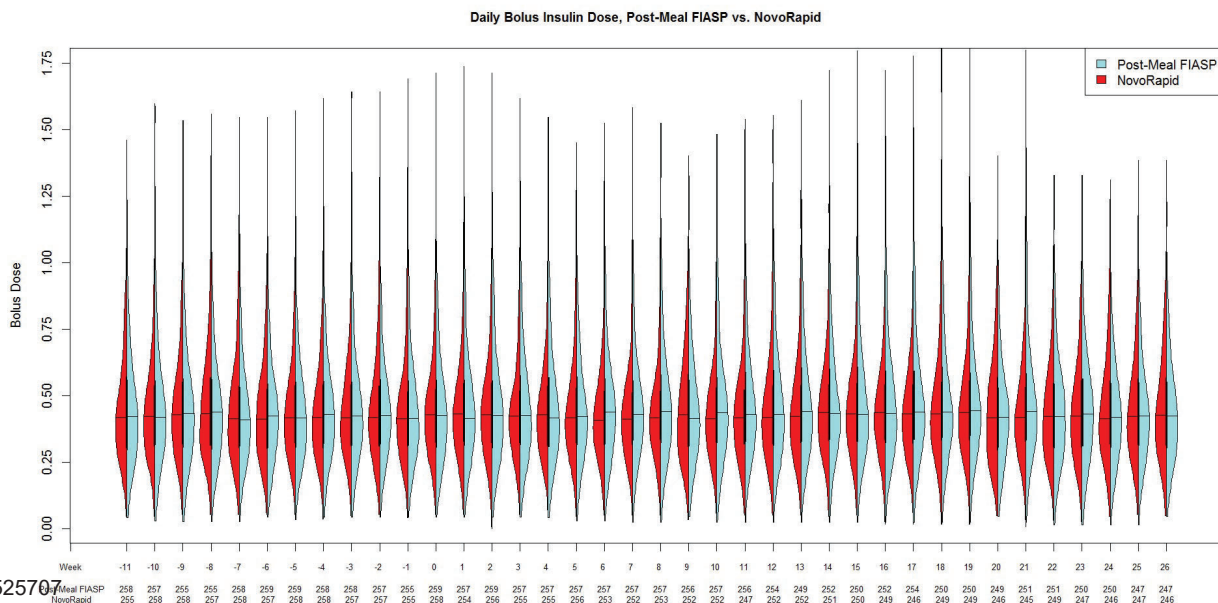


Figure 8: Bolus Dose Over Time, Post-meal FIASP and NovoLog

Source: Statistical reviewer's analysis

Daily Basal Doses Over Time

The figures below show the distribution of daily basal insulin doses throughout the run-in and treatment periods of the study. The doses of post-meal FIASP and NovoLog are relatively well matched in distribution with post-meal FIASP slightly higher at different time-points; at the



primary week 26 timepoint the distributions appear quite similar. Mealtime FIASP appears to have slightly higher median values throughout much of the study periods including at week 26. However, this trend also seems to hold during the run-in period, pre-randomization when everyone is on the same study treatment, so it is likely not due to purposeful dosing strategies to increase the study treatment effect. The patterns seen here and with HbA1c is likely due to imperfect randomization with more patients with lower HbA1c and lower basal doses randomized to NovoRapid. There is the possibility that randomization was done in an unblinded manner to have patients with lower HbA1c randomized to NovoLog, which would thereby compromise the integrity of the study and all results. However, given the amount of oversight for these types of trials, this seems an unlikely option and would be beyond the scope of this review to detect.

Figure 9: Basal Dose Over Time, Mealtime FIASP and NovoLog

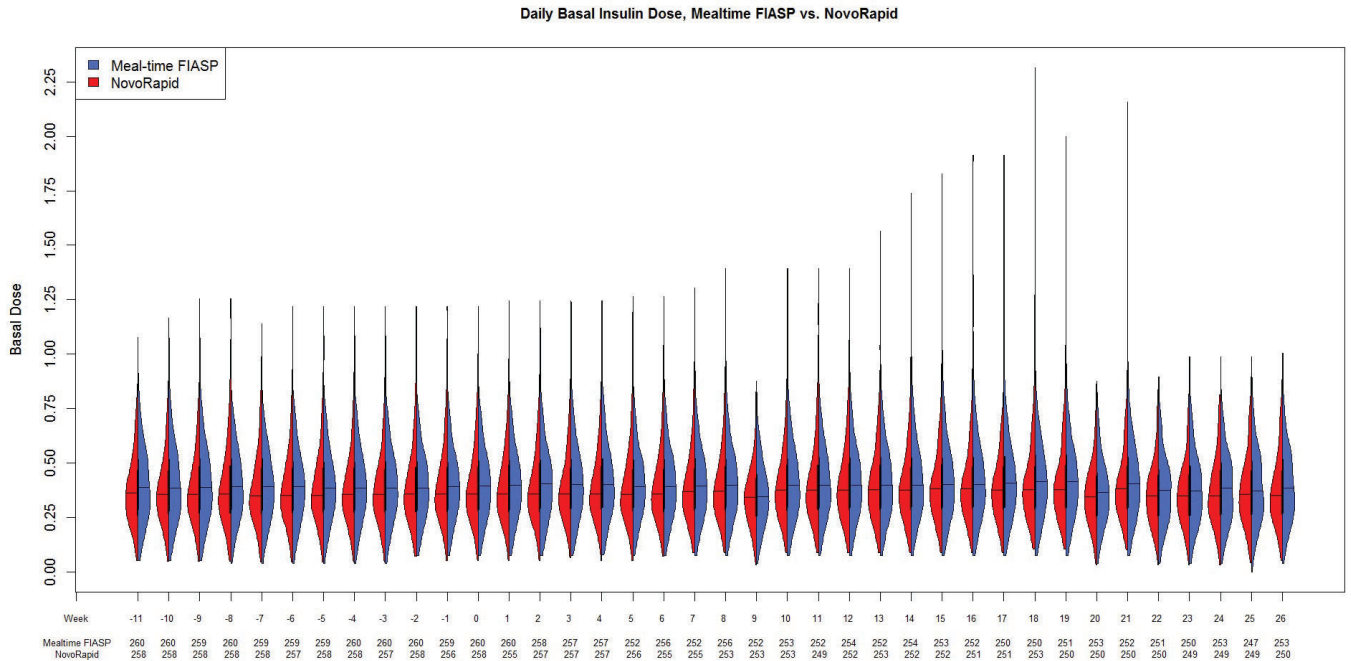
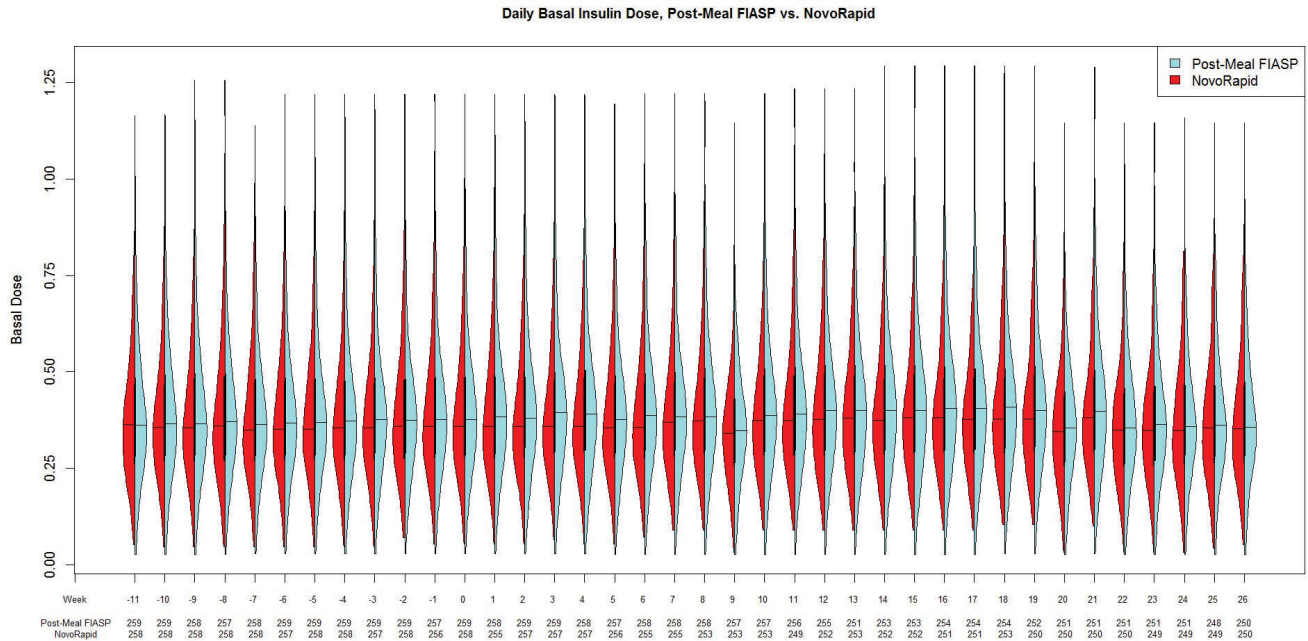


Figure 10: Basal Dose Over Time, Post-meal FIASP and NovoLog



Source: Statistical reviewer’s analysis

3.3.8 Adult Study Device Extrapolation

Study 3852, T1DM Adult Study Results

Pediatric study results seen in Table 5 are different from what was seen in the adult studies where HbA1c decreased at week 26. Table 6 shows results for the adult study as they appear in the current FIASP label.

Table 6: Results from the Adult T1DM Study as they appear in the current label

	Mealtime FIASP + insulin detemir	Post-meal FIASP + insulin detemir	Mealtime NovoLog + insulin detemir
Number of subjects randomized (N)	381	382	380
HbA_{1c} (%)			
Baseline (mean)	7.6	7.6	7.6
Adjusted mean change from baseline	-0.32	-0.13	-0.17
Estimated treatment difference vs. mealtime NovoLog [95% CI]*	-0.15 [-0.23;-0.07]		
Estimated treatment difference vs. mealtime NovoLog [95% CI]*		0.04 [-0.04;0.12]	

Baseline is based on the mean of the observed last available values prior to randomization.

*Tested for non-inferiority

7.6% of subjects on the Mealtime FIASP arm, 7.6% of subjects on the Post-meal FIASP arm, and 5.3% of subjects on the Mealtime NovoLog arm were missing the final HbA_{1c} assessment.

Source: Current FIASP label, Section 14

Study 3852, an efficacy and safety study of FIASP compared to NovoLog both in combination with insulin detemir in adults with T1DM, is currently in the label from the original approval and is similarly designed to the current pediatric study but done in adults with ages ranging from 18 to 83. This used a similar treat-to-target approach throughout the study, but with different targets in the adult population than what are set for the pediatric population, please see the clinical review by Dr. Hyon Kwon for more information. The basal insulin dose was titrated during the run-in period, but with adult targets of 71-90 mg/dL for the pre-breakfast glycemic target, and a pre-dinner target of 71-108 mg/dL if a twice daily regimen was specified. The target for the pediatric study during the basal titration 12-week run-in period were specified for a pre-breakfast self-measured plasma glucose glycemic target of 71-145 mg/dL.

At randomization the bolus insulin was titrated in a treat-to-target approach to a preprandial or bedtime SMPG target of 71-108 mg/dL at the subsequent meal or bedtime for the adult study. In the pediatric study, the treatment period had pre-breakfast and pre-lunch glycemic targets of 71-145 mg/dL, and a pre-dinner target of 120-180 mg/dL for the bolus insulin titration. Although the treat-to-target approach in the study design is similar between the adult and pediatric study, the differences in the targets complicates comparability between the study treatment effects. However, the studies do separately suggest that there is a treatment effect within the adult and pediatric population. For more information on the adult studies and the results, please see the clinical review by Dr. Hyon Kwon, signed on 7 October 2016, and the statistical review by Dr. Cambon, signed on 2 September 2016.

Differences seen in the change from baseline in each of the treatment arms could be due to the titration targets being different for the pediatric population. Since the increase is smallest in the mealtime FIASP arm, treatment effect is maintained when compared to NovoLog. Post-meal FIASP has the largest increase, however, since the upper limit is below the NIM of 0.4%, it is still considered non-inferior to NovoLog. Results show a noticeably deteriorating treatment effect with an increased effect towards the control arm relative to post-meal FIASP; the treatment effect is over three times favoring control from what was seen in the comparable adult study (0.04 [-0.04, 0.12] vs. 0.13 [-0.01, 0.26]).

Even though the change from baseline to week 26 was considerably different in the pediatric study when compared to results from the comparable adult study, the overall treatment effect was somewhat preserved and similar when comparing mealtime FIASP to NovoLog. Differences between the adult and pediatric populations in treatment targets and compliance make extrapolation of the actual treatment effect seen in the adult device study, currently under review under the same NDA, difficult to determine. However, the treatment effect seen in the current pediatric study is highly indicative that there would be a treatment effect for the pediatric population using a device with this treatment if the current adult device study shows a beneficial treatment effect. While I would not recommend that the actual treatment effect seen in the adult device study be extrapolated to the pediatric population, it would be reasonable, to extrapolate that there would be a beneficial effect for the pediatric population using this treatment with a device if there is a benefit seen in the adult population.

3.4 Evaluation of Safety

Hypoglycemia

Only events classified as treatment emergent (event had an onset date on or after the first day of exposure to randomized treatment, and no later than 7 days after the last day of randomized treatment) were used to determine the total number of hypoglycaemic episodes while subjects were on study treatment. Table 7 has the classifications for each hypoglycemic event. Patients can have none or multiple events, all of the events captured in the study were included in the table. A majority of these events could not be classified for all treatment arms. While the proportion of classifications for hypoglycemic events were similar between treatment arms, there were numerically more events in the mealtime faster aspart arm.

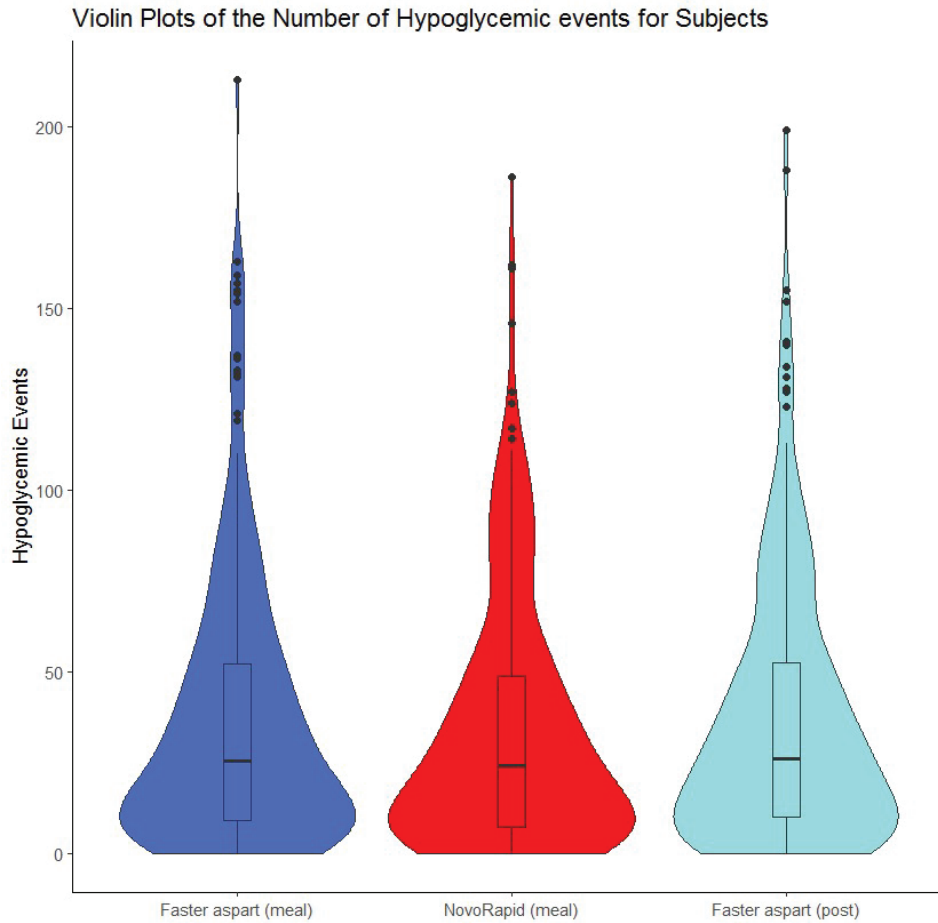
Table 7: Number of Hypoglycemic Events in each arm

	Faster Aspart (Meal)	Faster Aspart (Post)	NovoLog
Symptomatic BG Confirmed	2233 (23.08%)	2425 (25.33%)	2190 (24.6%)
Asymptomatic BG Confirmed	1338 (13.8%)	1170 (12.22%)	1082 (12.15%)
Severe	3 (0.03%)	8 (0.08%)	4 (0.04%)
Unclassifiable	6103 (63.07%)	5971 (62.37%)	5626 (63.2%)
	9677	9574	8902

Source: Statistical reviewer's analysis

Of the 777 patients in the study, only 27 did not experience a hypoglycemic event (10 (3.9%) mealtime FIASP, 8 (3.1%) post-meal FIASP, 9 (3.5%) NovoLog). Figure 11 shows violin plots which contain box plots in black for the distribution of the number of hypoglycemic events experienced by each patient in each treatment arm. So, while there were more events in the mealtime FIASP arm, the distributions for the number of events experienced by patients in the study were fairly similar, the numeric imbalance appears to be due to more outliers in the FIASP arm who also tended to have more events.

Figure 11: Violin Plots of the number of Hypoglycemic Events Experienced by Patients in each treatment arm



Source: Statistical reviewer's analysis

Most patients experiencing hypoglycemia during the study had 10 or fewer episodes in all arms. This can be seen in the overlaying histograms in Figure 12 and Figure 13 comparing each FIASP arm to NovoLog. The number of outliers, which can be seen in the tails of the histograms with the number of events (x-axis) experienced by patients within each treatment arm (y-axis), seems to be slightly higher for the mealtime FIASP arm. While there tended to be a few more outliers who tended to experience more hypoglycemic episodes in the mealtime FIASP arm which led to a numerically higher number of hypoglycemic episodes, the overall distribution patterns between the three arms are fairly similar.

Figure 12: Histogram of the number of Hypoglycemic Events Experienced by Patients, Mealtime FIASP and NovoLog

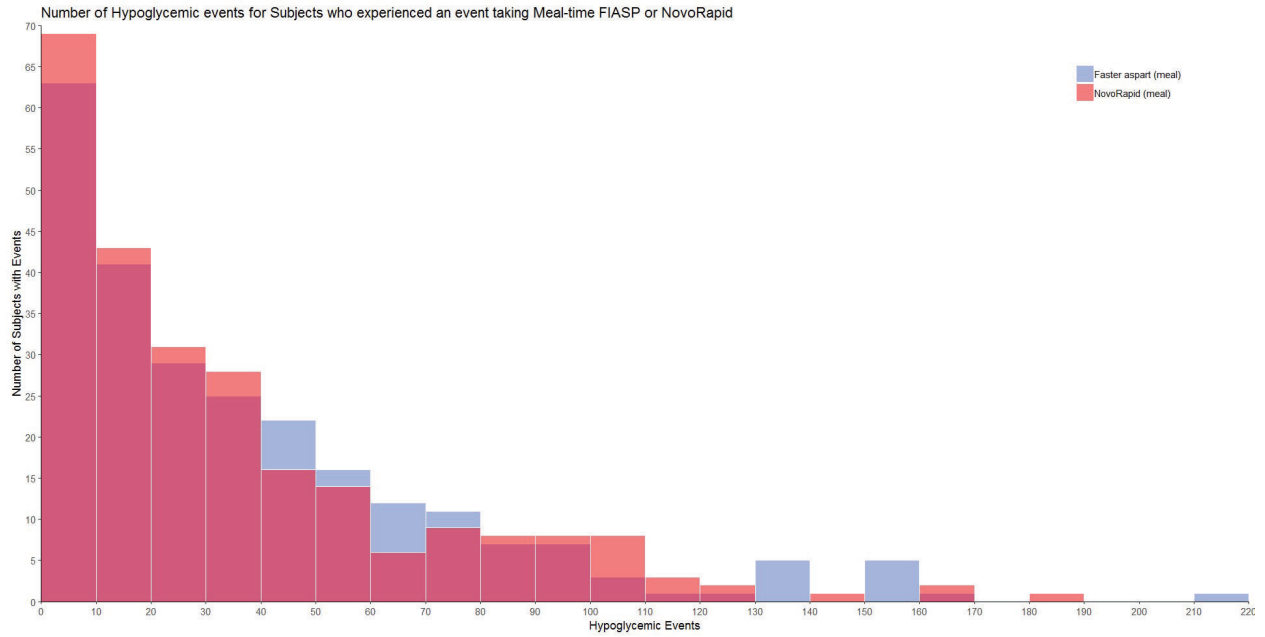
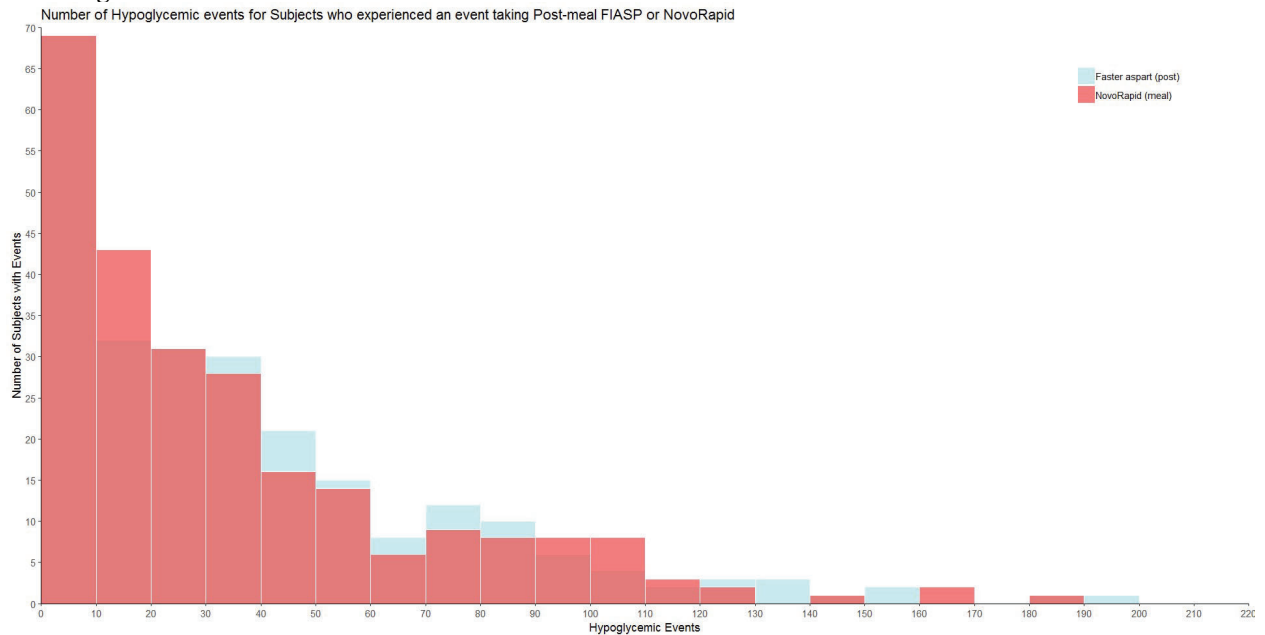


Figure 13: Histogram of the number of Hypoglycemic Events Experienced by Patients, Post-meal FIASP and NovoLog



Source: Statistical reviewer’s analysis

3.5 Benefit-Risk Assessment

While HbA1c did increase from baseline, it did so in all three treatment arms and is likely indicative of the unique titration treatment targets which tend to be higher for the pediatric population. The treatment effect in this randomized trial is still preserved when comparing

blinded mealtime FIASP to mealtime NovoLog, so this population does seem to derive a benefit from mealtime FIASP. There were a few more patients in this arm that had a larger number of hypoglycemic events which led to a higher number of overall events in this arm. The numerically higher number of patients experiencing more events could be due to natural variability. If, however, there is a certain subset of patients who tend to have more hypoglycemic episodes on mealtime FIASP, there are typically no long-term consequences to these AEs, and these patients can switch to a different treatment if the risk of hypoglycemia outweighs the glyceemic benefits.

There did not seem to be any additional benefit in the post-meal FIASP when compared to Novolog. While the treatment was considered non-inferior, the magnitude and direction of the treatment effect warrants further investigation for less ambiguous results. The NI design with a margin of 0.4 indicates there is likely some treatment effect preserved when comparing post-meal FIASP to placebo. The number of hypoglycemic events is similar to NovoLog with some patients who are already experiencing a moderate to higher level of events experiencing a few more events. While additional hypoglycemia does not seem to be a concern with this arm, the possible decrease of glyceemic benefit makes it reasonable to recommend either of the mealtime dosing arms over this one.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

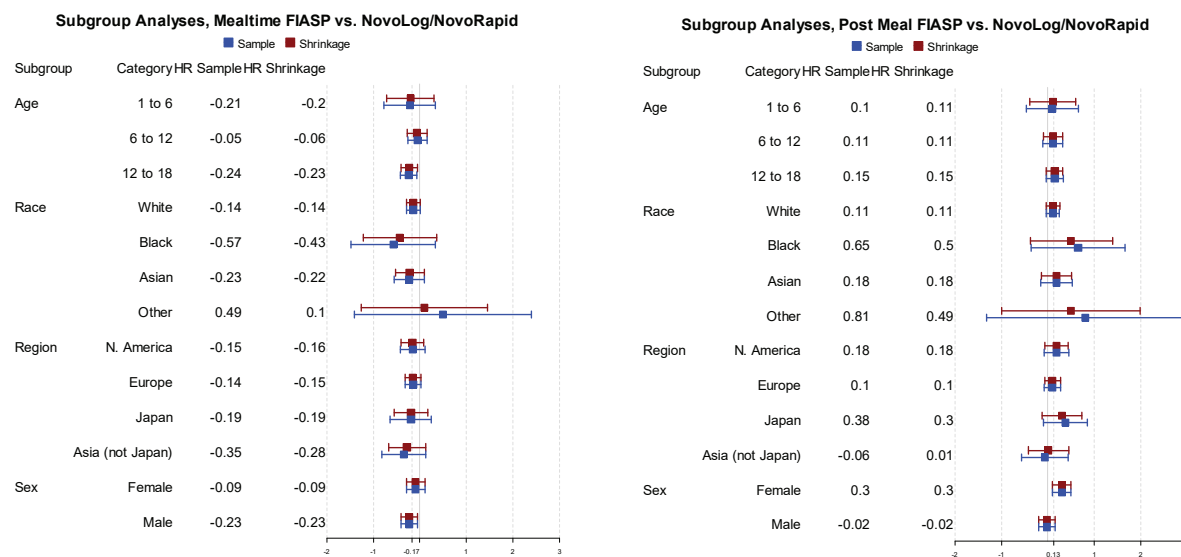
Subgroup analyses were done for age, race, sex, and geographic region. Analyses were first run using the same ANCOVA model with MAR MI for missing data for the primary endpoint with the subgroup and treatment by subgroup interaction added to the model and a contrast statement used to estimate the treatment effect for each subgroup. For subgroups which had some adjustment in the primary endpoint model (ie, age and region), the subgroup variable was used in lieu of the adjusting covariate if they were not the same. There are some random highs and random lows in sample estimates of subgroup treatment effects due to small sample sizes and large variability for some subgroups. To address this, shrinkage estimates of subgroup treatment effects were derived using a Bayesian hierarchical model based on summary sample estimates. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a “weighted” average of the sample estimate and overall estimate. We used the same flat prior to derive shrinkage estimates for all subgroups. The Bayesian hierarchical model assumptions are:

For $i = 1, 2, \dots$ Y_i represents the observed sample estimate of treatment effect in a subgroup level i , assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(0, 16)$, $\tau^2 \sim \text{Half-Cauchy}(25)$

Results with the sample and shrinkage estimates are shown below in Figure 14 with hazard ratios comparing mealtime FIASP and post-meal FIASP to NovoLog. In addition to reference lines, a line is drawn at the overall estimated treatment effect of -0.17 (mealtime FIASP vs. NovoLog) and 0.13 (post meal FIASP vs. NovoLog). Most results are similar between the sample and shrinkage estimates. Subgroups with the smallest sample sizes are the ones that are most affected by the shrinkage analysis as they will borrow more heavily from other subgroups. This can most easily be seen in the “Other” race subgroup which only has four patients, so the sample estimates may not be a very good estimate of the treatment effect. Subgroups with larger sample sizes and smaller variance had less shrinkage and were more like the sample estimates.

Figure 14: Forrest Plots of Subgroup Analysis Results



Source: Statistical reviewer’s analysis

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

While there were a number of statistical issues analyzed and discussed throughout this review, none seemed to change the efficacy results for mealtime FIASP and post meal FIASP vs. NovoLog. The most impactful issues discussed were:

- An increase from baseline in HbA1c at Week 26
- Differences in HbA1c results when compared to the original adult study. Whether we can extrapolate results from this study and adult device study to support use of FIASP in device for pediatric patients

5.2 Collective Evidence

Evidence from the pediatric FIASP study indicates there is an improved treatment effect when comparing mealtime FIASP to NovoLog. Evidence is less conclusive comparing post meal FIASP to NovoLog, although it may be termed “non-inferior” to NovoLog with the pre-specified non-inferiority margin of 0.4%. Further exploration on this treatment effect is needed for any sort of conclusive interpretations. However, it is likely that there is some treatment effect preserved for mealtime FIASP if it were compared to placebo. There is also the possibility that a few patients may experience a higher number of hypoglycemic events on mealtime FIASP (section 3.4). It is possible that differences seen in basal doses could be due to non-blinded randomization with more subjects having lower HbA1c at baseline randomized to NovoLog. However, if we are confident in the randomization process and that the proper blinding procedures in the protocol were followed for randomization, then this is most likely due to arbitrary randomization.

The observed FIASP treatment effect in this pediatric study (Table 5) is qualitatively better than what was observed in adult device study reviewed in Supplement 8 (Table 9 in FIASP Label) and quantitatively slightly better than what was observed in adult study (Table 6). While I would not recommend that the actual numeric treatment effect seen in the adult device study be extrapolated to the pediatric population, it would be reasonable to extrapolate that there is a beneficial effect of FIASP in a device for the pediatric population (Supplement 11), since the Agency approved FIASP for use in insulin infusion pump for adults with Type 1 and 2 diabetes on October 22, 2019, based on the adult device study (Supplement 8).

5.3 Conclusions and Recommendations

Statistical evidence of efficacy from this submission support approval for a pediatric indication for mealtime FIASP. While evidence is less conclusive concerning post meal FIASP, results from this arm should be included if this will be a viable option that patients may choose when prescribed this treatment (Supplement 10).

If extrapolation of benefit can be made without inferring extrapolation of the numeric treatment effect, then this study can be considered supportive for extrapolation for the pediatric population (Supplement 11).

5.4 Labeling Recommendations

Statistical methods and models used to calculate results (adjusted mean change, estimated treatment difference, etc.) should be included in the label. This can be added as a footnote in the table containing the results. This should be done for this (study 4101) and all other studies already included in the label. Currently, statistical methods and adjusting covariates and models are not included and I had to look back at previous reviews to infer what statistical methodology was used for the label (Supplement 10).

It is reasonable to infer that there is some benefit for the pediatric population if there is benefit for the adult population. However, it should not be inferred that the pediatric population will have a similar treatment trajectory as to what is seen in the adult population (Supplement 11).

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/

JENNIFER J CLARK
11/26/2019 11:23:47 AM

YUN WANG
11/26/2019 11:43:00 AM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208751Orig1s011

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology Review

NDA Number	208751/S-10, S-11
Link to EDR	\\CDSESUB1\evsprod\NDA208751\208751.enx
Submission Date	2/21/2019 (S-010) & 2/25/2019 (S-011)
Submission Type	NDA 505(b)(1); Standard
Brand Name	FIASP®
Generic Name	Insulin Aspart
Dosage Form and Regimen	Solution for injection
Route of Administration	Subcutaneous injection and continuous subcutaneous insulin infusion
Proposed Indication	To improve glycemic control in children with diabetes mellitus
Applicant	Novo Nordisk Inc.
OCP Review Team	Renu Singh, Ph.D.; Manoj Khurana, Ph.D.
OND Division	Metabolism and Endocrinology Products

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Executive Summary

The applicant, Novo Nordisk Inc., has submitted a prior approval efficacy supplement (Supplement 10 & 11) under NDA 208751 for Fiasp (insulin aspart injection), to support use of Fiasp subcutaneous injections (S-10) and the continuous subcutaneous insulin infusion (CSII) (S-11) in pediatric patients with diabetes mellitus.

Fiasp was approved to improve glycemic control in adults with diabetes mellitus on September 29, 2017 for subcutaneous (SC) and intravenous (IV) use. Fiasp was recently approved on October 21, 2019 for CSII use in adults (S-8). Fiasp was developed as a meal-time insulin with the claim of a 'greater early glucose lowering effect' compared to the currently approved NovoLog (global trade name of NovoRapid® reflected in the Applicant's tables and figures; hereafter, comparator referred to as NovoLog in the review text). Following PMR was included in the approval letter:

1. 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).

The clinical development program for pediatric use for Fiasp is comprised of three pharmacokinetic (PK)/ pharmacodynamic (PD) studies (3888, 4371 and 4265) and one confirmatory efficacy and safety study (study 4101).

1.1. Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed the information submitted under NDA 208751, Supplement 10 & 11 and has the following recommendations:

- The clinical pharmacology data submitted under Supplement 10 is acceptable to support the approval of this supplement.
- The clinical pharmacology data submitted to support Supplement 11 is acceptable. However, the final approvability of this supplement is deferred to the assessments by Clinical and CDRH review disciplines.

1.2. Post Marketing Requirement

None.

1.3. Summary of Important Clinical Pharmacology Findings

The following data were included in this submission to support the pediatric indication (S-10) for SC injection:

- **NN1218-4101:** Efficacy and Safety of Fiasp compared to NovoLog® both in Combination with Insulin Degludec in Children and Adolescents with T1DM
- **NN1218-3888:** A study investigating the Pharmacokinetic Properties of Fiasp in Children, Adolescents and Adults with T1DM
- **NN1218-4371:** A study comparing the Pharmacokinetic Properties of Fiasp between Children, Adolescents and Adults with T1DM (same study design as study 3888 except the insulin aspart concentration was measured by total ELISA assay)
- **NN1218-4265:** A study Investigating the Pharmacokinetic and Pharmacodynamic Properties of Fiasp in Subjects with T2DM

In addition, prior approval efficacy supplement (S-11) is submitted to support CSII use in Insulin pump for Fiasp in pediatric patients with diabetes mellitus. In accordance with agreed initial pediatric study plan (iPSP) (dated 08/28/2015 in DARRTS), Novo Nordisk proposes to extrapolate efficacy results from the adult pump study in T1DM to pediatric T1DM based on the following:

- Efficacy data from the completed Phase 3b pump efficacy and safety study in adult subjects with T1DM (NN1218-3854). This study was submitted under Supplement 08 (NDA 208751).
- The completed single dose pump PK/PD study in adult subjects with T1DM (NN1218-4349). This study was also submitted under Supplement 08 (NDA 208751).
- Efficacy data from the completed subcutaneous pediatric efficacy and safety study in subjects with T1DM (NN1218-4101). This study is submitted in the current submission.

Novo Nordisk has also proposed to leverage the safety and dosing information from studies NN1218-3854 and 4101 to support the CSII use of Fiasp with pediatric patients. Furthermore, study NN1218-3852 (long-term efficacy) is used to provide reference data for supporting dosing recommendations.

Studies 4371 and 3888 were important PK/PD studies to support pediatric development (S-10) as SC injection. While studies 4371 and 3888 had similar design, study 3888 measured only free serum insulin aspart concentrations whereas repeat study 4371 measured both free and total serum insulin aspart. During the original NDA submission, the free serum insulin aspart assay was deemed to be unreliable (Refer to the review in DARRTS by Dr. Shalini Wickramaratne Senarath Yapa dated 09/06/2017; hereafter OCP review dated 09/06/2017), hence only total serum insulin aspart concentration were relied for PK conclusions from study 4371, as was done for the original NDA resubmission. Therefore, this review is focused on the PK/PD results from study 4371 and only PD results from study 3888.

Study 4371 and 3888 were randomized, single-center, double-blind, single-dose, two-period cross-over studies investigating the PK properties of Fiasp and NovoLog® in children (6-11 years), adolescents (12-17 years) and adults (18-64 years) with T1DM. In addition, PD properties were investigated using a meal test setting. In studies 4371 and 3888 (pediatric and adult subjects with T1DM), a SC dose of 0.2 Unit/kg body weight was used for both Fiasp and NovoLog®.

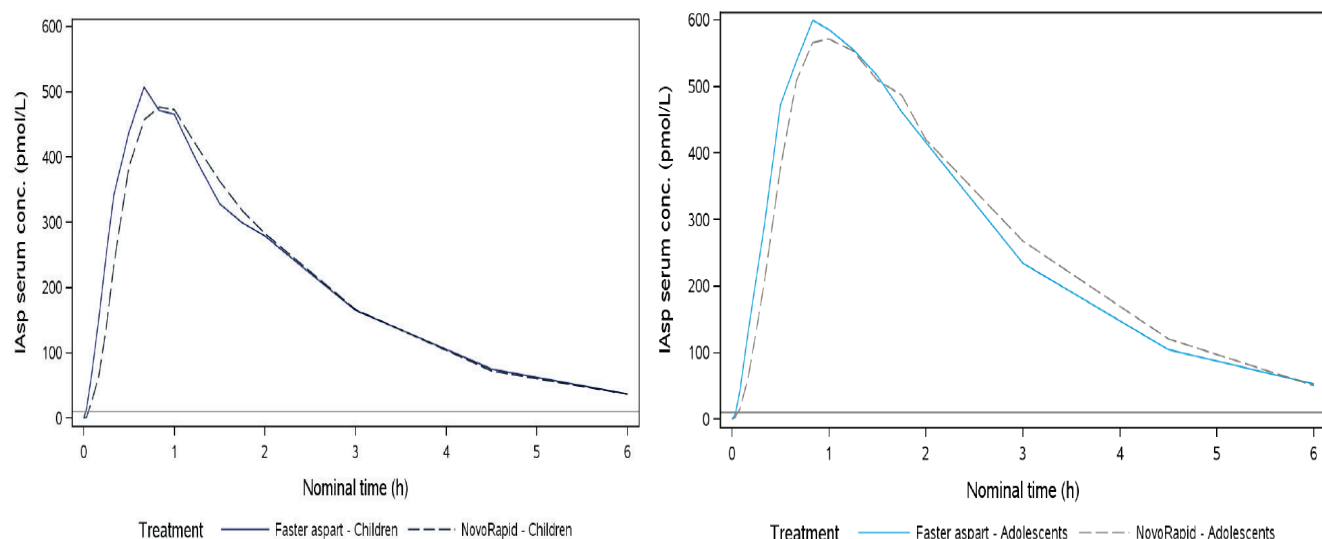
The mean profiles for total serum insulin aspart concentration after SC administration of Fiasp in children and adolescents were slightly shifted to the left compared to NovoLog, indicating a faster absorption and greater early insulin exposure with Fiasp (Figure 1). In children, estimates of mean onset of appearance were 2.4 minutes with Fiasp and 5.4 minutes with NovoLog®. The estimates of mean time to 50% $C_{max, IAsp}$ were 20.8 minutes with Fiasp and 27.1 minutes with NovoLog® in children. In adolescents, estimates of mean onset of appearance were 3.2 minutes with Fiasp and 5.0 minutes with NovoLog®. Estimates of mean time to 50% $C_{max, IAsp}$ were 21.9 minutes with Fiasp and 28.1 minutes with NovoLog® in adolescents. Both children and adolescents showed statistically significantly greater early total insulin aspart exposure (assessed using endpoints $AUC_{IAsp,0-15min}$, $AUC_{IAsp,0-30min}$) with Fiasp than NovoLog.

The duration of exposure for total insulin aspart (measured as time to late 50% $C_{max, IAsp}$) was comparable between Fiasp and NovoLog in children but in adolescents 12.3 minutes shorter for Fiasp than for NovoLog. In children and adolescents, the total exposure of insulin aspart ($AUC_{IAsp,0-12h}$) and the maximum insulin aspart concentration ($C_{max, IAsp}$) were comparable for Fiasp and NovoLog®.

For children and adolescents with T1DM in the clinical pharmacology studies 4371 and 3888, the PG profiles for the first 2 hours after meal test were lower for Fiasp compared to that for NovoLog®.

The results from study 4371 demonstrated that PK from SC injection in children and adolescents preserved the initial (0-30 minutes) absorption differences with the SC delivery of the Fiasp versus NovoLog. These relative PK/PD differences between Fiasp and NovoLog, when administered in pediatric T1DM patients were consistent with the observations after SC administration in adults in the original NDA submission (see OCP review dated 09/06/2017). When compared to the adult group within study 4371, the PK analysis indicated that AUC_{12h} and C_{max} was higher in pediatrics (~25-50%) compared to adults. This difference was due to the higher baseline mean total antibody level for children (30.3 %B/T) and adolescents (36.0 %B/T) than for adults (18.9 %B/T). After adjusting for antibody level AUC_{12h} and C_{max} were comparable for children and adolescents compared to adults. Additionally, other PK parameters like onset of appearance, time to 50% $C_{max,IAsp}$, t_{max} and duration of exposure were also similar to adults.

Figure 1. Mean children PK (left) and mean adolescent PK (right) profiles of Fiasp and NovoLog in study 4371.



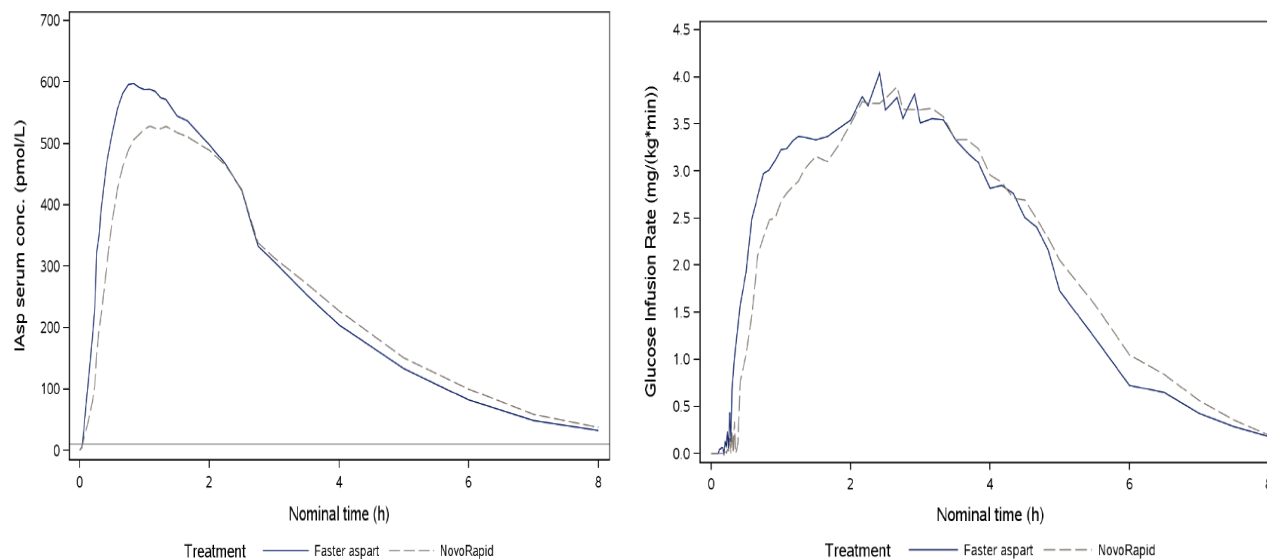
Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Pages 19 and 20

To support indication in pediatric T2DM patients the sponsor conducted study 4265 to evaluate the PK/PD in adult 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 in a euglycemic clamp setting in subjects with T2DM. In adults with T2DM, Fiasp showed earlier onset of exposure, greater early and maximum exposure compared to NovoLog® with a comparable total insulin exposure (Figure 2). In adults with T2DM, the mean onset of appearance of insulin aspart was 3.1 minutes for Fiasp compared to 4.3 minutes for NovoLog®. The time to reach 50% C_{max} (time to 50% $C_{max,IAsp}$) of insulin aspart was 19.0 minutes for Fiasp compared to 26.7 minutes for NovoLog®.

The estimated time to late 50% $C_{max,IAsp}$ (duration of exposure) was 30 minutes shorter with Fiasp compared with NovoLog®. Exposure during the last part of the PK profile ($AUC_{IAsp,2-12h}$) of Fiasp was statistically significantly lower by 11% compared to NovoLog®. In adults with T2DM, the total insulin exposure (measured as $AUC_{IAsp,0-12h}$) was similar between Fiasp and NovoLog®, while the maximum insulin aspart concentration ($C_{max,IAsp}$) was 12% higher for Fiasp compared to NovoLog®, however these differences were not considered clinically meaningful. In adults with T2DM, the median terminal half-life was 80.6 minutes for Fiasp and 85.9 minutes for NovoLog®.

The mean GIR profiles for Fiasp were left-shifted compared to NovoLog®, indicating a greater early glucose-lowering effect with Fiasp compared to NovoLog®/ NovoLog® (Figure 2). Fiasp showed earlier onset of glucose-lowering effect, greater early glucose-lowering effect compared to NovoLog® while maintaining a comparable total and maximum glucose-lowering effect. Onset of action was 22.4 minutes for Fiasp compared to 31.3 minutes for NovoLog®. Time to 50% GIR_{max} was 39.3 minutes for Fiasp and 51.1 minutes for NovoLog. The tGIR_{max} was 150.9 minutes for Fiasp compared to 155.7 minutes for NovoLog®. However, the estimated time to late 50% GIR_{max} was 14.4 minutes earlier with Fiasp compared to that with NovoLog®. In study 4265, the total glucose-lowering effect (measured as AUC_{GIR,0-t}) and the maximum observed GIR (GIR_{max}) for Fiasp was comparable to NovoLog®.

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



Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Pages 27 and 40

Efficacy and safety of Fiasp in pediatric population was assessed in study 4101. This was a 26-week, randomized, partly double-blind, multicenter, multinational, active controlled, treat-to-target, 3-armed parallel-group study with a 12-week run-in period. The study compared effect and safety of mealtime Fiasp versus mealtime NovoLog®, both in combination with insulin degludec once daily in a basal-bolus regimen, in subjects with T1DM aged 1 year to less than 18 years of age. Fiasp and NovoLog were titrated following the same recommendations.

Sponsor reported that the results of the hierarchical testing procedure showed that mealtime Fiasp was non-inferior to mealtime NovoLog®, both in combination with insulin degludec, in terms of change from baseline to 26 weeks after randomization in HbA1c (-0.17 % [-0.30; -0.03]95% CI). Non-inferiority of postmeal Fiasp versus mealtime NovoLog®, both in combination with insulin degludec, was confirmed in terms of change from baseline to 26 weeks after randomization in HbA1c (0.13 % [-0.01; 0.26]95% CI). Superiority of mealtime Fiasp versus mealtime NovoLog®, both in combination with insulin degludec, was confirmed in terms of change from baseline to 26 weeks after randomization in HbA1c.

The comparability in the PK/PD with respect to overall unit dose-response of Fiasp and NovoLog, corroborates with the observation of non-inferior glycemic control vis-à-vis comparable total insulin dose utilization from the 4101 study. The clinical relevance of the initial PK/PD differences between Fiasp and NovoLog as claimed by the sponsor is uncertain towards efficacy differences in the clinical use setting.

The acceptability of the efficacy claims and risk-benefit assessment from the study 4101 are further deferred to the reviews by Statistical and Clinical disciplines.

Overall, Clinical Pharmacology data submitted for supplement 10 and 11 of NDA 208751 is acceptable to support the use of Fiasp in pediatrics.

2. Question-Based Review

2.1. Background

Fast-acting insulin aspart, tradename Fiasp, for improvement of glycemic control in adults with diabetes mellitus was approved on September 29, 2017 under NDA 208751 for subcutaneous (SC) and intravenous (IV) use. Fiasp is currently not approved for CSII in pump systems in the US. Compared to NovoLog, Fiasp contains two additional excipients: nicotinamide (also known as niacinamide or vitamin B3) and L-arginine hydrochloride (an amino acid). The addition of (b) (4)

(b) (4) Both Fiasp and NovoLog contain the same API (insulin aspart) and therefore, once systemically absorbed, no difference in biological action at the insulin receptor is anticipated.

Based on the clinical pharmacology program conducted for the original NDA for Fiasp in adults (Refer to OCP review dated 09/06/2017), the following attributes about Fiasp were concluded:

PK properties:

- Following SC administration of 0.2 Unit/kg single dose of Fiasp in patients with T1DM, the mean onset of appearance was ~2.5 minutes post-dose and mean time to maximum insulin aspart concentration was achieved ~63 minutes post-dose
- Following SC administration of single doses ranging from 0.06 to 0.28 Unit/kg in patients with T1DM, a proportional increase in total insulin aspart exposure and maximum concentrations of insulin aspart was observed with an increase in Fiasp dose
- The absolute SC bioavailability of insulin aspart in healthy subjects following administration of a 0.2 Unit/kg Fiasp dose in the abdomen, deltoid, and thigh was 85%, 76%, and 75%, respectively
- Following IV administration of 0.02 Unit/kg Fiasp in healthy subjects, the geometric mean volume of distribution for insulin aspart was 0.15 L/kg
- Insulin aspart has a low binding affinity to plasma proteins (<10%), similar to that seen with regular human insulin
- Following SC administration of 0.2 Unit/kg single dose of Fiasp in patients with T1DM, the geometric mean terminal half-life for Fiasp was 68.1 minutes (median: 65.5 minutes)
- Following IV administration of 0.02 Unit/kg Fiasp in healthy subjects, the geometric mean clearance and elimination half-life was 0.90 (L/hr)/kg, and 7.2 minutes, respectively

PD properties

- In 3 euglycemic clamp studies, following SC administration of 0.2 Unit/kg single dose of Fiasp in patients with T1DM, the geometric mean onset of action was 11 to 17 minutes (range) and time to maximum glucose lowering effect was 109 to 119 minutes (range). The geometric mean duration of action was 342 to 476 minutes (range) for Fiasp
- The total glucose lowering effect and maximum glucose lowering effect increased in slightly less than linear manner within increasing dose of Fiasp (0.1, 0.2, 0.4 Unit/kg)

- Following SC administration of 0.2 Unit/kg Fiasp, the within-subject variability for total glucose lowering effect and maximum glucose lowering effect was 18.3% and 19.3%, respectively

2.1.1. What are the Clinical Pharmacology and Biopharmaceutics studies submitted in this NDA?

The clinical pharmacology program for pediatric SC injection consisted of the following:

Table 1. Summary of clinical pharmacology development program.

Study	Description
NN1218-3888	Pharmacokinetic Properties of Fiasp (free) in Children, Adolescents and Adults with T1DM
NN1218-4371	Pharmacokinetic Properties of Fiasp (total) between Children, Adolescents and Adults with T1DM
NN1218-4265	Pharmacokinetic and Pharmacodynamic Properties of Fiasp in Subjects with T2DM
NN1218-4101	Efficacy and Safety of Fiasp compared to NovoLog® both in Combination with Insulin Degludec in Children and Adolescents with T1DM

Source: Reviewer's summary of information submitted in Module 2.7.2. Summary of Clinical Pharmacology Studies

2.2. General Attributes

2.2.1. What was the formulation/device used in the clinical studies?

The formulation of the Fiasp drug product used in the clinical studies supporting this application is the same as the Fiasp drug product used in the clinical development program supporting the original NDA and is identical to the marketed Fiasp drug product. The investigational medicinal products (IMPs) used in study 4371 and 3888 are below:

- Fiasp, 100 U/mL, solution for injection, 3 mL PDS290 pen-injector, 0.2 Unit/kg body weight administered subcutaneously.
- Insulin aspart (NovoLog®), 100 U/mL, solution for injection, 3 mL PDS290 pen-injector, 0.2 Unit/kg body weight administered subcutaneously.

In study 4265 the investigational study product was Fiasp, 100 U/mL in 3 mL Penfill® (batch EP51006 and FP53116). The active comparator was NovoLog®, 100 U/mL in 3 mL Penfill® (batch EP51136 and GP51088). The dose level was 0.3 Unit/kg body weight and was administered SC (single dose) in the abdomen.

In study 4101 the investigational study product was Fiasp, 100 U/mL in 3 mL Penfill® (batch EW5F973, EW5F974 and FWN773). The active comparator was NovoLog®, 100 U/mL in 3 mL Penfill® (batch FWSR240).

2.3. General Clinical Pharmacology

2.3.1. Do the clinical pharmacology information submitted support the pediatric indication for use of Fiasp via multiple daily subcutaneous injection?

The sponsor seeks indication for SC injection in T1DM and T2DM pediatric population. Studies conducted for T1DM pediatric population are shown in Table 1. According to iPSP (dated 08/28/2015 in

DARRTS), it was agreed to extrapolate efficacy results from pediatric T1DM subjects to pediatric T2DM patients age 10 and above. The extrapolation was based on the following:

- 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 (Study 4265 in this submission).
- The efficacy results from a planned pediatric T1DM study, NN1218-4101

Note that the PK/PD study in T2DM was requested at the initial PSP stage (see DARRTS document dated 05/01/2015) and following concerns were listed in the iPSP:

- We acknowledge that trial NN1218-3824 in adults indicated similarity between T1DM and T2DM with regards to the differences in the pharmacokinetic profile of NN1218 and Novolog. However, the PD results in adult T2DM do not indicate if these PK differences translated to a meaningful difference in the PD profile of NN1218 to support the proposed pre-meal/post-meal use in adult T2DM patients.
- The study used a different formulation of NN1218 that differs in composition from the to-be-marketed formulation.

There are three important aspects of the Fiasp PK/PD data as it compares to NovoLog to support the SC use in pediatric T1DM and T2DM patients:

1. Do Fiasp PK/PD differences from Novolog observed in adults preserved in pediatric population?
2. Are Fiasp PK/PD properties observed in pediatric population comparable to adults?
3. Do Fiasp PK/PD differences from Novolog observed in T1DM adults preserved in T2DM population?

These three PK/PD aspects are discussed below.

1. Are Fiasp PK/PD differences from Novolog observed in adults preserved in pediatric population?

The PK/PD properties for Fiasp in pediatric T1DM patients were assessed in two studies 4371 and 3888. Study 4371 and 3888 were randomized, single-center, double-blind, single-dose, two-period cross-over study investigating the PK properties of Fiasp and NovoLog® in children (6-11 years), adolescents (12-17 years) and adults (18-64 years) with T1DM (Figure 3). In addition, PD properties were investigated using a meal test setting. In studies 4371 and 3888 (pediatric and adult subjects with T1DM), a SC dose of 0.2 Unit/kg body weight was used for both Fiasp and NovoLog®. This dose is close to the average pre-meal dose administered in the therapeutic confirmatory efficacy and safety studies with pediatric subjects (study 4101) and adult subjects.

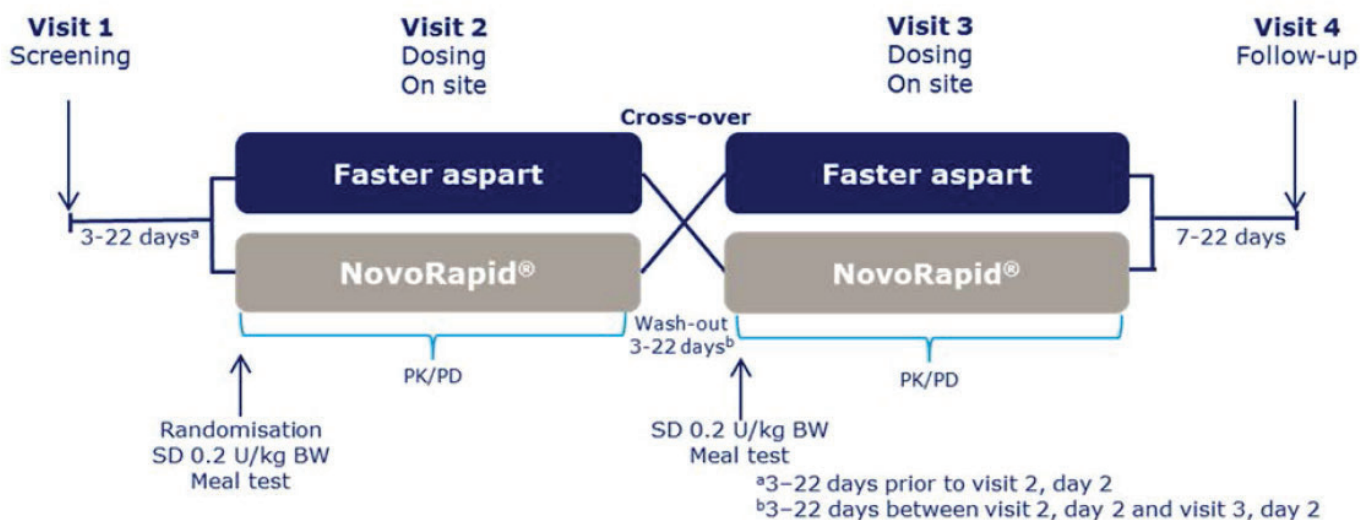
The subjects received an overnight infusion of human soluble insulin (Actrapid®) or glucose to ensure the PG level was within the target range 5.6–8.9 mmol/L (100–160 mg/dL). Fiasp or NovoLog® was administered immediately before intake of a standardized liquid meal. The liquid meal (Composition in study 4371: 62% carbohydrates, 16% protein, and 22% fat; Composition in study 3888: 68% carbohydrates, 17% protein, and 15% fat) was to be ingested as fast as possible preferably within 8 minutes after dosing. The amount of the meal was adjusted to subjects' body weight at visit 2 day 1. The PK and PD properties of Fiasp and NovoLog® were assessed by collecting blood samples for insulin aspart analysis for 6-12 hours after study product administration.

In study 4371, free as well as total serum insulin aspart was analyzed for the assessment of PK profiles. In study 3888, only free serum insulin aspart was analyzed. During the original NDA submission, the free

insulin aspart assay was deemed to unreliable (see OCP review dated 09/06/2017), and only total serum insulin aspart concentration were relied for PK conclusions. Thus, for description of comparative PK properties of Fiasp and NovoLog, study 4371 was relied upon, whereas for PD properties both studies 4371 and 3888 were utilized.

In order to describe the PK properties of Fiasp, elements of the PK profiles were evaluated by analyzing selected temporal components (i.e., onset, early, late and total exposure/action). The PD endpoints used to evaluate the PD properties of Fiasp based on meal test was analyzed focusing on the first 2 hours after dose administration. No interventions were made during the first 60 minutes following study product administration, and most of the interventions in children and adults occurred between 120 minutes and 180 minutes in study 4371 and 120 minutes and 300 minutes in study 3888.

Figure 3. Schematic of study design



Source: Module 5.3.3.3. Study report 4371, Page 31

The PK profile of Fiasp in children and adolescents with T1DM (study 4371) was left-shifted compared to that of NovoLog®, showing a greater early insulin absorption and exposure with Fiasp (Figures 4 and 5).

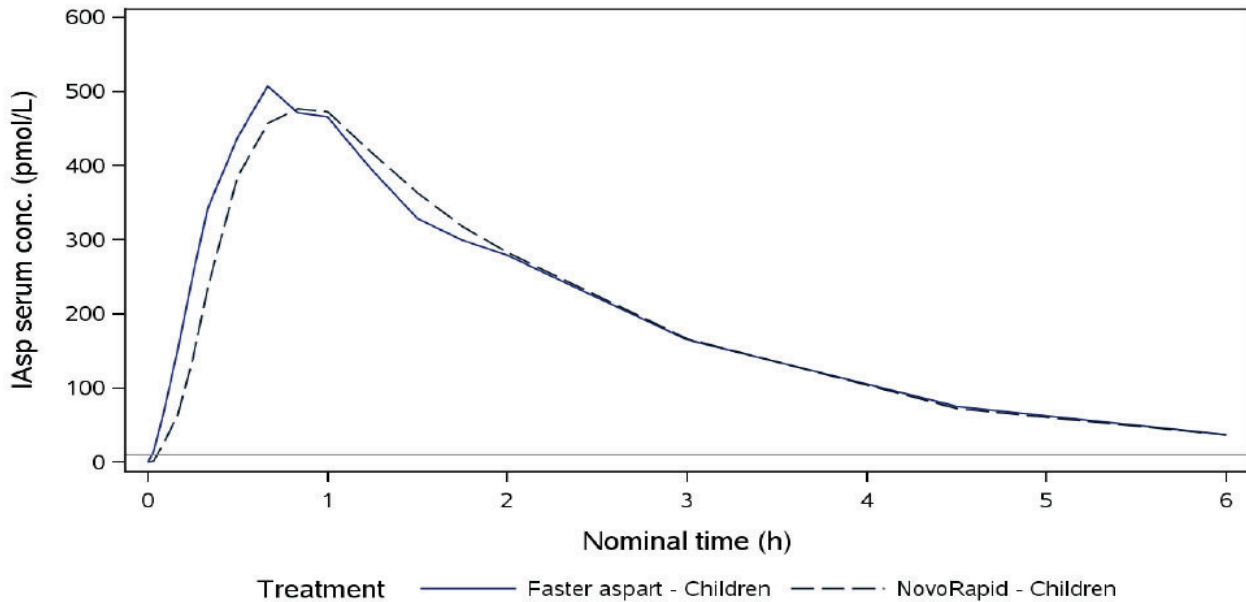
In children, estimates of mean onset of appearance were 2.4 minutes with Fiasp and 5.4 minutes with NovoLog®. The estimates of mean time to 50% $C_{max, IAsp}$ were 20.8 minutes with Fiasp and 27.1 minutes with NovoLog® in children. In adolescents, estimates of mean onset of appearance were 3.2 minutes with Fiasp and 5.0 minutes with NovoLog®. Estimates of mean time to 50% $C_{max, IAsp}$ were 21.9 minutes with Fiasp and 28.1 minutes with NovoLog® in adolescents (Table 2). In children and adolescents, the estimated early insulin aspart exposure was statistically significantly greater for Fiasp compared to NovoLog® for the first 30 minutes after administration (Table 3). This difference was less at 1 and 2 hours after SC administration.

In children, both duration of exposure (measured as time to late 50% $C_{max, IAsp}$) of insulin aspart and late insulin aspart exposure ($AUC_{IAsp, 2-12}$ hours) were comparable between Fiasp and NovoLog®. In adolescents, the estimated time to late 50% $C_{max, IAsp}$ was 12.3 minutes shorter for Fiasp compared to NovoLog®. Exposure during the later part of the PK profile ($AUC_{IAsp, 2-12h}$) of Fiasp was statistically significantly lower by 14% compared to NovoLog® (Table 4).

In children and adolescents, the total exposure of insulin aspart ($AUC_{IAsp,0-12h}$) and the maximum insulin aspart concentration ($C_{max,IAsp}$) were comparable for Fiasp and NovoLog® (Table 5).

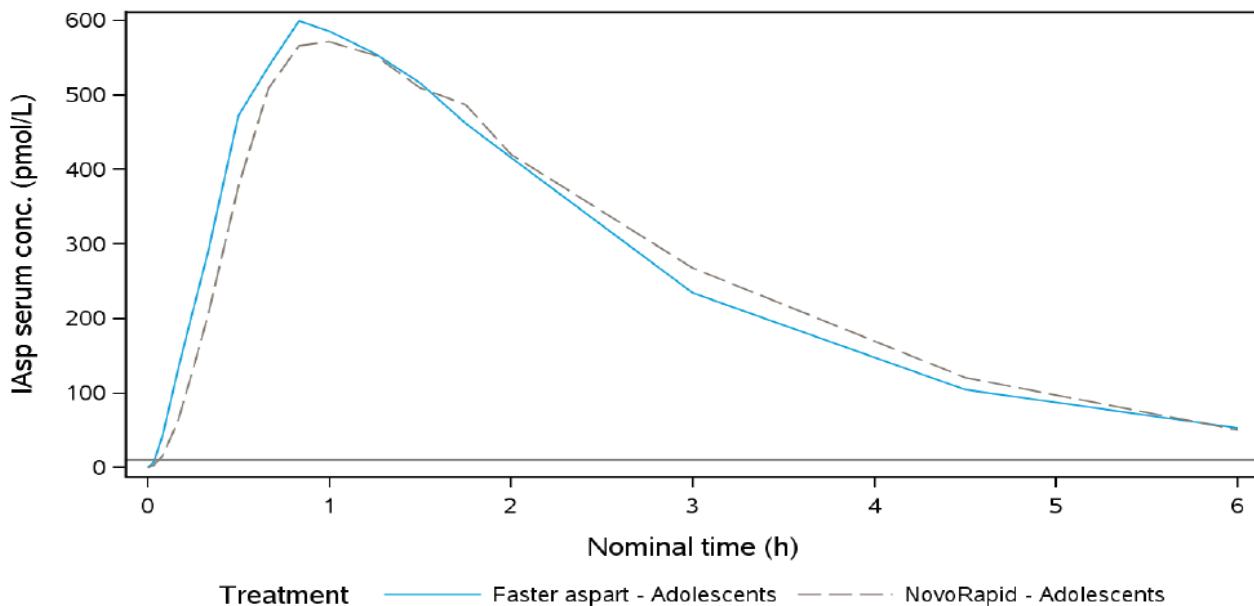
These PK differences between Fiasp and NovoLog® were generally similar to that observed in adults SC injection in the original NDA for Fiasp in adults (Refer to OCP review dated 09/06/2017).

Figure 4. Mean total insulin aspart profiles (0 to 6 hours) in children with T1DM (study 4371)



Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 19

Figure 5. Mean total insulin aspart profiles (0 to 6 hours) in adolescents with T1DM (study 4371)



Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 20

Table 2. Mean onset of exposure in adults with T1DM in pediatrics T1DM (study 4371)

Children

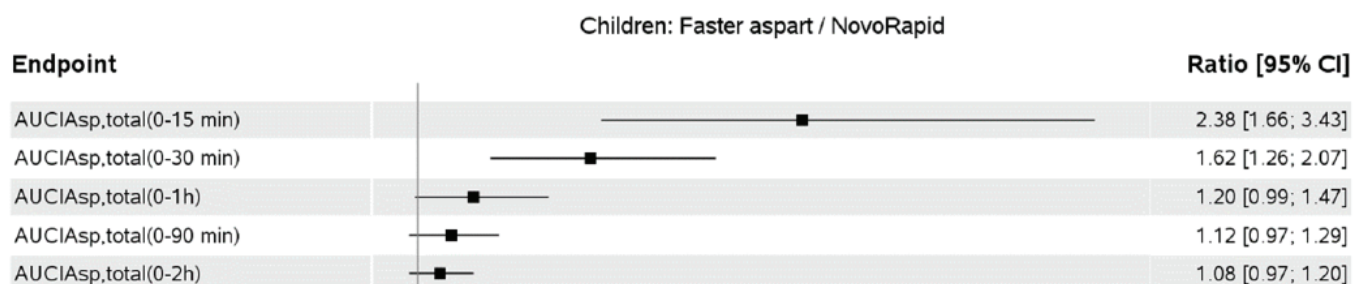
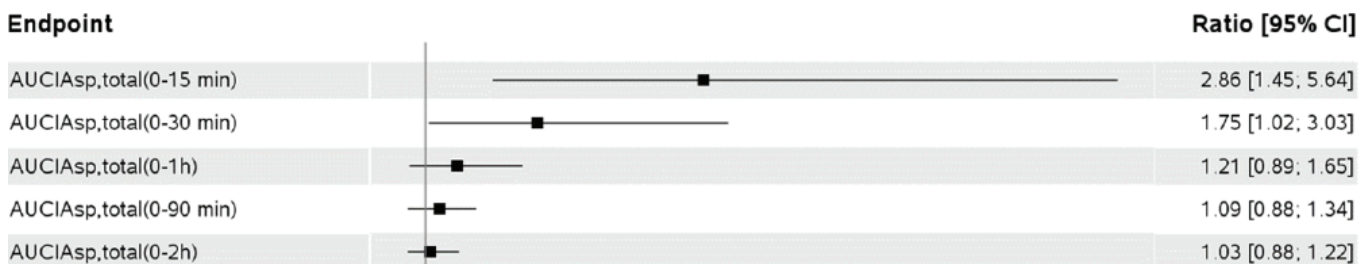
Endpoint	Number of subjects		Estimated mean (minutes)		Treatment difference [95% CI] (min)	Treatment ratio [95% CI]
	Faster aspart	Novo Rapid®	Faster aspart	Novo Rapid®	Faster aspart- NovoRapid®	Faster aspart/ NovoRapid®
Onset of appearance	12	12	2.4	5.4	-2.9 [-4.4; -1.5]	0.45 [0.24; 0.68]
Time to 50% C _{max,IAsp}	12	12	20.8	27.1	-6.3 [-13.1; 0.6]	0.77 [0.56; 1.01]
t _{max,IAsp}	12	12	48.1	64.8	-16.7 [-33.9; 0.6]	0.74 [0.53; 0.99]

Adolescents

Endpoint	Number of subjects		Estimated mean (minutes)		Treatment difference [95% CI] (min)	Treatment ratio [95% CI]
	Faster aspart	Novo Rapid®	Faster aspart	Novo Rapid®	Faster aspart- NovoRapid®	Faster aspart/ NovoRapid®
Onset of appearance	16	16	3.2	5.0	-1.8 [-3.2; -0.5]	0.64 [0.43; 0.88]
Time to 50% C _{max,IAsp}	16	16	21.9	28.1	-6.3 [-10.1; -2.5]	0.78 [0.66; 0.90]
t _{max,IAsp}	16	16	65.6	63.3	2.3 [-13.2; 17.8]	1.04 [0.81; 1.32]

Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Pages 21 and 22

Table 3. Treatment ratios and 95% CI for insulin exposure (AUC_{IAsp}) in pediatrics T1DM (study 4371)



Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 23

Table 4. Duration of exposure and late exposure in pediatrics T1DM (study 4371)**Children**

Endpoint	Number of subjects		Estimated mean		Treatment difference [95% CI]	Treatment ratio [95% CI]
	Faster aspart	Novo Rapid®	Faster aspart	Novo Rapid®	Faster aspart- NovoRapid®	Faster aspart/ NovoRapid®
Time to late 50% C_{max,IAsp} (min)	12	12	130.5	130.9	-0.5 [-34.1; 33.1]	
AUC_{IAsp,2-12h} (pmol*h/L)	12	12	446	438		1.02 [0.85; 1.21]

Adolescents

Endpoint	Number of subjects		Estimated mean		Treatment difference [95% CI]	Treatment ratio [95% CI]
	Faster aspart	Novo Rapid®	Faster aspart	Novo Rapid®	Faster aspart- NovoRapid®	Faster aspart/ NovoRapid®
Time to late 50% C_{max,IAsp} (min)	16	16	152.3	164.6	-12.3 [-39.0; 14.5]	
AUC_{IAsp,2-12 h} (pmol*h/L)	16	16	653	702		0.93 [0.80; 1.08]

Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 24

Table 5. Treatment ratios and 95% CI for total (AUC_{IAsp,0-t}) and maximum (C_{max,IAsp}) insulin exposure in pediatrics T1DM (study 4371)**Children**

Endpoint	Number of subjects		Estimated mean		Treatment ratio [95% CI]
	Faster aspart	Novo Rapid®	Faster aspart	Novo Rapid®	Faster aspart- NovoRapid®
AUC_{IAsp,0-12h} (pmol*h/L)	12	12	1161	1139	1.02 [0.95; 1.10]
C_{max,IAsp} (pmol/L)	12	12	536	534	1.00 [0.76; 1.33]

Adolescents

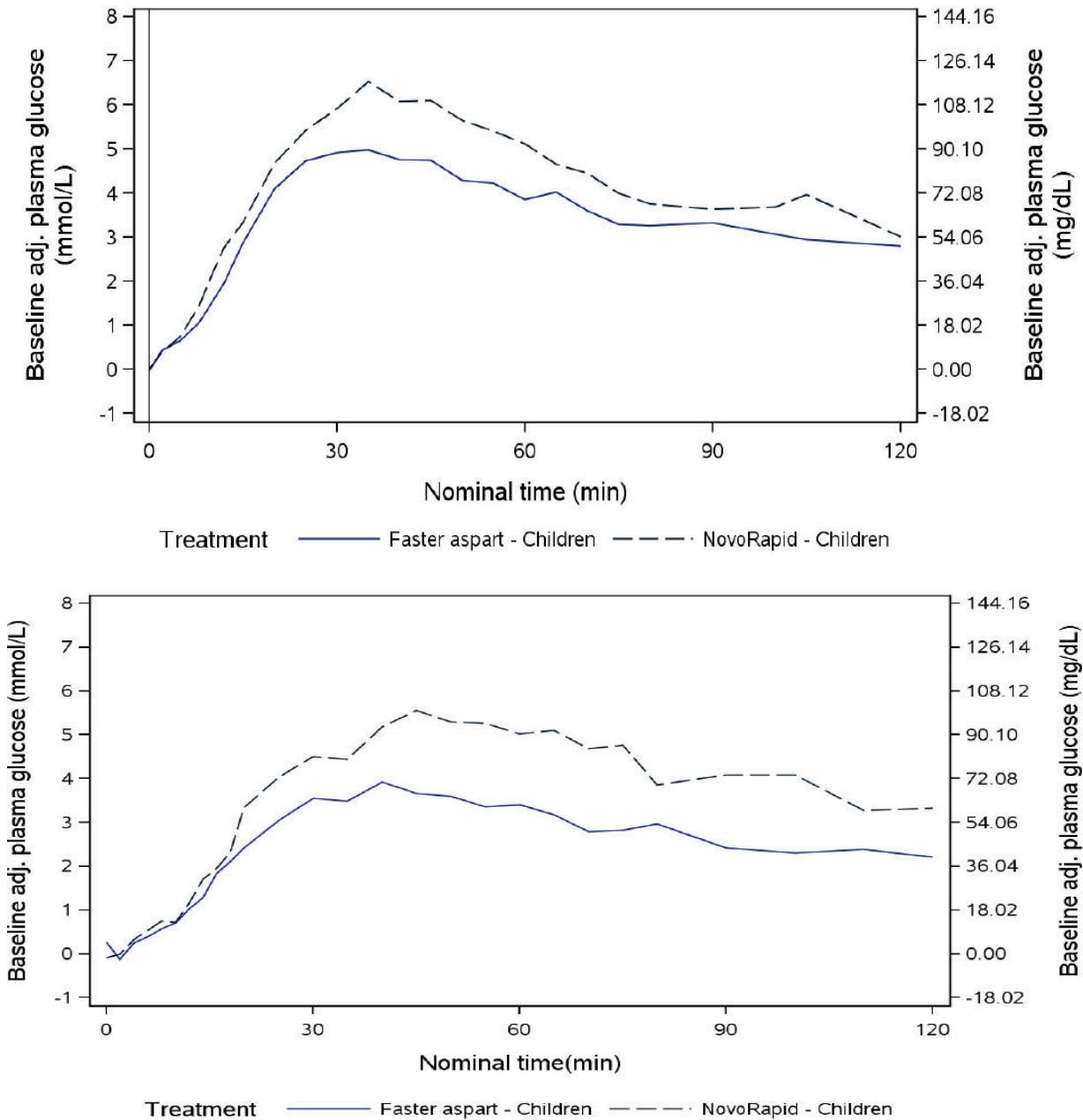
Endpoint	Number of subjects		Estimated mean		Treatment ratio [95% CI]
	Faster aspart	Novo Rapid®	Faster aspart	Novo Rapid®	Faster aspart- NovoRapid®
AUC_{IAsp,0-12h} (pmol*h/L)	16	16	1461	1448	1.01 [0.96; 1.06]
C_{max,IAsp} (pmol/L)	16	16	555	540	1.03 [0.88; 1.20]

Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 25

The PD properties of Fiasp and NovoLog® were compared in children and adolescents with T1DM during a meal test in the clinical pharmacology studies 4371 and 3888, as well as in a subgroup of pediatric subjects aged ≥8 years with T1DM in the therapeutic confirmatory study 4101 (see Figure 8 and

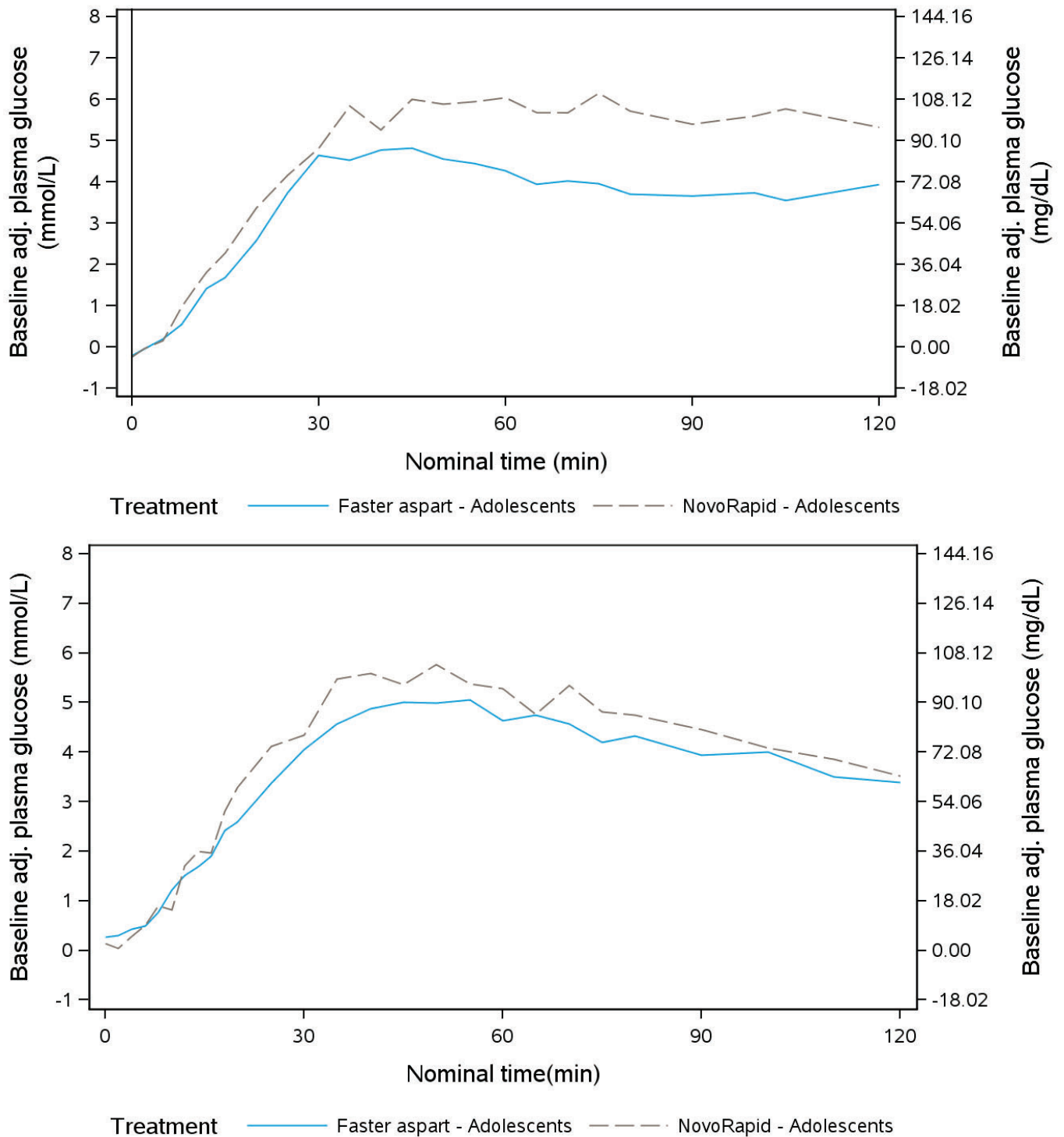
section 2.3.2 for further details on study 4101). For children and adolescents with T1DM in the clinical pharmacology studies 4371 and 3888, the plasma glucose (PG) profiles for the first 2 hours were lower for Fiasp compared to that for NovoLog®, indicating a trend for numerically lower PG excursion with Fiasp compared to NovoLog® (Figure 6 and 7). Note that beyond 2 hours the PD profile was impacted by oral carbohydrate interventions. No insulin or glucose infusions were given as intervention during the meal test. Given that meal test studies are less controlled as compared to euglycemic studies, the PD conclusions from studies 4371 and 3888 are limited in nature.

Figure 6. Mean baseline adjusted plasma glucose profiles for children with T1DM (top: study 4371; bottom: study 3888)



Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 34

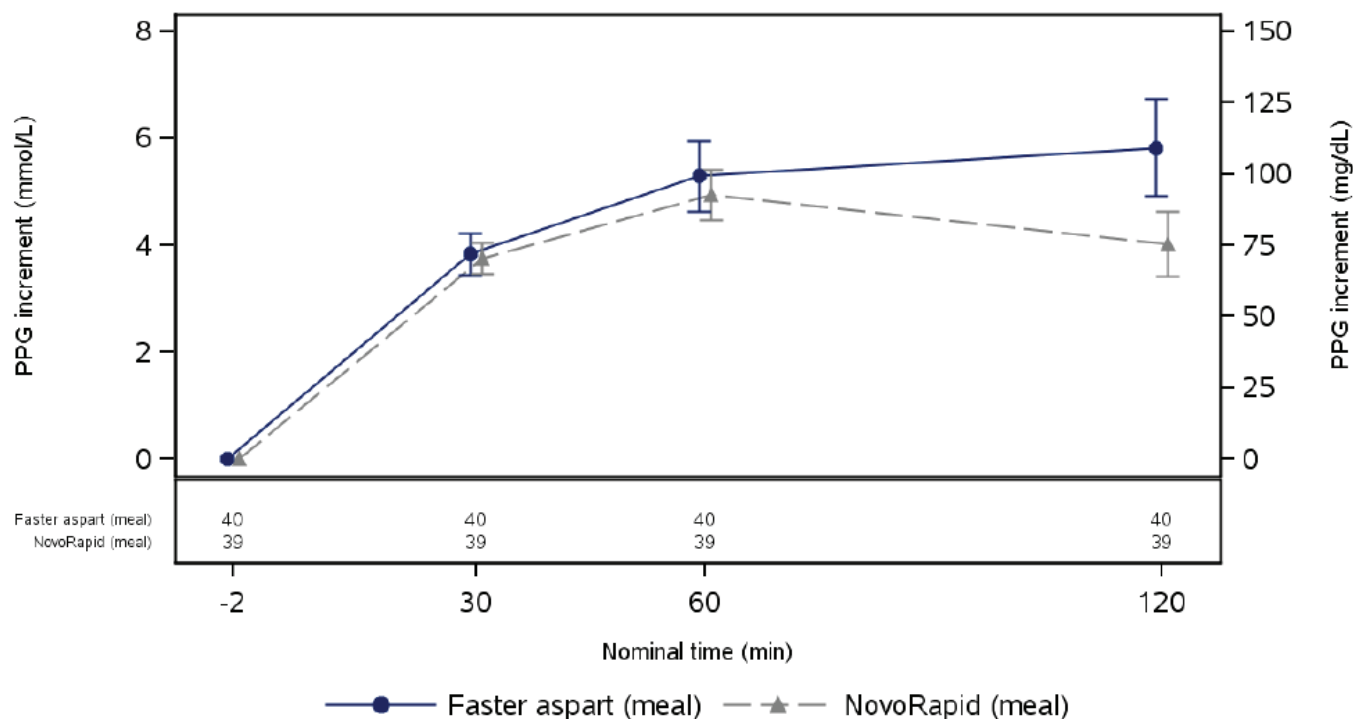
Figure 7. Mean baseline adjusted plasma glucose profiles for adolescents with T1DM (top: study 4371; bottom: study 3888)



Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 35

In the therapeutic confirmatory study 4101, PPG in a standardized meal test was evaluated at baseline and after 26 weeks of treatment in a subset of the study population aged 8 to <18 years of age. The PG profiles for the first 2 hours after 26 weeks of treatment are shown in Figure 8 and are generally similar up to 60 min for Fiasp and NovoLog.

Figure 8. Post prandial glucose increments at week 26, 0–2 hours in children and adolescents with T1DM (study 4101)



Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 36

2. Are Fiasp PK/PD properties observed in pediatric population comparable to adults?

The PK/PD profile of Fiasp was generally comparable between children, adolescents, and adults. This comparison was supported by data from studies 4371 and 3888. The study design for these two studies has been described above in section 2.3.1. The PK analysis indicated that AUC_{12h} and C_{max} was higher in pediatrics (~25-50%) compared to adults (Table 6 and Figure 9). The baseline mean total antibody level for children (30.3 %B/T) and adolescents (36.0 %B/T) were higher than for adults (18.9 %B/T). After adjusting for antibody level AUC_{12h} and C_{max} were comparable for children and adolescents compared to adults (Table 6). These findings are not unusual considering the total insulin assay measures free and antibody bound insulin and are consistent with the observations from original NDA submission where a trend for an increase in total insulin aspart exposure with an increase in the level of total anti-insulin aspart antibodies was observed following SC administration of Fiasp (Refer to OCP review dated 09/06/2017). Total glucose lowering effect for Fiasp did not appear to be affected by the level of total anti-insulin aspart antibodies.

Note that for all the results of age group comparisons in study 4371 presented below, the PK endpoints based on total insulin aspart concentrations were adjusted for antibody level.

The estimated onset of appearance of Fiasp and estimated time to 50% $C_{max, IAsp}$ were comparable across children, adolescents, and adults (Table 7). Likewise, the total exposure ($AUC_{IAsp, 0-12h}$) of Fiasp was comparable across age groups, with estimated age group ratios of 0.97 [0.80; 1.17]95%CI for children versus adults and 1.07 [0.85; 1.34]95%CI for adolescents versus adults (Table 7). The estimated age group ratio for the maximum concentration ($C_{max, IAsp}$) was 1.12 [0.82; 1.53]95%CI for children versus adults and 1.04 [0.77; 1.40] 95%CI for adolescents versus adults (Table 7).

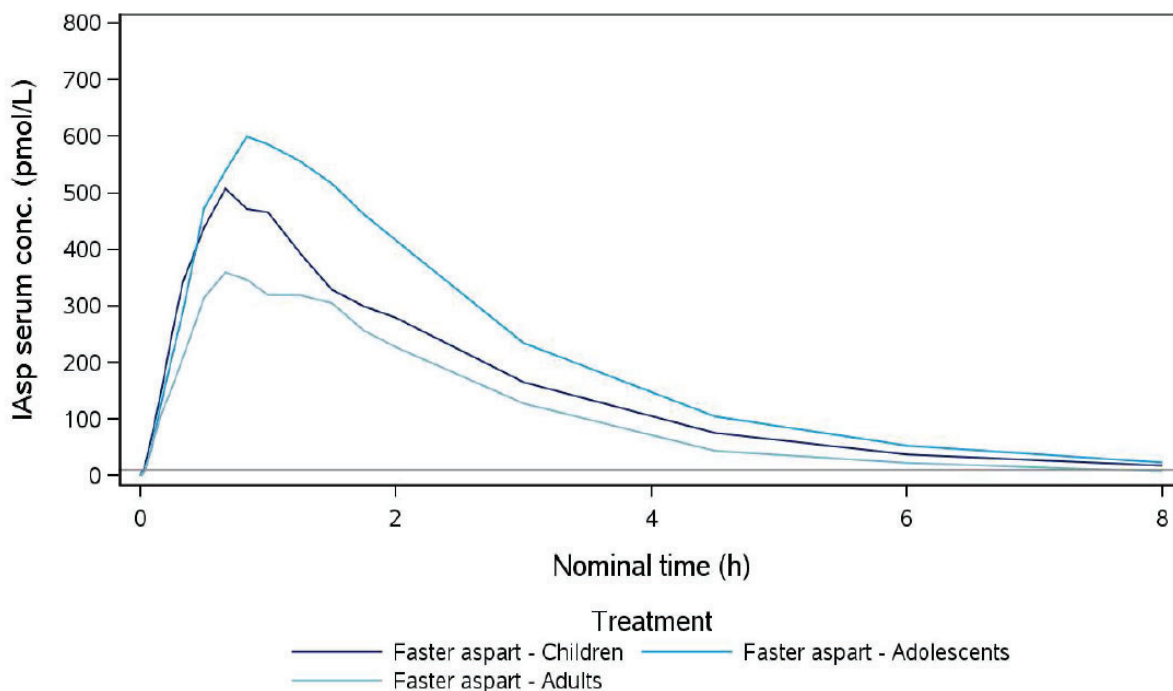
A similar pattern was observed for NovoLog® (see Study 4371). When comparing the total exposure and maximum concentration for Fiasp versus NovoLog® (Study 4371), the estimated treatment ratio was similar across age groups and there was no statistically significant interaction between age group and treatment.

Table 6. AUC and C_{max} comparison in age groups by ADA status.

Total Fiasp exposure	Estimate [95% CI]	
	Not ADA adjusted	ADA adjusted
AUC_{0-12hr}		
Fiasp: Children / Adults	1.24 [0.90; 1.71]	0.97 [0.80; 1.17]
Fiasp: Adolescents / Adults	1.56 [1.13; 2.17]	1.07 [0.85; 1.34]
NovoLog: Children / Adults	1.15 [0.84; 1.58]	0.89 [0.74; 1.08]
NovoLog: Adolescents / Adults	1.47 [1.06; 2.03]	1.00 [0.79; 1.25]
C_{max}		
Fiasp: Children / Adults	1.36 [0.96; 1.94]	1.12 [0.82; 1.53]
Fiasp: Adolescents / Adults	1.41 [1.00; 2.00]	1.04 [0.77; 1.40]
NovoLog: Children / Adults	1.38 [0.98; 1.97]	1.10 [0.80; 1.50]
NovoLog: Adolescents / Adults	1.40 [0.99; 1.98]	0.99 [0.74; 1.33]

Source: Reviewer’s summary of data submitted in Module 5.3.3.3. Study report 4371

Figure 9. Mean total insulin aspart profiles – Fiasp (IASptotal), 0-8 hours.



Source: Module 5.3.3.3. Study report 4371, Page 109

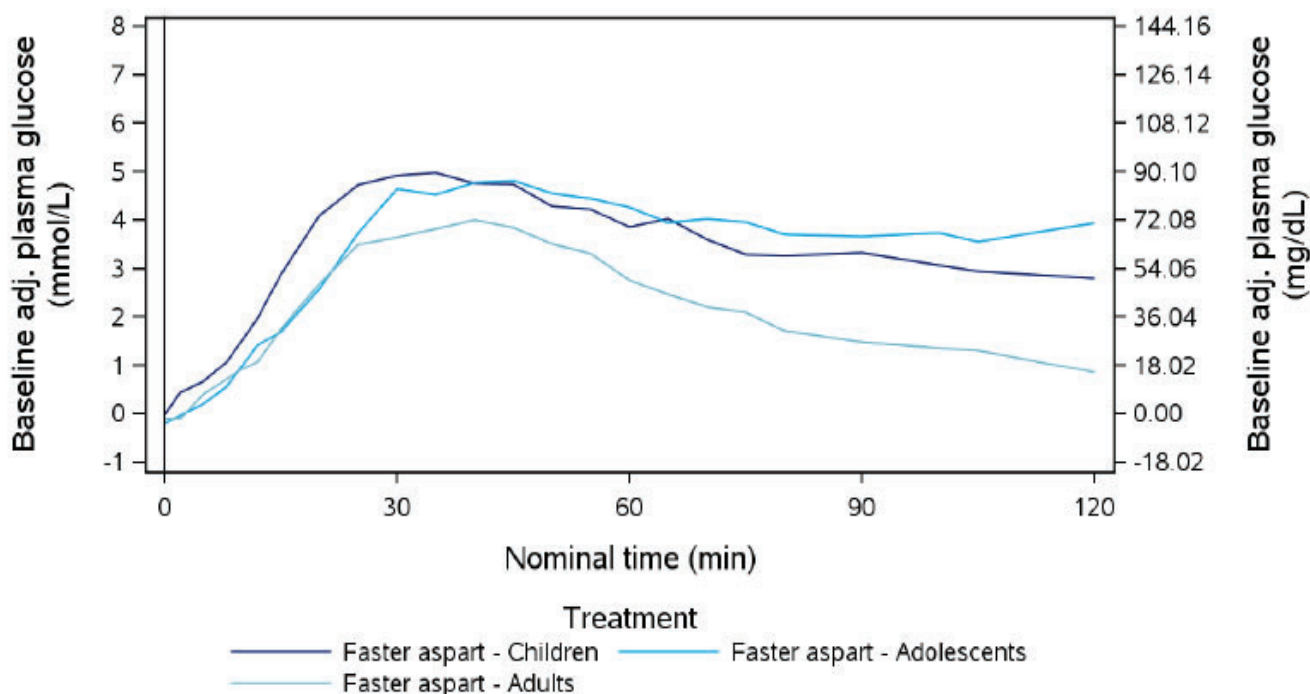
Table 7. Onset and total exposure of insulin aspart across age groups in subjects with T1DM (study 4371)

Endpoint	Children	Adolescents	Adults
Number of subjects	12	16	13
Onset of appearance (min)	2.5	3.2	3.3
Time to 50% C _{max,Iasp} (min)	20.7	21.1	22.6
Total exposure	Ratio Children vs adults [95% CI]	Ratio Adolescents vs adults [95% CI]	Age-by-treatment interaction p-value
AUC _{IAsp, 0-12h}	0.97 [0.80; 1.17]	1.07 [0.85; 1.34]	0.095
C _{max,Iasp}	1.12 [0.82; 1.53]	1.04 [0.77; 1.40]	0.850

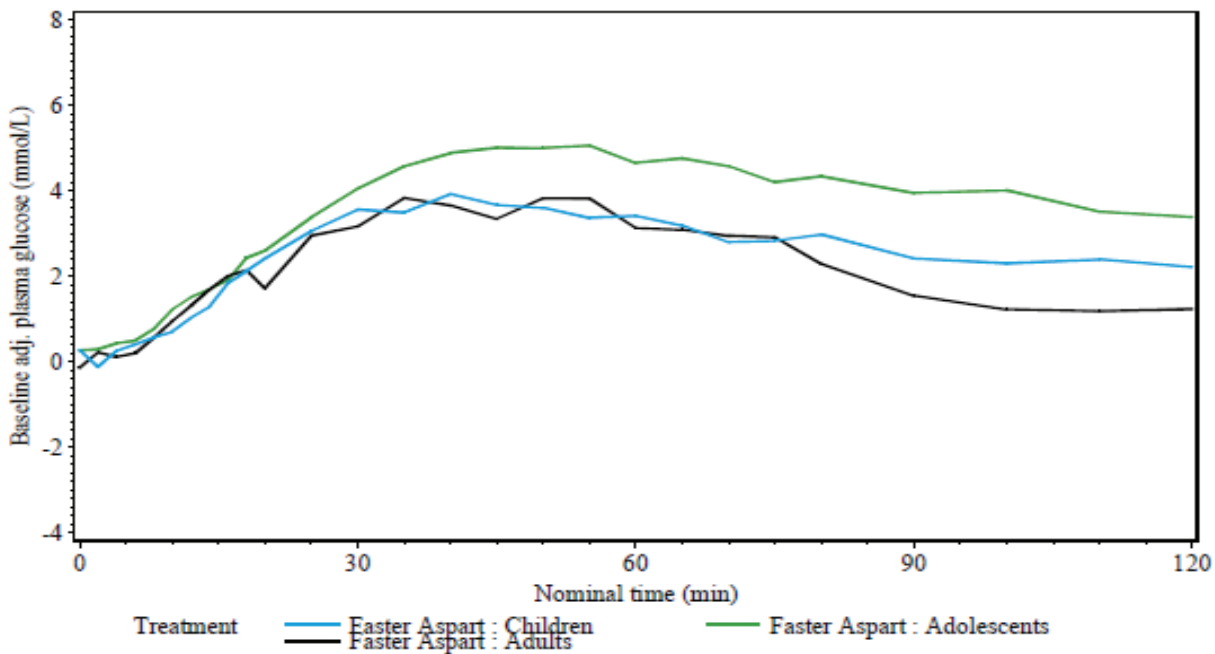
Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 26

Mean baseline adjusted PG profiles for all age groups for Fiasp from 0 to 120 minutes are shown in Figure 10. During the first 2 hours after administration of Fiasp, the PG profile for children and adolescents appeared to be higher compared to that for adults in study 4371 but not in study 3888.

Figure 10. PD - plasma glucose - single-dose - baseline adjusted mean profiles (-1 to 6 hours), study 4371 (top) and study 3888 (bottom)



Source: Module 5.3.3.3. Study report 4371, Page 120

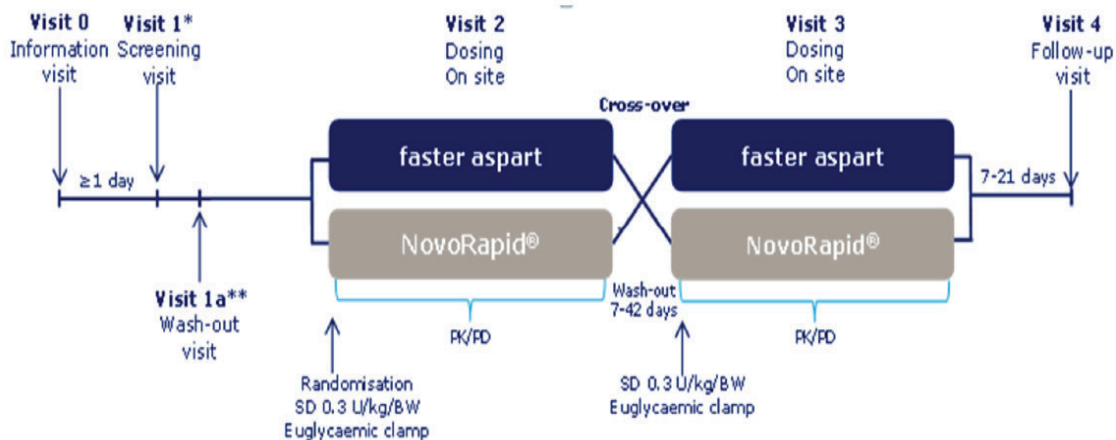


Source: Module 5.3.3.3. Study report 3888, Page 92

3. Do Fiasp PK/PD differences from Novolog observed in T1DM adults preserved in T2DM population?

To support the relevance of the safety and efficacy data from pediatric T1DM and adult T2DM to pediatric T2DM patients the sponsor conducted study 4265 in adult T2DM patients. Study 4265 evaluated the PK/PD of Fiasp and Novolog in adult 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 in a euglycemic clamp setting in subjects with T2DM (Figure 11). The dosing visits were separated by a wash-out period of 7–42 days during which the subjects could resume the insulin regimen followed immediately before the first dosing visit (i.e. with no oral antidiabetic drug therapy except metformin in any of the subjects). For both the IMPs, the dose level was 0.3 Unit/kg body weight.

Figure 11. Schematic of study 4265 design



Source: Module 5.3.4.2. Study report 4265, Page 26

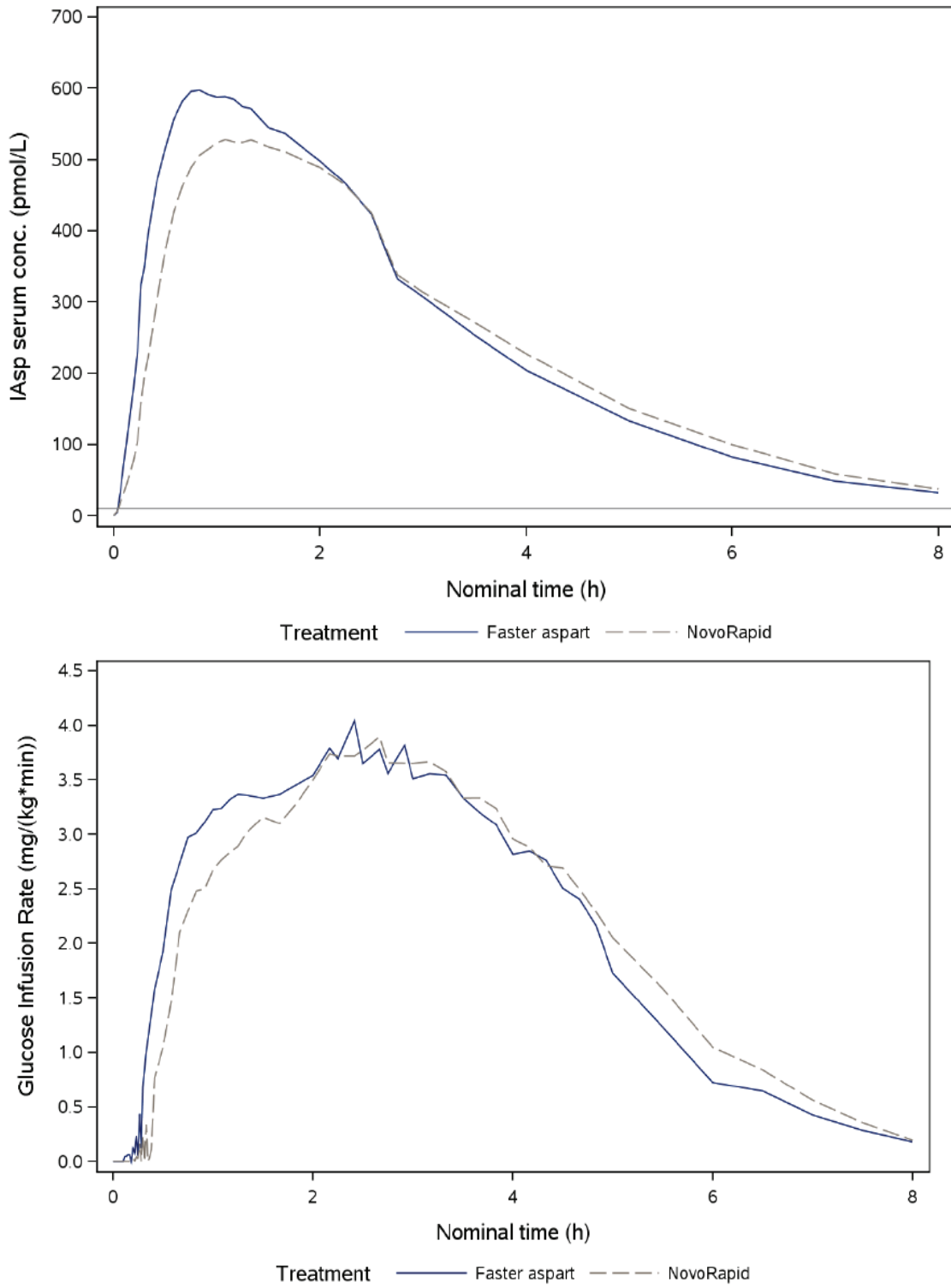
The mean age of the 61 subjects randomized and exposed to treatment was 61.8 years. The majority of subjects were male (73.8%), and all subjects were white. The mean BMI was 29.6 kg/m². Mean duration of diabetes was 20.8 years, and mean HbA1c at baseline was 7.6%. In total, 19 subjects had C-peptide value <0.3 nmol/L, 33 subjects between ≥0.3 – <0.6 nmol/L and 9 subjects between ≥0.6 – ≤0.9 nmol/L. No subject had C-peptide value >0.9 nmol/L.

The PK profiles of Fiasp in study 4265 in adults with T2DM was left-shifted compared to NovoLog®, showing a greater early insulin exposure with Fiasp (Figure 12).

In adults with T2DM, Fiasp showed earlier onset of exposure, greater early exposure compared to NovoLog® with a comparable total insulin exposure (Table 8). In adults with T2DM, the mean onset of appearance of insulin aspart was 3.1 minutes for Fiasp compared to 4.3 minutes for NovoLog®. The time to 50% C_{max,IAsp} was 19.0 minutes for Fiasp compared to 26.7 minutes for NovoLog®. However, the estimated time to late 50% C_{max,IAsp} (duration of exposure) was 30 minutes shorter with Fiasp compared to NovoLog®. Exposure during the last part of the PK profile (AUC_{IAsp,2-12h}) of Fiasp was statistically significantly lower by 11% compared to NovoLog®. In adults with T2DM, the total insulin exposure (measured as AUC_{IAsp,0-12h}) was similar between Fiasp and NovoLog®, while the maximum insulin aspart concentration (C_{max,IAsp}) was 12% higher for Fiasp compared to NovoLog®. However, this 12% difference is not considered to be a clinically relevant difference, supported by the observation that total glucose-lowering effect in study 4265 was similar for Fiasp and NovoLog (see below). In adults with T2DM, the median terminal half-life was 80.6 minutes for Fiasp and 85.9 minutes for NovoLog®.

The mean GIR profiles for Fiasp were left-shifted compared to NovoLog®, indicating a greater early glucose-lowering effect with Fiasp compared to NovoLog®/ NovoLog® (Figure 12). Fiasp showed earlier onset of glucose-lowering effect, greater early glucose-lowering effect compared to NovoLog® while maintaining a comparable total and maximum glucose-lowering effect (Table 8). Onset of action was 22.4 minutes for Fiasp compared to 31.3 minutes for NovoLog®. Time to 50% GIR_{max} was 39.3 minutes for Fiasp and 51.1 minutes for NovoLog. The tGIR_{max} was 150.9 minutes for Fiasp compared to 155.7 minutes for NovoLog®. However, the estimated time to late 50% GIR_{max} was 14.4 minutes earlier with Fiasp compared to that with NovoLog®. In study 4265, the total glucose-lowering effect (measured as AUC_{GIR,0-t}) and the maximum observed GIR (GIR_{max}) for Fiasp was comparable to NovoLog®. Overall, the PK/PD profile of Fiasp and differences observed with Novolog in subjects with T2DM were consistent with those observed in subjects with T1DM.

Figure 12. Mean PK (top) and mean GIR (bottom) profiles of Fiasp and NovoLog in study 4265.



Source: Module 5.3.4.2. Study report 4265, Pages 111 and 120

Table 8. PK (left) and PD (right) parameters from study 4265.

	Fiasp	NovoLog		Fiasp	NovoLog
	Estimated mean (min)			Estimated mean (min)	
Onset of Appearance	3.1	4.3	Onset of Action	22.4	31.3
Time to 50% C _{max}	19	26.7	Time to 50% GIR _{max}	39.3	51.1
T _{max}	62.7	84.5	TGIR _{max}	150.9	155.69
Time to late 50% C _{max}	180	210	Time to late 50% GIR _{max}	283.3	297.7
	Ratio [95% CI]			Ratio [95% CI]	
AUC _{15min}	2.5		AUC _{GIR,30min}	2.47	
AUC _{30min}	1.85		AUC _{GIR,60min}	1.48	
AUC _{1hr}	1.4		AUC _{GIR,90min}	1.35	
C _{max}	1.12 [1.3,1.2]		GIR _{max}	1.03 [0.9,1.1]	
AUC ₀₋₁₂	1.00 [0.9,1.1]		AUC _{GIR,0-12}	1.01[0.9,1.1]	

Source: Reviewer's summary of data submitted in Module 5.3.4.2. Study report 4265

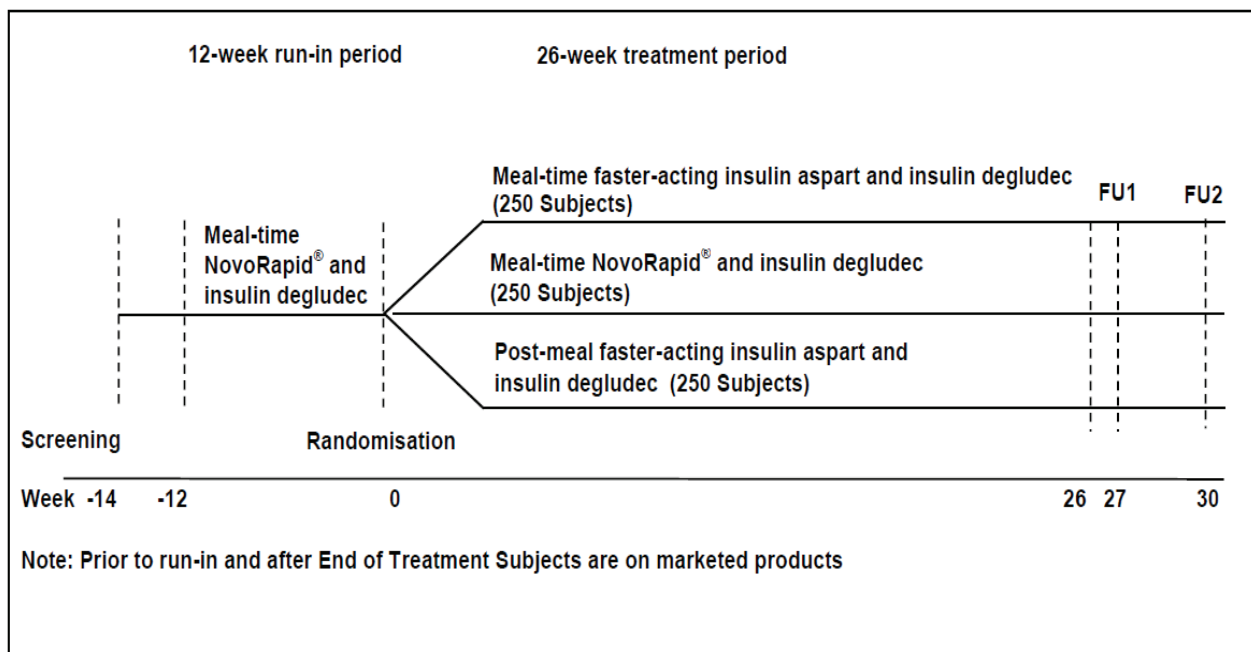
2.3.2. What are the relevant components of the efficacy comparison between Fiasp and NovoLog in study 4101 as they may relate to the PK/PD observations?

While the acceptability of the efficacy/safety claims is deferred to Statistical/Clinical reviews, certain relevant observations from Study 4101 are described here. This was a 26-week, randomized, partly double-blind, multicenter, multinational, active controlled, treat-to-target, 3-armed parallel-group study with a 12-week run-in period (Figure 13). The study compared effect and safety of mealtime Fiasp versus mealtime NovoLog®, both in combination with insulin degludec once daily in a basal-bolus regimen, in subjects with T1DM aged 1 year to less than 18 years of age.

The study also included a 26-week open-label postmeal Fiasp dosing group in combination with insulin degludec. Mealtime dosing was defined as injecting the bolus insulin 0–2 minutes before the meal and postmeal dosing was defined as injecting the bolus insulin 20 minutes after the start of the meal. During the treatment period, the bolus insulin was titrated to the pre-meal glycemic target of 4.0–8.0 mmol/L [71–145 mg/dL] and bedtime glycemic target of 6.7–10.0 mmol/L [120–180 mg/dL] in a treat-to-target approach. The study also compared glycemic control of mealtime Fiasp or postmeal Fiasp versus mealtime NovoLog® in relation to a standardized meal test and continuous glucose monitoring (CGM) in a subgroup of subjects aged ≥ 8 years at the time of screening. A total of 833 subjects were planned to enter the run-in period, and 750 subjects were planned for randomization.

The population consisted of male (53.9%) and female (46.1%) children and adolescents aged 2 to < 18 years with T1DM, with a mean age of 11.68 years (range 2 to 17 years), mean BMI of 19.66 kg/m² (range 11.8 to 33.5 kg/m²), mean duration of diabetes of 4.38 years (range 0.52 to 16.3 years) and mean HbA1c of 7.56 % (range: 4.9–10.6 %) (59.13 mmol/mol; range: 30.1 to 92.4 mmol/mol). The majority of the subjects were White (81.3%) or Asian (16.2%) and of non-Hispanic or non-Latino ethnicity (94.2%). The majority of subjects were enrolled in the US (25.1%), Russia (13.4%) and Japan (8.5%). There were ~143 patients in 12 to <18 years age category, ~100 patients in 6 to <12 years category and ~16 patients in 1 to <6 years category, in each treatment arm.

Figure 13. Schematic of study 4101 design



Source: Module 5.3.5.1. Study report 4101, Page 55

At week 26, insulin doses for Fiasp versus NovoLog® were as follows:

- The mean daily bolus insulin dose at week 26 was 23.3 Units (0.48 Unit/kg) for mealtime Fiasp, 23.5 Units (0.49 Unit/kg) for postmeal faster as part and 22.5 Units (0.47 Unit/kg) for NovoLog®. No apparent differences between treatment groups were identified among the observed doses at each main meal.
- The mean daily basal insulin dose at week 26 was 21.6 Units (0.43 Unit/kg) for mealtime Fiasp, 21.5 Units (0.43 Unit/kg) for postmeal faster as part and 20.7 Units (0.41 Unit/kg) for NovoLog®.
- The mean daily total insulin dose at week 26 was 44.8 Units (0.92 Unit/kg) for mealtime Fiasp, 45.0 Units (0.9 Unit/kg) for postmeal faster as part and 43.2 Units (0.88 Unit/kg) for NovoLog®.

At week 26, the mean basal: bolus split ratio was similar between treatment groups (47: 53 for mealtime Fiasp, 47: 53 for postmeal Fiasp and 46: 54 for NovoLog®). For further understanding of dose, the daily dose was separated by various pediatric age categories. The mean plots for daily bolus, basal and total dose for insulin in study 4101 for various pediatric age categories are shown in Figure 14. Note that in age category of 1 to <6 years only 16 patients received Fiasp whereas 14 received NovoLog. Out of these 16 patients, only 2 patients between 1 to < 3 years age received Fiasp, therefore the interpretation of the difference observed in daily dose in this age category is limited by the small sample size. Overall, there were no clinically meaningful differences apparent in the mean daily doses between Fiasp as compared to NovoLog in age categories.

The main results of the study, as reported, are as follows:

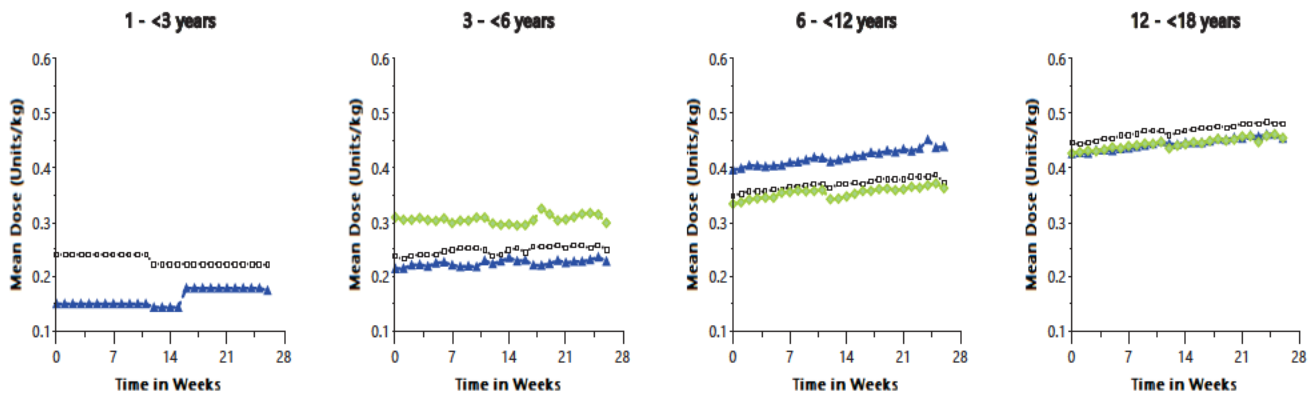
- Fiasp dosed at mealtime (estimated treatment difference (ETD): -0.17 % [-0.30; -0.03]95% CI) or postmeal (ETD: 0.13 % [-0.01; 0.26]95% CI) was confirmed to be effective, as both

administrations were confirmed to be non-inferior to mealtime NovoLog®, with regards to change from baseline to 26 weeks in HbA1c (Figure 15).

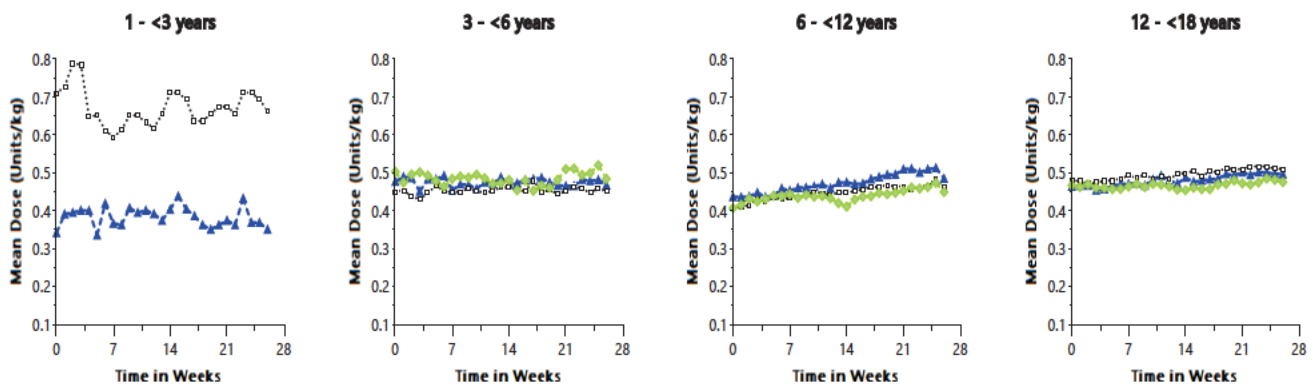
- Superiority of mealtime Fiasp versus mealtime NovoLog® was also confirmed for change from baseline to 26 weeks in HbA1c with ETD -0.17 % [-0.30; -0.03]95% CI.
- A statistically significant difference was demonstrated for mean 1-hour PPG increment over all 3 meals (SMPG) in favor of mealtime Fiasp compared to mealtime NovoLog® after 26 weeks of treatment. For postmeal Fiasp, this comparison was statistically significantly different in favor of mealtime NovoLog®.
- No statistically significant differences in overall rate of severe or BG confirmed hypoglycemic episodes were seen between mealtime Fiasp and NovoLog® or between postmeal Fiasp and NovoLog®. No statistically significant difference in rate of nocturnal severe or BG confirmed hypoglycemic episodes was observed between mealtime Fiasp and NovoLog®; for postmeal Fiasp, the rate was statistically significantly higher compared to mealtime NovoLog®. The overall safety profiles for Fiasp and NovoLog® were similar and as expected for insulin aspart.

Figure 14. Mean plot of daily insulin dose (basal, bolus and total) in Unit/kg by treatment week in study 4101. Black line shows Fiasp post meal, blue lines show Fiasp mealtime and green lines show Novolog mealtime.

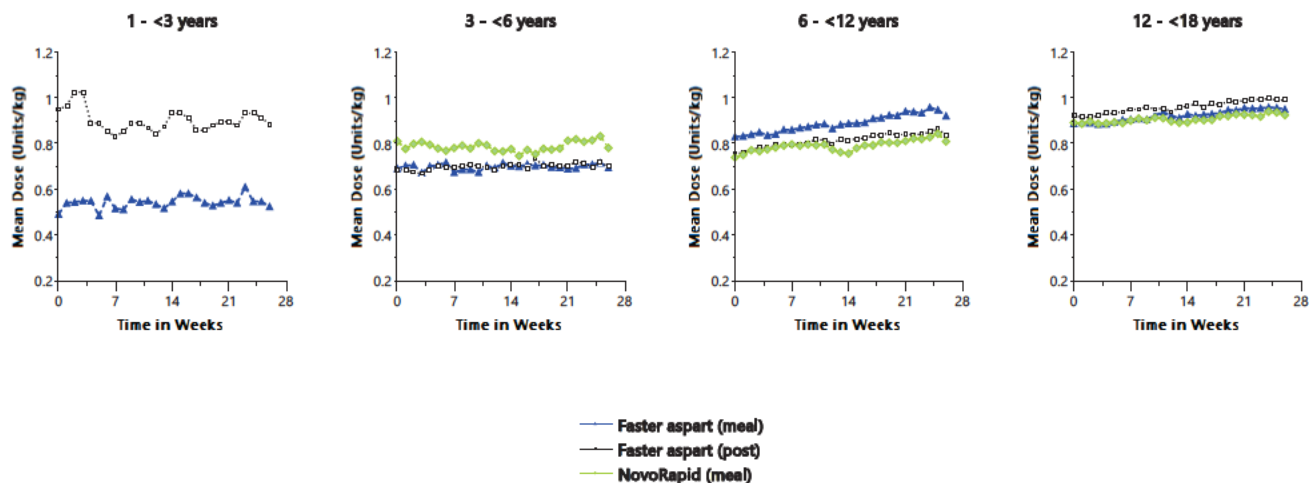
Daily Basal Insulin dose



Daily Bolus Insulin dose

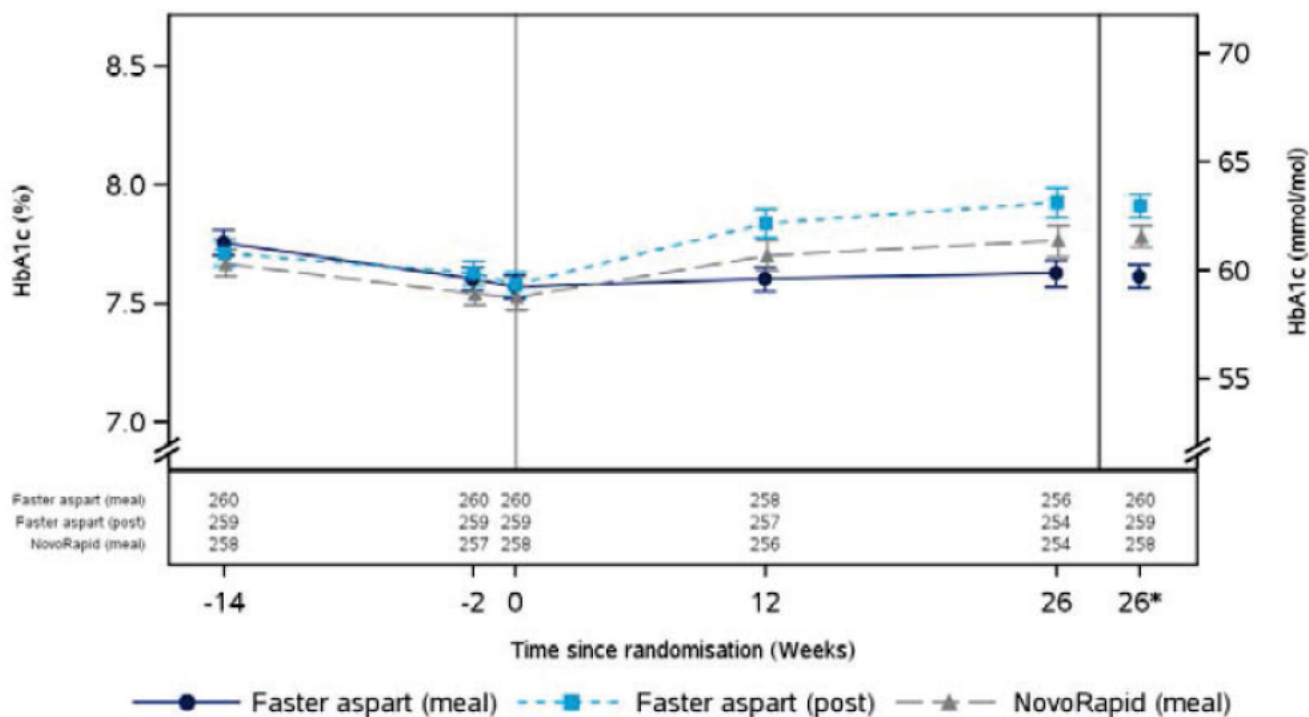


Total daily insulin dose



Source: Reviewer's analysis of data submitted within module 5.3.5.1. study report 4101

Figure 15. HbA_{1c} by treatment week - observed mean and ls mean plot in study 4101

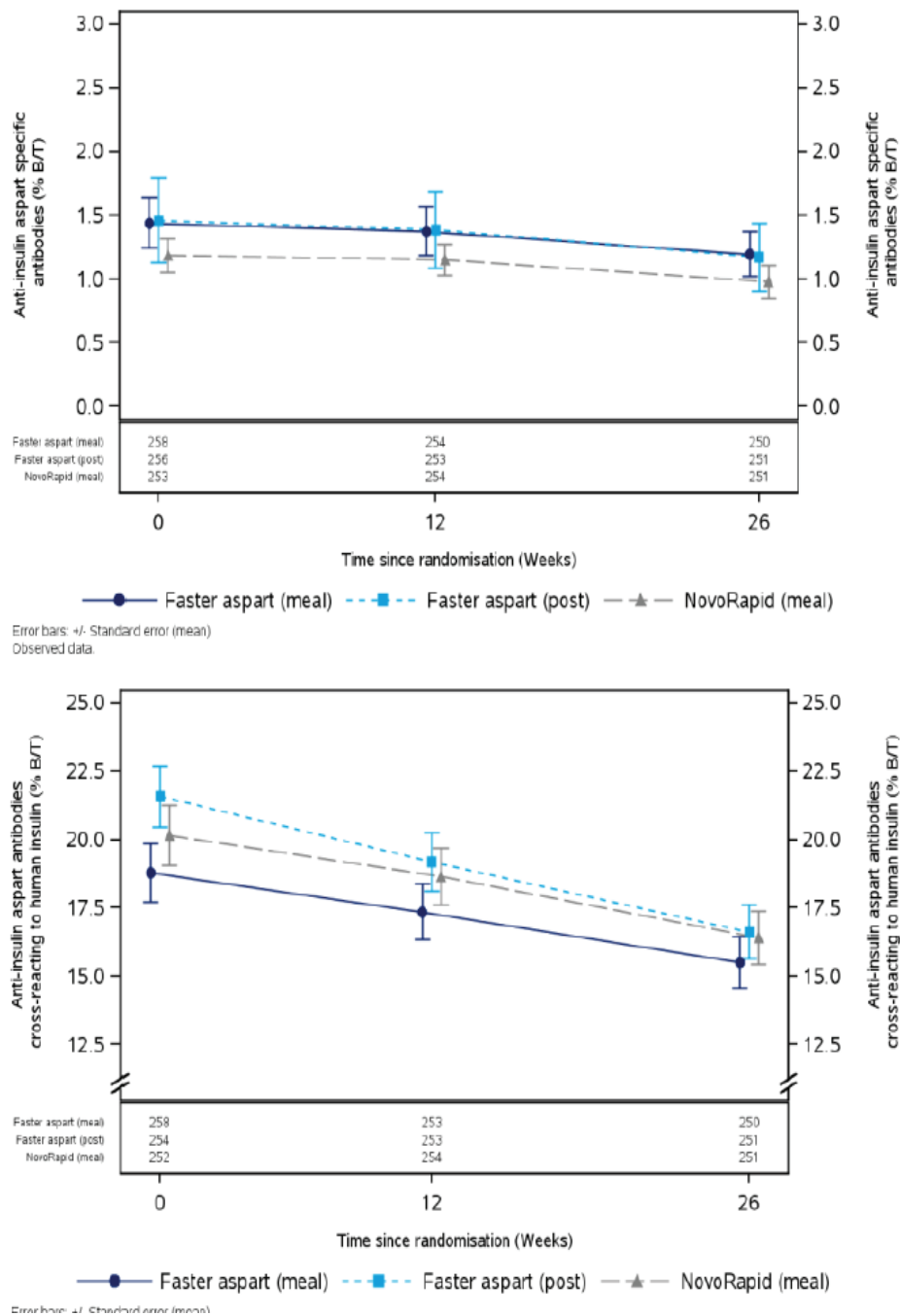


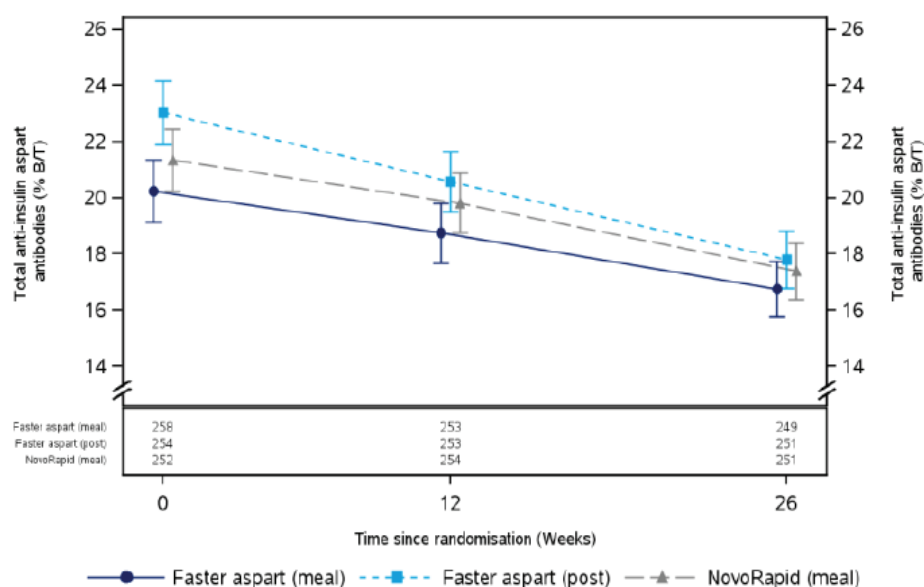
Source: Module 5.3.5.1. Study report 4101, Page 138

Samples for antibodies were collected at baseline (week 0), approximately half way through the study (week 12) and at the end-of-study visit (week 26). Overall, there were no differences in anti-insulin aspart specific antibodies, anti-insulin aspart antibodies cross-reacting to human insulin and total anti-insulin aspart antibodies (specific and cross-reacting with human insulin) across the 3 treatment groups at baseline and after 12 and 26 weeks of treatment (Figure 16). The percentage of subjects categorized as

positive for specific antibodies was similar between the 3 treatment groups (13.6–20.5%), irrespective of the timing of the sample or whether the response was sustained or a single occurrence (Table 9). At baseline, the percentage of subjects categorized as positive for cross-reacting antibodies was 93.0–96.2%, and 96.1–98.1% of the subjects were categorized as positive at any time during the treatment period. In line with the results for specific antibodies, the percentage of subjects categorized as positive for cross-reacting antibodies was similar between the 3 treatment groups. There was no apparent relation between the level of antibodies and either bolus or total daily insulin dose.

Figure 16. Anti-insulin aspart specific antibodies (top), anti-insulin aspart antibodies cross-reacting to human insulin (middle) and total anti-insulin aspart antibodies (bottom) – safety analysis set





Source: Module 2.7.4 Summary of clinical safety page 64

Table 9. Incidence of anti-insulin aspart antibody positive subjects – safety analysis set

	Anti-insulin aspart antibody positive			
	Safety Set	Baseline N (%)	Anytime N (%)	Sustained N (%)
Anti-insulin aspart antibodies cross-reacting to human insulin (% B/T)				
Faster aspart (meal)	261	251 (96.2)	256 (98.1)	252 (96.6)
Faster aspart (post)	258	240 (93.0)	248 (96.1)	241 (93.4)
NovoRapid (meal)	258	244 (94.6)	251 (97.3)	246 (95.3)
Anti-insulin aspart specific antibodies (% B/T)				
Faster aspart (meal)	261	41 (15.7)	48 (18.4)	41 (15.7)
Faster aspart (post)	258	42 (16.3)	51 (19.8)	35 (13.6)
NovoRapid (meal)	258	44 (17.1)	53 (20.5)	43 (16.7)
Total anti-insulin aspart antibodies (% B/T)				
Faster aspart (meal)	261	241 (92.3)	250 (95.8)	240 (92.0)
Faster aspart (post)	258	234 (90.7)	241 (93.4)	236 (91.5)
NovoRapid (meal)	258	238 (92.2)	248 (96.1)	244 (94.6)

#: Percentage of subjects, N: Number of subjects

Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms. Limits: Cross-reacting antibodies > 0.7 % B/T, Specific antibodies > 1.9 % B/T, Total antibodies > 1.9 % B/T.

Source: Module 2.7.4 Summary of clinical safety, page 65

2.3.3. Does the clinical pharmacology information submitted support the pediatric indication for the use of Fiasp as CSII?

The sponsor has submitted prior approval efficacy supplement (S-11) to support CSII use in Insulin pump for Fiasp in pediatric patients with diabetes mellitus. In accordance with the agreed iPSP (dated 08/28/2015 in DARRTS), Novo Nordisk has proposed to extrapolate efficacy results from the adult pump study in T1DM to pediatric T1DM based on the following:

- Efficacy data from the completed Phase 3b pump efficacy and safety study in adult subjects with T1DM (NN1218-3854). This study was submitted under Supplement 08 (NDA 208751).

- The completed single dose pump PK/PD study in adult subjects with T1DM (NN1218-4349). This study was also submitted under Supplement 08 (NDA 208751).
- Efficacy data from the completed subcutaneous pediatric efficacy and safety study in subjects with T1DM (NN1218-4101)

Novo Nordisk has also proposed to leverage the safety and dosing information from studies NN1218-3854 and 4101 to support the CSII use of Fiasp with pediatric patients. Furthermore, study NN1218-3852 (long-term efficacy) is used to provide reference data for supporting dosing recommendations. From clinical pharmacology perspective the observed consistency in PK/PD profile of Fiasp among children, adolescents, and adults, supports the proposed extrapolation of adult CSII data towards an indication for CSII use in pediatric patients. However, the final acceptability of S-11 is deferred to Clinical and CDRH review disciplines.

2.4. Bioanalytical

2.4.1. Are the bioanalytical methods properly validated to measure Fiasp in the plasma samples?

The methods of bioanalysis for the studies included in this application were the same as in the original NDA. In brief, samples were analyzed by an indirect sandwich ELISA using an analyte-specific capture antibody and a biotinylated analyte-specific detection antibody. Following addition of avidin-peroxidase, the antibody-antigen complex is visualized by 3,3',5,5'-Tetramethylbenzidine substrate. The quantification is performed using the optical density values at 450 nm.

The analytical method for determination of insulin aspart (also referred to as “total insulin aspart”) is described in SM3-349 and was validated in (b) (4) method validation studies. The assay validation and analysis of samples were performed in accordance with current practice and were reviewed at the time of original NDA submission (see OCP review dated 09/06/2017 for further details).

From study 4371, a total of 1720 samples were received frozen on dry ice and stored (b) (4) at -20°C. Study samples were stored from sample collection (first collection date 16-Jan-2018) to the end of sample analysis (last analysis date 27-Jul-2018) for a duration not exceeding 192 days. Study samples were analyzed without exceeding long-term, short term or freeze-thaw stability. The %bias for QC samples was -1.8% to 1.2% and CV% was 7.1 to 8.0%. The overall performance of the ELISA method met the acceptance criteria and the results obtained were of the required integrity and quality.

From study 4265, a total of 4718 samples were received frozen on dry ice and stored (b) (4) at -20°C. Study samples were stored from sample collection (first collection date 17-Nov-2016) to the end of sample analysis (last analysis date 28-Mar-2018) for a duration not exceeding 497 days. Study samples were analyzed without exceeding long-term, short term or freeze-thaw stability. The %bias for QC samples was -0.1% to -6.1% and CV% was 5.7 to 8.7%. The overall performance of the ELISA method met the acceptance criteria and the results obtained were of the required integrity and quality.

3. Label Recommendations

The following proposed clinical pharmacology related labeling is acceptable.

Specific Populations

Age (b) (4), gender, BMI, and race did not meaningfully affect the pharmacokinetics and pharmacodynamics of FIASP.

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/

RENU SINGH
11/08/2019 11:39:17 PM

MANOJ KHURANA
11/10/2019 09:56:08 AM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208751Orig1s011

OTHER REVIEW(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Office of New Drugs
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Ndidi Nwokorie, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)
Office of Drug Evaluation IV (ODE IV)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ODE IV, OND

John J. Alexander, MD, MPH, Deputy Director
Division of Pediatric and Maternal Health (DPMH)
ODE IV, OND

To: Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Subject: Pediatric Labeling Review

Applicant: Novo Nordisk Inc.

Application # NDA 208751/S-010 and S-011

Drug: FIASP (insulin aspart)

Approved Indications To improve glycemic control in adults with diabetes mellitus

Proposed Indication: To improve glycemic control in adults and pediatric patients with diabetes mellitus¹

Approved Dosage Forms: 10 ml multiple-dose vial
3 ml single-patient use FIASP Flex-Touch® pen
3 ml single-patient use PenFill® cartridges for use in a PenFill® cartridge device

Approved Dosage Strengths: 100 units/ml (U-100)

Approved Route of Administration: subcutaneous (SC) and intravenous (IV) infusion

Proposed Pediatric Dosing: Individualize and adjust the dosage of FIASP based on route of administration,² individual's metabolic needs, blood glucose monitoring results and glycemic control goal

Consult Request:

DDLO consulted DPMH to conduct a labeling review for sNDA 208751/S-010 and S-011 for the expansion of the approved indication to pediatric patients and to provide recommendations for pediatric use information in labeling.

Materials Reviewed:

Documents tracked under NDA 208751 (S-010-S-011) in DARRTS or the Electronic Document Room (EDR)

- October 24, 2019 Proposed Prescribing Information (PI) submitted by the applicant (eCTD# 0130)
- February 21, 2019 "Labeling history" document submitted by the applicant (eCTD# 0072)
- February 25, 2019 Clinical Overview of the Pediatric Pump Indication submitted by the applicant (eCTD# 0073)
- December 15, 2019 Division Summary Memo for Regulatory Action and CDTL Review of NDA 208751 S- 010 and S-011 (DARRTS)

¹ *Underlined text* is the proposed expansion of the existing indication in pediatrics

² SC or IV

- November 10, 2019 Clinical Pharmacology Review of NDA 208751 S-010 and S-011 (DARRTS)
- December 13, 2019 Clinical Review of NDA 208751/S-010 and S-011 (DARRTS)

Documents tracked under IND 106878 in DARRTS

- August 11, 2015 Agreed Initial Pediatric Study Plan (DARRTS)

Brief Regulatory Background of NDA 208751:

FIASP is an insulin aspart formulation approved by FDA on September 29, 2017 for subcutaneous (SC) and intravenous (IV) administration to improve glycemic control in adults with diabetes mellitus (DM). The applicant submitted a Prior Approval Efficacy Supplement (S-010) on February 21, 2019 to support use of FIASP in pediatric patients with diabetes mellitus 6 years of age and older and fulfill their Postmarketing Requirements under the Pediatric Research Equity Act (PREA). The applicant submitted a Prior Approval Labeling Supplement (S-011) on February 25, 2019 to support use of FIASP administered by continuous subcutaneous infusion in pediatric patients.

Brief Overview of FIASP (NDA 208751)

The approved FIASP formulation contains two novel excipients: nicotinamide (also known as niacinamide or vitamin B3) and L-arginine hydrochloride. The applicant asserts that the nicotinamide (b) (4) while L-argininine (b) (4) (b) (4)

The pediatric development program included three phase 1 pharmacokinetic (PK)/pharmacodynamic (PD) trials (i.e., trial NN1218-3888, trial NN1218-4371, trial NN1218-4265) and a phase 3 trial (i.e., NN1218-4101).

Study 4371 was a randomized, single-center, double-blind, single-dose, two-period cross-over trial comparing the PK profiles of a single 0.2 unit (U)/kg dose of FIASP versus NovoLog® in children (6-11 years), adolescents (12- 17 years) and adults with T1DM. The trial also evaluated PD data using a meal test. Results showed:⁴

- Faster absorption and greater early insulin exposure in pediatric patients 6 to 17 years of age with FIASP than with NovoLog based on mean total serum insulin aspart concentration (assessed using endpoints $AUC_{IASp,0-15min}$, $AUC_{IASp,0-30min}$).

³ Division Summary Memo for Regulatory Action and CDTL Review of NDA 208751 S- 010 and S-011. DARRTS entry December 15, 2019.

⁴ Clinical Pharmacology Review of NDA 208751 S-010 and S-011. DARRTS entry November 10, 2019

- Lower plasma glucose profiles for the first 2 hours after meal test in pediatric patients 6 to 17 years of age with FIASP than NovoLog®.
- Comparable AUC_{12h} and C_{max} in children and adolescents compared to adults.

DDLO concluded that the differences in PK and PD between FIASP and NovoLog (administered as SC injections) observed in adults with T1DM were preserved in children and adolescents with T1DM.⁵

Study 4265 was a randomized, single-center, double-blind, single-dose, two-period, cross-over, active-comparator trial comparing the PK and PD of FIASP versus NovoLog in adults with T2DM in the context of a euglycemic clamp. Results showed earlier onset of exposure and higher maximum exposures with FIASP compared with NovoLog, but comparable total insulin exposure. Results also showed FIASP resulted in an earlier onset of glucose lowering effect and greater early glucose lowering effect while maintaining comparable total and maximum glucose-lowering effect. The total glucose-lowering effect (measured as AUC_{GIR,0-t}) and the maximum observed GIR (GIR_{max}) for FIASP was comparable to NovoLog®. The division concluded that the differences in the PK/PD profiles of the two products that were initially observed with T1DM were preserved in adults with T2DM.⁶

The division concluded that Studies 4101, 4371, and 4265 supported the safety and efficacy of both mealtime FIASP and post-meal FIASP in improving glycemic control in pediatric patients with diabetes.⁷

Brief Summary of the Data Supporting IV infusion (S-011)

The Office of Biotechnology Products in the Office of Pharmaceutical Quality and the Office of Health Technology 7 (OHT-7), Division of Chemistry and Toxicology Devices (DCTD), Diabetes Branch (DB) reviewed the pump device and concluded there were no objections to the addition of CSII as a condition of use for FIASP in the pediatric population. CDRH confirmed that there are no outstanding issues specific to the delivery of FIASP using the pump labeled for use with FIASP. The division concluded that extrapolation of efficacy from the result of Study 3854 (previously reviewed and found to be safe and effective in adults with T1DM),⁸ as

⁵ Division Summary Memo for Regulatory Action and CDTL Review of NDA 208751 S- 010 and S-011. DARRTS entry December 15, 2019

⁶ *Ibid.*

⁷ *Ibid.*

⁸ sNDA 2018751/S-008

negotiated during the IND phase of development, is adequate to support approving the pump device as a condition of use in pediatric patients with diabetes.⁹

DPMH Recommendations for Pediatric Use Information in FIASP Labeling:

Pediatric use information must be described in the Pediatric Use subsection and included in other sections of labeling as appropriate. The information must include what is known and unknown about the use of the drug, differences in safety and efficacy in the pediatric population compared to adults, and any limitations of use in that pediatric population. When evidence supports the use of a drug for a pediatric indication, pediatric use information must be placed in all relevant sections of labeling which include: Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, and Clinical Studies, as well as any other sections that may be appropriate. (21 CFR 201.57(c)(9)(iv)(B), (C), and (D)).¹⁰

The pediatric efficacy study, 4101, was summarized in section 14.3 of FIASP labeling. This DPMH Labeling review will focus primarily on the following sections: 1 (Indications and Usage), 6 (Adverse Reactions), 8.4 (Use in Specific Populations -Pediatric Use), and 12 (Clinical Pharmacology). DPMH's proposed deletions are represented as strikethrough text and additions as underlined text.

Applicant's Proposed Labeling:

1. INDICATIONS AND USAGE

FIASP is a rapid-acting human insulin analog indicated to improve glycemic control in adults and ^{(b) (4)} pediatric patients with diabetes mellitus.

DPMH Comments:

DDLO concluded the efficacy of FIASP in pediatric patients with T1DM is supported by results from Study 4101, which was conducted in patients down to 2 years of age. Additionally, DDLO concluded that results from Study 4265 supported extrapolating the efficacy data from Study

⁹ Division Summary Memo for Regulatory Action and CDTL Review of NDA 208751 S- 010 and S-011. DARRTS entry December 15, 2019

¹⁰ Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling. FDA Guidance for Industry. March 2019

4101 to pediatric patients with T2DM 10 years of age and older.¹¹ DPMH suggested specifying the approved pediatric range for the T1DM population separately from the T2DM population in accordance with the final 2019 Pediatric Labeling Guidance, which suggests specifying the age range for which a drug or biologic is approved in pediatric patents if the approval will not be for the full pediatric population. The broader language drafted in this section by DDLO is consistent with the labeled indication statement for other insulin products.

Applicant’s Proposed Labeling:

6. ADVERSE REACTIONS

6.1 Clinical Trial Experience

Table 3: Adverse Reactions (%*) in Pediatric Patients with Type 1 Diabetes

	Mealtime FIASP + Insulin degludec (N=261)	Postmeal FIASP + Insulin degludec (N=258)
Viral upper respiratory tract infection	23.0	20.5
Upper respiratory tract infection	8.4	12.4
Influenza	7.7	5.8
Rhinitis	3.8	6.2
Headache	6.1	10.1
Pyrexia	8.4	6.2
Vomiting	3.4	8.1

*Incidence $\geq$ 5% and occurring at the same rate or greater with FIASP than comparator

	Mealtime FIASP + Insulin degludec (N=261)	Postmeal FIASP + Insulin degludec (N=258)
<u>Viral upper respiratory tract infection</u>	<u>35.2</u>	<u>39.1</u>
<u>Influenza</u>	<u>7.7</u>	<u>5.8</u>
<u>Headache</u>	<u>6.1</u>	<u>10.1</u>
<u>Pyrexia</u>	<u>8.4</u>	<u>6.2</u>
<u>Vomiting</u>	<u>3.4</u>	<u>8.1</u>

DPMH Comments:

DPMH notes that use of the Preferred Terms, “Viral Upper Respiratory Infection”, “Upper Respiratory Infection”, and “Rhinitis” appeared to overlap and recommended these terms be

¹¹ Clinical Review of NDA 208751/S-010 and S-011.DARRTS entry December 13, 2019

consolidated to the single term, “Viral Upper Respiratory Infection” to minimize prescriber confusion when reading this section of the labeling.

Weight Gain

Weight gain can occur with insulin therapy, including FIASP, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria. In Study A, adult patients with type 1 diabetes treated with FIASP gained an average of 0.7 kg and in Study B, adult patients with type 2 diabetes treated with FIASP gained an average of 2.7 kg.

Peripheral Edema

Insulin, including FIASP, may cause sodium retention and edema, particularly if previous poor metabolic control is improved by intensified insulin therapy. In the clinical program, peripheral edema occurred in 0.8% of adult patients treated with FIASP.

DPMH Comments:

DPMH notes that, if peripheral edema was a safety measure in Study 4101 or 4371, then these subsections should include a statement describing the frequency of this observed adverse event in pediatric patients. Alternatively, if the frequency of peripheral edema was similar in the studied pediatric patients to that observed in adults, then a statement could be added to note this similarity.

Applicant’s Proposed Labeling:

8. USE IN SPECIFIC POPULATIONS

8.4 Pediatric use



The safety and effectiveness of FIASP have been established to improve glycemic control in pediatric patients with diabetes mellitus. Use of FIASP for this indication is supported by evidence from an adequate and well-controlled study in 777 pediatric patients with type 1

diabetes mellitus aged 2 to 17 years, and from studies in adults with diabetes mellitus [see Clinical Pharmacology (12.3) and Clinical Studies (14)].

Pediatric patients with type 1 diabetes treated with mealtime and postmeal FIASP reported a higher rate of blood glucose confirmed hypoglycemic episodes compared to patients treated with NovoLog; the imbalance was greater during the nocturnal period. Monitor blood glucose levels closely in pediatric patients [see Warnings and Precautions (5.3), Clinical Trial Experience (6.1)].

DPMH Comments:

DPMH agrees with DDLO's revisions to this subsection. The revised language is consistent with the final Pediatric Labeling Guidance which states the Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population.¹⁰

Applicant's Proposed Labeling:

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

The Applicant did not include specific pediatric pharmacokinetic or pharmacodynamic information for FIASP.

DPMH Comments:

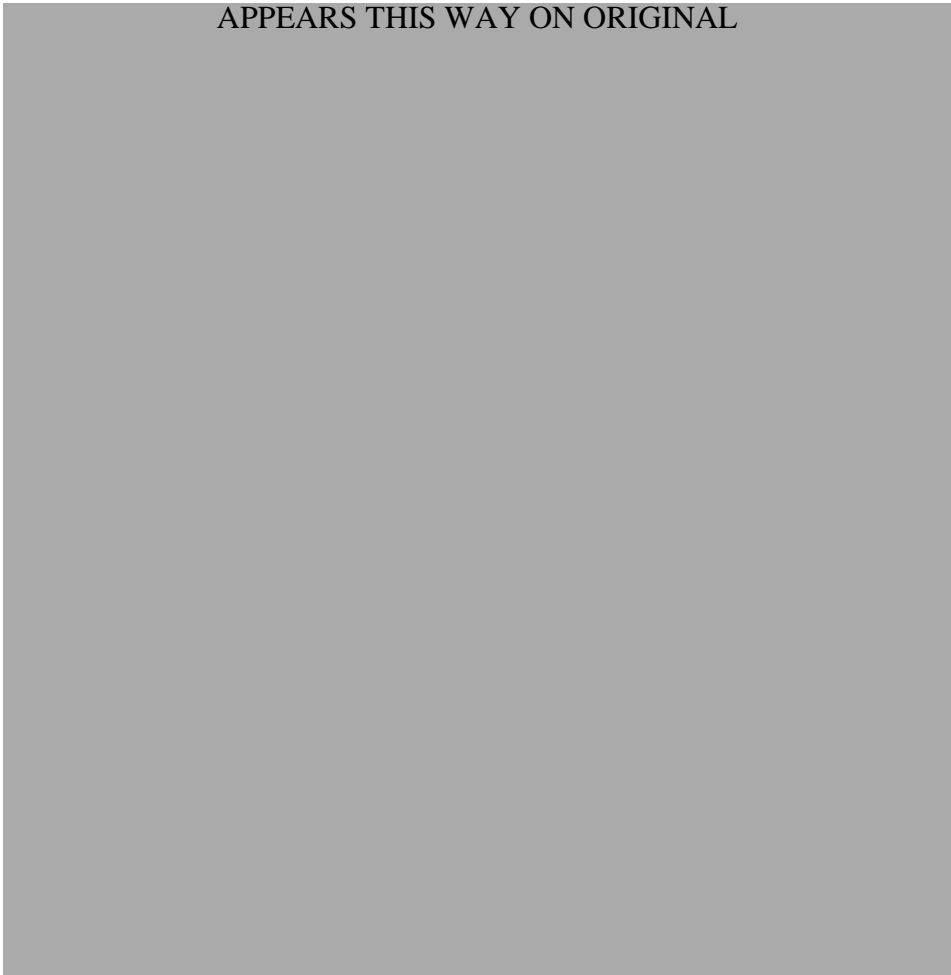
The March 2019 guidance for industry document, "Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling-Guidance for Industry" states that descriptions of pediatric pharmacokinetic, pharmacodynamic, and/or pharmacogenomic study data; relevant data obtained from modeling, simulation, or bridging studies; and dose response information should be included in the CLINICAL PHARMACOLOGY section. (21 CFR 201.57(c)(13)).¹⁰ DPMH suggested adding the following language to this subsection of the labeling.

"Pharmacokinetic properties for FIASP in pediatric patients with type 1 diabetes mellitus were assessed in two randomized, single-center, double blinded, single dose, two period crossover study in children 6-11 years, 12-17 years and over 18 years. The PK/PD profile of FIASP was generally comparable between pediatric patients 6 to 17 years of age and adults."

DPMH Actions

DPMH reviewed the applicant's proposed labeling and attended internal meetings from November 6, 2019 until December 20, 2019. Several comments were recommended to the Division based on 21 CFR 201.57(c)(9)(iv). Final labeling will be negotiated with the applicant and may not reflect suggestions made in this review.

APPEARS THIS WAY ON ORIGINAL



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/s/

NDIDI N NWOKORIE
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MONA K KHURANA
02/26/2020 02:30:37 PM

JOHN J ALEXANDER
02/26/2020 04:27:39 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: December 5, 2019

To: Callie Cappel-Lynch, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

Monika Houstoun, Associate Director for Labeling, (DMEP)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for FIASP® (insulin aspart injection) for subcutaneous or intravenous use

NDA: 208751 S-10 & S-11

In response to DMEP's consult request dated March 4, 2019, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for FIASP® (insulin aspart injection) for subcutaneous or intravenous use. These supplements (S10 and S11) provide for changes to the labeling regarding the addition of a pediatric indication and a pediatric pump use.

PI and PPI: OPDP's review of the proposed labeling is based on the draft PI received by electronic mail from DMEP on December 2, 2019, and we have no comments.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on December 4, 2019.

Thank you for your consult. If you have any questions, please contact Ankur Kalola at (301) 796-4530 or Ankur.Kalola@fda.hhs.gov.

24 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ANKUR S KALOLA
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: December 04, 2019

To: Callie Cappel-Lynch
Regulatory Project Manager
Office of Drug Evaluation II

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Ankur Kalola, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: DMPP and OPDP Concurrence with Submitted: Patient
Package Insert (PPI)

Drug Name (established name): FIASP (insulin aspart injection)

Dosage Form and Route: injection, for subcutaneous use
for injection, for subcutaneous use

Application Type/Number: NDA 208751

Supplement: S-010 and S-011

Applicant: Novo Nordisk, Inc.

1 INTRODUCTION

On February 21, 2019 and February 25, 2019 respectively, Novo Nordisk, Inc. submitted for the Agency's review Prior Approval Efficacy Supplements for FIASP (insulin aspart injection). The purpose of the submissions is to seek approval for the expansion of the currently approved FIASP (insulin aspart injection) indications to include the treatment of pediatric patients with diabetes mellitus and to support the use of Continuous Subcutaneous Insulin Infusion (CS II) use in insulin pump for FIASP (insulin aspart injection) in pediatric patients with diabetes mellitus.

On March 4, 2019, the Office of Drug Evaluation II requested that the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) review the Applicant's proposed PPI for FIASP (insulin aspart injection).

This memorandum documents the DMPP and OPDP review and concurrence with the Applicant's proposed PPI for FIASP (insulin aspart injection).

2 MATERIAL REVIEWED

- Draft FIASP (insulin aspart injection) PPI received on February 21, 2019 and received by DMPP and OPDP on December 2, 2019.
- Draft FIASP (insulin aspart injection) Prescribing Information (PI) received on February 21, 2019 revised, by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 2, 2019.

3 CONCLUSIONS

We find the Applicant's proposed PPI is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP and OPDP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/

SHARON W WILLIAMS
12/04/2019 10:51:36 AM

ANKUR S KALOLA
12/04/2019 10:58:50 AM

LASHAWN M GRIFFITHS
12/04/2019 01:22:12 PM



OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date:	11/18/2019		
To:	Callie CappelLynch, Sr. Regulatory Program Manager		
Requesting Center/Office:	CDER/OND	Clinical Review Division:	DMEP
From:	Nikhil Thakur, Assistant Director, Infusion Systems OPEQ/OHT3/DHT3C		
Through (Team):	Alain Silk, Branch Chief OPEQ/OHT7/DCTD/Diabetes Branch		
Through (Division): *optional			
Subject:	Management Review of Consult for Submission: NDA 208751, Fiasp, Novo Nordisk		
Recommendation:	Approvable, with comments regarding Team Recommendation regarding the addition of the use of an Infusion Pump for Pediatrics to the Drug Labeling.		

Digital Signature Concurrence Table		
OHT3/DHT3C Assistant Director	OHT7/DCTD/Diabetes Branch, Chief	Division (optional)
Nikhil Thakur -S3 Digitally signed by Nikhil Thakur -S3 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nikhil Thakur - S3, 0.9.2342.19200300.100.1.1-1300215196 Date: 2019.11.18 14:15:45 -05'00'	Alain D. Silk -S	

1. SUBMISSION OVERVIEW

Table 1. Submission Information	
Consult Identification #	00006826
Consult Request Link	https://force-dsc.lightning.force.com/lightning/r/Case/500t000000IDLgyAAH/view
ICC tracking #	ICC1900179
Submission Number	NDA 208751/S-11
Sponsor	Novo Nordisk
Drug/Biologic	FIASP
Indications for Use	FIASP is a rapid acting human insulin analog indicated to improve glycemic control in adults with Diabetes mellitus
Device Constituent	Infusion Pump
Related Files	IND 106878

2. CDRH REVIEW

On November 12, 2019, the CDRH Review Team completed their review of NDA 208751/S-11. Their review resulted in the identification of the following concerns deemed to be outstanding device issues (ODI):

ICC Review Request from CDER/OND, DMPEP:	Novo Nordisk has submitted a supplement for Fiasp to include pump use in pediatrics. Please review the pump studies included in the submission and provide a recommendation for approval. Please also provide any labeling recommendations you may have. We also ask that you attend the internal milestone meetings list below. Filing: April 4, 2019 Mid Cycle: July 17 2019 Wrap Up/Labeling: November 14 2019
Device Presentation(s) being evaluated:	Infusion Pump
Objective of this Memo:	Evaluation of the following changes: Addition of the Use of an Infusion Pump for a Pediatric Patient Population to the Drug Labeling.

Review by OHT3/DHT3C Assistant Director:

Based on my review of the CDRH's review of NDA 208751/S-11, it appears that the team has identified relevant issues that raise concerns regarding the labeling of the device constituent (Insulin Omnipod DASH Insulin Management System (Omnipod DASH)) as it relates to pediatric use, the characterization of the leachables and extractables associated with the Omnipod DASH in light of the specific purpose for marketing to the pediatric population, and Medical Device Report (MDRs) associated with the Omnipod DASH related to usability in the pediatric population.

Regarding the pediatric labeling for the Omnipod DASH, the device was not specifically assessed for the delivery of FIASP with the pediatric population. I concur that this information was not provided in NDA 208751/S-11 to satisfy

our concerns regarding the system's use with pediatric patients. However, it is noteworthy that other rapid acting insulin such as Novolog (Novo Nordisk), and Humalog (Ely Lilly Corporation), also contain formulations of rapid acting insulin which are indicated for delivery through a subcutaneous infusion system (i.e. insulin infusion pump).¹ These drug products have been on the market for over 10 years without any specific signal related to pediatric adverse events related to infusion delivery of insulin. It is also noteworthy that when the most recent 510(k) premarket clearance for the Omnipod DASH system was cleared by CDRH on October 21, 2019 (K192659), the "Indications For Use" statement did not specifically indicate any intent to specifically indicate device usage with the pediatric population. CDRH cleared the 510(k) submission with general indications for use, with the understanding that pediatric usage for this product would be at the discretion of the prescribing physician (as opposed to the Insulet Corporation (Device Sponsor) marketing the product for pediatric use). Ultimately, CDRH will continue to work with the Device Sponsor to assess concerns related to the required testing associated with specifically marketing the Omnipod DASH to the pediatric population. I do not believe that this concern should affect the approvability of NDA 208751/S-11.

Regarding the characterization of leachables and extractables associated with the Omnipod DASH, the review team's concerns were heightened with the knowledge that Insulet Corporation and Novo Nordisk are specifically marketing the delivery of FIASP through the Omnipod DASH to the pediatric population. The concern regarding leachables and extractables was raised during the review of 510(k), K192659. The review team's concern at the time (consistent with their concerns expressed in the review of NDA 208751/S-11) was that the original leachables study did not capture repeated use of the device, and that the insulin might mask additional extractables and leachables from the device's drug fluid pathway. However, at the time the Sponsor's 510(k) did not identify the firm's intent to market the product specifically to the pediatric population. Thus, CDRH's risk based decision to accept the study was based on our observation that there were no identified adverse impacts on the drug product's quality as a result of the leachables study, and that the drug fluid pathway was the same as the predicate device cleared under 510(k) K182630. CDRH will continue to work with Insulet Corporation to address concerns related to the leachables data, and its implication to the marketing of the device for pediatric use, outside of our review scope for NDA 208751/S-11. I do not believe that this concern should affect the approvability of NDA 208751/S-11.

Regarding MDR data that the review team identified, these MDR's appeared to indicate a significantly higher occurrence of use-related failures in the pediatric population (e.g. lack of adhesion of the Omnipod DASH to the pediatric patient, dosing errors, and usability with the pediatric population). However, the MDR data was unable to identify whether the dosing errors were specific to an insulin type. I agree with the review team that these MDR's must be addressed by the Medical Device Sponsor, and that the firm's assessment might have an impact on a broader segment of the diabetic patient population who rely on the Omnipod DASH to deliver rapid acting insulin products. CDRH will address our concerns with the Medical Device manufacturer. I do not believe that this concern should affect the approvability of NDA 208751/S-11.

¹ Approved Labeling for Novo Nordisk's Novolog Insulin and Ely Lilly's Humalog insulin indicates that it is intended for subcutaneous delivery by injection or infusion to both the adult and pediatric patient population –

(Novolog Labeling - <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3a1e73a2-3009-40d0-876c-b4cb2be56fc5>)

(Humalog Labeling - <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c8ecbd7a-0e22-4fc7-a503-faa58c1b6f3f>)

ICC1900179

NDA 208751, Fiasp, Infusion Pump

Novo Nordisk

Conclusion:

Based on the assessment provided above, I believe that although concerns related to the Omnipod DASH system exist at-large, the issues are not specifically relegated to the delivery of FIASP. These concerns should be addressed by CDRH through collaboration with the Medical Device Sponsor (Insulet Corporation). If necessary, CDRH will work with FDA partners to seek a regulatory solution. The issues identified above should not affect the approvability of NDA 208571/S-11.

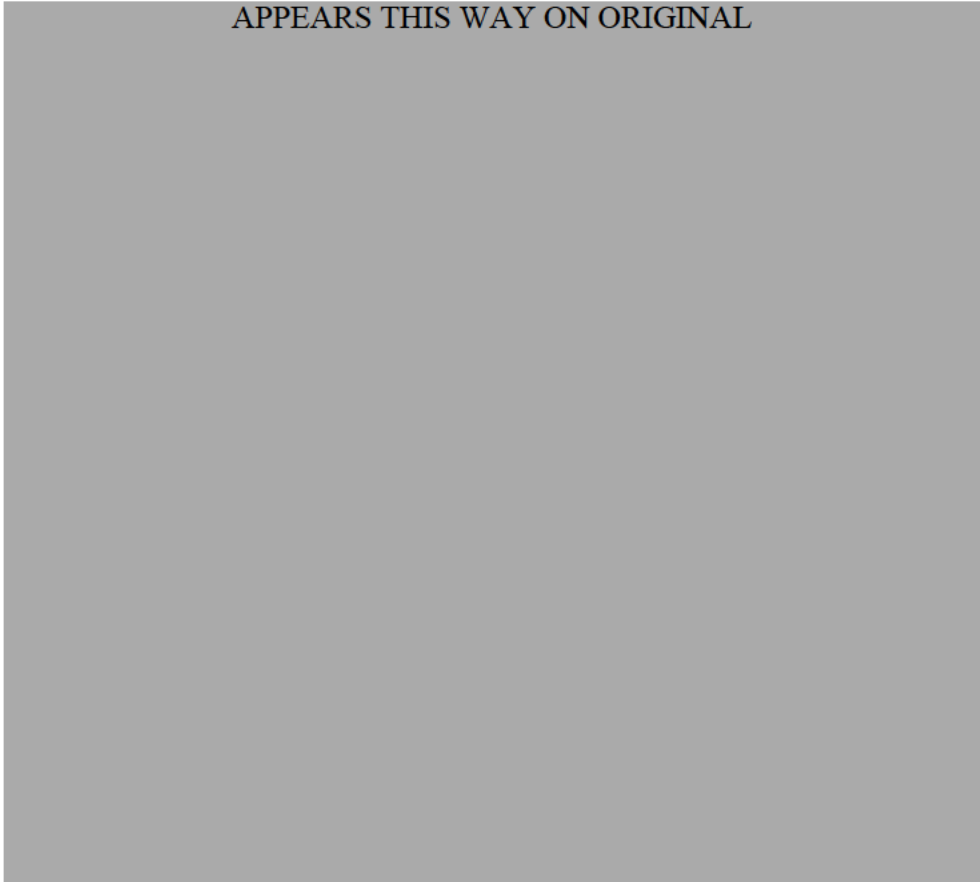
---END OF REVIEW---

3. APPENDIX

3.1. DOCUMENTS REVIEWED

Documents
K192659 – 510(k) for Omnipod DASH & Associated Reviews
K182630 – 510(k) for Omnipod DASH (Predicate Device) & Associated Reviews
NDA 280751/S11 - CDRH Review Team Memorandum

APPEARS THIS WAY ON ORIGINAL





DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – STREAMLINED

Date:	11/12/2019		
To:	Callie CappelLynch, Sr. Regulatory Program Manager		
Requesting Center/Office:	CDER/OND	Clinical Review Division:	DMEP
From:	David Wolloscheck, PhD, Senior Staff Fellow OPEQ/OHT3/DHT3C		
Through (Team):	Carolyn Dorgan, MS, Team Lead, Infusion Team OPEQ/OHT3/DHT3C		
Through (Division): *optional	CDR Nikhil Thakur, Assistant Director OPEQ/OHT3/DHT3C		
Subject:	Consult for Submission: NDA 208751, Fiasp, Novo Nordisk		
Recommendation:	The Addition of the use of an Infusion Pump for Pediatrics to the Drug Labeling is <u>not</u> Approvable		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (optional)
David Wolloscheck -S Digitally signed by David Wolloscheck -S Date: 2019.11.13 13:29:58 -05'00'	Carolyn C. Dorgan -S Digitally signed by Carolyn C. Dorgan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001800814, cn=Carolyn C. Dorgan -S Date: 2019.11.13 13:36:45 -05'00'	

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Device Constituent	
Related Files	IND 106878

2. CDRH REVIEW

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Device Presentation(s) being evaluated:	Infusion Pump
Objective of this Memo:	Evaluation of the following changes: Addition of the Use of an Infusion Pump for a Pediatric Patient Population to the Drug Labeling.
Review Comments:	This labeling change was originally reviewed by Rumi Young (CDRH/OHT3/DHT3C). Her review will be references throughout this document and is attached to this memo. Novo Nordisk filed Supplement 11 to NDA 208751 to add a pediatric indication to Fiasp for the use with an infusion pump. The Sponsor intends to use Omnipod (most recently cleared under K192659) as one possible option to administer Fiasp to a Pediatric patient population using an infusion pump. However, Omnipod has not received clearance under Section 510(k) of the act for the specific use in pediatrics. The following are the indications for use for the Omnipod infusion system from the most recent FDA clearance: <i>“The Omnipod® Insulin Management System is intended for subcutaneous delivery of insulin at set and variable rates for the management of diabetes mellitus in persons requiring insulin and for the quantitative measurement of glucose in fresh whole capillary blood (in vitro) from the finger.</i>

The glucose measurements should not be used for the diagnosis or screening for diabetes. The PDM glucose meter is intended for single patient use and should not be shared.

Abbott FreeStyle® test strips are used with the built-in FreeStyle meter for the quantitative measurement of blood glucose in fresh whole capillary blood from the finger, upper arm and palm. Abbott Freestyle Control Solutions are used to verify that the meter and test strips are working together properly and that the test is performed correctly.

Omnipod DASH Insulin Management System

The Omnipod DASH™ Insulin Management System is intended for subcutaneous delivery of insulin at set and variable rates for the management of diabetes mellitus in persons requiring insulin.

Additionally, the Omnipod DASH System is interoperable with a compatible blood glucose meter to receive and display glucose measurements.”

In order to approve the supplement, there should be at least one legally marketed device that is compatible with the drug for the intended patient population. Omnipod has a general indication for “persons” which leaves it up to the prescribing physician to determine the appropriateness of the device for the specific patient. To date, no 510(k) was filed by Insulet (manufacturer of OmniPod) to add pediatrics to the indications for use of the device. This interpretation of the intended use was confirmed with CDRH’s 510(k) staff.

Data provided by Novo Nordisk to support the change:

Novo Nordisk intends to support the pediatric claim using four clinical trials NN1218-3854, NN1218-4349, NN1218-4101, and NN1218-3852. Of these, NN1218-4101 and NN1218-3852 were carried out in a pediatric subpopulation (NN1218-4101 Efficacy Pediatric Study ≥ 8 years and NN1218-3852 Supporting Pediatric Dose Recommendations ≥ 18 years). However, Both NN1218-4101 and NN1218-3852 were carried out by administering Fiasp using **Pen-Injectors** and not an infusion pump. Hence, these studies do not yield any validation data that could support the use of an infusion pump in a pediatric patient population. The other two studies (NN1218-3854 and NN1218-4349) were conducted with an infusion pump but only in adult patients. Novo Nordisk intends to extrapolate results of this study to a pediatric population. However, it is not clear how a study conducted in adult patients correlates to the usability of the device in a pediatric population. Overall, the conducted studies do not sufficiently demonstrate that an infusion pump can be used to administer the drug to a pediatric population using an infusion pump.

In addition to the lack of validation data, there are biocompatibility and postmarket safety concerns for the use of the device in a pediatric population.

Biocompatibility/Toxicological concerns regarding use of OmniPod in Pediatrics

Ms. Young consulted Drs. Berk Oktem and Alan Hood (CDRH/OSEL) to evaluate an extractables and leachables study provided by Insulet for the Omnipod Infusion Pump System. The Omnipod Insulin pump is intended for the treatment of diabetic patient. Per the labeling of the device, each pod should be replaced at least once every 72 hours or after delivering 200 units of insulin. However, due to the high potential of repeated use of the device on a single patient (i.e., after 3 days the patient will dispose of the pod and use another one), the device should be classified as permanently contacting. As such, any chemical characterization study on the device should be done using exhaustive extractions (Per ISO 10993-12 and ISO 10993-18) with a polar, mid-polar, and non-polar solvent. In previous submissions (K162296 and K182630), extractables studies were submitted using either 100% water or a 50%/50% water and ethanol mixture under non-exhaustive conditions. However, this is not appropriate to address the concerns of any non-polar extractables/leachables or that the extraction should be done under exhaustive conditions. To address the Agency's concerns, Insulet provided an extractables study using Fiasp drug solution as the solvent and an extraction at 37°C for 96 hours. However, Dr. Oktem noted several deficiencies including that the extraction conditions are not exhaustive and that Fiasp, a large macromolecular compound, may potentially mask any extractable findings on the provided spectra. Overall, although there is no evidence that specifically suggests that Omnipod is not appropriate for the use in pediatrics, Insulet has not responded to the concerns of the Agency and there is not sufficient toxicological evidence that would support the use in this vulnerable patient population. For details regarding the described extractables and leachables study, please see Dr. Oktem's consult memorandum attached to this memo in Appendix 3.

Postmarket Data on the use of Omnipod in Pediatrics

Ms. Young consulted Helen Yousefi (CDRH/OHT3/DHT3C) to conduct an MDR search using the following criteria (the full memo is attached in Appendix 3):

Summary of Analysis:

The System for Unified Surveillance (SUS) was used to run a query of MDRs filed under product code: LZG, manufacturer name: "INSUL%", brand name: OMNI% (to cover OmniPod and OmniPod dash) and report create date: 01/01/2016 to 07/31/2019. Due to the large number of MDRs per year, the same criteria were used to run four separate queries of MDR

data for report create date: from the beginning to end of 2016, 2017, 2018 and then 01.01.2019 to 07.31.2019 respectively.

The total number of MDRs per year are as follow:

Year	Total number of MDRs
2016	4283
2017	6737
2018	9192
2019	7055

The search yielded the following results:

	2016	2017	2018	2019
Total MDRs	4283	6737	9192	7055
Total Pediatrics	1654	2988	4158	3345
Total Text Term Pediatric	1645	2978	4123	3320
Age group:				
<1	0	2	1	1
1 year	7	21	15	15
2-12 years	1063	738	2767	2131
13-18 years	470	1981	1078	963
19-21 years	105	236	262	210

The results suggest that the amount of MDRs are higher in younger patient subpopulations. However, the usefulness of this search is unclear since it did not include infusion pumps from other manufactures and does not consider how MDRs are distributed for these patient populations for medical devices in general (i.e., it is unclear whether the identified trend is reflective of medical devices in general).

The most common reported MDRs for the pediatrics were related to usability, adhesion, and dosing errors. Since this is a patch pump, adhesion to the skin is vital for the functionality of the device. Partial or complete dislodgement can lead to an under dose which can result in death in type 1 diabetics. There is no evidence to support that the design is or is not safe for use in the pediatric population.

Conclusion

There does not appear to be a legally marketed infusion pump indicated for a pediatric patient population that is compatible with the proposed drug product. The provided clinical studies were not conducted with an infusion pump in pediatric patients and does not provide any insight into the usability, adhesive quality, or dosing of the pump in these patients. In addition, there are biocompatibility/toxicological concerns for the use of Omnipod in pediatrics that

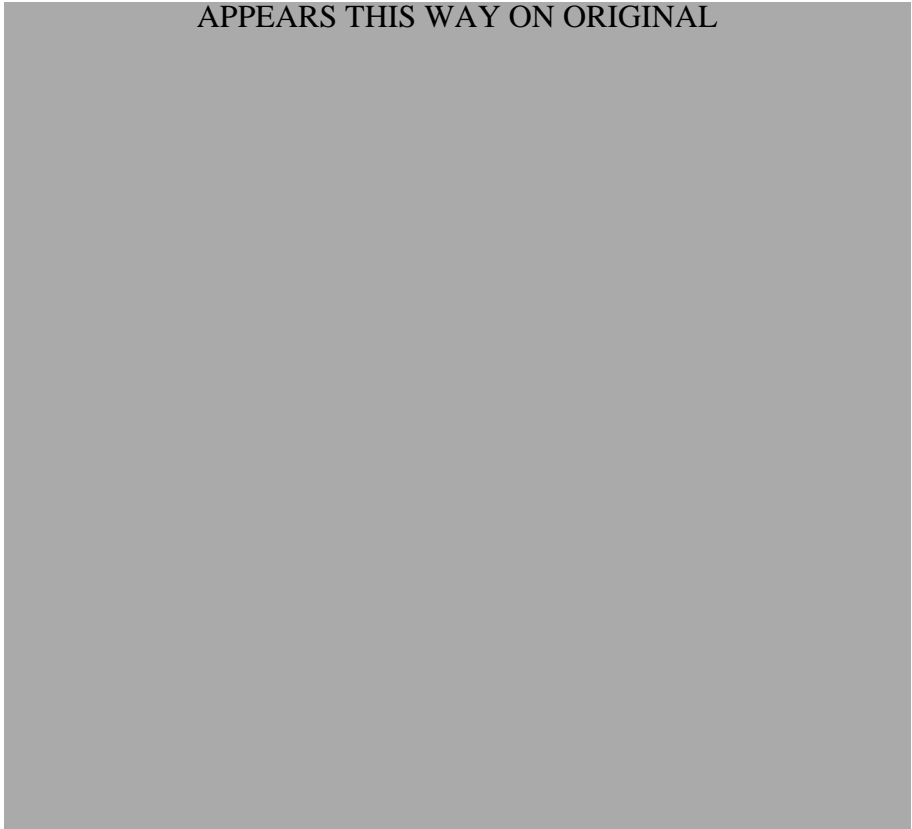
	were not resolved during the review and the device is not cleared for the use in pediatrics. <u>Hence, although there is no specific evidence that suggests that Omnipod poses a safety concern for a pediatric patient population, not enough data is available to support the safe use of the device in these patients.</u> The Sponsor of FIASP should ensure there is at least one CSII pump that is approved for use in the pediatric population prior to approval of this supplement.
Review Recommendation:	No Approvable.

---END OF REVIEW---

3. APPENDIX

- 3.1. Review Memorandum from Rumi Young regarding use of Fiasp with Omnipod (including Memo's from Dr. Berk Oktem and Helen Yousefi for the extractables/leachables and MDR analysis respectively).**

APPEARS THIS WAY ON ORIGINAL



OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

**GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM**



Date	September 21, 2019
To	Callie CappelLynch, Senior Regulatory Health Project Manager CDER/OND/ODEII/DMEP
Requesting Center/Office	CDER/OND
OND Review Division	DMEP
From	Rumi Young CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	Carolyn Dorgan CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CAPT Alan Stevens CDRH/ODE/DAGRID/GHDB
Subject	Consult for NDA208751 Adult indication: ICCR2019-04230 ICC1900084 Pediatric indication: ICCR2019-04552 ICC1900179
Filing Recommendation	Recommendation Date: Device Constituents Parts of the Combination Product are Acceptable for Filing
Mid-Cycle Recommendation	Recommendation Date: 7/17/2019 CDRH has Information Requests related to the device constituents parts of the combination product - See Section 11.3 for Information Requests
Final Recommendation	Recommendation Date: 9/21/19 Device Constituents Parts of the Combination Product are Approvable for the Adult (S008) Indication

Digital Signature Concurrence Table	
Reviewer	Rumi Young -S Rumi Young -S c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rumi Young -S, 0.9.2342.19200300.100.1.1=2002467913 2019.09.21 01:17:55 -04'00'
Team Lead	Carolyn Dorgan -S Digitally signed by Carolyn C. Dorgan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001800814, cn=Carolyn C. Dorgan -S Date: 2019.09.24 10:18:38 -04'00'
Branch Chief	C. Dorgan -S C. Dorgan -S Digitally signed by Carolyn C. Dorgan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001800814, cn=Carolyn C. Dorgan -S Date: 2019.09.24 10:18:38 -04'00'

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2019-04230 and ICCR2019-04552
ICC tracking # (Lead)	ICC1900064
Submission Number	NDA208751-SUPP008 and NDA 208751-SUPP-011
Sponsor	Novo Nordisk
Drug/Biologic	FIASP
Indications for Use	FIASP is a rapid acting human insulin analog indicated to improve glycemic control in adults with Diabetes mellitus
Device Constituent	Infusion Pump
Related Files	IND106878

Table 2. Review Team					
Were other disciplines consulted?				☒ Yes	☐ No
Below is a list of the Discipline Specific ICCR#, ICC# and CON#.					
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	ICCR #	ICC #	CON #	
Extractables /Leachables	Berk Oktem (CDRH/OSEL/DBCMS)	N/A	ICC1900084	CON1917508	
DP Quality	Anjali Shukla (CDER/OBP/DBRRII)	00011791	N/A	N/A	

Table 3. Important Dates		
Interim Due Dates	S-8 (Adult) Due Dates	S-11 (Pediatric) Due Dates
Filing	2/19/2019	4/4/2019
Mid-Cycle	5/21/2019	7/17/2019
Primary Review	9/21/2019	11/14/2019
PDUFA/GDUFA Due Date	10/21/2019	12/20/2019

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2. PURPOSE/BACKGROUND

2.1. Scope

Novo Nordisk is submitting SUPP008 and SUPP011 for FIASP. There is no specific device constituent (brand/ model).

CDER/OND has requested the following consult for review on 01/30/2019:

This submission contains a prior approval efficacy supplement to add a CSII indication for Fiasp. Please review the submitted data and provide a recommendation on approvability and labeling (if necessary).

CDER/OND also requested the following consult for review on 3/4/2019:

Novo Nordisk has submitted a supplement for Fiasp to include pump use in pediatrics. Please review the pump studies included in the submission and provide a recommendation for approval. Please also provide any labeling recommendations you may have.

The goal of this memo is to provide a recommendation of the adequacy of the proposed changes: Update labeling to include indication of CSII to deliver FIASP and pediatric indication.

The two consult requests were combined since the analysis (labeling adequacy), review team and reviewers will be the same.

2.2. Prior Interactions

ICC1500680

Below were the outstanding device issues:

CDRH Comment 1

CDRH does not currently have a device that is labeled for continuous subcutaneous infusion of the insulin – faster aspart (FIASP) – proposed in this NDA. Insulin infusion pump labeling must designate the specific insulins they are compatible. Therefore, FIASP cannot be approved for subcutaneous infusion due to an outstanding device issue. Please note that there may be other outstanding issues requiring a response which may need to be addressed prior to or in conjunction with resolving this outstanding device issue. You must work with a pump manufacturer to update the labeling of a currently approved or cleared subcutaneous infusion pump for use with the proposed new FIASP. This labeling update must occur in parallel with the drug approval process. The labeling update may reference in-pump use stability data and clinical data collected as part of the NDA. Depending on which pump manufacturer you wish to work with to obtain the labeling update, additional stability and clinical studies may be needed.

CDRH Comment 2

You have not provided the information required to claim that the proposed faster aspart insulin (FIASP) drug can be safely used in an insulin infusion pump. The clinical studies and bench data provided are insufficient. Reference CDRH Comment 3 for what additional bench testing is needed. To support safe use of FIASP in insulin infusion pumps you will need to propose a new clinical study that addresses the following areas:

- a. *Clinical studies to demonstrate the interval of infusion set change; which is controlled under the insulin label and not the device label. These studies should be based not on microscopic or macroscopic occlusion of the infusion sets because this approach has not been shown to be sufficiently sensitive to detect infusion set occlusion that can*

result in serious harm. The studies should be designed to use the insulin under the desired conditions of use that include the interval of reservoir change (b) (4) studied in clinical trials 3 days). The assessment of occlusion should include strict evaluation of hyperglycemia to detect unexplained hyperglycemia, failure to correct hyperglycemia with an appropriate bolus of insulin, and the rate of infusion set changes.

- b. An accurate assessment of the PK/PD of FLASP. Understanding of this information is critical for the safe use of FLASP in insulin infusion pumps not only because the timing of insulin administration in relationship to meals is important to avoid insulin to carbohydrate mismatch but also because the pumps have software that controls the profile of bolus insulin administration and performs bolus dose calculations based on patient specific requirements of insulin sensitivity and consideration for insulin on board.
- c. A new clinical study to examine the rate of infusion set occlusion and describe any changes in pump profiles that were required over the course of the study to support the safe use of FLASP in insulin pumps. You will need to provide the necessary PK/PD information, either by reanalysis or restudy, to describe the FLASP including an insulin on board profile for subjects with varied rates of FASP clearance.

The proposed claims (b) (4) currently approved for use in pumps, are not consistent with the indications for insulin infusion pumps which are limited to the ability to deliver basal (fixed or variable) and bolus insulin in the subcutaneous space. Therefore, no claims other than the ability to be used in a pump (either cleared or approved) are appropriate. If you wish to pursue specific (b) (4) additional studies will be required under an IDE to support these claims. You are encouraged to discuss these goals with CDRH (ODE and OIR) through the pre-submission process.

CDRH Comment 3

The in-use pump stability data supports compatibility of the FLASP with the infusion sets evaluated (Medtronic Silhouette Paradigm 60 and 110 cm and the Unomedical Inset II 60 and 110cm) for the recommended duration of 3 days. However, clinical data should be collected to confirm occlusion rates and failure as it has been determined that bench testing is not solely sufficient (See CDRH Comment 2). The in-use pump stability data you have provided for the faster aspart is not sufficient to recommend a (b) (4) reservoir pump in-use time for all CSII pumps. In-use pump studies should be conducted for twice the claimed duration to challenge the specification. You will need to conduct in-use pump stability test for at least twice the duration you intend to claim or reduce the in-use pump reservoir time you wish to claim. Ultimately, the pump labeling will dictate which insulin products are appropriate for use with the pump. You may need to work with the device manufacturer to establish the most appropriate pump reservoir duration based on the data you have collected or any new data you wish to collect.

2.2.1. Related Files

N/A

2.3. Indications for Use

Table 1: Indications for Use

Combination Product	Indications for Use

FIASP	FIASP is a rapid acting human insulin analog indicated to improve glycemic control in adults and children with Diabetes mellitus
Infusion Pump	Delivery of the drug product

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Location
0065 Cover Letter 20181221 PAS – NN1218-3854 Adult Pump	Sequence 0065/1.2 Cover Letters
Reviewers Guide – Pump Indication	Sequence 0065/1.2 Cover Letters
0065 Annotated PI – Pump Indication	Sequence 0065/1.14.1.2 Annotated Draft Labeling Text
Clinical Overview – Pump Indication	Sequence 0065/2.5 Clinical Overview
Summary of Clinical Pharmacology Studies – Pump Indication	Sequence 0065/2.7.2 Summary of Clinical Pharmacology Studies
Summary of Clinical Efficacy – Pump indication	Sequence 0065/2.7.3 Summary of Clinical Efficacy
Summary of Clinical Safety – Pump Indication	Sequence 0065/2.7.4 Summary of Clinical Safety
Report Body	Sequence 0065/5.3.5.1 nn1218-3854 – Efficacy and Safety of Continuous Subcutaneous Insulin Infusion of Faster-acting Insulin Aspart compared to NovoRapid in Adults with Type 1 Diabetes
Report Body	Sequence 0065/5.3.4.2 NN1218-4349 – A trial investigating the pharmacokinetic and pharmacodynamic properties of Faster-acting Insulin Aspart when administered as a bolus in a continuous subcutaneous infusion regimen in subjects with type 1 diabetes
Insulet Letter of Authorization	Sequence 0065/1.4.1 Letter of Authorization
Annotated PI- Pediatric Pump	Sequence 0073/1.12.1.2 Annotated Draft Labeling Text
Clinical Overview – Pediatric Pump Indication	Sequence 0073/2.5 Clinical Overview
In-vitro Pump In-use Stability data	Sequence 0000/3.2.P.8.3 Stability data
007 Att 5 TR17-462 Fiasp In Use Stability Study	MAF (b) (4)/Email from MAF holder
See Contact History for documents received interactively from the sponsor	Emailed documents from MAF holder

4. DEVICE DESCRIPTION in Clinical Studies

4.1. Device Descriptions in Clinical Studies

The following information was taken from:

- *Clinical Overview – Pump Indication*
- *Report Body* [Efficacy and Safety Clinical Study]
- *Report Body* [Pk/Pd Clinical Study]
- *Clinical Overview – Pediatric Pump indication*

CSII Pump Adult

The sponsor submitted NN1218-3854 confirmatory clinical trial to support the pump indication. In addition, they conducted two exploratory trials (NN1218-3930 and 3931) and two PK/PD studies (NN1218-3890 and 4349) to support FIASP pump use. Trials 3930, 3931 and 3890 were submitted under the original NDA.

CSII Pump Adult + Pediatric

To support the addition of a pediatric indication the sponsor extrapolated efficacy results from the adult pump trail in T1DM to pediatric T1DM based on the following:

- Efficacy from NN1218-3854 Phase 3b pump efficacy and safety trial in adult subjects
- Completed single dose from NN1218-4349 in adult subjects
- Efficacy data from completed subcutaneous pediatric efficacy and safety trial NN1218-4101
- Trial NN1218-3852 will provide reference data for supporting dosing recommendations

Reviewer Comment:

- In IND 106878 the sponsor proposed (b) (4) to provide further guidance regarding the (b) (4). We agreed that it was “generally appropriate to provide further guidance” However, it appears that the sponsor decided to file without this additional data.
- To support the pediatric indication the sponsor referenced two new trials (NN1218-4101 and NN1218-3852). All other data provided is adult data extrapolated to pediatric (NN1218-3854 and NN1218-4349).
- The devices used in all referenced trials will be reviewed below as well as age of participants to support the pediatric indication. This is critical since physiological differences in pediatric patients may impact the device performance (e.g. dermis and subcutaneous thickness).

NN12-3854 -Safety and Efficacy

The safety/efficacy clinical study -3854 used Medtronic infusion pumps that the participants have been using for the past 6 months (minimum). The Medtronic pumps were:

- Minimed 530G (551/751)
- Paradigm Veo (554/754)
- Paradigm Revel (523/723)
- Paradigm (522/722))

The sponsor then allowed the study subjects a choice of one of the following Medtronic infusions sets:

- Quick-Set®
- Mio®
- Silhouette®
- Sure-T ® (Easy-set®)

The also provided insulin reservoir 1.8/3.0mL

They also provided the following CGM supplies:

Novo Nordisk provided the following:

- CGM device (receiver and transmitter)
- CGM user guide and quick user guide (for site use)
- Instructions for subjects

CGM equipment was returned to Novo Nordisk at end of treatment (Visit 22).

The CGM manufacturer provided the following:

- CGM installation link to CGM software
- CGM sensors
- CGM training (webinar or on-site)

Patient Population: males and females age ≥ 18 years

Reviewer Comment:

- The device description for this clinical trial is adequate. The infusion pump and sets used are described.
- This study did not evaluate a pediatric population.
- IRs related to the CGM will be deferred to OIR.

NN1218-4349 PK/PD Clinical Study

The PK/PD study (-4349) used the following infusion pump devices and accessories:

Insulin Pump: Medtronic MiniMed 640G

Insulin Reservoir: MiniMed 640G Reservoir 3.0 mL

Infusion Set: Quick Set, 6mm cannula – 60 cm (23 in) tubing

Patient population: Male or Female 18-64 years (inclusive)

Reviewer Comment:

- The device descriptions for clinical trial -4349 is adequate. The infusion pump and sets used are.
- This study did not evaluate a pediatric population.
- IRs related to the CGM will be deferred to OIR.

NN1218-4101 Efficacy Pediatric Study

Insulin Pumps, Reservoirs, Sets: N/A

Insulin Pens:

- Bolus: Faster aspart, 100 u/mL, 3mL Penfill ®
- Bolus: Insulin apart (NovoRapid/Novolog) 100u/mL, 3mL Penfill ®
- Basal: Insulin degludec, 100 u/mL, prefilled 3mL PDS290 pen-injector (FlexTouch®)

CGM: A subgroup of 150 patients aged ≥ 8 years used a blinded device for CGM for two periods during the trial. At baseline: 11 to 13 consecutive days before randomization and before randomized treatment. During treatment: 11 to 13 consecutive days before the end of the 26 week treatment period.

Novo Nordisk will provide the following:

- CGM devices (receiver and transmitter)
- CGM user manual and quick guides (for site use)
- Instructions for Subjects and the LAR(s)

CGM devices should be returned to Novo Nordisk at end of trial.

The CGM manufacturer will provide the following:

- CGM Installation link to CGM software
- CGM sensors (customs clearance must be expected)
- CGM Training (webinar or on-site)

Patient Population: 1 years to less than 18 years old (Serbia only: 2 years to less than 18 years)

Reviewer Comment:

- This clinical study only used **pen injectors** to deliver basal-bolus regimen. No pump or infusion set was used. They state that they do not consider there will be difference in the benefit-risk profile of faster aspart administer as CSII in children. They also rely on data from NovoRapid/Novolog approved for use with CSII (NDA20986/S-047)
- Limited information was provided regarding the CGM. I defer adequacy of the CGM device description to OIR.

NN1218-3852 supportive pediatric dosing recommendations

Insulin Pumps, Reservoirs, Sets: N/A

Insulin Pens: [treat to target dose for all]

- Faster aspart, 100U/mL, 3mL PDS290 pen-injector
- NovoRapid®/NovoLog®, 100 U/mL, 3mL PDS290 pen-injector
- Insulin detemir (Levemir®) 100 U/mL, 3mL Flexpen

CGM: A subset of subjects in each treatment group had interstitial glucose profiles generated for 10–14-day periods twice during the trial: during the run-in (2–5 weeks before randomization) and again during randomized treatment (24–26 weeks after randomization). A frequently sampled meal test was performed for the subgroup of subjects within each of these two periods.

Novo Nordisk A/S will provide the following:

- CGM system
 - CGM equipment including sensors
 - CGM user manual and quick guides (for site use)
 - Instructions for Subjects
 - Guideline on how to transfer CGM data
- CGM diary (included in the trial diary)

CGM equipment should be returned to Novo Nordisk at EoT.

Patient Population: Males and females age ≥ 18 years

Reviewer Comments:

- The device description was adequate.
- All of the devices used were **pen-injectors**.
- The pediatric population was limited to 18-21(inclusive).

5. FILING REVIEW

CDRH performed Filing Review	☒
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

Filing Review Checklist				
Description		Present		
		Yes	No	N/A
Description of Device Constituent		X		
Essential Performance Requirements				X
Release Specifications				X
Letters of Authorization		X		
Design Control Check	Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer			X
	Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.			X
	Risk Analysis supplied in the NDA / BLA by the Combination Product Developer			X
	Traceability			X
Full Test Reports for Verification and Validation Testing				
Release Specifications Defined	Dose Accuracy (Fill Volume)			X
	Beak loose/ Glide Force			X
	Audible/Visual Information on injection status			X
Device Constituent Labeling		X		

Reviewer Comment:

They sponsor included a LOA from Insulet for omnipod in this supplement. The purpose of this was to provide data demonstrating that FIASP is stable in Omnipod reservoirs for up to six days. MAF ^{(b) (4)} Section 7.2 provided a high-level summary of the study and referred to Attachment 5: Fiasp In-Use Stability TR17-462 test report located in the MAF. However, this attachment is missing from the MAF. Therefore, the sponsor did not provide adequate information to review the in-use stability of FIASP in a pump reservoir. This can be resolved with the MAF holder. I defer to CDER for communicating this deficiency. See Comment to CDER #1. RESOLVED - The MAF holder provided this data and it will be reviewed in Section 7 of this memo.

A review of the data shows that it was only performed on tubeless pumps. However, given their labeling or any infusion pumps they should provide In-Use stability for pumps with tubes. See IR #2 issued on 4/4/2019. The sponsor resolved this IR by referencing the data provided in Sequence 0000 3.2.P.8.3 Stability data

Filing Recommendation	
Filing Information Requests	Section 11.1 Filing IRs - # None Section 11.2 74-Day-letter IRs - # None
The device constituent content in the submission for the combination product is acceptable for filing	☒
The device constituent content in the submission for the combination product is acceptable for filing, CDRH has Information Requests to include in the 74-Day letter, See Section 11.2	☐
The device constituent content in the submission for the combination product is acceptable for filing, See Section 11.1 for Filing Information Requests	☐

6. LABELING REVIEW

6.1. Proposed Change – CSII for Adults(S-08) and Pediatric (S-11)

The purpose of this supplement is to update the Physician insert to include a CSII indication on the labeling which would be supported by clinical data. Therefore, the sponsor provided an annotated PI with redlines of the changes and reference to the clinical data supporting the claim. The following excerpts were taken from *Annotated PI – Pediatric pump (SEQ 0073)* as it would contain both the adult and pediatric labeling considerations .

Reviewer Comment: There are currently no CSII pumps indicated for use with FIASP. Therefore, there is an ODI. However, there were previous discussion with the MAF holder and sponsor regarding this issue. It may be useful to send a reminder. See [Comment to CDER #8](#). This was communicated at the midcycle review (5/21/2019)

The following is an excerpt from the -3854 clinical study regarding infusion set changes.

Table 12-19 Infusion set changes - summary - on-treatment - safety analysis set

	Faster aspart				NovoRapid			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	236				236			
Total exposure (yrs)	72.8				71.7			
All changes	236 (100.0)		9653	13267	236 (100.0)		9360	13057
Routine change	236 (100.0)		9113	12525	236 (100.0)		8868	12370
Non-routine change	168 (71.2)		507	697	135 (57.2)		479	668
A perceived occlusion by the subject	50 (21.2)		120	165	50 (21.2)		112	156
Any problems related to the infusion set	108 (45.8)		201	276	75 (31.8)		206	287
Any technical issues with the pump	23 (9.7)		31	43	17 (7.2)		22	31
Changes in the insulin solution in the infusion set or reservoir	3 (1.3)		3	4	8 (3.4)		8	11
High BG with no other explanation which made the subject change the infusion set	66 (28.0)		121	166	60 (25.4)		119	166
Infusion site reaction	16 (6.8)		28	38	8 (3.4)		11	15
Missing	3 (1.3)		3	4	1 (0.4)		1	1
Missing	11 (4.7)		33	45	10 (4.2)		13	18

#: Percentage of subjects, BG: Blood glucose, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years

Reviewer Comment:

- **Reservoir Change:** The sponsor recommends changing the pump reservoir **at least every 6 days**. This is adequate for pumps *with tubing* since the Sponsor provides 15 days of stability under worse case (pediatric) conditions. However, the data provided in MAF (b)(4) only supports 3 days (72 hrs) since the MAF holder only provides 6 days of stability data. Tubing pumps may be considered worse case. Therefore, the proposed recommendation of at least every 6 days is adequate assuming the stability testing conducted (pumps with tubing) is adequate. **See Comment to CDER #2.** See Section 7 for analysis of stability data.
- **Infusion set change:** Clinical study report for -3854 Section 12.10 *Infusion set changes* states that the mean infusion set change was 2.55 with FIASP, 2.49 with NovoRapid/NovoLog during the 16-week randomization. However, FIASP had a high proportion of infusion set changes with FIASP(71.1%) than with Novorapid/Novolog(57.2%). The reasons for the infusion set changes were *perceived occlusion by subject* (same rate between FIASP and Novorapid/Novolog), *infusion site reaction* (2X higher in FIASP), any problems with infusion set (same rate between FIASP and Novorapid). It appears that the drug may impact the infusion set change rate based on the data provided. The sponsor may refer to NDA 20986/S-047 approval of NovoRapid/Novolog for CSII but since AE for infusion site reactions were higher for FIASP the sponsor should address the concern. In addition, the labeling for NovoLog states that the reservoir and infusion set should be change at **at least every 48 hours** and even more often if you notice high blood sugar, pump alarms or occlusions. This was recently updated to every 72 hours. **See comment to CDER #3.** This was communicated at the midcycle review (5/21/2019)
- **Infusion set change Pediatric:** It is also noted that this study was done with adults and they do not extrapolate this for pediatric which may be more susceptible to infusion site reactions. The study -4101 with pediatric patients assessed pen injectors which would not show safety data relating to infusion set changes/infusion site reactions. The sponsor can claim a pediatric indication if they limit it to injection not CSII infusion assuming the efficacy/safety data supports it. **See Comment to CDER #4.** This was communicated at the midcycle review (5/21/2019)

ICC1900064
NDA208751 , FIASP ,
Novo Nordisk

(b) (4)



Reviewer Comments:

- The instructions regarding training and infusion site location are consistent with infusion pump labeling (MAF (b) (4)).
- The temperature recommendations are consistent with the stability testing conditions (Section 7) and clinical study storage conditions.

Reviewer Comments: The AE reported are misleading because they do not state that it was done with Pen injectors. It can be misconstrued to believe it was done with pumps. Therefore, some AEs may not be reported. E.g. infusion site reactions. See [Comments to CDER #5](#) This was communicated at the midcycle review (5/21/2019)

ICC1900064
NDA208751 , FIASP ,
Novo Nordisk

(b) (4)



Reviewer Comments: The infusion site reactions section is not specific to pediatric AEs related to infusion pumps. See **Comment to CDER #4 and 5.** This was communicated at the midcycle review (5/21/2019)

Reviewer Comment: The first sentence is misleading because no studies were performed to assess the AEs for pediatric using CSII pumps. See Comment to CDER #5. This was communicated at the midcycle review (5/21/2019)

ICC1900064
NDA208751 , FIASP ,
Novo Nordisk

(b) (4)



ICC1900064
NDA208751 , FIASP ,
Novo Nordisk

(b) (4)



Reviewer Comment: The sponsor did not provide any dose accuracy data in their clinical study to support a pediatric infusion pump use. The pediatric testing only used pen injectors which would have a much tighter dose accuracy performance. **Comment to CDER #6.** This was communicated at the midcycle review (5/21/2019)

MiniMed 530G system

Infusion set Change: 2-3 days

Reservoir change

Enlite Glucose Sensor: 6 days

Reviewer Comment:

- The annotated labeling has a reference for each of the proposed changes made. The referenced documents are included in the submission.
- In addition, it appears that the sponsor provided information regarding 2 clinical studies to address CDRH's original comments (2 and 3). It may address comment 1 (device labeling) during the formal review. Therefore, there are no filing review issues at this time.

Device Description Stock IR

Labeling Recommendation	
The Sponsor Provided Complete Labeling for the Device Constituent	☒
The Sponsor DID NOT Provide Complete Labeling for the Device Constituent	☐
Device Description Information Requests	Section 11.1 Filing IRs - # None Section 11.2 74-Day Letter IRs - # None Section 11.3 Mid-Cycle IRs - # None Section 11.4 Interactive IRs - # None
All Information Requests were Resolved over the course of the review	☐
There are Complete Response Deficiencies, See Section 9	☐

7. PERFORMANCE TESTING REVIEW

7.1. Dose Accuracy in Clinical Studies

The following infusion was obtained from Clinical Trial Report NN1218-3854 regarding bolus and basal doses.

APPEARS THIS WAY ON ORIGINAL

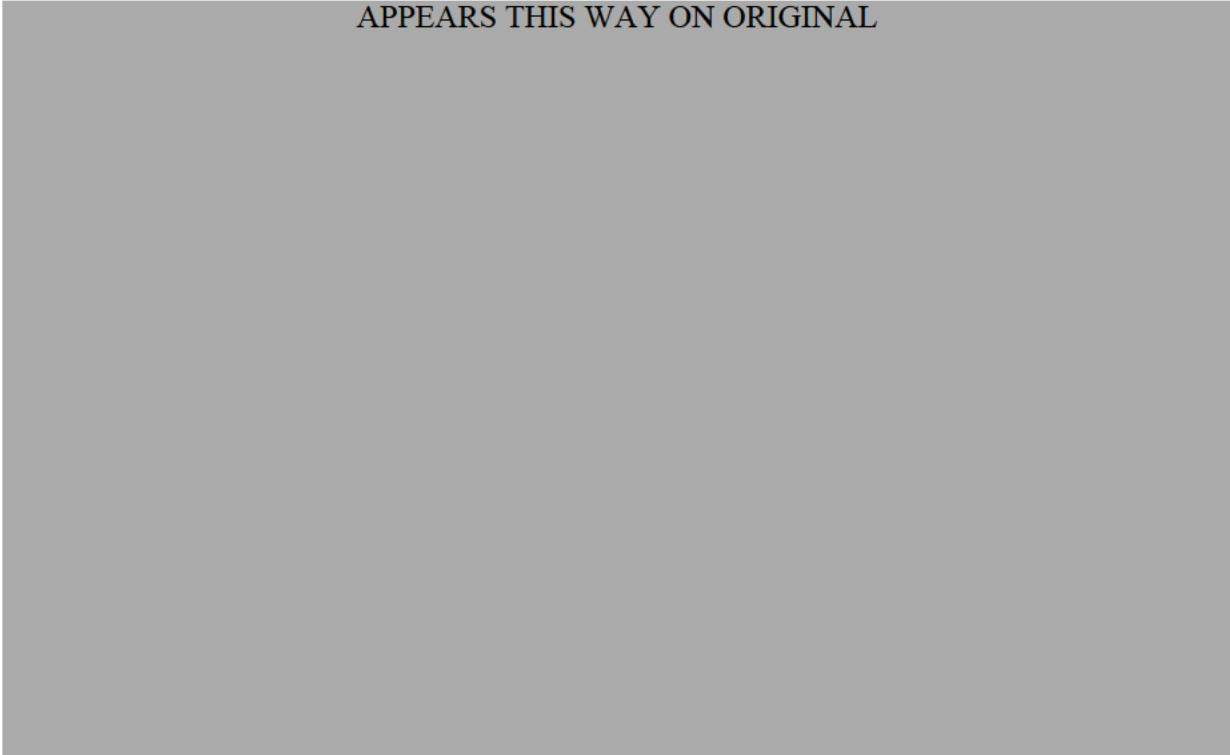


Table 12-2 Daily bolus, basal and total insulin dose (actual) at week 0 and after 16 weeks – on-treatment observation period

Visit (Week)	Treatment	Safety analysis set	Descriptive statistics					
			N	Mean	SD	Median	Min	Max
Daily bolus dose (all meals) in U								
Visit 6 (Week 0)	Faster aspart	236	236	24.90	14.73	22.60	2.1	90.0
	NovoRapid	236	236	25.85	15.10	23.05	4.0	107.8
Last on-treatment value	Faster aspart	236	236	25.91	17.46	21.90	3.2	150.4
	NovoRapid	236	236	25.27	15.33	22.35	4.3	104.7
Daily basal dose in U								
Visit 6 (Week 0)	Faster aspart	236	236	23.21	12.18	19.78	5.7	77.5
	NovoRapid	236	236	23.91	11.70	21.84	4.1	83.8
Last on-treatment value	Faster aspart	236	236	23.82	12.82	19.86	5.7	92.7
	NovoRapid	236	236	23.87	11.38	22.08	7.6	76.5
Total daily insulin dose in U								
Visit 6 (Week 0)	Faster aspart	236	236	48.06	28.71	42.35	15.5	162.1
	NovoRapid	236	236	49.76	24.07	45.40	16.5	191.7
Last on-treatment value	Faster aspart	236	236	49.72	27.08	44.29	15.2	228.0
	NovoRapid	236	236	49.12	23.75	43.60	18.1	173.1
Daily bolus dose (all meals) in U/kg								
Visit 6 (Week 0)	Faster aspart	236	236	0.32	0.16	0.29	0.0	1.1
	NovoRapid	236	236	0.32	0.16	0.30	0.0	1.5
Last on-treatment value	Faster aspart	236	236	0.33	0.17	0.30	0.0	1.3
	NovoRapid	236	236	0.31	0.16	0.25	0.0	1.1
Daily basal dose in U/kg								
Visit 6 (Week 0)	Faster aspart	236	236	0.30	0.12	0.27	0.1	0.7
	NovoRapid	236	236	0.30	0.12	0.28	0.1	1.1
Last on-treatment value	Faster aspart	236	236	0.30	0.12	0.27	0.1	0.8
	NovoRapid	236	236	0.30	0.11	0.26	0.1	1.0
Total daily insulin dose in U/kg								
Visit 6 (Week 0)	Faster aspart	236	236	0.61	0.23	0.56	0.2	1.5
	NovoRapid	236	236	0.62	0.24	0.60	0.2	2.6
Last on-treatment value	Faster aspart	236	236	0.63	0.24	0.58	0.2	1.8
	NovoRapid	236	236	0.61	0.23	0.56	0.3	2.1

N: Number of subjects, SD: Standard deviation, Last on-treatment value contains the last available measurement in the on-treatment period.

Cross-reference: Adapted from EOT Tables 14.2.16, 14.2.17, 14.2.29, 14.2.30, 14.2.33 and 14.2.34

Reviewer Comment: The table reported what was delivered. It does not demonstrate what was intended to be delivered vs. what was delivered. Therefore, there was not clinical dose accuracy data provided. However, a review of the Medtronic pumps (pumps with tubing) used in the study claim a (b)(4) % delivery accuracy (bolus and basal). In addition, the referenced MAF (b)(4) Omnipod (tubeless pump) claims a (b)(4) % delivery accuracy (bolus and basal) as well. Therefore, both tubeless and pumps with tubing pumps have the same delivery accuracy specifications and no additional data is needed to support the use of tubeless pumps.

7.2. Infusion Pumps with Tubing

The following information was provided by the sponsor in In-vitro Pump In-use Stability data/SEQ0000 3.2.P.8.3 Stability Data.

Table 6 Study design

Pump system	Drug product Batch	Basal infusion rate	Bolus per 24 hour	Infusion set	Study duration (days)	Study ID
MiniMed Paradigm® 722	DW5B443	0.3 U/h	3x2.5 U	Medtronic Silhouette® Paradigm®, 110 cm	14	P-1
	DW5B444	0.9 U/h	3x7.5 U	Medtronic Silhouette® Paradigm®, 110 cm	5	P-2
	CW57091	0.3 U/h	3x2.5 U	Medtronic Silhouette® Paradigm®, 60 cm	15	P-3
	CW57091	0.3 U/h	3x2.5 U	Medtronic Silhouette® Paradigm®, 110 cm	14	P-4
Animas® Vibe™	DW5B444	0.3 U/h	3x2.5 U	Unomedical Inset™ II, 110 cm	9	A-1
	DW5B443	0.9 U/h	3x7.5 U	Unomedical Inset™ II, 110 cm	3	A-2
	CW57091	0.3 U/h	3x2.5 U	Unomedical Inset™ II, 60 cm	9	A-3
	CW57091	0.3 U/h	3x2.5 U	Unomedical Inset™ II, 110 cm	9	A-4

Reviewer Comment:

- To support at 6 day reservoir change, the sponsor should provide at least 12 days of stability (2x). The study design allows for 15 day at longest infusion set (110cm) length and lowest flow rate (0.3 U/h). The study tested various flow rates and pump systems (2 total).
- The flow rates of 0.3 U/h with 3x2.5 U/day bolus was used to simulate pediatric use while 0.9 U/h with 3x 7.5 u/day bolus was used to simulate adult use.

Study Conditions/Simulate patient use: placed on reciprocating table at 37C (b)(4) and movement (b)(4) (b)(4) Light exposure was (b)(4) minutes per day during bolus and during handling samples during infusion set changes.

Reviewer Comment:

- The simulated patient use appears representative of intended use.
- Infusion sets were changed every third day per the manufacturers recommendations. However, the first change occurred at day 6 instead of day 3 for MiniMed Paradigm 722 P1, P3 and P4 studies and Animas Vibe Study A1, A2, A3 and A4.
- No occlusions/alarms were identified during the study.
- The sponsor concludes that the 15 days stability would support a (b)(4) pump in-use time. However, 15 days is only sufficient to support a (b)(4) proposed 6 days. The data is adequate to support 6 days.

7.3. Tubeless Infusion pumps

The sponsor referred to MAF (b) (4) for in-use stability of FIASP in tubeless pumps. Below are is list of assays conducted and study design.

Test	Testing at T=0 Days	Testing at T= 2 Days	Testing at T=4 Days	Testing at T=6 Days
Potency (Assay)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control (2-8°C)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)
Total Other Impurities	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control (2-8°C)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)
High Molecular Weight Proteins	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control (2-8°C)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)
Preservatives	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control (2-8°C)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)
Zinc	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control (2-8°C)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)
Appearance and Clarity	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control (2-8°C)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)	-1 Device Lot L43356 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)
pH	-1 Device Lot L43636 -1 Device Lot L43636 -1 Device Lot L43534 - Insulin Control (2-8°C)	-1 Device Lot L43636 -1 Device Lot L43636 -1 Device Lot L43534 - Insulin Control - Insulin Control Quiescent	-1 Device Lot L43636 -1 Device Lot L43636 -1 Device Lot L43534 - Insulin Control - Insulin Control Quiescent	-1 Device Lot L43636 -1 Device Lot L43636 -1 Device Lot L43534 - Insulin Control - Insulin Control Quiescent
Particulate Matter	-1 Device Lot L43534 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control (2-8°C)	-1 Device Lot L43534 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)	-1 Device Lot L43534 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)	-1 Device Lot L43534 -1 Device Lot L43454 -1 Device Lot L43365 - Insulin Control - Insulin Control (b) (4)

Devices were filled with 3 different lots of FIASP, gently agitated (b) (4) and removed from stability conditions (37C (b) (4)) at 0 (no agitation), 2, 4 and 6 days. The controls were insulin vials stored at 2-8C (T=0 testing only) or 37 (b) (4) (b) (4) with or without gentle agitation (b) (4).

Reviewer Comment:

- There was no light exposure since the pod does not permit light exposure.
- The MAF holder did not specify the agitation time. I defer to CDER for adequacy of the shaker time period. Comment to CDER #7. This was communicated at the midcycle review (5/21/2019)

Performance Testing Recommendation

The Sponsor Provided Complete Performance testing for the Device Constituent	☒
The Sponsor DID NOT Provide Complete Performance Testing for the Device Constituent	☐
Device Description Information Requests	Section 11.1 Filing IRs - # None Section 11.2 74-Day Letter IRs - # None Section 11.3 Mid-Cycle IRs - None Section 11.4 Interactive IRs - None
All Information Requests were Resolved over the course of the review	☐
There are Complete Response Deficiencies, See Section 9	☐

8. REFERENCED MAF ^{(b)(4)} REVIEW

The sponsor references MAF ^{(b)(4)} which is for: Omnipod Insulin Management System and OmniPod DASH Insulin Management System. The MAF content is reviewed below to assess if the content is adequate to support use with FIASP.

It is noted that the insulin infusion pump was recently cleared under **K182630 on 1/8/2019**.

8.1. Proposed changes

At a high level, the sponsor is adding FIASP U100 insulin to their labeling. As a result they are making the following changes:

- Labeling - addition of FIASP

Reviewer Comment: Based on the information provided in the MAF, it is unclear exactly what changes are being made to the device, why the changes would not raise new questions of safety and effectiveness and data references and test reports to substantiate the changes. They can submit a draft 510k summary to summarize this information. **See IR #6 to the MAF holder.** Resolved – the MAF holder clarified that the only change from K182630 is the labeling. They provided a 510(k) summary with this statement.

8.2. Device Description

The omnipod system is a single use disposable device. It uses an adhesive to attach via a biocompatible acrylic that keeps the pod in place for 3 days.

Figure 1: The Omnipod System

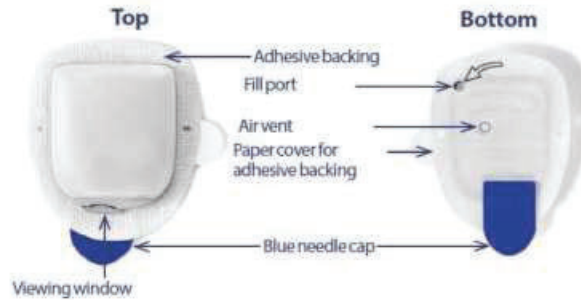


Figure 2: The Omnipod DASH System

Figure 3: Features of the Omnipod Pod



Figure 4: Features of the Omnipod DASH Pod



The pod is filled by the user through a port using a syringe. The pod delivers the medication subcutaneously through a cannula. It has a cannula insertion mechanism designed to place the soft cannula into the subcutaneous tissue at an angle to an insertion depth of 6mm. The insertion needle serves to puncture the skin and stiffen the soft cannula during the insertion process.

The PDM manages all processes for the operation of the system. The LCD allows the use of full text to prompt the user through the set-up and use processes. It is also used to initialize the program in the Pod with the user's custom basal insulin delivery profile, to check the Pod status, initiate a bolus dose of insulin or make changes to a patient's insulin delivery profile. After set-up and initiation the Pod will run at the programmed basal rate independent of the PDM. The PDM provides the ability to calculate a suggested bolus dosage, which otherwise is typically done manually by the user. This Suggested Bolus calculation feature is provided as a convenience to the user to aid in determining the bolus dosage needed based on carbohydrates ingested, most recent blood glucose reading, programmable correction factor, insulin to carbohydrate ratio, target blood glucose value and Insulin on Board.

The PDM incorporates a blood glucose measurement capability. Blood glucose readings are made using Abbott FreeStyle® blood glucose meter technology. The PDM displays blood glucose readings from the incorporated FreeStyle® blood glucose meter design via an internal serial interface/protocol. The blood glucose data is stored, and displayed on the PDM.

The OmniPod DASH PDM is a locked-down android mobile device where a majority of the smart phone characteristics are locked out, allowing only the blue tooth and WIFI to be accessed by the user.

Reviewer Comment: The Device description appears complete. No additional changes required.

8.3. Performance Testing

8.3.1. Biocompatibility

Reference is made to biocompatibility testing. Although, the sponsor is not changing any of the materials they should still provide a table summarizing the materials of construction, contact classification and summary of the endpoints. See IR #7 to the MAF holder. Resolved- the sponsor provided the biocompatibility information. Regardless, their response to IR#6 address biocompatibility because the design and manufacturing is identical to K182630 which was cleared in Jan 2019.

8.3.2. DP Stability

The sponsor provided stability testing in Attachment 007_Att 5 TR1717-462 FIASP In Use Stability Study. In Section 7.2 of this memo stability testing with tubing was considered “worse case”. However, for a future 510(k) the sponsor would need to demonstrate that their device (OmniPod) stability is adequate.

Anjali Shukla of CDER/OBP/DBRRI was consulted to review the MAF stability testing report . Her full review memo is attached in Section 13 Appendix of this memo

Recommendation: The information provided in the MAF (b) (4) supports the compatibility of OmniPod and OmniPod Dash systems for use with FIASP U100 and support the approval of the proposed 510k.

Reviewer Comment: The consultant supported their recommendation by referencing the in-pod stability studies. The consultant noted that while the studies omitted drug product quality data dispensed from the cannula this was adequate since the design itself has virtually no infusion set and there would be minimal degradation of the insulin from the reservoir to the patient.

8.3.3. EMC/Software

The sponsor states in the MAF

“The OmniPod and OmniPod Dash Pods are identical with the exception of the PCBA which was updated on OmniPod Dash to accommodate a (b) (4) The power budgets of OmniPod and OmniPod Dash were reviewed by engineering where a power consumption comparison was generated and summarized in Table 9.”

Reviewer Comment: It is unclear if the PCBA is a design change from the recently cleared device K182630. Also, we need the full reports for the testing to assess if we agree with the conclusion that it does not impact the Insulin stability test results. See IR#8 to the MAF holder. Resolved – the sponsor’s clarified that the design and manufacturing is identical to K182630. Therefore, this PCBA design change was reviewed and cleared in K182630.

8.3.4. Leachables

The sponsor provided a summary of leachables testing and reports in the MAF:

- Att6 Fiasp Leachables from OmniPod System Pods TR17-464
- Att7 Fiasp Leachables ICH Q3D Testing Tr18-521

The study consistent of subjecting Eros Devices to the Fiasp U100 drug. The Eros device has an identical fluid path/drug contact as the OmniPod system. The extractions were performed at 37 (b) (4) for 96 (b) (4) hours. The study also included control extractions. The volatile and non-volatiles were assessed.

A separate leachables study was conducted to assess ICH Q3D Class 1 metals in Fiasp. Testing was conducted using Eros devices that had the identical fluid path as the OmniPod systems. Metal extraction was performed (b) (4)

(b) (4) The following metals were analyzed by ICP-MS: Cd, Pb, As, Hg.

Berk Oktem of CDRH/OSEL was consulted to review the leachables studies. A series of IRs were issued to resolve questions regarding the proposed extraction methods. See IR#11 and 11.1. Resolved. The sponsor provided additional justification to conduct a final review of the leachables. His recommendation is below

Recommendation: *Additional Information needs to be requested from the sponsor.*

His final review memo is attached in Section 13 Appendix of this memo

Reviewer Comment:

The consultant disagreed with the leachables testing approach because it was performed at conditions with limited time and extraction power. For example, while the sponsor performed the leachables testing at 96 (b) (4) hours which is longer than the intended use (72 hours), it does not consider the repeated use (new pump each time) of a user's lifetime. In addition, it was noted that additional extractables may have been masked by FIASP in TR17-463. Therefore, an exhaustive extraction would be more appropriate.

However, the additional information requests will not be issued and the leachables data will be **deemed adequate** for the following reasons:

- No adverse impact on DP quality - If there were leachables at harmful levels being removed from the fluid path they could have impacted the DP quality. However, a review of the DP quality data showed that there was no adverse effect on FIASP after being exposed to the OmniPod fluid path materials under agitation.
- Predicate extractables testing and toxicological assessment – The materials of construction and design of the fluid path for the future 510(k) is identical to the predicate K182630. In addition, the test methodology proposed by the MAF holder is the same used for the clearance of K182630. Therefore, the request for additional exhaustive extractables testing, even though the materials and design are identical to the predicate, is superfluous unless the sponsor made changes to the materials of construction or design of the fluid path.

8.4. Safety Assurance Case

Reviewer Comment:

The sponsor did not provide a Safety assurance case. They only provided a risk assessment summary. **See IR #9 to the MAF holder.** The sponsor addressed this IR #9 by providing the following SAC addendums:

- Attachment 4 _ Q4 Eros Safety Assurance Case
- Attachment 5 _ Q4 Dash Safety Assurance Case

The Eros system is the OmniPod that is approved in Europe. Attachment 4 is an addendum to the SAC in K166296. Attachment 5 is an addendum to the SAC in K180045. Both focus on the hazards and mitigations relating to the addition of FIASP to the labeling.

K182630 (cleared Jan 2019) was a bundled submission for OmniPod and OmniPod dash where the predicates were K162296 (OmniPod) and K180045 (OmniPod Dash). The scope of K182630 was the addition of Admelog U100 and cannula design (holes, cannula depth of insertion, depth of infusion specifications only). While K182630 SAC would contain information regarding the cannula design change, limiting the scope of the addendums to just the addition of FIASP compared to K166296 and K180045 is adequate since the risks associated with cannula design were addressed in K182630 and do not impact FIASP compatibility with the OmniPod or OmniPod DASH.

In addition, they provided the signed System level requirements (product definition document, Attachment 6) for the Eros (OmniPod). The requirement for the addition of FIASP will be leveraged for the OmniPod DASH, since the addition of FIASP would result in the same design requirement (2.1.3 in Attachment 6) but will be confirmed in the 510(k).

Overview

My review accomplishes the following with respect to the addition of FIASP:

- Identify the design specification documents describing the subject device
- Assure traceability of the requirements / specifications to the design verification / validation documentation
- Verify appropriate hazards analyses (e.g., both patient / user centric and technology centric) and mitigation efforts have been completed.
- Assure traceability of hazards – mitigations – evidence is complete.
- Review key pieces of evidence, as determined by the time available and review team priority.

The applicant's assurance case follows a risk-based argument structure, as shown in the safety case top-level claim,

Eros System

The OmniPod Insulin Management System with blood glucose monitor is acceptably safe for the infusion of U100 insulin that is approved for use in pumps, for use in the home setting by people with diabetes mellitus who require insulin on a daily basis.

OmniPod Dash

The OmniPod Dash Insulin Management System with dose calculator is acceptably safe for the infusion of U100 insulin that is approved for use in pumps, for use in the

home setting by people with diabetes mellitus who require insulin on a daily basis.

Safety Assurance Case Administrative Review

Top Level Structure

The importance of top-level structure is found in the content of claims and contextual information that constrains the review of the lower-level argument structures.

The following table documents the lead reviewer assessment of the OmniPod (i.e., Eros) and OmniPod DASH assurance case top-level structure and supporting assurance strategy with respect to the addition of FIASP.

Top Level Goal Review	Present (Y/N)	Reviewer Comments
There is a top-level goal asserting device safety, is propositioned as a true/false statement and is consistent with FDA definitions (i.e. Device X is safe for its intended use)	Y	The top-level goals are complete
Context for top-level goal is provided and includes at a minimum: specific devices (i.e. model numbers) covered by the SAC, intended use, environment of use, patient population, predicate context, and use assumptions.	Y	The top-level goal doesn't specifically state adult, but a separate IR(3.2) was issued and resolved to ensure the labeling of both systems limit the use to adults. From a SAC perspective, it is adequate as written.
Argument structures for top-level goal	Present (Y/N)	Reviewer Comments
Acceptability of risk mitigations.	Y	
Adequate design verification and validation of device specifications.	Y	Conducted through DP stability and leachables testing
Adequate device reliability.	N/A	Addition of FIASP to the labeling does not impact the reliability of the device that was established in the predicate(s)
Hierarchic structure down to relevant domains (preferred but not mandated)	Y	
Evidence Review (i.e. Requirements / Specifications Documents)	Present (Y/N)	Reviewer Comments

Hazard Analysis and Risk Management documents are provided in full	Y	MAF ^{(b) (4)} Section 5 Risk Assessment
System Level Requirements and Specification Documents are provided	N/A	Attachment 6_Q4 Attachment INSPR017-(PDD) Eros Product Definition Document
Component Level Requirements / Specification Documents are provided.	N/A	Design unchanged from predicate. Therefore, they are leveraging the existing component level requirements/ specification documents provided in previous SAC.
Safety-related Requirements (specific requirements for safety, or requirements not achieved resulting in unsafe situation) are Identified	Y	
Reliability Specifications are defined for the system and components	N/A	Leveraged from previous 510k and not impacted by addition of FIASP.
Traceability Documentation demonstrates verification / validation of all requirements	Y	
All referenced evidence is provided in full	Y	
Traceability Review (i.e. Requirements / Specifications Documents)	Present (Y/N)	Reviewer Comments
The safety case includes System Level Requirements and corresponding traceability to the performance testing and hazard analysis.	Y	The Maf holder provided a separate hazard analysis for OmniPod and OmniPod Dash in the MAF (Attachment3 and 4). They link the identified risks to PRS (Product Requirement Specifications). In addition, their argument structure clearly links the performance testing and risks.

Tag	Component (SMA)	Mission Phase (SMA)	Cause Category (SMA)	Potential Cause (SMA)	Hazard Category (SMA)	Hazard (SMA)	Sequence of Events (SMA)	Unmitigated PS (SMA)	Hazardous Situation (SMA)	Unmitigated PS (SMA)	Unmitigated POB (SMA)	Severity (SMA)	Harm (SMA)	Unmitigated Risk Region (SMA)	Risk Control Measures (SMA)	PS to SVA, Unmitigated Harms	Verification Reference (SMA)	Mitigated PS (SMA)	Mitigated PS (SMA)	Mitigated POB (SMA)	Mitigated Risk Region (SMA)	SBA Note 1	PSA (SMA)	Analysis of Risk (Unmitigated) (SMA)
510k-5006	Pump	Activating/Charging a Pod	Human Factors	Improper syringe filling	Biocompatibility	Allergen in fluid path	1. The syringe is contaminated with allergen during fill process by user 2. The user fills the reservoir with insulin 3. The fluid is contaminated with the allergen 4. The allergen is infused into the patient.	2	Allergenic - Critical	3	1	5	Severe urticaria (hives and/or swelling) and/or anaphylactic shock	Medium	System is for and by prescription only. User guide provides instruction on transfer of insulin to Pump.	PRS-5630, PRS-4065, PRS-4068	See INSP0041 systems STM	2	5	1	Medium	SBA Note 1		

4.4. The use of a fast-acting U100 insulin, Fiasp, due to its faster onset of action, may require adjustment to the insulin duration of action setting in the PDM. The outcome for the user if this is not correct could be hyperglycemia.

4.4.1. The PDM is designed with a setup wizard that is used to program the insulin duration of action and other critical factors. The settings are written out on a prescription form Pump Therapy Orders Form, 14838-AW that captures the critical settings in the same order and terminology as the PDM Setup Wizard. The user is trained by the Health Care Provider (HCP) or a Certified Pump Trainer (CPT) to input the settings. This form was evaluated in a summative human factors test for the predicate, and was cleared under K162296, and has not changed since. The results of this human factors testing demonstrated that users were able to perform the tasks and program the PDM. The results of this human factors testing demonstrated that users were able to perform the tasks and program the PDM. The Supplemental Summative Usability Test of Next Generation OmniPod Insulin Management System (TR12-191) included having subjects go through the setup wizard at first-time setup.

Supporting Evidence

Document Number	Document Title	Location
TR12-191	Supplemental Summative Usability Test of Next Generation OmniPod Insulin Management System	K162296 Section 22-3

The safety case includes references to the traceability of the design requirements to the verification and validation documents.

Y

The sponsors system level document refers to testing which their SAC list as supporting evidence for the addition of FIASP.

Specification Description	Design Requirement	Rationale (For Design Requirement)	Verification
2.1.3. Type of use	Rapid-acting U100 insulin, e.g. Eli Lilly Humalog (Lispro), Fiasp, Novo Nordisk Novolog (Aspart), Sanofi Aventis Apidra and Ademlog	Marketing requirement	See 2.7.1
2.7.1. Drug integrity & Compatibility	The stored and delivered insulin shall be tested in accordance with the current USP standard Extractables shall be tested according to USP<1653> Leachables shall be tested according to USP<1664> Preservatives shall be tested to ensure adequate levels are present to maintain bacteriostasis.	To confirm insulin delivered by the device maintains its integrity and is compatible with the fluid path materials.	Refer to Document # INSPR017 PRODUCT DEFINITION TRACEABILITY MATRIX for Reference Traceability Matrix

Supporting Evidence

Document Number	Document Title	Location in Submission
TR17-462	Fast-acting Insulin Aspart Stability in Eros Pod	Attachment 5
TR17-464	Fast-acting Insulin Aspart Leachables from Omnipods	Attachment 6
TR18-521	Fiasp Leachables ICH Q3D Testing	Attachment 7

The safety case identifies the reliability requirements and corresponding traceability to the performance testing.

N/A

Reliability is not impacted by the addition of FIASP. Therefore, the addendums do not provide reliability requirements. This can be leveraged from the predicate SACs.

Part 1: Acceptability of Risk Mitigations

Risk Management Plan/Strategy

They follow ISO 14971 for the identification of hazards sources. After implementation of mitigations, they then perform a risk benefit analysis for each risk identified.

Hazards Identification

The Sponsor has identified the following hazards and hazardous situations within the safety conditions/goals:

System Hazards	Present (Y/N)	Reviewer Comments
<u>Infusion Delivery Error</u> (examples include – Intended medication selected and delivery attempted, but failure to deliver within the right time, dose, volume, patient, or anatomical or physiologic site specifications. This can include over-delivery, under-delivery or delay in delivery situations.)	Y	
<u>Incorrect Therapy</u> (examples include – Failure to select or deliver the intended medication because the wrong substance was selected for delivery.)	Y	
<u>Biological/Chemical Contamination</u> (examples include – Unintended contact with biological or chemical substance, or unintended patient or provider physiologic response to intended biological or chemical substance.)	Y	
<u>Traumatic Injury</u> (examples include – Burns, cuts, abrasions, air embolisms, electric shock, etc.)	Y	
<u>Harm due to insecure transmission of Data or incompatibility with digitally connected device</u>	Y	

Hazardous Situations	Present (Y/N)	Reviewer Comments
Operational	Y	
Environmental	Y	
Electrical	Y	
Hardware	Y	
Software	Y	
Mechanical	Y	
Biological and Chemical	Y	
Use	Y	

Reviewer Comment: The MAF holder’s risk assessments addressed the risks associated with the entire system and did not limit their assessment to the addition of FIASP. This approach ensures they did not miss any risks that may be related to the addition of FIASP.

Hazard Analysis Review

The following are Hazards obtained from Attachment 3 and 4 in the MAF for the OmniPod and OmniPod DASH related to the addition of FIASP.

System/Sub-System Hazard	Source/cause	RCM	RCM effective in mitigating hazard	Verification Method appropriate and acceptance criteria met
Chemical	Toxin in Fluid Path/ Toxic pump material leaches into the insulin. Insulin is infused into the user exposing the user to contaminated insulin	TR11-178, Rev. A, Extractables of Fluid Path TR12-014, Rev. A, Toxicological Assessment of Extractables TR11-178, Rev. B, Leachables of Fluid Path TR17-462, Rev. A, Fast-acting insulin aspart (Fiasp) stability in Eros pod TR17-463, Rev.A, Full Fill Dash Extractables TR17-464, Rev. A, Fiasp Leachable Study in Eros TR18-300, Rev. A, Admelog in Pod Stability Study TR18-301, Rev. A, Admelog in Use Stability Study in the Omnipod system TR18-302, Rev. A, Admelog in Pod Leachables Study	Yes, as determined by a review of the DP quality data, leachables testing and design (unchanged from predicate).	Yes, see section 8.3 of this memo.
User Error	User programs meal bolus prematurely. User is using Fiasp insulin a more rapid acting U-100 insulin and the insulin begins to act prior to food update	1. User guide provides a warning that Fiasp is a faster acting brand of U-100 insulin. 2. Patients should always consult with their healthcare provider and refer to the insulin labeling.	Yes, the labeling contains this warning. See Section 8.5.	FIASP is prescribed to the patient and the drug labeling also contains information regarding proper use.

Reviewer Comment: The risk regarding faster acting raised questions regarding the Pk/Pd compared to Novo (IR #4). However, this was resolved by the sponsor explaining while different it is not clinically relevant. FIASP dosing can be managed using the existing dose calculator with modifications.

Part 2: Adequate Design Verification & Validation of the Device Specifications

Verification & Validation of Design Requirements Summary

The summarized V&V plan is specific to the addition of FIASP

Design Requirement	Verification & Validation Method			Acceptance criteria met
The stored and delivered insulin shall be tested in accordance with the current USP standard	Document Number	Document Title	Location in Submission	Yes, See Section 8.3 of memo for review
	TR17-462	Fast-acting Insulin Aspart Stability in Eros Pod	Attachment 5	
	TR17-464	Fast-acting Insulin Aspart Leachables from Omnipods	Attachment 6	
	TR18-521	Fiasp Leachables ICH Q3D Testing	Attachment 7	

Part 3: Adequate Device Reliability

Reliability Plan

The sponsor is leveraging the predicate reliability since the functional performance would not be hindered by the labeling change and no design changes were made to the device.

8.5. Labeling

In addition to adding FIASP to the labeling, the labeling refers to children using the device. The user population age is not defined. Below are snapshots of the labeling.

003_Att 1 OmniPod User Guide Redlines

Pg. 13

Safe Use

Pump therapy requires substantial caregiver involvement, especially with children. Work with your healthcare provider to establish diabetes management guidelines and settings that best fit your, or your child's, needs. These may include:

Pg. 38.

Warnings:

Do NOT use a Pod if you are sensitive to or have allergies to acrylic adhesives, or have fragile or easily damaged skin.

If you are a first-time Omnipod System user, your Omnipod System Trainer will guide you through the steps for initializing and applying your first Pod. Do NOT attempt to apply or use a Pod until you have been trained by your Omnipod System Trainer. Use of the System with inadequate training or improper setup could put your health and safety at risk.

Because the Pod uses only rapid-acting U-100 insulin, you are at increased risk for developing hyperglycemia if insulin delivery is interrupted. Severe hyperglycemia can quickly lead to diabetic ketoacidosis (DKA). DKA can cause symptoms such as breathing difficulties, shock, coma, or death. If insulin delivery is interrupted for any reason, you may need to replace the missing insulin usually with an injection of rapid-acting insulin. Ask your healthcare provider for instructions for handling interrupted insulin delivery, which may include an injection of rapid-acting insulin.

Keep the Pod and its accessories, including the needle cap, away from young children, as they contain small parts that may be dangerous if swallowed.

Pg. 50.

Warnings:

Keep the blood glucose testing accessories away from young children, as they contain small parts that may be dangerous if swallowed.

Only use FreeStyle® test strips and FreeStyle® control solution with the Omnipod® System. Using other brands of test strips and control solutions with the System can produce inaccurate results.

Never attempt to test your blood glucose while your PDM is connected via a USB cable to a computer. Doing so could result in electrical shock.

If you are experiencing symptoms that are not consistent with your blood glucose reading and you have followed all instructions described in this *User Guide*, call your healthcare provider immediately.

Blood circulation is different between the finger and other test sites such as the upper arm and hand. You may see differences in blood glucose measurements between the other test sites and your finger after eating, taking insulin medication, or exercise.

You may see changes in blood glucose in blood samples from the finger sooner than in blood samples from alternate sites. Vigorous rubbing of the alternate test sites before lancing helps to minimize these differences.

Measurements obtained from sites other than the finger, palm or upper arm should not be used to calculate insulin doses with the Omnipod® System.

Do not use during xylose-absorption testing.

Objects that may be soiled with blood may then transmit pathogens. See "PDM cleaning and disinfecting" on page 111 for instructions on how to disinfect your PDM.

Follow the guidance of your healthcare provider for proper blood glucose monitoring.

Severe dehydration and excessive water loss can cause falsely elevated blood glucose results. If you believe you are suffering from severe dehydration, consult your healthcare provider immediately.

Pg. 124.

If the PDM is not safe from children or others who may press the buttons by accident, consider using the optional PDM lock safety feature to prevent unwanted program changes (see "Lock or unlock the PDM buttons" on page 61).

Reviewer Comment: IR# 3, 3.1 and 3.2 were issued to clarify the intended patient population of their device to determine its compatibility with the FIASP labeling claims (CSII for pediatric down to 1 years old). The sponsor did not define the specific ages. **RESOLVED for S008.** It was determined that the OmniPod and OmniPod Dash were not cleared for a

pediatric patient population. They were cleared for general use. While a physician can prescribe the subject device to determine adequacy, from a regulatory perspective, the subject device was never evaluated for safety and effective use with pediatric patients. However, the MAF holder updated their labeling (IR 3.2) to restrict FIASP to adults only to allow for the S008 supplement. For S011 (pediatric CSII), the FIASP indications for use statement would need to change to general use to enable a general use for FIASP with OmniPod and OmniPod Dash systems . **See IR 10#**

Below is the 510(k) history of the Insulet OmniPod pump.

Subject K#	Primary History	Secondary History	Tertiary History
K182630 Children in labeling. Not in IFU or 510(K) Summary			
	K180045 Children in labeling. Not in IFU or 510(K) Summary		
		K162296 Children in labeling. Not in IFU or 510(K) Summary	
			K122953 Review memo stated Not for pediatric use (checklist). However, labeling was approved with children being mentioned.

It is also noted that the sponsor included the following warning in the OmniPod and OmniPod DASH user guide redlines labeling.



(b) (4)

This instruction is used to mitigate the identified risk of the user delivering a meal bolus too soon relative to their food intake because FIASP is faster acting. Labeling alone is an effective mitigation for this risk because the prescribing physician and drug labeling will communicate proper use of FIASP.

8.6. MAF REVIEW CONCLUSION

Based on the information provided in the MAF there should be not clearance issues for the future 510k to support adults using FIASP (Supplement 008 208751) unless the sponsor provides new information regarding the design or data provided.

9. INTERACTIVE REVIEW

9.1. Filing Information Requests

Are there filing review information requests? No Yes

9.2. 74-Day letter Information Requests

Are there 74-Day Letter information requests? No Yes

9.3. Mid-Cycle Information Requests

Are there Mid-Cycle review information requests? No Yes

9.4. Interactive Review

Are there other interactive review information requests? No Yes

See *Section 12 Contact History* for summary of interactions and list of documents provided by the MAF holder. The documents sent should be provided in the future 510(k). Regardless, they will be stored in DOCMAN folder associated with the future 510k.

Agency Information Request # 1(Sent on 03/05/19) - **ADEQUATE**/INADEQUATE

The following was sent to the MAF holder

Per LOA dated December 6, 2018, Novo Nordisk referred to your MAF (b) (4) for their submission for FIASP. In Section 7.2 of MAF (b) (4) you provided a high-level summary of in-use stability and refer to Attachment 5: Fiasp In-Use Stability TR17-462 test report. However, Attachment 5 is missing from your MAF. Therefore, there is insufficient information to review the in-use stability of FIASP in the pump reservoir. Please update MAF (b) (4) to include Attachment 5 by March 12, 2019 . In addition, please send a searchable PDF copy via email.

MAF holder Response (received on 03/05/2019)

It appears as though the eCopy file for that attachment is missing an underscore in the name – I am assuming therefore it appears to be missing.

Attached is the Attachment 5. We will submit a new eCopy record for the MAF

Reviewer Comments: The sponsor provided the missing data via email. The MAF holder addressed this request. See Section 7.3 and 8.3.2 DP Stability for a review of the data.

Agency Information Request #2 (Sent on 04/04/19) - ADEQUATE/INADEQUATE

You provided a LOA dated December 6, 2018 that allows you to reference MAF (b) (4) for OmniPod and OmniPod Dash for submissions with FIASP. OmniPod and OmniPod Dash are tubeless pumps. However, your labeling is for *Continuous Subcutaneous Infusion (Infusion Pumps)*, which consists of tubeless pumps and pumps with tubing. Therefore, the referenced data does not cover the scope of your proposed labeling. Provide In-Use stability of FIASP for infusion pumps with tubing.

Sponsor Response (received on 04/04/19)

The pump in-use stability report was submitted in the original NDA (sequence 0000) Module 3.2.P.8.3. The stability testing was conducted with MiniMed Paradigm® 722 insulin pump and the Animas® Vibe™ insulin pump. Both are pumps with tubing. This report is also cross-referenced from the annotated labeling provided in S-008 to support the proposed pump in-use time. Attached is a copy of the stability report.

Reviewer Comments: The sponsor addressed the request. See Section 7 for a review of the data.

Agency Information Request #3 (Sent on 06/20/19) - ADEQUATE/INADEQUATE

The following was sent to the MAF holder

In you MAF (b) (4) redlined user guide it does not specify the pediatric age ranges. In Novo Nordisk submission they are claiming a pediatric indication and I need to confirm they are consistent with one another. If not, additional data may be required which may fall outside the scope of a special 510(k) (new patient population). Please confirm the specific pediatric age ranges for the currently cleared OmniPod and what you plan to propose in the future submission

MAF holder Response (received 7/8/2019)

The OmniPod system does not have a contraindication on the age range of users. The current system is cleared for all age groups, including pediatrics, as prescribed by a health care professional.

Reviewer Comment: In Att 1 OmniPod User Guide Redlines, Att 2 OmniPod Dash User Guide Redlines the sponsor refers to “children” or a child using the device. Since the sponsor did not address the question an assessment will be made based on the information provided in the recently cleared 510(k) and labeling claims. They claim children in their age range. Therefore, their pump is cleared down to 2 years old. An IR will be issued to the sponsor to ask them to identify a continuous insulin infusion pump cleared down to 1 years old. Alternatively, they should adjust their labeling to 2 years old. See IR #3.1- Resolved. MAF holder updated labeling to limit FIASP to adults only to reflect S008. Additional review is needed for S011 for general use.

Agency Information Request #3.1 (Sent on 07/18/19) - ADEQUATE/INADEQUATE See IR #3.2

The following was sent to the MAF holder

After a review of the 510(k) predicate history for your infusion pump, it was determined that your device was cleared with a general use indication which would allow a physician to determine suitability of your device for a patient (adult or

pediatric). However, this is not the same as having a pediatric specific indication because your device was never evaluated or cleared for that patient population in a 510(k) submission. Therefore, you cannot claim your device is intended for a pediatric patient population, only for general use. If you want update the indications for use from general to specific (pediatric), please submit a 510(k) with evidence demonstrating your device is suitable for a pediatric patient population. For additional guidance we recommend you review FDA Guidance for Industry General/Specific Intended Use (<https://www.fda.gov/media/71966/download>).

We are working separately with the NDA sponsor Novo Nordisk as it relates to their pediatric labeling claims for FIASP with CSII.

MAF Holder Response (Received 7/25/2019)

At this time, Insulet does not intend to file a 510(k) to have a pediatric specific indication.

Reviewer Comments:

For Supplement 008 this response is not adequate because that supplement is limited to adults only. See IR #3.2. Resolved. MAF holder updated labeling to limit FIASP to adults only to reflect S008. Additional review is needed for S011 for general use.

Agency Information Request 3.2 (Sent on 9/5/2019) – ADEQUATE/INADEQUATE

The following was sent to the MAF holder

Your OmniPod and OmniPod Dash user guide redlines add ‘FIASP’ to the list of Rapid-acting insulins safe for use in the Pod. However, the referenced Novo NDA supplement(PDUFA date 10/21) scope is limited to adults only. Therefore, please update your user guide labeling to state ‘FIASP (Adults only)’ or similar wording. The patient population needs to be specified for FIASP because the proposed indications for FIASP (Novo NDA PDUFA 10/21) is limited to adults and is not general. Please provide updated user guide redlines specifying the patient population restriction for FIASP. Please note that you can amend your labeling in a future 510k if the FIASP NDA is updated for general use or pediatrics.

MAF holder Response (received 9/6/2019)

Updated labeling with the following wording:

(b) (4)

Reviewer Comments:

Resolved. MAF holder updated labeling to limit FIASP to adults only to reflect S008. Additional review is needed for S011 for general use (IR#10).

Agency Information Request #4 (Sent on 06/20/19) - ADEQUATE/INADEQUATE

The following was sent to the MAF holder

In you MAF ^{(b) (4)} Section 5 Risk Assessment you state that you included a labeling mitigation because of a new risk of ^{(b) (4)}

Please clarify if you are indicating that FIASP has a different IOB or PK/PD profile.

Sponsor Response (received 7/8/2019)

The PK/PD profile of FIASP is different, which is described in the sNDA and relevant in terms of timing of the bolus related to meal consumption. Clinical studies conducted by Novo Nordisk indicate that there was no difference in the duration of insulin action (DIA) setting for FIASP as compared to NovoLog. The PK/PD characteristic that is relevant to the bolus calculator is the duration of insulin action, which is similar for Fiasp® U100 as compared to NovoLog® (3-5 hours). The duration of insulin action is user settable and is used to calculate the IOB.

Reviewer Comment: Pk/Pd difference is apparent, but unclear if it is clinically relevant. They are dosing slightly higher than novolog. The FIASP dosing can be managed using the existing dose calculator with modifications. Not statistically compelling that would require new dose calculator.

Agency Information Request #5 (Sent on 06/20/19) - ADEQUATE/INADEQUATE

The following was sent to the MAF holder

In MAF ^{(b) (4)} Section 8 Software you state that no software changes are required for addition of FIASP U100. However, wouldn't it require an updated drop down menu to include FIASP? Please clarify what changes are being made to the software.

MAF holder Response (received 7/8/2019)

There is no drop down menu for insulin brand/type. As was discussed in the pre-submission meeting with the Agency in Q171840, based on the Novo Nordisk clinical studies, there was no difference in the duration of insulin action pump setting for Fiasp® U100 as compared to NovoLog®. The PK/PD characteristic that is relevant to the bolus calculator is the duration of insulin action, which is similar for Fiasp® U100 as compared to NovoLog® (3-5 hours). Insulet does not believe that any software modification is necessary as any differences are accommodated for by the programmable bolus calculator settings, which are determined by the health care professional specifically for each individual patient. The duration of insulin action for Fiasp® U100 lasts for 3–5 hours, which is within the settable parameter range of 2 –6 hours for the Omnipod bolus calculator. During the CSII clinical study to support European approval, a commercial insulin pump was used with the clinician making adjustments to insulin to carb ratios, correction factors, and the active insulin time setting if there were any signs of insulin stacking or any other sign of an incorrect setting. Based on the pharmacological and clinical data for Fiasp® U100 and the programmable settings of the Omnipod bolus calculator, Insulet believes that no modifications to the software are necessary. Currently, no change to bolus calculators has been required for pump use in Europe with Fiasp® U100.

Reviewer Comment: This is adequate. Changes may be made to the labeling to change the timing of when to take FIASP. Note that the sponsor's response to IR #8 states that there are no design changes between the future 510k and the predicate K182630.

Agency Information Request #6 (Sent on 07/08/19) - **ADEQUATE**/INADEQUATE

The following was sent to the MAF holder

In you MAF ^{(b) (4)} you 002_Omnipod and OmniPod Dash Device Master File Submission you provide a device description and overview of changes/non-changes. However, it is unclear exactly what these changes (indications, intended use population, environment of use, technological characteristics) are compared to the recently cleared 510(k) version (K182630 on 1/8/2019), if they raise different questions of safety and effectiveness, and the performance testing provided to demonstrate substantial equivalence for each technological characteristic. To effectively communicate this information, we recommend that you provide this information in the format of a 510(k) summary with the required content per 21 CFR 807.92.

MAF holder Response (received 7/12/2019)

A 510(k) summary is provided in Attachment 1 comparing the systems for use with Fiasp U100 to the most recently cleared systems in K182630.

Reviewer Comment: The response was adequate.

Agency Information Request #7 (Sent on 07/09/19) - **ADEQUATE**/INADEQUATE

The following was sent to the MAF holder

In Section 7.0 Biocompatibility, you state that there were no changes to the PDM or Pod, including the patient-contacting materials. However, you do not specify what the materials are or the proposed patient contact classification per ISO 10993-1 Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process. Please provide a table summarizing the materials of construction and patient contact classification for each component of your device and compare it to the recently cleared device (K182630).

MAF holder Response (received 7/12/2019)

A table of materials of construction and patient contact classification is located in Attachment 2.

Reviewer Comment: This response is adequate. See response to IR #8.

Agency Information Request #8 (Sent on 07/09/19) - **ADEQUATE**/INADEQUATE

The following was sent to the MAF holder

In Section 7.1 Biocompatibility Introduction you state, "The Omnipod and Omnipod Dash Pods are identical with the exception of the PCBA which was updated on Omnipod Dash to accommodate a ^{(b) (4)} ^{(b) (4)} The power budgets of Omnipod and Omnipod Dash were reviewed by engineering where a power consumption comparison was generated and summarized in Table 9." We need the full reports for the testing referred to in Table 9 to assess if we agree with the conclusion that it does not impact the Insulin stability test results. Please provide the full reports for the testing referred to in Table 9.

MAF holder Response (received 7/12/2019)

The assessment of the effect of the (b) (4) on the impact of insulin stability was done as an analysis of power consumption between the Omnipod and Omnipod DASH systems. As this was done by an analysis of specifications, no formal testing was conducted. The analysis is included in Attachment 3.

Reviewer Comment: It was still unclear why the 510k summary provided (IR #6) stated that there were no changes in design and manufacturing to the device, but they provided this data. Therefore, a follow-up email was sent to the maf holder. Over the phone and email (7/15/2019) the regulatory contact (Julie Perkins), confirmed the following statement: *Per your 510k summary, the subject and predicate device design, manufacturing, sterilization, and software are identical. The only change is a labeling change for the addition of FIASP and data (e.g., DP quality) to support that change. The change you refer to in your MAF with respect to the PCBA has already been reviewed and cleared in K182630 bundled 510k.*

Therefore, the response is adequate and addresses IRs 5-8

Agency Information Request #9 (Sent on 07/09/19) - ADEQUATE/INADEQUATE

The following was sent to the MAF holder

Your MAF (b) (4) did not have a Safety Assurance Case. Device assurance cases submitted for infusion pumps should include a top-level goal with supporting assurance arguments. We recommend that you structure the assurance case to include the following:

- a. Provide a top-level assurance goal that is supported with appropriate contextual information, which includes the following:
 - i. Indications for use
 - ii. Patient types
 - iii. Users
 - iv. Use conditions (e.g., how are the devices actually used in practice)
 - v. Environments of use
 - vi. List of specific devices (by model) covered by the assurance case and identification of the design specification and labeling documents (version and date).
- b. Provide three separate argument structures to support the top level goal, which address the following:
 - i. Adequate design verification and validation of device specifications.
 - ii. Acceptability of risk mitigations.
 - iii. Adequate device reliability.

Each argument structure should be inclusive of all of top level assurance goals' contextual information and should support the adequacy of the provided information, including specifications, mitigations, test methods, acceptability criteria, etc.

- c. In addition to other forms of evidence that might be included, such as test reports, it is expected that the report will contain the actual design specification document(s) (signed and dated), traceability, and risk assessment(s) documents for the devices included in your MAF (b) (4)

MAF holder Response (received 7/12/2019)

As was done for K182630, we have provided 2 SAC addendums to the SACs referenced in the attached documents that focus on the arguments for support of the use of Fiasp. Please note that we do not have all the design specifications, reports, and risk assessments complete for the Omnipod DASH system as they will be signed off before we go to market. The Omnipod (Eros) system design documents are signed and dated as the use of the system with Fiasp U100 is released for the European market. The SAC addendums are provided in Attachments 4 and 5. The risk analysis and reports were provided in the original Master File submission and the updated specification for Fiasp U100 for the Omnipod (Eros) system is located in row 2.1.3 of the Product Definition Document in Attachment 6

Reviewer Comment: The MAF holder provided sufficient information to conduct the SAC review. See review of SAC materials in Section 8.4.

Agency Information Request #10 (Sent on 07/18/19) - ADEQUATE/INADEQUATE – S011 only

While there are continuous insulin infusion (CSII) pumps with general use indications for diabetes mellitus, there are no currently marketed CSII pump specifically indicated for a pediatric patient population down to 1 years old. Therefore, there is a potential outstanding device issue with your pediatric CSII labeling claims. Identify a CSII infusion pump that is specifically indicated for a pediatric patient population down to 1 years old.

Sponsor Response (received 7/29/2019)

*According to international paediatric consensus guidelines continuous subcutaneous insulin infusion (CSII) pump therapy can be used safely and effectively in children with type 1 diabetes (T1D) regardless of age. CSII reduces chronic complications of T1D in children and provides similar glycaemic control as measured by HbA1c as multiple daily injection (MDI) therapy.1 Novo Nordisk considers the use of CSII in the paediatric population to be an important therapeutic option. Novo Nordisk expects Fiasp® to be used in a range of marketed insulin pump devices and has worked in collaboration with pump manufacturer Insulet, to ensure that Fiasp® can be safe and effectively used with the currently marketed OmniPod® pump system. The OmniPod® pump has been on the market since 2013 and is indicated for general use without any age limitation, allowing physicians to have the flexibility to determine whether OmniPod® is suitable for an adult or paediatric patient (<https://www.myomnipod.com/become-a-podder/pediatric>). An estimate of a representative subset of current OmniPod® users under 12 years of age is provided by Insulet from post-marketing database in Figure 1. The data shows there are a total of 3,314 users ≤ 6 years of age (~25%) among the 14,387 users ≤ 12 years of age, demonstrating that OmniPod® pump is used in children across a range of age groups. **No safety concerns from the paediatric use of OmniPod® have been observed based on Insulet's extensive post-marketing data.** As OmniPod® is indicated for general use without a specific paediatric age range, it is suitable for paediatric patients use.*

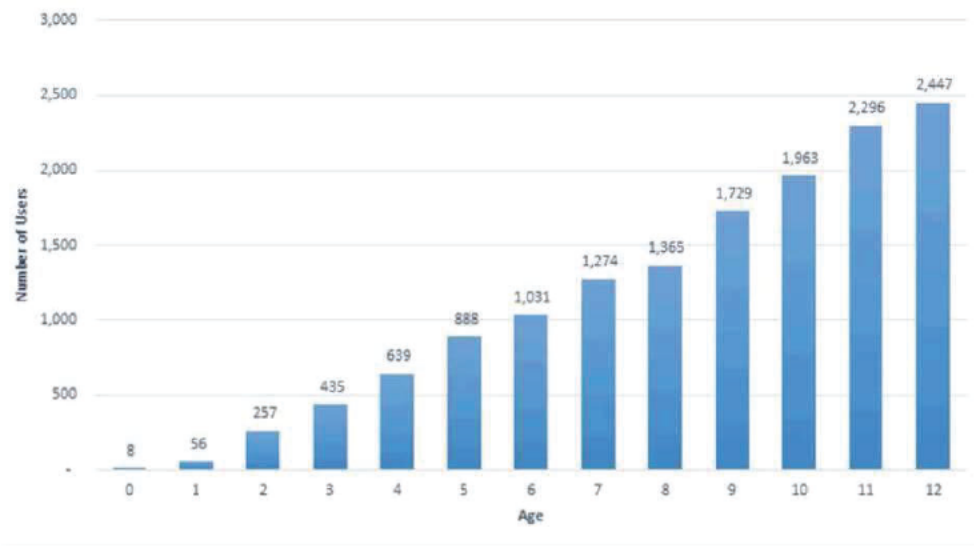


Figure 1 Age distribution of a representative subset of current users of OmniPod® in USA by age ≤12 years

The use of CSII therapy in children is also supported by a recent study by Blair et al (2019), which showed CSII to be safe and effective in providing glycaemic control in children aged ≤16 years including in a subgroup of 33 children aged 7 months to 5 years in different CSII pump systems.2 These findings are consistent with studies which have included children aged 1-6 years of age. 3, 4 Novo Nordisk is seeking collaboration with a number of different insulin pump manufactures so Fiasp® can be used in various CSII systems. Due to different features and functionality such as threshold suspend and CGM integration, CSII systems are either indicated for general use or have specific age limits for use in the paediatric population. As such Novo Nordisk proposes not to specify the age range of Fiasp® use in CSII, instead to cross refer to the individual pump user manual to determine the suitable paediatric age range. Therefore, the proposed PI section 8.4 is revised to include the text

(b) (4)
 (b) (4) (Module 1.14.1.3 - Proposed Physician Insert,
 Section 8.4 (b) (4)
 (b) (4)

Reviewer Comment: Under Review for S011. Response does not impact S008 (adult CSII) indication since a general indications for use would not prohibit adult use of FIASP with CSII devices.

Agency Information Request #11 (Sent on 8/20/19) - ADEQUATE/INADEQUATE see IR 11.1

The following was sent to the MAF holder

You provided the report TR17-464 REV.A which included leachables testing performed using Fiasp Insulin solution 37 (b) (4) C for 96 (b) (4) hours. We believe the study is insufficient. The study is simply a screening study with limited time and

limited extraction power. The length of the study is far shorter than the clinically relevant contact time. Therefore, please address following concerns:

- a. Please provide justification that Fiasp Insulin solution extraction power and polarity is comparable to the extractables study performed originally under prior submission TR17-463 Rev A.
- b. The extractables study TR17-463 Rev A found several more extractables. They were possibly not observed in this study since the insulin solution contents masks a good portion of the chromatogram, making it impossible to determine if any additional components co-elute. Please perform another blank extraction with higher purity extraction vehicle what is comparable to the Fiasp Insulin solution extraction power.
- c. You included an Analytical Evaluation Threshold (AET) calculation that is based on United States Pharmacopeia (USP) literature yet not quite applicable to medical devices. The Agency in several public platforms publicized an approach that is more applicable to medical devices, based on the following formula :

$$\text{AET } (\mu\text{g/mL}) = \text{DBT } (\mu\text{g/day}) \times (\text{A} \div (\text{B} \times \text{C} \times \text{D})) \div \text{UF}$$

Where DBT is the Dose-Based Threshold; A is the number of medical devices extracted, B is the extract volume, C is the number of medical devices that contact the body, D is the dilution factor and UF is the uncertainty factor of the analytical methods. (not to be confused with any uncertainty factors used in Toxicology) The UF depends on the analytical method and needs to be determined for that particular method accounting for the level of variation of the response factors of compounds found in the observed extractables (Jordi et al. Journal of Pharmaceutical and Biomedical Analysis 150 (2018) 368–376; and Jenke and Odufu, Journal of Chromatographic Science 2012;50:206–212).

MAF holder Response (received 8/27 and 9/4)

Response to a.:

The length of the study was discussed and agreed upon with the Agency during the December 17, 2017 pre-submission meeting (Page 7 “The study will be conducted under conditions similar to those utilized for stability studies”; Page 10 “conducting the insulin in-use stability testing for 4 days to support 80 hours in-use period is acceptable”).

The extractables study (report) TR17-463 Rev A used both de-ionized water and 50/50 v/v ethanol/water as extraction solvents at (b) (4) 72 hours. The organic component ethanol in the ethanol/water mixture is a much stronger solvent than water itself as demonstrated in the study. Fiasp insulin solution 100unit/mL is an aqueous solution (b) (4) similar to the deionized water. Therefore, the polarity and extraction power of the insulin solution should be between the two extraction solvents we had conducted in the extractable study TR17-463 Rev A. In other words, extractables seen in the de-ionizable water are very likely to be seen in the Fiasp insulin solution extractable study and extractables seen in the ethanol/water 50/50 mixture may not be seen in the Fiasp insulin solution extractable study.

Response to b

We agree that the insulin solution has some profound peaks in both GC and LC chromatograms; however, as demonstrated below, the extractables that have retention time close to these insulin related peaks have minimal interference with no detected value or less than the AET value.

- *Report TR17-463 Rev A showed that water and ethanol/water mixture extracted the known extractable (b) (4) substantially at (b) (4) device, respectively. It demonstrated that ethanol/water has stronger*

extraction power. On the other hand, TR17-464 Rev A showed that insulin solution extracted about (b) (4) (b) (4) device with very similar leachable/extractable pattern to that of de-ionized water extraction. Therefore when the water extract and insulin extract GCMS chromatograms are compared as shown below, the insulin solution related peaks are not overlapping/interfering with extractables that are likely to be greater than (b) (4) peak and the (b) (4) calibration solution as markers. Additional extractables observed in the ethanol/water mixture with very close retention time to the insulin related peaks will be re-evaluated based on the new AET value calculated by the recommended formula for medical device (as responded in regarding to question C). The new revised report will demonstrate that they are either not detected or lower than the AET value.

- Regarding the LCMS chromatograms (see below) for insulin solution control and three replicate extracted samples: they are right on top of each other. The extractable peaks (b) (4) observed in the water extracted sample, if present in the insulin extracted sample, are likely to distort the peak shape around the insulin related peak region. But, as shown below, that is not the case indicating that these extractables are not observed as leachables in insulin solution. We believe that we have demonstrated that the extractable studies performed in TR17-463 Rev A is comprehensive and the leachable study performed in TR17-464 Rev A is sufficient.

Response to c

We agree to follow the agency's new approach to calculate the AET value that is more applicable to medical devices. Based on that formula, we realized that the AET value will be different from what is reported. Please see attached response (Attachment 1) from our contract lab addressing the AET values where different analytical methods were used to evaluate extractables. Thus the leachables in the insulin solution extract will also re-evaluated by our contract lab and a revised report will be provided as soon as possible.

Reviewer Comment: The consultant had additional comments regarding the extraction method. Additional IRs were issued See IR# 11.1 – Resolved. The sponsor provided additional justification to complete the review. See Section 8.3.4 for final review of the leachables study.

Agency Information Request #11.1 (Sent on 9/12/19) - ADEQUATE/INADEQUATE

The following was sent to the MAF holder

1. You indicated responding to the deficiency that “ The length of the study was discussed and agreed upon with the Agency during the December 17, 2017 pre-submission meeting (Page 7 “The study will be conducted under conditions similar to those utilized for stability studies”; Page 10 “conducting the insulin in-use stability testing for 4 days to support 80 hours in-use period is acceptable”). The discussion in the meeting minutes does not refer to biocompatibility testing: the context was “Pump in-use insulin stability discussion”.

Moreover, you indicated “TR17-464 Rev A showed that insulin solution extracted about (b) (4) device with very similar leachable/extractable pattern to that of de-ionized water extraction” The amount of (b) (4) device appears to be the main source of your conclusion that the extraction power of water was sufficient. Basing the extraction power only to (b) (4) amounts is insufficient since the purpose of extraction is to exaggerate the release of material for all possible extractables not just a specific one.

Therefore, please provide additional information to justify the existing study or perform new experiments to provide sufficiently exaggerated extraction. Please also perform a blank (i.e. solvent only) extraction with Ethanol or Hexane.

2. You provided a revised draft report J14030-1 Rev. 4 that has updated AET calculation. The information provided is insufficient to determine if AET approach is applied appropriately. The calculation is missing appropriate volume information since the extract is processed and volume did not remain the same. Please provide Protocol P18-21 Rev. A. and Protocol P7.1.1.226 Rev. B.

You further indicate in the report for LC-MS results “No AET threshold was used and all compounds detected were reported, since a suitable number of standards is not available for calculating a UF. This would be a worst case approach, protective of safety, and would provide a complete list of all compounds observed by QToF-LCMS-UV-CAD.”. An AET calculation is regardless needed to determine if the limit of quantification (LOQ) of the method is sufficiently low to achieve the AET level. Please provide an AET calculation. For the LC-UV-CAD-MS. An additional concern is the selection of the compounds to determine response factor RSD for GC/MS (b) (4) appear insufficiently diverse to make a response factor assessment. Please provide justification or additional data that includes expected or observed extractables with semi-polar and non-polar solvent.

MAF holder Response (received 9/16 and 9/17)

Response to Q1

We acknowledge that the meeting minutes referred to the 96 hours time for in-use stability, however, we believe the 96 hour leachables study is also appropriate. The device is physically unable to be used beyond 80 hours. As soon as insulin is added to the reservoir, an internal clock begins that automatically stops use of the pump after 80 hours. As it is impossible for the insulin and device to interact for longer than 80 hours, we believe it is appropriate that leachables testing conducted after 96 hours of use is appropriate. This method was identical for that for the leachables testing with Admelog submitted and cleared with the FDA in K182630.

We would like to clarify the above statement. We are not basing on the (b) (4) amount to conclude the extraction power of water was sufficient. We did both ethanol/water and water extraction and those results reported in our TR17-463 is the base of our design for leachable study. We based on the holistic evaluation of GCMS and LCMS-UV-CAD data in the insulin leachable study to conclude that (b) (4) detected leachable in the insulin extract. The exact same method/protocol was used to perform Ademlog leachable study and the same result with similar leachable found in similar concentration was concluded as was provided in K182630. A table of comparison of the test method and test results are shown in the table below.

Comparison Table of Fiasp and Admelog leachable studies [not shown]

We have demonstrated in our extractable study TR17-463 that 50/50 ethanol/water is stronger solvent than water and it is a common nonpolar solvent used by the industry based on the USP 1663 (chemical nature of the extracting medium) as explained below.

Many drug products are compositionally intermediate between the polar and nonpolar examples just discussed. Examples of such products include “aqueous” drug products that contain stabilizers, solubilizing agents, chelating agents and buffers, lipid-containing products, and biotechnology products containing proteins, peptides, and blood-derived products.

Such products have a characteristic polarity which establishes their “extracting power”. Thus, an appropriate simulating solvent will have a polarity that matches that of the drug product. Binary mixtures of miscible solvents (such as alcohol/water) have been utilized as simulating solvents for these types of drugs product.

Response to Q2

The use of a triple detection QTOF-LCMS-UV-CAD system reduces substantially the risk of under reporting due to the independent responses for each detector for a single compound combined with the use of GCMS. Triple detection substantially mitigates the need for a UF factor. The analytical sensitivity was demonstrated to be (b) (4). When considered in the context of the QTOF-LCMS-UV-CAD strategy, the overestimate of the maximal patient exposure (3.5X) and an unmodified AET of (b) (4) it is our position that the current analysis is protective of safety and provides a very low risk of under reporting of compounds.

The selection of the standards for GCMS was considered suitable based on initial screening assessments of the leachables solution and results from a prior extractables assessment of the Omnipod device (J13190-1). During the previous extractables study (b) (4) unique extractables were identified using the same GCMS method applied here demonstrating the suitability of the method for detecting a wide range of extractables (polar and non-polar) from the OmniPod device. Since only (b) (4) compounds were observed during screening analyses, formal quantitation was used as it provides higher accuracy than relative quantitation for (b) (4) (b) (4) since both have very similar functional groups (b) (4) and have similar retention times (i.e. similar volatility, (b) (4) respectively) and it is therefore reasonable to conclude they would have a similar response factor. Finally, a number of additional conservative factors were built into the analysis providing an additional margin of safety including (b) (4) (b) (4) for the patient exposure (b) (4) maximal exposure provides a 3.5X safety margin) and the analysis of standards down to a concentration of (b) (4) (nearly 5X lower than the revised AET). This would provide an additional conservative factor of (b) (4)

Reviewer Comment: The sponsor addressed the questions of the consultant. For review of the final responses see Section 8.3.4 Leachables of this memo.

10.COMPLET RESPONSE DEFICIENCIES

N/A

11.RECOMMENDATION

Device Constituents Parts of the Combination Product are Approvable for the Adult (S008) Indication

11.1. Comments to CDER/OND

CDRH has the following comments that were conveyed to the CDER/OND review team at the midcycle on **May 21, 2019**

Comment to CDER/OND #1

They sponsor included a LOA from Insulet for OmniPod MAF (b)(4) to reference FIASP In-Use stability data. Although the MAF had a high-level summary of the study in Section 7.2, it was missing the reference test report *Attachment 5: Fiasp In-Use Stability TR17-462*. Therefore, we cannot adequately review in-use stability of FIASP in a pump reservoir. CDRH defers to CDER whether to communicate this to the sponsor as an additional comment in the refuse to file or 74 day letter.

Comment to CDER/OND #2

The sponsor submitted stability data to support the “at least 6 days” reservoir change for pumps with tubing. The sponsor also referred to MAF (b)(4) to support the reservoir change for pumps without tubing (b)(4) days claim, 15 days stability). The sponsor can claim at least 6 days since pumps with tubing are worse case when compared with tubeless pumps. A review of the stability study design provided appears to support the label claim. However, we defer adequacy of the stability data endpoints to support the reservoir labeling claim to CDER.

Comment to CDER/OND #3

The labeling proposes infusion set changes per the manufacture’s manual and refer to clinical study -3854 as supportive evidence. While your clinical study report (-3854) shows that the mean infusion set change for FIASP was similar (2.55 days vs. 2.49 days) to NovoRapid/Novolog, infusion site reaction, one of the main reasons for infusion set change, was ~2X higher with FIASP than with NovoRapid/Novolog. Therefore, infusion set changes appears to be impacted by the drug being delivered. We recommend that the sponsor specify the specific infusion set change time in their labeling. This is also consistent with Novolog (20986).

Comment to CDER/OND #4

The sponsor proposes to add a pediatric patient population to their indications. However, the clinical studies presented did not assess the use of an infusion pump with pediatric patients. While the provided clinical -4101 with pediatric patients, the study was conducted with pen injectors, which would not show safety data relating to infusion set changes/infusion site reactions. In addition, the sponsor did not provide justification why the clinical study outcomes for adults (-3854) using infusion pumps could be extrapolated to pediatric patients, which could be more vulnerable/susceptible to infusion pump related adverse events (e.g., infusion site reactions). Therefore, we recommend that the sponsor provides justification or clinical data addressing the safety concerns associated with pediatric patients using infusion pumps.

Comment to CDER/OND #5

The AE reported in Table 3 for pediatric patients are misleading because they do not state that the information was collected with pen injectors not infusion pumps. Therefore, it can be misconstrued to believe it the AEs presented took into account infusion pump related AEs. I defer adequacy of the content presented in Table 3 to CDER clinical team.

Comment to CDER/OND #6

The sponsor did not provide any dose accuracy data to support infusion pump use for pediatric patients. The only study presented that assessed the pediatric patient population used pen injectors, which may have a tighter dose accuracy

performance than infusion pumps. Consider how the differences in dose accuracy performance impacts the clinical study outcomes.

Comment to CDER/OND #7

The sponsor referred to MAF (b)(4) FIASP in-use stability for OmniPod (tubeless pump). A review of the protocol shows that they agitated samples at (b)(4). However, they do not specify the agitation time. The time of agitation may impact the reported reports. Therefore, the MAF holder should clarify the agitation time used for their study (samples and control). I defer adequacy of the response to CDER.

Comment to CDER/OND #8

A reminder should be sent to the sponsor stating that there are currently no continuous subcutaneous insulin infusion pumps (CSII) on the market that are indicated for FIASP. There would be an outstanding device issue that would prevent approvability of their NDA supplements (S008 and S011) if they cannot identify a CSII pump indicated for use with FIASP for S008 and for pediatrics for S011.

11.2. Recommended Post-market commitments/post-market requirements

CDRH has Post-Market commitments/requirements	☐
CDRH does not have Post-Market commitments/requirements for S008	☒

12.MAF Contact History

Date	Contact	Attendees	Deficiencies/ Topics Discussed	Interactively Received Documents
3/5	Email	MAF holder/Reviewer	Missing FIASP In-Use Stability Report	3/7 Email Response <u>Attachments</u> 1) 007 Att 5 TR17-462 Fiasp In Use Stability Study
6/20	Email	MAF holder/Reviewer	Indications for Use-Pediatric Risk assessment – labeling Software changes	7/8 Email Response
7/9	Email	MAF holder/Reviewer	Software/hardware differences Biocompatibility	Email Response 7/12 & 7/15 <u>Attachments</u>

Date	Contact	Attendees	Deficiencies/ Topics Discussed	Interactively Received Documents
			Safety Assurance Case	Attachment 1_Q1 Fiasp MAF 510k summary Attachment 2_Q2 MAF Patient-Contacting Materials Table Attachment 3_Q3 Dash PCBA Analysis Attachment 4_Q4 Eros Safety Assurance Case Fiasp Attachment 5_Q4 Dash Safety Assurance Case fiasp Attachment 6_Q4 Attachment INSPR017-(PDD) Eros Product Definition Document
7/15	Email & Phone	MAF holder/Reviewer	Additional clarification regarding 510(k) predicate and subject device differences from IR issued (email) on 7/9.	Email response 7/15
7/18	Email	MAF holder/Reviewer	Pediatric indication	Email response 7/25
8/20	Email	MAF Holder/Reviewer	Leachables	Email Response 8/27 & 9/4 <u>Attachments</u> 1) Insulet response to FDA inquiries on FIASP 2) Attachment 1 FDA response 2) Final Report Insulet Corporation 08022019 J14030-1 Rev 3(1)

Date	Contact	Attendees	Deficiencies/ Topics Discussed	Interactively Received Documents
9/5	Email	MAF holder/Reviewer	Labeling	Email response 9/5 and 9/6 <u>Attachments</u> 1) 17845_Eros_US_Rev002-Redline FIASP 2) 17845_Eros_US_Rev002pdf FIASP
9/12	Email	MAF holder/Reviewer	Leachables IRs based on their response on 8/27 to the 8/20 communication	See teleconference below*
9/17	Teleconference	MAF holder/Reviewer, Carolyn Dorgan, David Wolloscheck, Berk Oktem, Alan Hood	Leachables/Extractables testing approach and response to IR issued 9/12	Email Response 9/16 <u>Attachments</u> 1) Summary of FDA response 09122019 2) Attachment 1 Response to Question #2

13.APPENDIX – CONSULTANT MEMOS

13.1. Anjali Shukla Drug Product Review Memo



PRODUCT REVIEW – CDRH Consult Request

SUBMISSION #: 510(k) MAF (b) (4)

PRODUCT: Omnipod and Omnipod Dash

INDICATION: Diabetes mellitus

ROUTE OF ADMIN: Subcutaneous injection

SPONSOR: Insulet Corporation

CONSULT REQUEST: 07/12/2019 ICCR 00011791 submitted on behalf of Rumi Young

CONSULT DUE DATE: 07/29/2019

AIM OF CONSULT: Review the Fiasp insulin compatibility provided in Attachment 5 of the submission.

PRIMARY ASSESSOR: Anjali Shukla, Ph.D., DBRRII/OBP/CDER

SECONDARY ASSESSOR: William Hallett, Ph.D., DBRRII/OBP/CDER

1. Summary basis of recommendation

- a. Recommendation
From an OBP perspective, the information provided in MAF (b) (4) supports the compatibility of Omnipod and Omnipod Dash systems for use with Fiasp U100 and support the approval of the proposed 510k.
- b. Justification
The sponsor proposes to add Fiasp U100 to the labeling for Omnipod and Omnipod Dash systems. To support the use of Fiasp U100 in Omnipod and Omnipod Dash systems, the sponsor performed in-pod stability studies analyzing Fiasp stability in the pods during storage. The attributes and methods selected are appropriate to evaluate potential changes in product quality during storage in pumps. Results demonstrate that Fiasp U100 remains stable over the duration of use in the device. The sponsor did not provide product quality data on product dispensed from the cannula. However, since the Omnipod systems have an integrated soft cannula and virtually no infusion set, minimal degradation of the insulin from the reservoir to the patient is expected. Therefore, from a product quality perspective, the data provided support compatibility of the Omnipod and Omnipod Dash devices for use with Fiasp U100.

2. ASSESSMENT

a. Background:

The Omnipod Insulin Management System and the Omnipod Dash insulin management system

Both the Omnipod® Insulin Management System with an integrated blood glucose meter (BGM) and the Omnipod Dash insulin management system are comprised of two primary components: the insulin pump (Pod) and a remote controller known as the Personal Diabetes Manager (PDM). The BGM is embedded in the PDM.

The Pod is controlled exclusively through the use of the PDM. The Pod is a single use disposable device. It is small, lightweight and designed to be attached to the body via a biocompatible acrylic adhesive pad that is welded to the bottom of the Pod. The Omnipod's biocompatible acrylic adhesive keeps it in place for up to 3 days. Insulin is delivered through an (b) (4) soft cannula that is inserted into the subcutaneous tissue by the Pod. The Pod is designed for one-time use. Once removed, a Pod cannot be reapplied.

The Pod is supplied sterile and is non-pyrogenic. There are no separate administration sets or reservoirs required for use with the system. The Pod incorporates a fully integrated insulin reservoir and cannula insertion system. The insulin reservoir is (b) (4) and holds up to 200 deliverable units of U100 insulin. Each Pod is supplied with a fill syringe and a fill needle that are used to fill the Pod with insulin. Piercing the fill septum on the bottom surface of the Pod with the fill needle enables transfer of the insulin into the Pod reservoir. The cannula insertion mechanism is a feature designed to place the soft cannula into the subcutaneous tissue at an angle to an insertion depth of 6mm. The rigid insertion needle and flexible soft cannula are contained within the body of the Pod. The insertion needle serves to puncture the skin and stiffen the soft cannula during the insertion process. Upon receiving a command from the PDM, the Pod activates the insertion mechanism, which drives both the insertion needle and the soft cannula forward into the subcutaneous tissue of the patient. Upon reaching the forward limit of travel, the insertion mechanism retracts and withdraws only the insertion needle, leaving the soft cannula in place at the infusion site and the needle contained within the Pod housing.

Device descriptions are illustrated as below:



Figure 1. The Omnipod Insulin Management System as currently marketed



Figure 4. The Omnipod DASH Insulin Management System as currently marketed



(b) (4)

b. Relevant Regulatory Background: The Omnipod systems are currently cleared for use with NovoLog, Humalog, Admelog and Apidra. The current submission aims to expand the Omnipod label to include the use of Fiasp U100 insulin. The Sponsor had a pre-submission meeting (Q171840/A001) with the Agency on December 15, 2017, to discuss Insulet’s proposal to add Fiasp U100 to the labeling. Muthukumar Ramaswamy from ONDP participated as the CDER product quality assessor. Novo Nordisk has submitted supplemental NDAs proposing use of Fiasp in CSII in adult and pediatric diabetic patients. These supplements are currently under review by the Agency.

c. Assessment of Fiasp compatibility

Fiasp insulin was full-filled into Pods, which were incubated at 37 °C with agitation for 2 days, 4 days, and 6 days and analyzed according to the USP for Insulin Aspart Injection. Omnipods were dispensed manually according to the drilling procedure outlined in protocol C19470-1 in MAF (b) (4). Three Omnipod lots were tested: L43356, L43454 and L43365. Test results are provided in the table below.

Table 10: Methods, Specifications and Summary of Results for Fast-Acting Insulin Aspart

Fiasp Test	Method	Specification	T = 0	T = 2 days	T = 4 days	T = 6 days
Potency - Insulin aspart	Novo Nordisk A3353b	(b) (4)	101%	101%	102%	101%
	(b) (4) Novo Nordisk A3353b		0.50%	0.60%	0.80%	1.0%
	Novo Nordisk A3353b		1.70%	2.00%	2.30%	2.50%
Total Other Impurities	Novo Nordisk A3353b		1.80%	2.40%	2.60%	2.90%
High MW Proteins	Novo Nordisk A3735a		0.10%	0.10%	0.10%	0.10%
Preservatives	(b) (4)		1.5	1.4	1.4	1.3
	SOP-00777		1.7	1.6	1.5	1.4
Zinc	USP<591>		19	19	19	19
Appearance Particulates/Foam	Visual		Pass	Pass	Pass	Pass
Clarity	Eur.2.2.1		Pass	Pass	Pass	Pass
pH	USP<791>		7.01	7.01	7.01	7.05
Particulate Matter	USP<788>		47	123	95	66
			2	3	12	4

Assessor's comment: The Omnipod system is preprogrammed to only function for 3 days at a time before pod change; therefore, the Omnipod reservoir storage stability data for 6 days provided in MAF (b) (4) is adequate to support this reservoir dwell time of 3 days. The results provided show that Fiasp is stable in the Omnipod reservoir during the in-use period. The sponsor's provided acceptance criteria for their study are not the same as the what the drug manufacturer uses for release/stability. However, the proposed AC adhere with USP guidelines for insulin aspart injection and are acceptable. The observed levels of metacresol and phenol have previously shown to be sufficient to maintain preservative efficacy and are therefore acceptable.

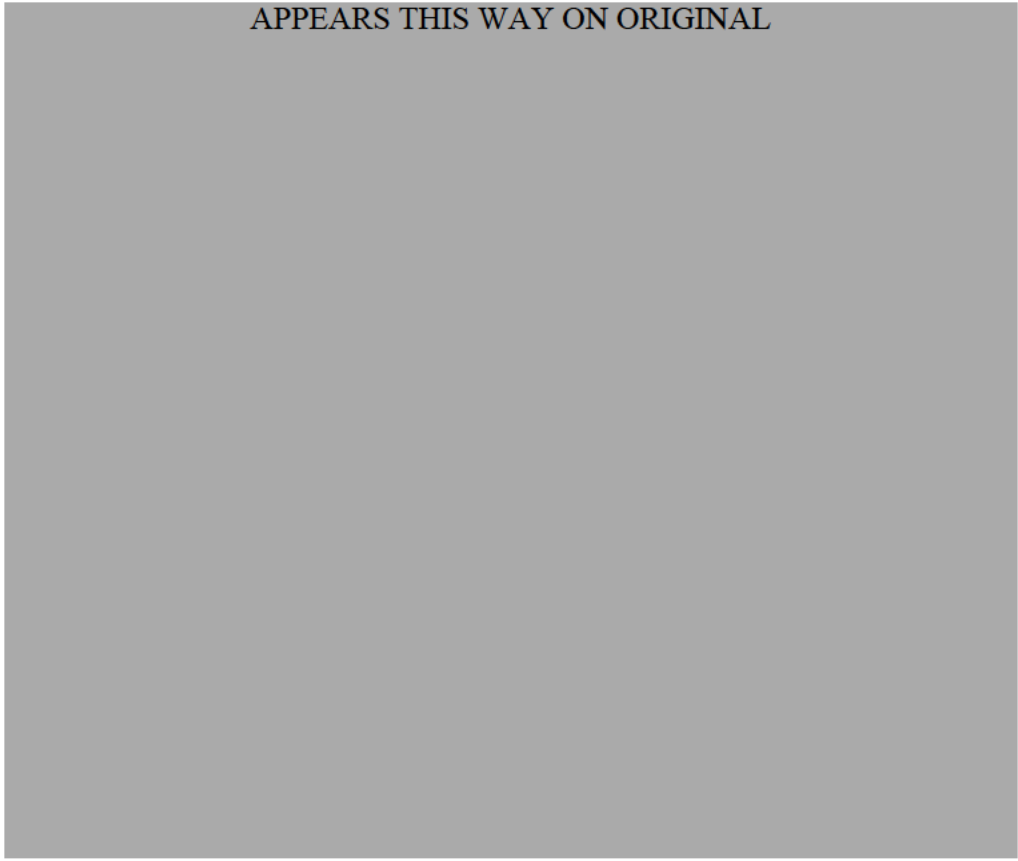
The Omnipod studies in the MAF do not test in-use stability of Fiasp after pumping. The MAF only provided product quality data on insulin within the reservoir. No information is provided regarding the quality of the insulin ejected from the cannula. In the presubmission meeting with the Agency held December 15, 2017, the sponsor explained that the quality attributes of the insulin product in the reservoir and cannula dispense of the Omnipod are expected to be similar due to the integrated soft cannula (shown in the figure above). A previous 510(k) submission K182630 for use of Admelog in Omnipod systems showed that stability test results

Page 5 –IDE G15256/S002, ICCR2019-0858 Consult

for in-pod and dispensed samples were comparable. Additionally, the Agency's experience is that longer infusion set lengths represent worst case for insulin pumps. The Omnipod has virtually no infusion set, thus minimal degradation of the insulin from the reservoir to the patient is expected. Therefore, lack of testing on cannula end samples is acceptable. Review of the biocompatibility is deferred to CDRH.

Assessor's conclusion: *The data provided are adequate to support in-use stability of Fiasp in pump use according to the proposed label.*

APPEARS THIS WAY ON ORIGINAL





eConsult Cover Sheet

Consult Number: CON1917508
Document Number: ICC1900084
Applicant:
Trade Name:
Consult Type: Chemistry
Requestor: Rumi Young [RUMLYOUNG]
rumi.young@fda.hhs.gov
Requestor Home: CDRH\OHT3\DHT3C\THT3C1
Requested Consultant:

Gatekeeper / Consultant: Berk Oktem [BERK.OKTEM]
berk.oktem@fda.hhs.gov ; 301-796-3542

Consultant Home: CDRH\OSEL\DBCMS

Date Requested: July 24, 2019

Due Date: August 12, 2019

Instructions: Hi Berk, Please review the leachables study in MAF (b) (4). The sponsor is adding FIASP to and insulin infusion pump label. The study was performed using the drug. I will provide additional instruction and review materials via email. Thanks,

Recommendation: Additional information needs to be requested from the sponsor.

SCOPE:

The sponsor, Novo Nordisk, has submitted NDA 208751 which includes a leachables report TR17-464 REV.A. The report is to document the qualitative and quantitative assessment of Fast acting Insulin Aspart (Fiasp) leachables from Omnipod System Pods. Testing was performed using Eros Omnipods.

The scope for CDRH is unclear: which biocompatibility endpoints are being addressed?

(b) (4)

Deficiencies:

- You provided the report TR17-464 REV.A which included leachables testing performed using Fiasp Insulin solution 37 (b) (4) C for 96 (b) (4) hours. We believe the study is insufficient. The study is simply a screening study with limited time and limited extraction power. The length of the study is far shorter than the clinically relevant contact time. Therefore, please address following concerns:
 - o Please provide justification that Fiasp Insulin solution extraction power and polarity is comparable to the extractables study performed originally under prior submission TR17-463 Rev A.
 - o The extractables study TR17-463 Rev A found several more extractables. They were possibly not observed in this study since the insulin solution contents masks a good portion of the chromatogram, making it impossible to determine if any additional components co-elute. Please perform another blank extraction with higher purity extraction vehicle what is comparable to the Fiasp Insulin solution extraction power.
 - o You included an Analytical Evaluation Threshold (AET) calculation that is based on United States Pharmacopeia (USP) literature yet not quite applicable to medical devices. The Agency in several public platforms publicized an approach that is more applicable to medical devices, based on the following formula :

$$\text{AET } (\mu\text{g/mL}) = \text{DBT } (\mu\text{g/day}) \times (\text{A} \div (\text{B} \times \text{C} \times \text{D})) \div \text{UF}$$

Where DBT is the Dose-Based Threshold; A is the number of medical devices extracted, B is the extract volume, C is the number of medical devices that contact the body, D is

the dilution factor and UF is the uncertainty factor of the analytical methods. (not to be confused with any uncertainty factors used in Toxicology) The UF depends on the analytical method and needs to be determined for that particular method accounting for the level of variation of the response factors of compounds found in the observed extractables (Jordi et al. Journal of Pharmaceutical and Biomedical Analysis 150 (2018) 368–376; and Jenke and Odofu, Journal of Chromatographic Science 2012;50:206–212).

RECOMMENDATION

Additional information needs to be requested from the sponsor.

Berk Oktem -S
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Date: 2019.08.16 13:42:30
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Berk Oktem, Ph.D.

Chemist, Division of Biology, Chemistry, and Materials Science; CDRH\OSEL

Consult 1918744, Parent Doc#ICC1900179

Background:

This consult was requested by Rumi Young on 07/25/2019. The purpose of the MDR analysis is to investigate the number of pediatric reports received for adverse events involving the OmniPod or OmniPod dash insulin pumps from 2016 to current date 2019. The consultant requests to categorize the pertinent pediatric MDRs based on different age groups.

Summary of Analysis:

The System for Unified Surveillance (SUS) was used to run a query of MDRs filed under product code: LZG, manufacturer name: “INSUL%”, brand name: OMNI% (to cover OmniPod and OmniPod dash) and report create date: 01/01/2016 to 07/31/2019. Due to the large number of MDRs per year, the same criteria were used to run four separate queries of MDR data for report create date: from the beginning to end of 2016, 2017, 2018 and then 01.01.2019 to 07.31.2019 respectively.

The total number of MDRs per year are as follow:

Year	Total number of MDRs
2016	4283
2017	6737
2018	9192
2019	7055

The MDRs for each year were exported to Excel for further analysis. A list of the total number of MDRs for each year is found in the “Original” worksheet in the Excel document per respective year.

The patient age was converted from “day” format to “Year/Month/Day” using a formula. The patient age in the “year/Month/Day” format is found in column “V” of the Excel worksheets. Pediatric MDRs were filtered and colored per age group. The following age groups and colors codes were used.

Age group	Color code
<1	Blue
1 year	Purple
2-12 years	Orange
13-18 years	Green
18-21 years	Tan

Pediatric MDRs were then separated from the adult MDRs and MDRs where no age was entered. The adult MDRs and no age entered MDRs are listed in the “Adult” and “No age” worksheet within the Excel document for each respective year.

A list of key words provided by the requester were used to text term filter the pediatric MDRs to pediatric MDRs of interest. The key words provided by the requester were:

Underdose, Overdose, Skin rash, Death, Adhesive, Hypoglycemia, Hyperglycemia, Ketoacidosis and Infection.

Once the suggested text terms were applied to the pediatric MDRs, the text term filtered MDRs were then separated into a worksheet named “Text Term Pediatric”. Then, the text term pediatric MDRs were divided into worksheets per the age groups. The Excel document for each year contains worksheets for each age group after the text terms were applied.

The table below provides the number of MDRs per age group per year.

	2016	2017	2018	2019
Total MDRs	4283	6737	9192	7055
Total Pediatrics	1654	2988	4158	3345
Total Text Term Pediatric	1645	2978	4123	3320
Age group:				
<1	0	2	1	1
1 year	7	21	15	15
2-12 years	1063	738	2767	2131
13-18 years	470	1981	1078	963
19-21 years	105	236	262	210

The MDR data from the past four years indicates an increased in the number of pediatric adverse events related to the OmniPod and OmniPod dash insulin pumps. The most increase in MDRs is seen in the 2-12-years and 13-18-years age groups.

The number of death MDRs from the past four years in the “Text Term Pediatric” list is as follow:

Year	Death MDRs in the “Text Term Pediatric” list
2016	0
2017	1
2018	3
2019	0

Helen Yousefi
MDR Analyst

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/

MICHAEL G WHITE

11/19/2019 08:22:22 PM

Filed on behalf of Carolyn Dorgan, MS, Infusion Devices Team Lead, Combination Products
Team Lead; OPEQ/OHT3/DHT3C

MEMORANDUM
REVIEW OF REVISED LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 8, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208751/S-011
Product Name and Strength:	Fiasp (insulin aspart) injection, 100 units/mL
Applicant/Sponsor Name:	Novo Nordisk Inc. (Novo)
FDA Received Date:	February 25, 2019 and October 24, 2019
OSE RCM #:	2019-437
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Novo Nordisk submitted an Efficacy Supplement for Fiasp (insulin aspart, NDA 208751/S-011) on February 25, 2019, which proposes to expand the indication to include continuous subcutaneous infusion in pediatric patients. We note that the sponsor also submitted supplement 010 on February 21, 2019, which proposes to expand the current indication for Fiasp to include pediatric patients with diabetes.

The sponsor submitted revised prescribing information on October 24, 2019, following the approval of NDA 208751/S-008 on October 21, 2019, which incorporated changes from the approved labeling for Fiasp. For S-011, they have proposed changes to various sections of the prescribing information (Highlights of Prescribing Information-Indications and Usage section; Full Prescribing Information-Section 1 Indications and Usage, Section 6 Adverse Reactions, Section 8 Use in Specific Populations, Section 12 Clinical Pharmacology, and Section 14 Clinical Studies) for Fiasp. In addition, they propose editorial changes to Section 5 Warnings and Precautions and Section 16 How Supplied/Storage and Handling.

2 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Fiasp is currently approved to improve glycemic control in adults with diabetes mellitus and can be administered via subcutaneous injection, intravenous infusion, or continuous subcutaneous

infusion^a. It is currently available as 100 units/mL (U-100) in 10 mL multiple-dose vials, 2 mL FlexTouch pen, and 3 mL PenFill cartridges for use in a PenFill cartridge device.

We note that the sponsor's proposal to expand the current indication for Fiasp to include pediatric patients with diabetes is consistent with the labeling of their other approved products (i.e., Novolog FlexTouch^b, Levemir FlexTouch^c, Tresiba FlexTouch^d, Novolog PenFill cartridges). All of these products use the FlexTouch device platform and are approved for use in pediatric patients. Thus, we determined that Novo Nordisk's proposal to expand the use of Fiasp to also include pediatric patients would be acceptable.

We performed a risk assessment of the revised prescribing information (Appendix A) to identify areas of vulnerability that may lead to medication errors and other areas of improvement and we have no recommendations at this time. We defer to the review team for analysis of the proposed changes to the various sections of the prescribing information.

3 CONCLUSION

The revised prescribing information for Fiasp is acceptable from a medication error perspective. We have no further recommendations at this time.

^a Administration via continuous subcutaneous infusion (insulin pump) was approved under S-008 on October 21, 2019.

^b Novolog (NDA 020986 approved June 7, 2000) is labeled for use in adults and pediatrics (older than 2 years). The Novolog FlexTouch device was approved on October 31, 2013 (under supplement 61).

^c Levemir (NDA 021536 approved June 16, 2005) is approved for use in adults and pediatrics (age 2 to 17 years). The Levemir FlexTouch device was approved on October 31, 2013 (under supplement 33).

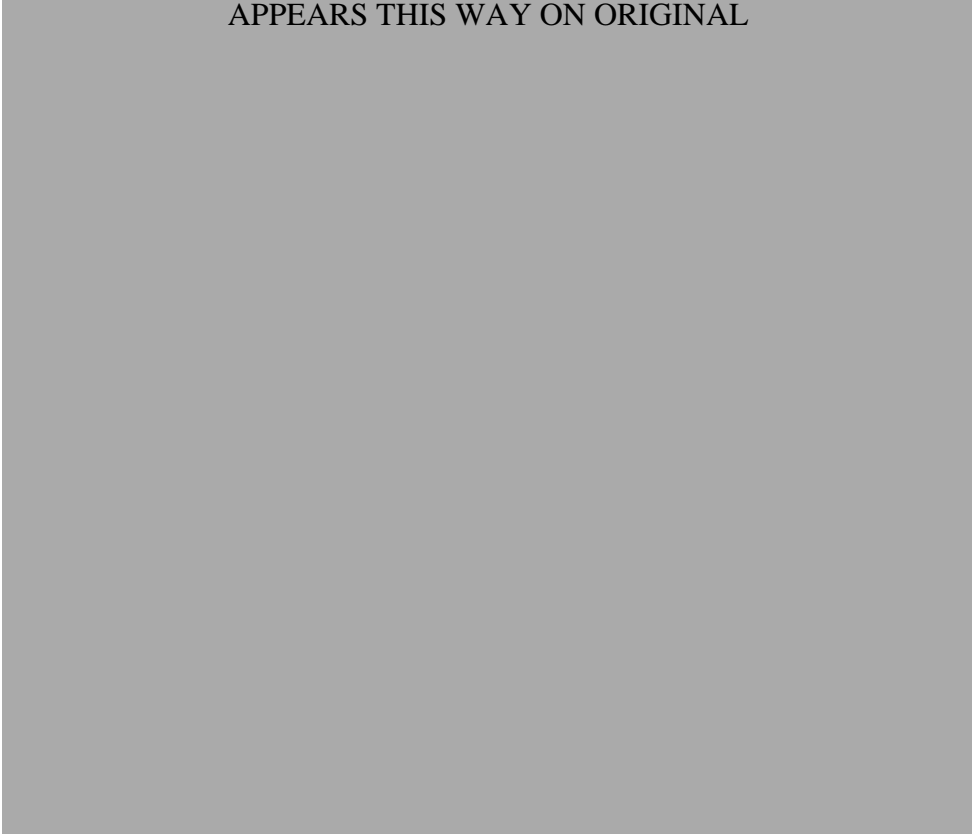
^d Tresiba (NDA 203314 approved September 25, 2015) is labeled for use in patients 1 year and older. The Tresiba FlexTouch device was approved in 2015 with the original NDA.

APPENDIX A. LIST OF LABELING RECEIVED ON OCTOBER 24, 2019

Using the principles of human factors and Failure Mode and Effects Analysis,^e along with postmarket medication error data, we reviewed the following Fiasp labels and labeling submitted by Novo Nordisk Inc. (Novo).

- Prescribing Information
 - <\\cdsesub1\evsprod\nda208751\0131\m1\us\prop-pi-clean-ped-pump.pdf>

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^e Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

ARIANE O CONRAD
11/13/2019 11:06:48 AM

HINA S MEHTA
11/13/2019 11:48:05 AM

CONSULTING REVIEW MEMORANDUM

To: Callie Cappel Lynch
CDER/OND/ODEII/DMEP

From: Jisun Yi, M.D., Medical Officer
FDA/CDRH/OHT-7/DCTD/DDDB

Through: Alain Silk, Ph.D., Branch Chief
CDRH/OHT-7/DCTD/DDDB

Applicant Name: Novo Nordisk, Inc.

Subject: InterCenter Consult (ICCR2019-04553)
Prior Approval Efficacy Supplement (sNDA) – Pediatric Pump Indication
(NDA 208751/S-11)

Date: October 18, 2019

Digitally signed by
Jisun Yi-S
Date: 2019.11.05
12:06:26 -05'00'

Jisun Yi-S

Alain D. Silk -S

REVIEW TEAM

- Jisun Yi, Medical Officer, CDRH/OHT-7/DCTD/DDDB
- Yiduo Wu, Artificial Pancreas Team Lead, CDRH/OHT-7/DCTD/DDDB
- Alain Silk, Branch Chief, CDRH/OHT-7/DCTD/DDDB

BACKGROUND

Novo Nordisk submitted a Prior Approval Efficacy Supplement (sNDA) (NDA 208751/S-11) to support Continuous Subcutaneous Insulin Infusion (CSII) use in insulin pump for Fiasp in pediatric patients with diabetes mellitus.

Novo Nordisk provides the following information relating to the clinical information in this submission to support the use of Fiasp in an insulin pump:

“In accordance with the extrapolation strategy in the agreed iPSP, Novo Norisk proposes to extrapolate efficacy results from the adult pump trial in T1DM to pediatric T1DM based on the following trials submitted under the NDA:

- The completed Phase 3b pump efficacy and safety trial in adult subjects with T1DM (NN1218-3854)
- The completed single dose pump Pk/Pd study in adult subjects with T1DM (NN1218-4349)
- The completed s.c. pediatric efficacy and safety trial in subjects with T1DM (NN1218-4101)

Additionally, as described in the agree iPSP, Novo Nordisk also proposes to leverage the safety and dosing information from trials NN1218-3854 and 41010 to support the CSII use of Fiasp with pediatric patients.”

Consult Scope

CDER has requested that OIR (OHT-7) in CDRH provide an intercenter consult review for this submission (NDA 208751/S-11) (which contains a prior approval efficacy supplement to add a pediatric CSII indication for Fiasp).

CDER/DMEP provided the following instructions in the intercenter consult request:

“Novo Nordisk has submitted a supplement for Fiasp to include pump use in pediatrics. Please review the pump studies included in the submission and provide a recommendation for approval. Please also provide any labeling recommendations you may have. We also ask that you attend the internal milestone meetings list below. Filing: April 4, 2019 Mid Cycle: July 17 2019 Wrap Up/Labeling: November 14 2019.”As discussed with CDER/DMEP, this consult will focus on the safety of the CSII indication for the pediatric population, specifically with regards to the pump programming parameters, as well as other device related safety related aspects, specifically occlusion.

Per discussion with OHT-3/CDRH, OHT-3/CDRH will provide a review and recommendations, and consult for any non-clinical device related components relating to the pediatric CSII indication for Fiasp (NDA 208751/S-11), or the related general pediatric indication.

This scope of this consult is limited to device specific clinical considerations around the pediatric pump indication for Fiasp.

INDICATIONS AND USAGE

The following information relating to indications and usage can be found in the proposed labeling for this submission:

“FIASP is a rapid-acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.”

CLINICAL STUDY TO SUPPORT THE CSII INDICATION (NN1218-3854)

SYNOPSIS

The sponsor provides the following synopsis of the clinical trial (NN1218-3854), which is reproduced below:

Please refer to the intercenter consult for the adult pump indication (NDA 208751/S-08), which discusses the above pump specific safety considerations within this study in detail, as well as summarizes relevant findings of the study.

CTR Synopsis Clinical Trial Report synopsis – ICH E3 Section 2

NAME OF SPONSOR Novo Nordisk, Novo Allé, 2880 Bagsværd, Denmark	
NAME OF ACTIVE SUBSTANCE Insulin aspart	
Trial ID NN1218-3854	
Trial registration ID-number NCT02825251	UTN – U1111-1118-2480 IND number – 106878 EudraCT number – 2010-024054-11
TITLE OF TRIAL Efficacy and Safety of Continuous Subcutaneous Insulin Infusion of Faster-acting Insulin Aspart* compared to NovoRapid® in Adults with Type 1 Diabetes (onset®5) *In the protocol the intervention name Faster-acting insulin aspart is used which is hereafter named 'faster aspart'	

INVESTIGATOR		
One principal investigator was appointed at each of the 92 trial sites in the trial. The following investigator was designated signatory investigator for the trial, and was responsible for reviewing and approving the clinical trial report: David C. Klonoff, M.D., FACP, FRCP (Edin), Fellow AIMBE Mills-Peninsula Medical Center 100 South San Mateo Drive, Room 5147 San Mateo, California 94401		
TRIAL SITES		
Country	No. of sites that screened subjects	No. of sites that randomised subjects
Belgium	7	7
Canada	8	8
France	10	10
Germany	9	9
Netherlands	9	8
Russian Federation	11	11
Slovenia	2	2
United Kingdom	6	6
United States	30	30
PUBLICATION		
No publications were available at the time of this clinical trial report synopsis.		
TRIAL PERIOD		DEVELOPMENT PHASE
Initiation date: 6 th July 2016		Phase 3b
Primary Completion Date: June 20, 2017 (Final data collection date for primary outcome measure)		
Global completion date: 21 st July 2017		
DATA CUT-OFF DATE		
The results presented reflect the data available in the clinical database as of 15 th September, 2017.		
DATE OF THE REPORT		
08 February 2018		
OBJECTIVES		
Primary objective:		
To confirm the effect of CSII treatment with faster aspart in terms of glycaemic control by comparing it to CSII treatment with NovoRapid®/NovoLog®, in adults with Type 1 Diabetes Mellitus (T1DM), using a non-inferiority approach.		
Secondary objectives:		
- To confirm superiority of CSII treatment with faster aspart compared to CSII treatment with NovoRapid®/NovoLog® in adults with T1DM, in terms of: - Postprandial glucose regulation (meal test) - Overall glycaemic control (HbA1c) - Postprandial glucose excursions (1,5-anhydroglucitol) - Time spent in low interstitial glucose (CGM) - To compare the effect and safety of CSII treatment with faster aspart vs. CSII treatment with NovoRapid®/NovoLog® in adults with T1DM.		
METHODOLOGY		
This was a double-blind, randomised, multicentre, multinational, active controlled, treat-to-target, parallel group trial in adult subjects with T1DM. The aim of the trial was to compare the effect and safety of continuous subcutaneous insulin infusion (CSII) of faster aspart and NovoRapid®/NovoLog®. The trial included a 4-week run-in period, a 16-week double-blind treatment period and a 30-day follow-up period. The 4-week run-in period was primarily for reinforcement of subject training in trial procedures, diabetes education and collecting baseline assessments. In the treatment period the investigators strived to achieve a glycaemic target of fasting and pre-prandial BG between 4.0-6.0 mmol/L [71-108 mg/dL] in a treat-to-target fashion based on frequent SMPG profiles and safety. No maximum dose of insulin was specified.		

NUMBER OF SUBJECTS PLANNED AND ANALYSED

A total of 666 subjects with type 1 diabetes were planned to be screened, and 506 were planned to enter the run-in period, of which 450 were expected to enter randomised treatment. The actual number of subjects randomised was slightly higher than the planned number.

Subject disposition

	Faster aspart		NovoRapid		Total	
	N	(%)	N	(%)	N	(%)
Screened					658	
Screening failures					162	
Run-in failures					24	
Randomised	236	(100.0)	236	(100.0)	472	(100.0)
Exposed*	236	(100.0)	236	(100.0)	472	(100.0)
Premature discontinued randomised treatment	7	(3.0)	10	(4.2)	17	(3.6)
Adverse event	2	(0.8)	1	(0.4)	3	(0.6)
Hypoglycaemic episode	0		0		0	
Protocol violation	2	(0.8)	2	(0.8)	4	(0.8)
Included in the trial in violation of criteria	2	(0.8)	2	(0.8)	4	(0.8)
Intension of becoming pregnant	0		0		0	
Participating in other clinical trials	0		0		0	
Other protocol violation	0		0		0	
Pregnancy	0		1	(0.4)	1	(0.2)
Decision of subject	3	(1.3)	6	(2.5)	9	(1.9)
Other	0		0		0	
Withdrawn from trial	3	(1.3)	6	(2.5)	9	(1.9)
Adverse event	0		1	(0.4)	1	(0.2)
Lost to follow-up	0		1	(0.4)	1	(0.2)
Withdrawal by subject	1	(0.4)	4	(1.7)	5	(1.1)
Other	2	(0.8)	0		2	(0.4)
Completed treatment period	229	(97.0)	226	(95.8)	455	(96.4)
Completed trial period	233	(98.7)	230	(97.5)	463	(98.1)

#: Percentage of randomised subjects, N: Number of subjects, *: Includes subjects 'as treated'. Treatment period: The period from visit 6 (Week 0) to visit 22 (Week 16) without premature discontinuation of randomised treatment. Trial period: The period from visit 6 (Week 0) to visit 22 (Week 16)

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION**Key inclusion criteria**

- Male or female, age at least 18 years at the time of signing the informed consent
- Diagnosed with T1DM (Type 1 Diabetes Mellitus) (based on clinical judgement and/or supported by laboratory analysis as per local guidelines) equal or above 1 year prior to the day of screening
- Using the same Medtronic pump (Minimed 530G (551/751), Paradigm Veo (554/754), Paradigm Revel (523/723), Paradigm (522/722)) for CSII in a basal-bolus regimen with a rapid acting insulin analogue for at least six months prior to screening and willing to stay on the same pump model throughout the trial (if the model is changed the change should not exceed 7 consecutive days.)
- HbA1c (glycosylated haemoglobin) 7.0-9.0% (53-75 mmol/mol) as assessed by central laboratory at screening
- Body mass index (BMI) below or equal to 35.0 kg/m² at screening
- Ability and willingness to take at least 3 daily meal-time insulin bolus infusions every day throughout the trial

Key exclusion criteria

- Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening
- History of hospitalization for ketoacidosis below or equal to 180 days prior to the day of screening

• Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before screening • Any condition which, in the opinion of the Investigator, might jeopardise a Subject's safety or compliance with the protocol
TEST PRODUCT BATCH NUMBER, DOSE AND MODE OF ADMINISTRATION The investigational trial product was faster aspart 100 U/mL solution in 10 mL vials; batch EW5H089. Faster aspart was to be infused subcutaneously using the patient's own insulin pump. During randomised treatment, the investigator reviewed and adjusted, if necessary, the bolus dose and basal infusion rate and other pump parameters.
DURATION OF TREATMENT The planned duration of the treatment period was 16 weeks. The mean duration of exposure was 0.31 years in the faster aspart group and 0.30 years in the NovoRapid®/NovoLog® group.
REFERENCE PRODUCT BATCH NUMBER, DOSE AND MODE OF ADMINISTRATION The reference therapy was insulin aspart (NovoRapid®/NovoLog®) 100 U/mL solution in 10 mL vials; batch EW5H087. NovoRapid®/NovoLog® was to be infused subcutaneously using the patient's own insulin pump. During randomised treatment, the investigator reviewed and adjusted, in necessary, the bolus dose and basal infusion rate and other pump parameters.
CRITERIA FOR EVALUATION – EFFICACY Key assessments for the efficacy evaluation were: HbA_{1c} Post-prandial glucose (PPG) based on meal test Fasting plasma glucose (FPG) 1,5-anhydroglucitol Self-measured plasma glucose (SMPG) Insulin dose Continuous glucose monitoring (CGM) of interstitial glucose (IG) Lipids
CRITERIA FOR EVALUATION – SAFETY Key variables/assessments for the safety evaluation were: Number of treatment-emergent adverse events (AEs) Number of treatment-emergent severe or blood glucose (BG) confirmed hypoglycaemic episodes Infusion site reactions Allergic reactions Infusion set changes Unexplained hyperglycaemia Laboratory safety parameters, vital signs and physical examination
STATISTICAL METHODS Analysis sets • Full analysis set (FAS) includes all randomised subjects. In exceptional cases, randomised subjects may be excluded from the FAS. In such cases, the reason for exclusion was justified and documented. Subjects in the FAS contributed to the evaluation “as randomised” • Safety analysis set includes all subjects receiving at least one dose of the test product or its comparator. Subjects in the safety analysis set contributed to the evaluation “as treated”. The primary estimand was defined as the treatment difference between subjects randomised to CSII treatment with faster aspart and CSII treatment with NovoRapid®/NovoLog® in adults with T1DM assessed by change from baseline in HbA_{1c} 16 weeks after randomisation for all randomised subjects regardless of treatment discontinuation or use of ancillary therapies. The secondary estimand is defined as the treatment difference in change from baseline in HbA_{1c} 16 weeks after randomisation between CSSI treatment with faster aspart and CSII treatment with NovoRapid®/NovoLog® in adult

subjects with T1DM if subjects continue on-treatment until 16 weeks.

Primary endpoint

- Change from baseline in glycosylated haemoglobin (HbA_{1c}) 16 weeks after randomisation.

Confirmatory secondary endpoints

- Change from baseline in 1-hour PPG increment 16 weeks after randomisation (meal test)
- Change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation
- Change from baseline of time spent in low IG (≤ 3.9 mmol/L [70 mg/dL]) during CGM 16 weeks after randomisation

Hierarchical testing procedure for the primary estimand

- Step 1 (Primary analysis): Change from baseline in HbA_{1c} 16 weeks after randomisation non-inferiority of faster aspart versus NovoRapid[®]/NovoLog[®] was analysed using an analysis of variance model after multiple imputations assuming treatment according to randomisation. The model included treatment, strata (use of own continuous glucose monitoring), previous insulin use, and region as factors, and baseline HbA_{1c} as a covariate. Multiple imputation is used to sequentially impute missing values of change from baseline in HbA_{1c} to subsequent planned post-baseline visits for each treatment group separately with strata, previous insulin use, and region as factors, and baseline HbA_{1c} and earlier changes from baseline in HbA_{1c} as covariates. Each imputed dataset was analysed separately and estimates were combined using Rubin's rules. The pre-defined non-inferiority margin for HbA_{1c} was 0.4%.
- Step 2: Change from baseline in 1-hour PPG increment 16 weeks after randomisation (meal test) superiority of faster aspart compared to NovoRapid[®]/NovoLog[®] was analysed using an analysis of variance model after multiple imputation assuming subjects on faster aspart switch to NovoRapid[®]/NovoLog[®]. The model included treatment, strata, previous insulin use and region as factors and baseline 1-hour PPG increment as covariate. Multiple imputation is used to impute missing values of change from baseline in 1-hour PPG increment to week 16 based on subjects in the NovoRapid[®]/NovoLog[®] arm who complete the trial period. Each imputed dataset was analysed separately and estimates were combined using Rubin's rules.
- Step 3: Change from baseline in HbA_{1c} 16 weeks after randomisation superiority of faster aspart compared to NovoRapid[®]/NovoLog[®] was analysed using the same model as in step 1 without the non-inferiority margin.
- Step 4: Change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation superiority of faster aspart versus NovoRapid[®]/NovoLog[®] was analysed using a model similar to step 1.
- Step 5: Change from baseline in time spent in low IG (≤ 3.9 mmol/L [70 mg/dL]) superiority of faster aspart versus NovoRapid[®]/NovoLog[®] was analysed using a model similar to step 1

Key supportive secondary endpoints:

The primary estimand was assessed using the in-trial observation period which includes data collected after a subject discontinued trial product. The secondary estimand was assessed using the on-treatment observation period. Efficacy endpoints except insulin dose and insulin pump parameters were presented using the in-trial observation period and repeated using the on-treatment observation period. Insulin doses and insulin pump parameters were presented using the on-treatment observation period.

Subjects achieving HbA_{1c} <7.0% or HbA_{1c} <7.0% without severe hypoglycaemic episodes were analysed using a logistic regression model with treatment, strata, previous insulin use, and region as factors, and baseline HbA_{1c} as a covariate. In the analysis of the in-trial observation period subjects without an HbA_{1c} measurement at week 16 was considered not to have achieved target. In the on-treatment observation period analysis subjects who either who prematurely discontinue treatment, withdrew from trial, or had no HbA_{1c} measurement at week 16 was considered not to have achieved target.

Change from baseline 16 weeks after randomisation in FPG and endpoints derived from the 7-7-9-point SMPG profile was analysed separately using a model similar to step 1. *Fluctuation in the 7-7-9-point SMPG profile 16 weeks after randomisation* was logarithmically transformed and analysed. *Change from baseline in PPG and PPG increment 16 weeks after randomisation* was analysed separately using a model similar to step 2. *Subjects achieving 1-hour PPG (SMPG) ≤ 7.8 mmol/L or 1-hour PPG (SMPG) ≤ 7.8 mmol/L without severe hypoglycaemic episodes* were analysed using a logistic regression model with treatment, strata, previous insulin use, and region as factors, and baseline PPG as a covariate. In the analysis of the in-trial observation period subjects without an PPG measurement at week 16 was

considered not to have achieved target. In the on-treatment observation period analysis subjects who either who prematurely discontinue treatment, withdrew from trial, or had no PPG measurement at week 16 was considered not to have achieved target. *Change from baseline in lipids-lipoproteins 16 weeks after randomisation* were logarithmically transformed and analysed using model similar to step 1. *Change from baseline in mean IG increment (0-30 min, 0-1 hour and 0-2 hours after start of the meal) 16 weeks after randomisation, change from baseline in mean IG peak after start of meal 16 weeks after randomisation and change from baseline in mean time to the IG peak after meal 16 weeks after randomisation* were analysed separately using a model similar to step 1. *Change from baseline in AUC of IG 16 weeks after randomisation, change from baseline in AUC of IG increment 16 weeks after randomisation, change from baseline in IG peak 16 weeks after randomisation and change from baseline in time to IG peak 16 weeks after randomisation* were analysed separately using an analysis of variance meal including treatment, strata, previous insulin use and region as factors, and with the corresponding baseline value as covariate. The remaining endpoints derived based on the IG profiles, insulin doses and insulin pump parameters (glucose sensitivity factor, insulin carbohydrate ratio and active insulin time) were summarised descriptively by treatment.

Safety endpoints:

All safety endpoints were compared using the on-treatment observation period. *A treatment-emergent adverse event* was defined as an event with an onset date on or after the first day of exposure to randomised treatment, and no later than seven days after the last day of randomised treatment. *A hypoglycaemic episode* was defined as treatment-emergent if the onset of the episode occurred on or after the first day of IMP administration after randomisation and no later than one day after the last day on IMP. Hypoglycaemic episodes were defined as nocturnal if the time of the onset was between 00:01 and 05:59 both inclusive. Severe or BG confirmed hypoglycaemia was defined as an episode that was severe according to the ADA classification or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with or without symptoms consistent with hypoglycaemia. Treatment emergent severe or BG confirmed hypoglycaemic were analysed based on the FAS using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model includes treatment, strata, previous insulin use and region as factors. *An unexplained hyperglycaemic episode* was defined as a confirmed PG value ≥16.7 mmol/L (300 mg/dL) that was unexplained (i.e. no apparent medical, dietary, insulin dose or pump failure reason). An unexplained hyperglycaemic episode was defined as treatment-emergent if the onset of the episode occurred on or after the first day of IMP administration after randomisation and no later than one day after the last day on IMP. The number episodes of unexplained hyperglycaemia were summarised in a frequency table. *Physical examination, Electrocardiogram, vital signs, fundus photography/fundoscopy and clinical laboratory assessments (haematology, biochemistry and urinalysis)* were summarised descriptively. *Change from baseline in body weight* was analysed using a model similar to step 1 in the hierarchical testing procedure with the corresponding baseline value as covariate. *Infusion set changes:* The number of change-of-infusion-sets per week during 16 weeks after randomisation was calculated for each subject as the total number of infusion sets used divided by the actual duration of the randomised treatment period in days, multiplied by seven and summarised descriptively. Non-routine infusion set changes were summarised descriptively categorised by reasons for change.

DEMOGRAPHY OF TRIAL POPULATION

The trial population consisted of men (43%) and women (57%) with T1DM with a mean age of 43.5 years (range: 18-76 years), mean BMI of 26.3 kg/m² (range: 17.9-36.6 kg/m²) and mean diabetes duration of 24.2 years (range: 2.2-62.0 years). The majority of subjects were White (88.8%). In general, the demography and baseline characteristics of subjects in the faster aspart and NovoRapid®/NovoLog® groups were similar.

Demographics and baseline characteristics

	Faster aspart N (%)	NovoRapid N (%)	Total N (%)
Number of subjects	236	236	472
Age group			
N	236 (100.0)	236 (100.0)	472 (100.0)
18 - 64 years	213 (90.3)	219 (92.8)	432 (91.5)
65 - 84 years	23 (9.7)	17 (7.2)	40 (8.5)
BMI group			
N	236 (100.0)	236 (100.0)	472 (100.0)

<25 kg/m ²	106 (44.9)	96 (40.7)	202 (42.8)
25-29.9 kg/m ²	87 (36.9)	92 (39.0)	179 (37.9)
30-34.9kg/m ²	37 (15.7)	45 (19.1)	82 (17.4)
=>35 kg/m ²	6 (2.5)	3 (1.3)	9 (1.9)
Sex			
N	236 (100.0)	236 (100.0)	472 (100.0)
Female	133 (56.4)	136 (57.6)	269 (57.0)
Male	103 (43.6)	100 (42.4)	203 (43.0)
Country of residence			
N	236 (100.0)	236 (100.0)	472 (100.0)
Belgium	20 (8.5)	16 (6.8)	36 (7.6)
Canada	20 (8.5)	25 (10.6)	45 (9.5)
France	20 (8.5)	15 (6.4)	35 (7.4)
Germany	32 (13.6)	31 (13.1)	63 (13.3)
Netherlands	14 (5.9)	6 (2.5)	20 (4.2)
Russia	26 (11.0)	29 (12.3)	55 (11.7)
Slovenia	17 (7.2)	16 (6.8)	33 (7.0)
United Kingdom	13 (5.5)	14 (5.9)	27 (5.7)
United States	74 (31.4)	84 (35.6)	158 (33.5)
Ethnicity			
N	236 (100.0)	236 (100.0)	472 (100.0)
Hispanic Or Latino	7 (3.0)	6 (2.5)	13 (2.8)
Not Hispanic Or Latino	210 (89.0)	215 (91.1)	425 (90.0)
NA	19 (8.1)	15 (6.4)	34 (7.2)
Race			
N	236 (100.0)	236 (100.0)	472 (100.0)
White	209 (88.6)	210 (89.0)	419 (88.8)
Black Or African American	2 (0.8)	5 (2.1)	7 (1.5)
Asian	3 (1.3)	3 (1.3)	6 (1.3)
American Indian Or Alaska Native	0	2 (0.8)	2 (0.4)
Other	2 (0.8)	1 (0.4)	3 (0.6)
NA	20 (8.5)	15 (6.4)	35 (7.4)

#: Percentage of subjects, BMI: Body mass index (kg/m²), N: Number of subjects, NA: Not applicable Baseline is at randomisation (Visit 6 - Week 0). Subjects from France did not provide information about race and ethnicity and are categorised under not applicable.

EFFICACY RESULTS

The efficacy results 16 weeks after randomisation with either faster aspart or NovoRapid®/NovoLog® in subjects with type 1 diabetes were:

Step-wise hierarchical testing procedure

- Faster aspart was confirmed to be non-inferior to NovoRapid®/NovoLog® with regards to change from baseline in HbA_{1c} 16 weeks after randomisation.
- Faster aspart was confirmed to be superior to NovoRapid®/NovoLog® in terms of change from baseline in the 1-hour PPG increment 16 weeks after randomisation.
- For Step 3, superiority of faster aspart to NovoRapid®/NovoLog® in terms of change from baseline in HbA_{1c} 16 weeks after randomisation was not confirmed, and the hierarchical statistical testing procedure was stopped.
- For Step 4: No confirmatory testing could be done for change from baseline in 1,5 anhydroglucitol.
- For Step 5: No confirmatory testing could be done for time spent in low interstitial glucose (IG) (≤3.9 mmol/L [70 mg/dL]) superiority of faster aspart versus NovoRapid®/NovoLog®.
- During the run-in period, the HbA_{1c} was lowered from 7.80% to 7.49%. At baseline, observed mean HbA_{1c}

was 7.49% in both the faster aspart group and the NovoRapid[®]/NovoLog[®] group.

- At 16 weeks, the observed mean HbA_{1c} was 7.44% in the faster aspart group and 7.35% in the NovoRapid[®]/NovoLog[®] group.
- The estimated treatment difference in HbA_{1c}, change from baseline, for faster aspart vs. NovoRapid[®]/NovoLog[®] was 0.09%-points [0.01; 0.17]_{95%CI}, confirming treatment with faster aspart to be non-inferior to treatment with NovoRapid[®]/NovoLog[®].
- At baseline, there were a similar proportion of subjects with HbA_{1c} <7% in the faster aspart (17.5%) and NovoRapid[®]/NovoLog[®] (17.4%) groups. At 16 weeks, there was an increase in the proportion of subjects achieving HbA_{1c} <7% in both the faster aspart (20.3%) and NovoRapid[®]/NovoLog[®] (23.3%) groups. There was no statistically significant difference (estimated OR: 0.76 [0.46; 1.26]_{95% CI}) between treatments in the odds of achieving HbA_{1c} <7% 16 weeks after randomisation.
- At 16 weeks, the proportion of subjects achieving HbA_{1c} <7% without severe hypoglycaemic episodes was 18.6% in the faster aspart group and 22.5% in the NovoRapid[®]/NovoLog[®] group. There was no statistically significant difference (estimated OR: 0.71 [0.43; 1.20]_{95% CI}) between treatments in the odds of achieving HbA_{1c} <7% without severe hypoglycaemic episodes 16 weeks after randomisation.

Change from baseline in 1-hour PPG increment 16 weeks after randomisation (meal test)

- At 16 weeks, the observed mean 1-hour PPG increment was 3.74 mmol/L (67.44 mg/dL) in the faster aspart group and 4.70 mmol/L (84.66 mg/dL) in the NovoRapid[®]/NovoLog[®] group.
- The observed mean change from baseline in 1-hour PPG increment 16 weeks after randomisation was -0.89 mmol/L (-15.99 mg/dL) in the faster aspart group and 0.05 mmol/L (0.98 mg/dL) in the NovoRapid[®]/NovoLog[®] group.
- There was a statistically significant treatment difference of -0.91 mmol/L [-1.43; -0.39]_{95% CI} (-16.39 mg/dL [-25.73; -7.06]_{95% CI}) in 1-hour PPG increment change from baseline to 16 weeks after randomisation between faster aspart and NovoRapid[®]/NovoLog[®] treatment, confirming superiority of faster aspart.

Change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation

- At 16 weeks, the observed mean 1,5-anhydroglucitol was 4.33 µg/mL in the faster aspart group and 4.41 µg/mL in the NovoRapid[®]/NovoLog[®] group.
- The observed mean change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation was 0.14 µg/mL in the faster aspart group and 0.25 µg/mL in the NovoRapid[®]/NovoLog[®].
- There was no statistically significant difference in estimated 1,5-anhydroglucitol change from baseline to 16 weeks after randomisation between treatments.

Change from baseline in time spent in low IG (≤3.9 mmol/L [70 mg/dL]) during CGM 16 weeks after randomisation

- At 16 weeks, the observed mean time spent in low IG (≤3.9 mmol/L [70 mg/dL]) was 78.61 min/day in the faster aspart group and 83.00 min/day in the NovoRapid[®]/NovoLog[®] group.
- The observed change from baseline in time spent in low IG (≤3.9 mmol/L [70 mg/dL]) during CGM 16 weeks after randomisation was -6.96 min/day in the faster aspart group and 2.85 min/day in the NovoRapid[®]/NovoLog[®] group.
- There was no statistically significant difference in estimated time spent in low IG (≤3.9 mmol/L [70 mg/dL]) change from baseline to 16 weeks after randomisation.

Change from baseline in fasting plasma glucose (FPG) 16 weeks after randomisation

- At 16 weeks, the observed mean FPG was 7.59 mmol/L (136.74 mg/dL) in the faster aspart group and 7.63 mmol/L (137.43 mg/dL) in the NovoRapid[®]/NovoLog[®] group.
- The observed change from baseline in FPG 16 weeks after randomisation was -0.03 mmol/L (-0.55 mg/dL) in the faster aspart group and 0.25 mmol/L (4.50 mg/dL) in the NovoRapid[®]/NovoLog[®] group.
- There was no statistically significant difference in estimated FPG change from baseline to 16 weeks after

randomisation between treatments.

Change from baseline in 30- min, 1- hour, 2- hour, 3- hour and 4- hour PPG 16 weeks after randomisation (meal test)

- There was a statistically significant difference between treatments in change from baseline in favour of faster aspart for:
 - 30-minute PPG (estimated treatment difference: -0.79 [-1.37; -0.22]_{95% CI})
 - 1-hour PPG (estimated treatment difference: -1.05 [-1.74; -0.35]_{95% CI})
 - 2-hour PPG (estimated treatment difference: -1.09 [-1.91; -0.28]_{95% CI})

Change from baseline in 30- min, 1- hour, 2- hour, 3- hour and 4- hour PPG increment 16 weeks after randomisation (meal test)

- There was a statistically significant difference between treatments in change from baseline in favour of faster aspart for:
 - 30-minute PPG increment (estimated treatment difference: -0.66 [-1.00; -0.31]_{95% CI})
 - 1-hour PPG increment (estimated treatment difference: -0.91 [-1.43; -0.39]_{95% CI})
 - 2-hour PPG increment (estimated treatment difference: -0.90 [-1.58; -0.22]_{95% CI})

Change from baseline in 7-7-9 point self-measured plasma glucose (SMPG) 16 weeks after randomisation profile assessed by mean of the 7-7-9 point SMPG profile

- At 16 weeks, the observed mean 7-7-9 point SMPG profile was 9.35 mmol/L (168.47 mg/dL) in the faster aspart group and 9.15 mmol/L (164.93 mg/dL) in the NovoRapid[®]/NovoLog[®] group.
- There was no statistically significant difference in estimated mean 0.16 mmol/L [-0.15; 0.47]_{95% CI} (2.89 mg/dL [-2.65; 8.42]_{95% CI}) of the 7-7-9 point SMPG profile change from baseline to 16 weeks after randomisation between treatments.

Pre-prandial plasma glucose (PG) (mean, pre-breakfast, pre-lunch, pre-main evening meal)

- The observed change from baseline in pre-prandial PG mean over all meals 16 weeks after randomisation was 0.39 mmol/L (7.10 mg/dL) with faster aspart and 0.21 mmol/L (3.71 mg/dL) with NovoRapid[®]/NovoLog[®].
- There were no statistically significant treatment differences for faster aspart versus NovoRapid[®]/NovoLog[®] in terms of change from baseline in pre-prandial PG at:
 - breakfast, estimated treatment difference: 0.22 mmol/L [-0.27; 0.71]_{95% CI} (4.00 mg/dL [-4.78; 12.78]_{95% CI}).
 - lunch, estimated treatment difference: 0.21 mmol/L [-0.32; 0.75]_{95% CI} (3.84 [-5.79; 13.46]_{95% CI}).
 - main evening meal, estimated treatment difference: -0.16 mmol/L [-0.73; 0.40]_{95% CI} (-2.94 [-13.07; 7.19]_{95% CI}).
 - mean over all meals, estimated treatment difference: 0.15 mmol/L [-0.20; 0.49]_{95% CI} (2.63 [-3.53; 8.79]_{95% CI}).

PPG (mean, breakfast, lunch and main evening meal)

- At 16 weeks, the observed mean PPG was reduced at breakfast and main evening meal but not for lunch in the faster aspart group and observed mean PPG was increased for all main meals (breakfast, lunch and evening meal) in the NovoRapid[®]/NovoLog[®] group.
- The observed change from baseline in PPG mean over all meals 16 weeks after randomisation was 0.06 mmol/L (1.14 mg/dL) with faster aspart and 0.13 mmol/L (2.31 mg/dL) with NovoRapid[®]/NovoLog[®].
- There were no statistically significant treatment differences for faster aspart versus NovoRapid[®]/NovoLog[®] in terms of change from baseline in PPG at:
 - breakfast, estimated treatment difference: -0.42 mmol/L [-1.06; 0.22]_{95% CI} (-7.60 mg/dL [-19.12; 3.91]_{95% CI}).
 - lunch, estimated treatment difference: 0.14 mmol/L [-0.50; 0.78]_{95% CI} (2.54 mg/dL [-9.00; 14.07]_{95% CI}).
 - main evening meal, estimated treatment difference: -0.32 mmol/L [-0.98; 0.34]_{95% CI} (-5.83 mg/dL [-

17.74; 6.07]95% CI).

- mean over all meals, estimated treatment difference: -0.05 mmol/L [-0.52; 0.43]95% CI (-0.86 mg/dL [-9.38; 7.67]95% CI).

PPG increment (mean, breakfast, lunch and main evening meal)

- At 16 weeks, the mean PPG increment was reduced at all main meals in the faster aspart group. In the NovoRapid®/NovoLog® group it was reduced for breakfast and lunch but not for the main evening meal.
- The observed change from baseline in PPG increment across all main meals 16 weeks after randomisation was -0.53 mmol/L (-9.60 mg/dL) with faster aspart and 0.12 mmol/L (2.12 mg/dL) with NovoRapid®/NovoLog®.
- There were no statistically significant treatment differences for faster aspart versus NovoRapid®/NovoLog® in terms of change from baseline in PPG increments at breakfast, lunch or main evening meal.
- There was a statistically significant treatment difference for faster aspart versus NovoRapid®/NovoLog® estimated treatment difference: -0.46 mmol/L [-0.90; -0.02] 95% CI (-8.27 mg/dL [-16.26; -0.28]95% CI) in terms of change from baseline in PPG increment mean over all meals.

Fluctuation in 7-7-9 point profile

- At 16 weeks, the geometric mean fluctuation was 2.10 mmol/L (37.91 mg/dL) in the faster aspart group and 2.03 mmol/L (36.57 mg/dL) in the NovoRapid®/NovoLog® group.
- There was no statistically significant difference in treatment ratio (1.03 [0.97; 1.10]95% CI) 16 weeks after randomisation.

Change in nocturnal SMPG measurements

- At 16 weeks, there were no statistically significant treatment differences between the faster aspart group and the NovoRapid®/NovoLog® group in terms of change from baseline in nocturnal PG increment at:
 - 04:00 to breakfast, estimated difference: -0.54 mmol/L [-1.34; 0.27]95% CI (-9.65 mg/dL [-24.22; 4.92]).
 - bedtime to 04:00, estimated difference: -0.15 mmol/L [-1.32; 1.02]95% CI (-2.72 mg/dL [-23.84; 18.41]).
 - bedtime to breakfast, estimated difference: -0.07 mmol/L [-1.07; 0.93]95% CI (-1.17 mg/dL [-19.19; 16.84]).

Subjects achieving PPG target (overall mean of daily post prandial glucose measurements in 7-7-9-point self-measured plasma glucose) 16 weeks after randomisation:

Overall PPG (1 hour) $\leq$ 7.8 mmol/L [140 mg/dL] or Overall PPG (1 hour) $\leq$ 7.8 mmol/L [140 mg/dL] without severe hypoglycaemia

- At 16 weeks, there was a decrease in the proportion of subjects achieving PPG targets in the faster aspart and NovoRapid®/NovoLog® groups.
- There was no statistically significant difference between treatments in the odds of achieving overall PPG (1 hour) target of $\leq$ 7.8 mmol/L [140 mg/dL] (OR: 1.15 [0.52; 2.54] 95% CI) or overall PPG (1 hour) $\leq$ 7.8 mmol/L [140 mg/dL] without severe hypoglycaemia (OR: 1.06 [0.47; 2.36] 95% CI) 16 weeks after randomisation.

Lipids-lipoproteins

- The estimated treatment difference between faster aspart and NovoRapid®/NovoLog® demonstrated no statistically significant difference between treatments after 16 weeks of randomisation for HDL (treatment ratio: 1.02 [0.99; 1.05]95% CI).
- The estimated treatment differences between faster aspart and NovoRapid®/NovoLog® demonstrated statistically significant difference between treatments after 16 weeks of randomisation for LDL (treatment ratio: 1.05 [1.02; 1.08]95% CI) and total cholesterol (treatment ratio: 1.02 [1.00; 1.05]95% CI).

Change from baseline in mean IG increment (0-30 min, 0-1 hour and 2 hours after start of meal) 16 weeks after randomisation

- For all meals and mean over all meals, there was a statically significant reduction in observed mean IG

increment for 0–1 hour and 0–2 hours for the faster aspart group compared to the NovoRapid®/NovoLog® group 16 weeks after randomisation.

Change from baseline in IG peak 16 weeks after randomisation

- There was no statistically significant treatment difference between faster aspart and NovoRapid®/NovoLog® for change from baseline in IG peak 16 weeks after randomisation at breakfast (0.08 mmol/L [-0.28; 0.44] 95%CI), lunch (-0.20 mmol/L [-0.54; 0.13] 95%CI), main evening meal (0.28 mmol/L [-0.06; 0.63] 95%CI) and mean over all meals (0.08 mmol/L [-0.20; 0.35] 95%CI).

Change from baseline in time to IG peak 16 weeks after randomisation

- There was no statistically significant treatment difference between faster aspart and NovoRapid®/NovoLog® for change from baseline in time to IG peak 16 weeks after randomisation at breakfast (-0.35 min [-5.54; 4.84] 95%CI), lunch (-2.01 min [-7.77; 3.76] 95%CI), main evening meal (-1.97 min [-4.24; 8.19] 95%CI) and mean over all meals (-0.05 min [-3.64; 3.54] 95%CI)

Change from baseline in mean time to the IG peak after start of meal 16 weeks after randomisation (related to meal test)

- At 16 weeks, change from baseline in observed mean time to the interstitial glucose peak increased by 1.2 minutes in the faster aspart group and decreased by 1.4 minutes in the NovoRapid®/NovoLog® group
- There were no statistically significant treatment differences (estimated treatment difference: -1.18 minutes [-9.51; 7.14] 95%CI) between the faster aspart group and the NovoRapid®/NovoLog® group in terms of change from baseline in mean time to the IG peak after start of meal 16 weeks after randomisation

Change from baseline in mean IG peak after start of meal 16 weeks after randomisation (related to meal test)

- At 16 weeks, observed mean interstitial glucose peak decreased in the faster aspart group and increased in the NovoRapid®/NovoLog® group.
- There was a statistically significant treatment differences between the faster aspart group and the NovoRapid®/NovoLog® group in terms of change from baseline in mean IG peak after start of meal 16 weeks after randomisation (-0.90 mmol/L [-1.64; -0.16] 95%CI)

Change from baseline in AUC of IG and AUC of IG increment 0-15 minutes, 0-30 minutes, 0-1 hour, 0-2 hours and 0-4 hours during meal test 16 weeks after randomisation (related to meal test)

- There was a statistically significant treatment difference in 0–2 hour AUC of IG (-0.66 mmol/L [-1.26; -0.06] 95%CI) and AUC of IG increment (-0.54 mmol/L [-0.97; -0.11] 95%CI) 16 weeks after randomisation between faster aspart and NovoRapid®/NovoLog®.

The results 16 weeks after randomisation were similar in both the faster aspart group and the NovoRapid®/NovoLog® with no significant difference from baseline values for the below endpoints:

- **Percentage of time spent in low IG range ($\leq 2.5, 3.0, 3.5, 3.9$ mmol/L [45, 54, 63, 70.2 mg/dL]) and high IG range ($>10.0, >12.0, >13.9$ mmol/L [180, 216, 250 mg/dL]) 16 weeks after randomisation**
- **Percentage of time spent within IG target range (4.0-7.8 mmol/L [71-140 mg/dL]) and 4.0-10.0 mmol/L [71-180 mg/dL] 16 weeks after randomisation**
- **Incidence of episodes with IG $\leq 2.5, 3.0, 3.5, 3.9$ mmol/L [45, 54, 63, 70 mg/dL]) and IG $>10.0, >12.0, >13.9$ mmol/L [180, 216, 250 mg/dL]) 16 weeks after randomisation**
- **Change from baseline in mean of the IG profile 16 weeks after randomisation**
- **Variation in the IG profile 16 weeks after randomisation**
- **Area under the curve (AUC_{3.9-IG}) for IG ≤ 3.9 mmol/L [70 mg/dL] 16 weeks after randomisation**

SAFETY RESULTS

Adverse events

Overall, there were no clinically relevant differences in the AE profiles across treatment groups.

- The overall AE rate per 100 patient years of exposure (PYE) was similar with faster aspart (604.7) and NovoRapid®/NovoLog® (574.7). The proportion of subjects reporting AEs was also similar with faster aspart (69.9%) and NovoRapid®/NovoLog® (65.7%).
- The vast majority of AEs were non-serious (98%), of mild or moderate severity (98%) and judged as unlikely related to trial products by the investigator (88%). Most AEs (86%) had resolved at the end of the 16-week treatment period.
- The observed rates of severe AEs and AEs judged as possibly or probably related to trial product by the investigator showed no clinically relevant differences between treatment groups. Overall, the most frequently reported AEs by PT were *viral upper respiratory tract infection, infusion site reaction, upper respiratory tract infection* and *gastroenteritis*.

Deaths, serious adverse events and other significant adverse events

- No deaths were reported during the trial.
- The rate of SAEs per 100 PYE was 6.9 for faster aspart, 15.3 NovoRapid®/NovoLog®. No SAEs (PT) occurred in more than 1% of the subjects. Three (3) were considered possibly related to treatment; 2 with faster aspart (*hypoglycaemic unconsciousness* and *drug eruption*) and one with NovoRapid®/NovoLog® (*hypoglycaemic seizure*).
- In total, 4 medication errors in 3 subjects were identified, based on a preferred term search. Three were reported as *accidental overdose* (1 faster aspart and 2 NovoRapid®/NovoLog®) and one as *other* (NovoRapid®/NovoLog®).

Hypoglycaemic episodes

- The overall rate of severe or BG confirmed hypoglycaemic episodes was not statistically significantly different between faster aspart and NovoRapid®/NovoLog® with estimated rate ratio 1.00 [0.85; 1.16]_{95%CI}. The observed rates were 4507 and 4529 episodes per 100 PYE with faster aspart and NovoRapid®/NovoLog® respectively.
- Daytime and nocturnal hypoglycaemic episodes: No statistically significant differences were seen in the estimated rates of daytime (estimated rate ratio: 1.00 [0.85; 1.18]_{95%CI}) or nocturnal (0.96 [0.76; 1.21]_{95%CI}) hypoglycaemic episodes between treatment groups. The observed rates of nocturnal severe or BG confirmed hypoglycaemic episodes per 100 PYE were 643 with faster aspart and 660 with NovoRapid®/NovoLog®.
- Hypoglycaemic episodes in relation to a meal: a higher rate of hypoglycaemic episodes was observed for faster aspart within the first 1 hour after start of a meal; the estimated rate ratio (faster aspart versus NovoRapid®/NovoLog®) was 1.78 [1.15; 2.75]_{95%CI}. The observed rate for severe or BG confirmed hypoglycaemic episodes within 1 hour after a meal was 126 episodes per 100 PYE (faster aspart) and 71 episodes per 100 PYE (NovoRapid®/NovoLog®). No statistically significant differences were observed between treatment groups for other intervals during the first 4 hours after the start of the meal.
- The observed rate of severe hypoglycaemic episodes was numerically higher with faster aspart (29 events per 100 PYE) than with NovoRapid®/NovoLog® (10 events per 100 PYE). The estimated rate ratio of 2.78 [0.78; 9.94]_{95%CI} (faster aspart versus NovoRapid®/NovoLog®) was not statistically significant.
- Three (3) subjects later randomised to faster aspart reported a total of 4 'severe' hypoglycaemic episodes during run-in. No severe hypoglycaemic episodes were reported during run-in by those subjects later randomised to NovoRapid®/NovoLog®.

Physical examination, fundoscopy, ECG, vital signs and laboratory assessments

- There were no clinically relevant differences from baseline to week 16 across treatment groups in physical examination, vital signs, fundoscopy, ECG or other laboratory assessments.

Body weight

- The treatment difference in body weight change from baseline at week 16 (-0.43 kg [-0.81; -0.06]_{95%CI}) was statistically significantly larger for NovoRapid®/NovoLog® than faster aspart. This small difference was not considered clinically relevant.

Pregnancies

- Two pregnancies were reported during the trial (1 faster aspart and 1 NovoRapid®/NovoLog®). No pregnancy complications were reported for either subject.

Infusion site reactions

- In total, 76 AEs in 45 subjects were identified as infusion site reactions, based on a preferred term search. The observed rate of infusion site reactions was numerically higher for faster aspart (60.5 events per 100 PYE) than for NovoRapid®/NovoLog® (44.6 events per 100 PYE), corresponding to an approximate rate difference of 0.16 infusion site reactions per patient year of exposure. The investigator judged 34 AEs in 22 subjects to be possibly or probably related to trial drug; 21 events (13 subjects) with faster aspart and 13 events (9 subjects) with NovoRapid®/NovoLog®.

Allergic reactions

- In total, 17 AEs in 17 subjects were identified as allergic reactions, based on a preferred term search. The event rate per 100 PYE was 13.7 with faster aspart and 9.8 with NovoRapid®/NovoLog®.
- Two (2) as allergic reactions lead to premature discontinuation of treatment in the faster aspart arm (*drug eruption and rash*).

Infusion set changes

- The mean number of changes of infusion sets per week was similar in both treatment groups; 2.55 with faster aspart and 2.49 with NovoRapid®/NovoLog®
- A similar rate of non-routine infusion set changes per 100 PYE was observed with faster aspart (697) and NovoRapid®/NovoLog® (668). A higher proportion of subjects with faster aspart (71.2%) than with NovoRapid®/NovoLog® (57.2%) reported non-routine changes.
- Changes in the category ‘*a perceived occlusion by the subject*’ were similar between faster aspart and NovoRapid®/NovoLog®
- Changes in the category ‘*infusion site reaction*’ were numerically higher for faster aspart
- A similar rate of changes in the category ‘*any problems related to the infusion set*’ was observed, however, in a higher proportion of subjects with faster aspart than with NovoRapid®/NovoLog®.

Unexplained hyperglycaemia

- The observed rate of unexplained hyperglycaemic episodes per 100 PYE was numerically higher with faster aspart (1629) than with NovoRapid®/NovoLog® (1476). The proportion of subjects reporting unexplained hyperglycaemia was similar in each arm.

CONCLUSIONS

- Faster aspart was demonstrated to be effective when administered via external continuous subcutaneous insulin infusion (CSII) as faster aspart was confirmed to be non-inferior to NovoRapid®/NovoLog® with regards to change from baseline in HbA_{1c}
 - The change from baseline in HbA_{1c} with faster aspart was statistically significantly smaller than with NovoRapid®/NovoLog®
- Faster aspart was confirmed to be superior to NovoRapid®/NovoLog® with regards to change from baseline in 1-hour PPG increment (meal test)
- Superiority of faster aspart versus NovoRapid®/NovoLog® could not be confirmed for change from baseline in HbA_{1c}. No confirmatory testing could be done for change from baseline in 1,5-anhydroglucitol or time spent in low IG (≤3.9 mmol/L)
- No statistically significant difference was seen in overall rate of severe or BG confirmed hypoglycaemic episodes, however:
 - A numerically higher rate of severe hypoglycaemic episodes was observed for faster aspart
 - The rate of severe or BG confirmed hypoglycaemic episodes during the first hour after starting a meal was statistically significantly higher for faster aspart
- A numerically higher rate of infusion site reactions was observed with faster aspart
- No other apparent safety issues were identified for faster aspart compared to NovoRapid®/NovoLog®

The trial was conducted in accordance with the Declaration of Helsinki Amended 2013 and ICH Good Clinical Practice (1996), including archiving of essential documents and 21 CFR 312.120.”

Reviewer Comment: Please refer to the intercenter consult previously provided by OHT-7 for the adult pump indication for Fiasp (NDA 208751/S-08) for detailed discussion about the device related clinical safety considerations.

Extrapolation strategy for pediatric pump indication

The sponsor has provided the following information about the extrapolation strategy for the pediatric pump indication (Module 1.6.3, NDA 208751 Faster-acting Insulin Aspart–Correspondence Regarding Meetings) meeting-correspondence, page 270-271/1342).

“Novo Nordisk proposes to extrapolate efficacy results from the adult pump trial in T1DM to pediatric T1DM based on the following:

- Efficacy data from a planned Phase 3b pump efficacy and safety trial in adult subjects with T1DM (NN1218-3854). This trial was reviewed by the Agency (submitted in Serial No. 0063) and is currently under revision based on the FDA’s Advice/Information Request (Reference ID 3746705)
- The completed single dose pump PK/PD study in adult subjects with T1DM (NN1218-3890, see synopsis provided in Appendix A)
- Efficacy data from a planned s.c. pediatric efficacy and safety trial in subjects with T1DM, NN1218-4101 (Section 9.1)

Novo Nordisk also proposes to leverage the safety and dosing information from trials NN1218- 3854 and 4101.

The planned Phase 3b pump trial NN1218-3854 is a 16-week multinational, multicenter, randomized, active-controlled, parallel, double blinded, efficacy and safety trial comparing external continuous subcutaneous infusion (CSII) of faster aspart and NovoLog® in 450 adult subjects with T1DM.

The single dose pump PK/PD trial in adults with T1DM (NN1218-3890) has characterized PK/PD properties of faster aspart during CSII. This will help to develop recommendations for physicians with regard to dosing in the CSII and setting of the pump parameters. With the CMC in vitro pump in-use stability data (to be available in the NDA) to support the stability in the infusion system with low dose infusion rates, in spite of smaller doses in children, Novo Nordisk does not expect any issues to arise in the pediatric pump users related to compatibility of faster aspart utilizing the same CSII systems as used in adults.

Assuming availability of efficacy and safety in the T1DM pediatric population from NN1218-4101 trial (Section 9.1) as well as pump compatibility, PK/PD and efficacy and safety data in the pump in the adult population with T1DM (NN1218-3854), Novo Nordisk considers that there will be sufficient data to justify faster aspart use in CSII system in pediatrics in the label. A further degree of assurance is provided by the frequent glucose monitoring and insulin dose adjustments in patients on the insulin pumps. Because of the growing importance of pump therapy in children, the proposed extrapolation of efficacy and leveraging of safety results will contribute to the early availability of faster aspart for pump use in pediatric population.

In addition, NovoLog® has been approved for use in CSII in the pediatric population since 2008 (NDA 20986/S-047). The two pediatric trials with use of the CSII systems (ANA-2181 n=298 children 4-18 years of age) and the supportive trial ANA-1507 (n=61, children < 7 years of age) submitted in S-047 showed that use of insulin aspart (NovoLog®) in CSII systems is safe and efficacious in pediatrics.

It is Novo Nordisk’s expectation that the Agency will determine the acceptability of the strategy to leverage adult pump data for the use of pumps in the pediatric population after review of the trial results from NN1218-3854, 3890 and 4101.”

Reviewer Comment: *The above information relating to the (from 2015) was taken into consideration during the clinical review for this intercenter consult request.*

DOCUMENTATION OF INTERACTIVE REVIEW

The following questions were sent through the sponsor through the Day 74 letter (April 22, 2019), and the following responses were received from the sponsor (May 28, 2019).

Introduction

Reference is made to NDA 208751 for Fiasp® (insulin aspart injection) approved on September 29, 2017. Reference is also made to the supplemental New Drug Application (sNDA) submitted on February 25, 2019 to support Continuous Subcutaneous Insulin Infusion (CSII) use in insulin pump for Fiasp in pediatric patients with diabetes mellitus and the Agency’s Information Request in the

Filing Communication letter dated April 22, 2019.

The FDA questions received on April 22, 2019 are provided below in italics, followed by the Novo Nordisk response.

1 FDA Question 1 – Occlusions

In the extrapolation strategy for the pediatric pump indication, you have proposed to extrapolate safety information, including catheter occlusions, from Trial 3854 in adult subjects with T1DM to support the pediatric pump indication. Catheter occlusion is a known important safety issue with respect to insulin pump use, which if undetected, and untreated, can lead to diabetic ketoacidosis (DKA), and complications of DKA.

From the information provided in this submission (NDA208751/S-011), it is unclear if pediatric occlusion rates during insulin pump use with Fiasp are anticipated to be comparable to adult occlusion rates during insulin pump use with Fiasp. Considering the relative vulnerability of the pediatric population with diabetes and the lower total daily insulin doses, additional information is required to effectively evaluate the risk-benefit profile of pediatric use of Fiasp in a pump. Please provide additional information separate from Trial 3854 for the proposed extrapolation from adult clinical pump use with Fiasp to support a pediatric pump indication with Fiasp, with respect to this important safety consideration (occlusions).

Information that may potentially help to support extrapolation from adults to pediatrics with respect to occlusions could include clinical trial data from other studies assessing the pediatric pump use, postmarket data from outside the US (OUS) where Fiasp may be approved in pumps for pediatric use, and clinical literature for pediatric pump use and occlusions in general. Additional rationale or justification may also be considered.

Novo Nordisk Response

To support the extrapolation of safety information from adults to pediatrics with respect to occlusions, Novo Nordisk has performed the following additional analyses from the adult pump trial 3854 (S-008) as presented in [Appendix 1](#). The analyses presented focus on subjects with low basal rates which is considered relevant for a pediatric population.

- 5 Non-routine infusion set changes due to perceived occlusion events by daily basal insulin dose at baseline-cumulative event plot
- 6 Non-routine infusion set changes by daily basal insulin dose at baseline-cumulative event plot
- 7 Non-routine infusion set changes due to any problems related to the infusion set by daily basal insulin dose at baseline-cumulative event plot
- 8 Daily basal insulin dose (actual) in units by treatment week
- 9 Infusion set changes - subjects having daily basal insulin dose (actual) < 15.29U at baseline

The cumulative number of non-routine infusion set changes due to perceived occlusion were similar between the faster aspart and NovoRapid®/ NovoLog® groups, with no trends towards the lower basal settings which are relevant for pediatric patients ([Figure 1, Appendix 1](#)).

The cumulative number of non-routine infusion set changes by daily basal insulin dose at baseline were similar between the faster aspart and NovoRapid®/ NovoLog® groups ([Figure 2, Appendix 1](#)).

Actual daily basal insulin dose in units by treatment week is provided in [Table 4, Appendix 1](#) and shows the doses remained stable and were similar between the faster aspart and NovoRapid®/ NovoLog® groups throughout the duration of the trial.

Subjects in the lower quartile for actual insulin daily basal dose (<15.29U), which are considered representative of pediatric dosing, had a lower rate of a non-routine infusion set change due to a perceived occlusion in the faster aspart group 123 events/100 PYE compared to the NovoRapid®/ NovoLog® group 217 events/100 PYE ([Table 5,](#)

Appendix 1). The cumulative number of non-routine infusion set changes due to any problems related to the infusion set by daily basal insulin dose at baseline were similar for the lower quartile (<15.29U) between the faster aspart and NovoRapid®/ NovoLog® groups, with no observable trend as daily basal insulin dose decreases (Figure 3, Appendix 1).

Furthermore, an *in-vitro* pump in-use compatibility and stability study which simulated infusion rates (both basal and bolus) expected in the pediatric population (as low as 8U per day with basal infusion rate of 0.3 U/hr) concluded that the flow rate of faster aspart through the pump system did not affect the formation of degradation products, as the level of degradation products at the needle end was comparable to the level in the reservoir. No occlusions of the infusion sets occurred. No obstruction or alarms of the pumps occurred while the pumps were running (Sequence 0000, 3.2.P.8.3 In-Vitro Pump In-use Stability Data).

Pediatric pump use was approved for NovoRapid®/ NovoLog® in the US under NDA 20986/S-047 on March 14, 2008. Trial ANA-2181, the confirmatory efficacy and safety trial to support the approval, was an open-label, parallel-group, multicenter study which included children and adolescents aged 4-18 years with diagnosed type 1 diabetes who were treated for 16 weeks with NovoRapid®/ NovoLog® CSII (n = 198) or insulin lispro CSII (n = 100).

In trial ANA-2181, occlusions were registered as part of 'Adverse Device Effects' and no imbalance was seen between the treatment groups (1 subject reporting an occlusion in the NovoRapid®/ NovoLog® group and 1 subject reporting an occlusion in the insulin lispro group).

A review of post marketing safety data since 2002 has shown the rate of perceived occlusions to be similar between adult and pediatric subjects using NovoRapid in a CSII setting with the rate in adults being 0.004 events/1000 PYE and 0.003 events /1000 PYE for pediatric subjects. As faster aspart is not yet approved in the pediatric population in any country, it's not possible to calculate corresponding rates for faster aspart. However, we have searched our global safety database for relevant cases in pediatric patients to identify any case reported with off-label use. As of 30 Apr 2019, we have cumulatively received 2 cases (1 serious case reporting "diabetic ketoacidosis" and 1 non-serious case reporting "hyperglycaemia") of faster aspart concerning occlusions in the pediatric population. Reported cases are reviewed on an ongoing basis as part of our routine surveillance and the available information from two cases do not warrant any safety concern regarding the risk of occlusions in the pediatric population.

No relevant literature was found with a clinical literature search for pediatric CSII use and occlusions.

Based on the totality of the data from trial 3854, NovoRapid®/ NovoLog® pediatric clinical trial experience in ANA-2181 and the many years of post-marketing experience of using NovoRapid®/ NovoLog® in CSII in adults and pediatric subjects, the pediatric occlusion rates with faster aspart in a CSII setting are expected to be comparable to adult occlusion rates with faster aspart in CSII. Furthermore, it is expected that the occlusion experience with faster aspart in CSII will be comparable to that of NovoRapid®/ NovoLog® in CSII in adult and pediatric subjects. Therefore, Novo Nordisk does not consider the use of faster aspart in CSII in pediatric subjects to present a safety risk with respect to perceived occlusions and these data can be extrapolated for use of faster aspart in a CSII setting in pediatric subjects, with no additional clinical study required.

Reviewer Comment:

The above information was requested, and provided by the sponsor interactively, relating to the potential for occlusion in Study 3854 study participants with low insulin flow rates, as the pediatric population would be expected to have overall lower flow rates (due to overall lower insulin requirements) compared to the adult population. A sub analysis of occlusion rates in those study subjects with low insulin flow rates (ie, low total daily insulin requirements) reported that those with low infusion rates experienced a comparable amount of occlusions, and

according to the additional analyses provided by the sponsor, there were no clear differences reported in occlusion rate in those with low infusion rates according to day of infusion set wear.

The sponsor's response (including additional analyses from Trial 3854) is, in my opinion, helpful information to extrapolate towards assessment of the potential for occlusion in the pediatric population.

Labeling

The following considerations relevant to labeling, relevant to clinical use of insulin pumps in the pediatric population, are raised in anticipation of further discussion during the labeling review:

- 1. As there was no clinical study specifically conducted to evaluate pump use of Fiasp in the pediatric population, the information in the labeling about clinical data relating to pediatric use of Fiasp should specify that clinical data about pump use was extrapolated from the adult study.*
- 2. Further internal discussion with CDER/DMEP and CDRH/OHT-3, as well as OCP would be helpful about any potential discrepancies between the minimum approved age of use of insulin pumps for home use and the requested minimum age of approval for Fiasp.*
- 3. My opinion is that the information in the drug label about the infusion set change duration and proposed reservoir change duration for use of Fiasp in adults applies to the pediatric population (for insulin pump use).*

DISCUSSION & CONCLUSION

I have reviewed the relevant information provided in this NDA supplement (NDA 208751/S-11) relating to the safety of Fiasp for clinical use in insulin infusion pumps in the pediatric population with diabetes mellitus. The discussed scope of this requested consult comprises a clinical review of device specific safety considerations, specifically considerations about pump programming parameters, as well as occlusion related information relating to use of Fiasp in insulin infusion pumps in the pediatric population (NDA 208751/S-11). The device related non-clinical review and evaluation is deferred to the appropriate reviewer and/or consult (from OHT-3/CDRH). I have made comments below regarding these elements to support the safety of Fiasp for use in insulin infusion pumps in the pediatric population.

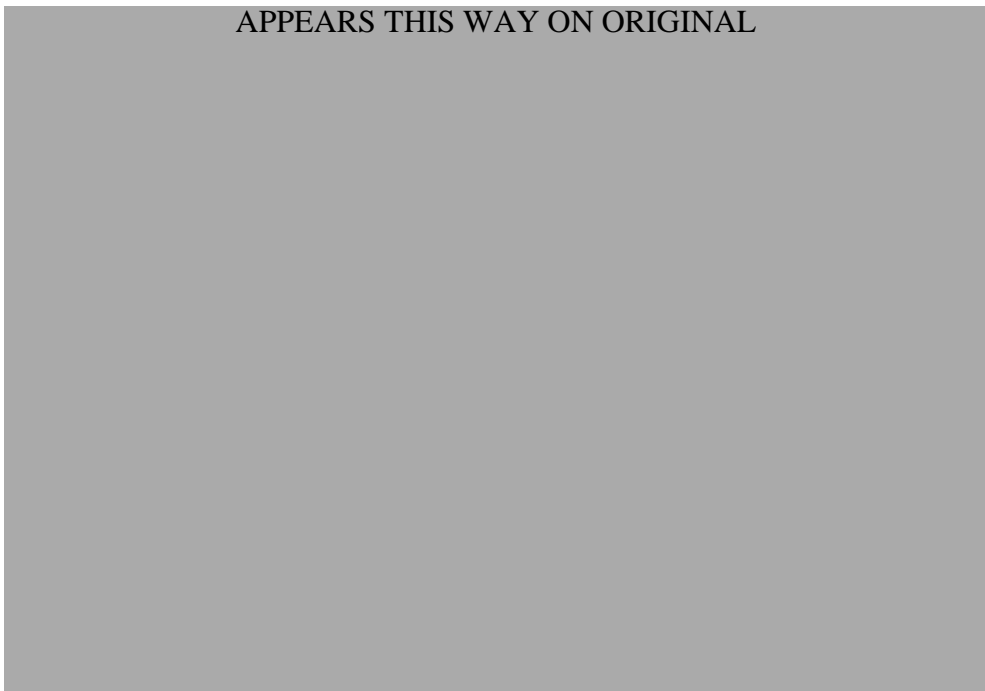
The sponsor has not conducted a clinical study evaluating the use of Fiasp in the pediatric population, but rather, proposes to extrapolate data from Trial 3854 to provide clinical support of safety and effectiveness for this NDA supplement (NDA 208751/S-11).

Based on the review and considerations discussed above, my opinion is that the information provided by the sponsor for this submission, supports that the safety of clinical use for these device specific safety elements of Fiasp in insulin infusion pumps in the pediatric population is comparable to the clinical use of Novolog (and Novorapid).

As discussed in detail in the CDRH/OHT7 consult for NDA 208751/S-11,

“Although in Trial 3854 there were several adverse events imbalances unfavorable to Fiasp relating to safety measures including unexplained hyperglycemia, severe hypoglycemia, non-routine infusion set changes, there is no indication that these imbalances relate specifically to pump programming parameters, and further, considering the reported magnitude and frequency, do not seem to be clinically meaningful.

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As for safety considerations relating to pump parameter programming, the sponsor provided analyses for the overall study population, as well as for a well controlled (baseline HbA1c level < 7.2%) subset of the population. Although there was a trend towards an increase in the daily total basal insulin requirement at the end of the study compared to the beginning (particularly in a subset of patients), considering the reported magnitude, this finding may not be clinically meaningful. Further, the analyses provided by the sponsor on this topic demonstrated that the majority of subjects did not make clinically significant changes to their basal rates, or other insulin pump settings affecting bolus doses (including insulin sensitivity factor, insulin carbohydrate ratio, and active insulin time). Individualization of pump parameters, based on individual response to Fiasp should occur on initiation of Fiasp pump therapy, as is the case for patients starting on any new insulin when using pump therapy. The information provided by the sponsor relating to individual pump parameter setting changes in Fiasp compared to Novolog supports the safety of use of Fiasp in insulin pumps (in the adult population) with individualization of pump parameters with Fiasp, when considering the reported differences in pharmacokinetics and pharmacodynamics between Fiasp and Novolog. Considering known individual variability in response to dietary glucose loads, variability in meal content and amount, as well as individual clinical differences in diabetes management, the reported differences in Pk and Pd in Fiasp (compared to Novolog) for pump use appear to be generally comparable to the scope of potential interindividual variations possible in physiology and clinical factors affecting insulin action in pumps.

Additional CGM analyses provided by the sponsor (blinded CGM values were collected in half the study population at baseline, halfway through and at the end of the study) were generally supportive of the above safety findings of the study.

Additional requested analyses were conducted by infusion set age (day of infusion set wear), and indicated that the safety measures assessed were generally comparable, when assessed by day of infusion set wear, between Novolog (and Novorapid), and thus there do not appear to be additional questions relating to safety of use of Fiasp when used in an insulin pump, according to infusion site age. There does not appear to be clinically meaningful differences in Fiasp compared to Novolog by infusion set day of wear that could be related to potential differences in pharmacokinetics and pharmacodynamics of insulin between Days 1 to 3 of infusion set wear. There do not appear to be clinically meaningful differences in reported safety event rates with Fiasp compared to Novolog, according to infusion set wear duration.”

My opinion is that there should not be additional questions of safety that arise from insulin pump programming parameters in the pediatric population above and beyond that in the adult population, so it is reasonable to extrapolate safety data relating to insulin dosing from Trial 3854 (in the adult population) to the pediatric population.

Additional information was requested, and provided by the sponsor, relating to the potential for occlusion in the pediatric population. A sub analysis of occlusion rates in those study subjects with low insulin flow rates (ie, low total daily insulin requirements) reported that those with low infusion rates experienced a comparable amount of occlusions, and there was no clear differences in occlusion rate in those with low infusion rates according to day of infusion set wear. My opinion is that information about the infusion set change interval is extrapolatable from the clinical study data from the adult insulin pump clinical study (Trial 3854).

Further, as young children requiring insulin therapy (primarily Type 1 diabetes mellitus) generally tend to have lower insulin requirements compared to the adult population, there may be potential benefits associated with the much finer dose increments achievable with use of an insulin pump (compared with

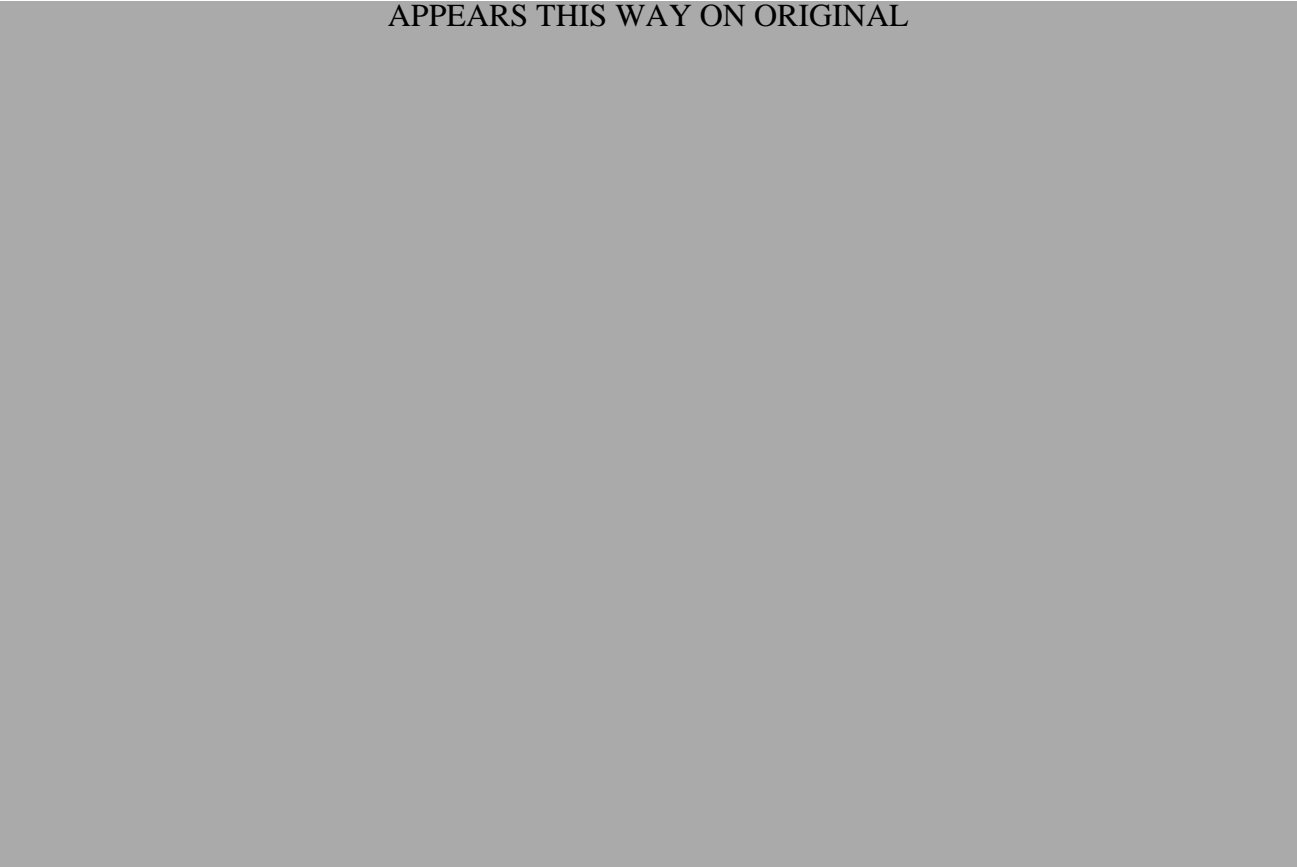
NDA 208751/S-8 Fiasp CSII Indication

insulin pen therapy), which would allow for more flexibility in insulin dosing and delivery in this patient population.

Based on my review and the considerations discussed above, my opinion is that Fiasp should receive Conditional Approval for use with insulin (CSII) pump(s) in the pediatric population, pending:

- i) Inclusion of Fiasp in labeling of at least one approved or cleared insulin pump by the time of NDA approval*
- ii) Agreement on labeling with CDER and Office of Combination Products (OCP)*

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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.

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