10 November 2016
EMA/CHMP/50360/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fiasp

International non-proprietary name: insulin aspart

Procedure No. EMEA/H/C/004046/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Fiasp
Applicant:	Novo Nordisk A/S Novo Alle 2880 Bagsvaerd DENMARK
Active substance:	INSULIN ASPART
International Non-proprietary Name/Common Name:	insulin aspart
Pharmaco-therapeutic group (ATC Code):	insulins and analogues, insulins and analogues for injection, fast-acting (A10AB05)
Therapeutic indication(s):	Treatment of diabetes mellitus in adults
Pharmaceutical form(s):	Solution for injection
Strength(s):	100 U/ml
Route(s) of administration:	Intravenous use, Subcutaneous use
Packaging:	cartridge (glass) (Penfill), pre-filled pen (glass) (FlexTouch) and vial (glass)
Package size(s):	10 cartridges, 5 cartridges, 1 pre-filled pen, 1 pre-filled pen + 7 NovoFine Plus needles, 1 pre-filled pen + 7 NovoFine needles, 1 pre-filled pen + 7 NovoTwist needles,), 5 pre-filled pens, 10 (2 x 5) pre-filled pens (multipack), 1 vial, 5 (5 x 1) vials (multipack) and 5 vials

Table of contents

List of abbreviations

$50\%GIR_{max}$	50% of maximum glucose infusion rate
1,5-AG	1,5-anhydroglucitol
ADA	American Diabetes Association
BG	blood glucose
BMI	body mass index
CGM	continuous glucose monitoring
CSII	continuous subcutaneous insulin infusion
Faster aspart	faster-acting insulin aspart (name used in some tables/figures for the Fiasp formulation)
FDA	Food and Drug Administration
FIA	previous abbreviation for Fiasp
FIA (R)	an earlier formulation of Fiasp not pursued for further clinical development
FPG	fasting plasma glucose
GIR	glucose infusion rate
HbA1c	glycosylated haemoglobin A1c
HDL	high-density lipoprotein
IDF	International Diabetes Federation
IG	interstitial glucose
i.m.	intramuscular
IV/WRS	Interactive Voice/Web Response Service
LDL	low-density lipoprotein
MACE	major adverse cardiovascular event
NPH	Neutral Protamine Hagedorn
OAD	oral antidiabetic drug
PG	plasma glucose
PP	per protocol
PPG	postprandial glucose
PRO	patient-reported outcome
PYE	patient years of exposure
s.c.	subcutaneous
SF-36v2	Short-Form 36 Health Survey version 2
SMPG	self-measured plasma glucose
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TRIM-D	treatment related impact measure – diabetes

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novo Nordisk A/S submitted on 4 December 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Fiasp, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: Treatment of diabetes mellitus in adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that insulin aspart was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

As Fiasp shares the same qualitative and quantitative composition in terms of active substance and the same pharmaceutical form as NovoRapid authorised to the same MAH on 7 September 1999, the assessment of the current application includes an assessment of the applicant's claim of significant differences in safety or efficacy versus NovoRapid due to difference in excipients. This is in line with the provision in the *EC note on Handling of Duplicate Marketing Authorisation Applications Ares(2011)1044649*, that a medicinal product containing different excipients resulting in significant differences regarding safety or efficacy would fall outside the scope of Article 82(1) of Reg 726/2004.

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 22 September 2011, 14 May 2013 and 17 October 2013. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Karsten Bruins Slot

CHMP Peer reviewer(s): Piotr Fiedor

- The application was received by the EMA on 4 December 2015.
- The procedure started on 31 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 21 March 2016 . The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 March 2016 . The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 4 April 2014 .
- During the meeting on 28 April 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 28 April 2016 .
- The applicant submitted the responses to the CHMP consolidated List of Questions on 1 July 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 24 August 2016 .
- During the PRAC meeting on 2 September 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP .
- During the CHMP meeting on 15 September 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 10 October 2016.
- During the meeting on 7-10 November 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Fiasp on 10 November 2016.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Chronic hyperglycaemia defines diabetes, and glycaemic control is fundamental to diabetes management. Improvement in long-term glucose control has been demonstrated to reduce the incidence and progression of complications in people with type 1 (T1DM) or type 2 diabetes mellitus (T2DM). Both fasting glycaemia and glycaemic excursions occurring after meals contribute to overall glycaemic burden, a major contributor to the microvascular and macrovascular complications of diabetes. According to the 2011 International Diabetes Federation (IDF) guideline for management of post-meal glucose in diabetes, hyperglycaemia after meals is associated with an increased risk of micro- and macrovascular complications and should be addressed as part of the diabetes treatment regimen.

2.1.2. Clinical presentation and diagnosis

Control of glycaemic excursions after meals contributes to lowering the glycosylated haemoglobin (HbA_{1c}) level. As HbA_{1c} decreases, the relative contribution of post-meal glucose control on HbA_{1c} levels increases. Thus, in order to achieve recommended HbA_{1c} targets (<7%), it is important to address post-meal hyperglycaemia in addition to fasting hyperglycaemia, and control of post-meal glucose excursions has received recognition as a therapeutic target for optimising glycaemic control in people with diabetes.

2.1.3. Management

A variety of pharmacological therapies can be considered to target post-meal glycaemic control, including many novel agents such as incretin-based therapies and SGLT-2 inhibitors. Still, for individuals with T1DM and for many with T2DM, rapid-acting insulin before meals is the only, or the most appropriate, means of achieving post-meal and overall glucose control.

Insulin, including mealtime insulin (i.e., short acting insulins and rapid-acting insulin analogues), is the most potent of all available therapies for diabetes. However, insulin is also one of the more challenging treatment options to utilise appropriately in clinical practice as it requires significant individualisation. Despite major advances in the development of rapid-acting insulin analogues that are absorbed more quickly than regular/soluble human insulin, currently available mealtime insulins are not able to completely control the rapid rise in glucose levels following a meal. An insulin product with a faster onset of action could potentially be of benefit via faster lowering of post-meal glucose concentrations, thereby improving postprandial glucose (PPG) control.

Dosing before the meal in order to maximise the efficacy of the currently available rapid-acting insulin analogues is not always the most optimal time of dosing as seen from the patient's perspective. Many patients with diabetes fear insulin-induced hypoglycaemia and since a delay in actual meal consumption or an unexpected change in meal size or composition may result in hypoglycaemia if insulin has already been injected pre-meal, patients might wait until they have eaten before injecting so they know exactly what and how much they have eaten. A more rapidly absorbed insulin would be likely to offer increased convenience and less concern about

hypoglycaemia for individuals with diabetes by allowing injection at the start of a meal and with the possibility to inject post-meal if necessary, without jeopardising overall glycaemic control. Importantly, mealtime insulin with an earlier glucose-lowering effect, may also offer particular advantages to patients treated with continuous subcutaneous insulin infusion (CSII) by external pump, as reduced lag-time between the s.c. insulin infusion and the glucose-lowering effect should enable better adjustment of bolus and basal rates according to individual need and lead to improved glycaemic control.

About the product

Fiasp is insulin aspart in a new formulation. Insulin aspart, with the global trade name NovoRapid, has been on the market worldwide for more than a decade for the treatment of diabetes mellitus. Compared to NovoRapid, Fiasp contains two additional excipients: nicotinamide (also known as niacinamide or vitamin B3) and L-arginine hydrochloride (an amino acid). The addition of nicotinamide is intended to result in a faster initial absorption of insulin aspart following subcutaneous (s.c.) injection. The addition of L-arginine hydrochloride should support stabilisation of the Fiasp formulation. The insulin aspart molecule in Fiasp and NovoRapid is identical and therefore, once systemically absorbed, it has the same biological action at the insulin receptor as that of NovoRapid.

Fiasp is intended to be used for the treatment of patients with diabetes mellitus (T1DM and T2DM) both for basal-bolus therapy in combination with intermediate- or long-acting basal insulin (± oral antidiabetic drugs; OADs), and for CSII by external pump, where both basal and bolus requirements can be covered by Fiasp. Fiasp can be injected at the start of a meal or postmeal (within 20 minutes after starting a meal). Moreover, Fiasp can also be delivered intravenously by health care professionals when the clinical situation requires this route of administration.

The indication sought is: "*Treatment of diabetes mellitus in adults*".

Type of Application and aspects on development

This application concerns a centralised procedure application submitted under Article 8(3) of Directive 2001/83/EC, known active substance.

The clinical development programme includes three therapeutic confirmatory trials evaluating efficacy and safety of Fiasp in subjects with T1DM and T2DM and two CSII (continuous subcutaneous insulin infusion) trials. In addition, nine clinical pharmacology trials evaluating the pharmacokinetic and pharmacodynamic properties of Fiasp in various settings have been performed.

More than 2500 subjects with T1DM or T2DM were included in the clinical development programme overall, including 2068 randomised subjects in the 3 therapeutic confirmatory trials, 80 randomised subjects in the CSII trials as well as 395 randomised subjects in the clinical pharmacology trials.

Table 1 Overview of previous CHMP Scientific Advice in the proposed indication or same product class

SA procedure No. including year	Product	Applicant	Indication

SA procedure No. including year	Product	Applicant	Indication
EMEA/H/SA/2136/1/2011/III	Insulin aspart (NN1218 (FIAsp - Faster-acting Insulin aspart))	Novo Nordisk	T1DM and T2DM in adults, adolescents and children older than 2 years of age
EMEA/H/SA/2136/1/FU/1/2013/III	Insulin aspart (NN1218 (FIAsp - Faster-acting Insulin aspart))	Novo Nordisk	T1DM and T2DM in adults, adolescents and children older than 2 years of age

SA was provided on Quality, Non-Clinical and Clinical aspects of the development programme. BWP, SWP and PDCO were involved.

The key topics of the 2011 SA concerned:

- adequacy of non-clinical data to support safety of new excipients (L-arginine hydrochloride, nicotinamide and trometamol)
- adequacy of clinical pharmacology investigations and phase 3 non inferiority (NI) studies
- clinical endpoints to support post-prandial dosing regimen
- Antibody measurements and immunogenicity data
- Inclusion of elderly (age ≥ 65 years) AND very elderly (age≥ 75 years) in the therapeutic confirmatory studies
- compatibility of Fiasp dosage administration to different insulin infusion pumps

The 2013 SA focused mainly on the paediatric development; non-clinical data for L-arginine and nicotinamide as excipients and monitoring of formation of the arginine-insulin impurity.

The advices given have in all essential parts been followed.

The development program is in general well in line with current guidelines, including the EMA guidance ("Guideline on the clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus", CHMP/EWP/1080/00 Rev.1).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a solution for injection containing 100 units/mL of insulin aspart as active substance.

Other ingredients are Phenol, Metacresol, Glycerol, Zinc acetate, Disodium phosphate dihydrate, Arginine hydrochloride, Nicotinamide (vitamin B3), Hydrochloric acid (for pH adjustment), Sodium hydroxide (for pH adjustment) and Water for injections.

The product consists of three different presentations: solution for injection in pre-filled pen; solution for injection in cartridge and solution for injection in vial. The cartridge consists of type 1 glass, closed with a plunger (halobutyl) and a stopper (halobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene, polyoxymethylene, polycarbonate and acrylonitrile butadiene styrene. The vial consists of type 1 glass closed with a halobutyl/polyisoprene rubber disc and a protective plastic cap in order to obtain a tamper-proof container.

Compared to the licensed product NovoRapid, which contains the identical active substance insulin aspart, two additional excipients nicotinamide (also known as niacinamide or vitamin B3) and L-arginine hydrochloride (an amino acid) are added.

2.2.2. Active Substance

The active substance included in this MAA is identical to insulin aspart as submitted and approved for NovoRapid, NovoMix and Ryzodeg.

General information

The INN name of the active substance is insulin aspart and the molecule has a molecular formula as follows $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5826 g/mole.

Insulin aspart is an analogue of human insulin where the amino acid proline has been replaced with aspartic acid in position B28 of the insulin β-chain. The lines represent the inter-chain disulphide bonds connecting the A and B-chain, and the intra-chain disulphide bond in the A-chain. Insulin aspart is produced using recombinant DNA technology in yeast (Saccharomyces cerevisiae). The amino acid sequence of insulin aspart is depicted in Figure 1.

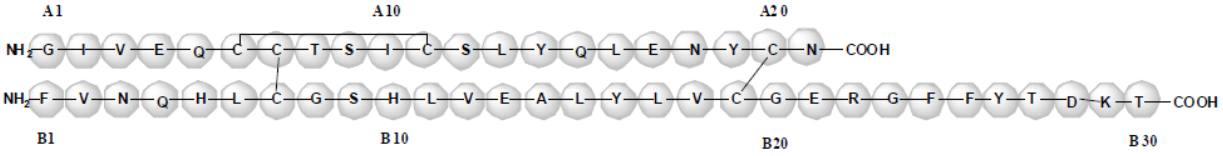


Figure 1 amino acid sequence of insulin aspart

Manufacture, characterisation and process controls

Insulin aspart is manufactured at Novo Nordisk A/S, Hallas Alle, 4400 Kalundborg, Denmark.The insulin aspart manufacturing process has been adequately described. Main steps are fermentation, recovery and purification.

The insulin aspart drug substance manufacturing process includes fermentation of yeast cells and recovery of insulin aspart precursor. The purification consists of the conversion of insulin aspart precursor followed by several purification steps to reach insulin aspart. Insulin aspart is stored at long term storage conditions.

Overall the control of source and starting materials is considered adequate. The construction of the expression plasmid, the source and history of S. cerevisiae strain and the generation of the S. cerevisiae strain producing insulin aspart precursor is described in sufficient detail. Description of preparation and testing of Master Cell Bank, Working Cell Bank and end of production cells are provided.

In general the fermentation, recovery, purification and storage have been described in sufficient details and are controlled by appropriate in-process controls and acceptance criteria of intermediate products.

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials have been presented. No human or animal derived materials are used in the active substance manufacturing process. No animal derived starting materials are used in the manufacture of Insulin Aspart, however, one raw material is used, for which animal derived raw materials were used for manufacture. Acceptable documents have been provided.

Control of critical steps

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the insulin aspart active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regards to critical, as well as non-critical operational parameters and in-process controls.

Process validation

Process validation of the manufacturing process for the fermentation, recovery and purification of insulin aspart was successfully carried out.

Consistency in production has been shown on full scale commercial batches. All acceptance criteria for the operational parameters and likewise acceptance criteria for the in-process controls are fulfilled demonstrating that the purification process consistently produces insulin aspart active substance of reproducible quality that complies with the predetermined specifications and in-process acceptance criteria.

Characterisation

Insulin aspart active substance has been sufficiently characterised by physico-chemical and biological state-of-the-art methods revealing that the active substance has the expected structure of insulin aspart. The analytical results are consistent with the proposed structure.

The insulin aspart active substance is tested by a range of physicochemical tests (identity, purity, assay and microbial content) to assure consistency in the production of the active substance.

All tests listed in the specification are specified in the Ph.Eur monograph for insulin aspart except for one method, which has been sufficiently described and validated.

The results from the all insulin aspart active substance batches used in the production of Fiasp finished product batches have been presented and meet the acceptance criteria according to the active substance specification. This shows that the insulin aspart manufacturing process is capable of consistently producing insulin aspart to the required quality.

Insulin aspart primary reference material (PRM) and secondary reference material (SRM) are used. PRM serves as reference for identification and determination of the insulin aspart content in insulin aspart SRM. The insulin aspart PRM is traceable to USP and Ph. Eur. insulin aspart current Chemical Reference Standard (CRS). SRM is used for analytical purposes as working reference for homogeneity, identification and as a calibrator for determination (assay) of insulin aspart content in insulin aspart active substance and finished product.

Stability

Stability data of production scale insulin aspart active substance batches are provided. All the stability results of insulin were within the specification limits. Supplementary stability data (long term and accelerated) are also provided. The proposed shelf life is acceptable.

Comparability exercise for Active Substance

Not applicable.

2.2.3. Finished Medicinal Product

The finished product intended for the market, Fiasp 100 U/ml, is a clear and colourless solution containing the active substance insulin aspart.

Fiasp 100 U/ml is intended for the market in three presentations:

- Fiasp 100 U/ml, Vial 10 ml
- Fiasp 100 U/ml, Cartridge (Penfill 3 ml)
- Fiasp 100 U/ml, Pre-filled pen (FlexTouch)

Description of the product and pharmaceutical development

Fiasp 100 U/ml is a clear, colourless solution. The solution is filled in a 3 ml cartridge or in a 10 ml vial. The 3 ml cartridge can be assembled into a pre-filled disposable peninjector.

The finished product contains 100 U/ml insulin aspart and the following excipients phenol and metacresol, glycerol, zinc (as zinc acetate), disodium phosphate dihydrate, arginine (as L-arginine HCl), nicotinamide, hydrochloric acid and sodium hydroxide and water for injections.

Compared to NovoRapid, two additional excipients nicotinamide (also known as niacinamide or vitamin B3) and L-arginine hydrochloride (an amino acid) are added. Both excipients are well-known and included in the European, US and Japanese pharmacopoeias .

All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation.

The intended commercial formulation is the same as that used during clinical studies.

Fiasp is presented in the container closure systems (1) 10 ml glass vials (primary packaging), (2) 3 ml cartridge (Penfill) for use as primary packaging in Novo Nordisk durable device such as NovoPen4 or NovoPen Echo, not supplied with the finished product and (3) a combination product consisting of a 3 ml cartridge (primary packaging) assembled in a prefilled pen, FlexTouch.

The vial (type 1 glass) is closed with a halobutyl/polyisoprene rubber disc and a protective plastic cap in order to obtain a tamper-proof container.

The cartridge (type 1 glass) contains a plunger (halobutyl) at the one end of the cartridge and a stopper (halobutyl/polyisoprene) at the opposite end.

The combination pack (3) contains a FlexTouch, which is a prefilled multidose delivery device. The device contains the finished product solution in a sealed 3 ml cartridge. The FlexTouch has a dose range of 1U to 80U with dose increments of 1U.

The device, prefilled FlexTouch, is covered by a certificate of approval , which has been included in the MAA dossier. The technical documentation for FlexTouch has been validated by Lloyd's Register Quality Assurance Limited (LRQA) to be in compliance with Annex 1 of Directive 93/42 EEC.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Fiasp at a 100U/ml is produced at Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark

Fiasp finished product is a clear solution of insulin aspart and is prepared by mixing an acidic insulin solution with a slightly alkaline excipients solution. The pH of the finished product is approx. 7.1

Fiasp is intended for subcutaneous injections and must be sterile.

The finished product formulation of Fiasp tested in phase 3 clinical trials is identical to the formulation of the product to be marketed. The manufacturing process of Fiasp of products for the clinical trials is identical to the manufacturing process for the product to be marketed.

The robustness of the final manufacturing process has been verified during process justification and the reproducibility has been demonstrated by manufacture of consecutive process performance qualification batches in 3 ml cartridges and 10 ml vials. The available data confirms the comparability between the process used to manufacture clinical phase material and the commercial process .

the proposed specifications are considered clinically qualified, and therefore accepted.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch analysis data of the active substance were provided. The results are within specifications and confirm consistency of the manufacturing process.

Reference material

The same reference material as described under active substance is used.

Stability of the product

The proposed shelf-life for vials, cartridges and pen-injectors is 30 months at 2°C - 8°C (in a refrigerator). The proposed in-use shelf life for vials, cartridges and pen-injectors is 28 days below 30°C. The cap on the pen should be kept on to protect from light.

Stability studies were performed in 3 mL cartridges and 10 mL vials. The containers used in the stability studies were identical to the ones intended for the market active substance manufactured at production scale.

All results comply with the proposed finished product shelf life specifications. Minor changes are observed for some well known impurities however these are not considered to impact the quality, safety and efficacy of the final product.

In-use stability studies have been performed for primary stability batches of both cartridges and vials at 30°C ± 2°C for 28 days.

In-use stability studies have been performed for primary stability batches, at 37°C ± 2°C for 9 days for pump in-use

The preservative efficacy of the finished product in the pump reservoir was evaluated using a modified Ph. Eur. Preservative Efficacy Test at conditions relevant for pump in-use. Finished product with levels of phenol and metacresol corresponding to the levels observed in the reservoir during the pump in-use studies was challenged with relevant microorganisms. The count of colony forming units of microbial test organisms fulfilled the acceptance criteria given in the Ph. Eur. (criteria B).

The compositions of Fiasp in 10 ml vial and 3 ml cartridge are identical. The available real-time stability data for finished product in 10 ml vial support a comparable stability profile with similar trends and similar levels as the available real-time stability data for 3 ml cartridge. The stability results from cartridges are comparable to the results for the vials.

Based on the available stability data, the shelf life and storage conditions are acceptable as stated in the SmPC. The shelf-life for vials, cartridges and pen-injectors is 30 months at 2°C - 8°C (in a refrigerator). The in-use shelf life for vials, cartridges and pen-injectors is 28 days below 30°C. The cap on the pen should be kept on to protect from light.

The applicant is requested to submit any new data from the ongoing stability studies and report any data on out-of-specification or out-of-trend to the EMA.

Comparability exercise for finished medicinal drug product

Not applicable

Adventitious agents

Viral and TSE safety

The TSE and virus safety evaluation covers the complete manufacturing process for insulin aspart, from cell bank production, fermentation, animal derived raw materials, recovery through to purification.

During the manufacturing process no primary animal derived raw material and only two secondary animal derived raw materials are used . The animal derived raw materials have been evaluated with regard to TSE and virus safety based on the source of the materials as well as on their production processes.

Insulin aspart is concluded to be safe with regard to both virus and TSE agents.

Bacteria, fungi and mycoplasma

Insulin aspart is tested for bacteria and fungi during fermentation when infection control is performed as in-process test at each step (fernbach flask, seed fermenter and main fermenter). No growth of foreign organisms is accepted.

The active substance is tested at release for total viable count by plate count (USP, Ph. Eur.) and bacterial endotoxins by Limulus Amoebocyte Lysate (Ph. Eur. method D).

GMO

The finished product Fiasp does not contain a genetically modified organism, therefore this section is not applicable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

No major objections have been identified during the procedure. A limited number of other concerns on finished product have been identified which could be satisfactorily resolved by the Applicant during the procedure. No recommendations for future quality development have been identified.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral and TSE safety.

2.2.6. Recommendation(s) for future quality development

None

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

The nonclinical pharmacology studies conducted for insulin aspart as part of development of NovoRapid demonstrated, in both *in vivo* and *in vitro* studies, that insulin aspart behaved in a manner that closely resembled human insulin. Studies also demonstrated that the dissociation of binding to the insulin receptor of insulin aspart is equivalent to human insulin. No separate pharmacology studies have been conducted with Fiasp, but plasma glucose was measured as part of a PK/PD study in pigs and compared to NovoRapid.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been performed with Fiaspor NovoRapid/NovoLog; this was accepted by the CHMP.

Safety pharmacology programme

A comprehensive set of safety pharmacology studies have been conducted for insulin aspart as part of development of NovoRapid/NovoLog including assessment of the nervous system, the cardiovascular and respiratory system as well as the gastrointestinal and urinary system. Effects were comparable to those produced by the same dose of human insulin. No safety pharmacology studies have been performed with Fiasp since it is insulin aspart in a new formulation.

Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies were investigated for insulin aspart with hexobarbital and ethanol in the development of NovoRapid/NovoLog. No important interaction was seen with with hexobarbital and ethanol. No studies have been performed with Fiasp since it is insulin aspart in a new formulation; this was acceptable to the CHMP.

2.3.3. Pharmacokinetics

After absorption, the active substance insulin aspart behaves in the same way as with NovoRapid, and the pharmacokinetics program provided with this product covers most important aspects.

Pharmacokinetic (PK) and pharmacodynamic (PD) profiles after subcutaneous (s.c.) dosing of insulin aspart were studied in pigs using faster-acting insulin aspart (Fiasp) compared to NovoRapid.

Early absorption of insulin aspart was statistically significantly increased for Fiasp compared to NovoRapid. Consistent with the faster absorption of insulin aspart, a more rapid decrease in plasma glucose was observed. The time difference is in the span of 5-10 minutes.

The mechanism by which the increased early absorption is achieved for Fiasp has been investigated i*n vitro* and *in vivo. In vitro* data demonstrated that nicotinamide impacts the self-association of insulin aspart, promoting a greater proportion of a more highly permeable monomeric form of insulin aspart.

2.3.4. Toxicology

A full nonclinical safety programme was conducted for insulin aspart and has been assessed for registration of NovoRapid. Findings were predominantly related to the pharmacological action of insulin or exaggerated pharmacology of insulin and no findings of toxicological concern were observed.

For this application the following additional toxicology evaluation has been performed:

- local tolerance studies in rats, rabbits and pigs
- safety assessment of L-arginine and nicotinamide by literature review
- safety assessment of impurities

Local tolerance studies are discussed below.

No safety issues have been identified for nicotinamide or L-arginine. The daily exposure after dosing in highly insulin-resistant patient is >10-fold / 100-fold lower than what is acceptable for normal intake from food and dietary supplements.

A number of drug product impurities and leachables were identified. They were shown to be of no toxicological concern, either by demonstrating a high margin to a calculated PDE-value or by showing that levels are below the TTC of 1.5 µg/day.

Single dose toxicity

No specific studies have been conducted with Fiasp, as studies have been conducted with NovoRapid/NovoLog.

Single subcutaneous and intravenous injections of insulin aspart were well tolerated by rodents (mice and rats) and dogs. Only few animals showed signs of hypoglycaemia even at very high doses given systemically. Acute deaths in mice were considered to be due to hypoglycaemia.

Repeat dose toxicity

No specific studies have been conducted with Fiasp, as studies have been conducted with NovoRapid/NovoLog.

Repeated dose toxicity studies were performed in Sprague-Dawley rats and beagle dogs with subcutaneous administration of up to 52 weeks duration. In the pivotal 52-week study in dogs, daily dose levels of 0.5, 1, and 2 U/kg were given bid; another group of dogs was given 2 U/kg/day of HI. Despite careful management between food intake and treatment hypoglycaemic episodes occurred in high dose animals and the dose level was therefore reduced to 1 U/kg/day from week 29 onwards. No significant antibody titres were detected and the only toxicity findings observed were those related to hypoglycaemia.

In the two 52-week studies performed in Sprague-Dawley rats (T12 and T13), deaths occurred especially in high dose animals in both HI and IAsp treated animals. The cause of deaths was considered to be the result from hypoglycaemia despite food access ad libitum. The primary pharmacological effect of IAsp, i.e. p-glucose depression, appeared to be maintained throughout the treatment periods of up to 52 weeks. Fasted p-glucose appeared to increase over time in a dose-related manner. Antibody determination revealed significant

immunological response against insulin aspart as well as HI (only in the 52-week studies). The antibodies detected did not appear to neutralise the primary effect of insulin aspart or HI. Other findings in the study T12 were elevated p-triglyceride levels, increased incidence of focal seminiferous epithelial atrophy in high dose males, and increased incidence of subcutaneous masses in the mammary gland region.

A statistical analysis (time-to-tumour method according to Peto et al.; incidental/non-incidental classification) of the data coming from both non-survivals and survivals revealed statistically significant increase in the incidence of all mammary gland tumours combined (fibroadenoma, adenoma and adenocarcinoma) and benign mammary tumours alone in insulin aspart female rats dosed 200 U/kg/day (~ 100-200 times maximum clinical dose) in comparison with that of the control group. There were no statistically significant differences when the incidence of mammary tumours in the 200 U/kg/day group was compared with that in the HI reference group (p=0.062). In the T13 study (non-GLP) in female Spraque-Dawley rats, no significant differences in incidence of mammary tumours were reported between the controls and rats treated with 200 U/kg/day of insulin aspart. There were no statistically significant differences when the incidence of mammary tumours in the high dose group was compared with that in the HI reference group (p=0.52). A Peto analysis on the combined incidence of mammary tumours in high dose animals of the two 52- week studies in Sprague-Dawley (T-12 and T-13) indicated that the tumourigenicity of insulin aspart was not different from human insulin (p=0.29).

It was concluded that both HI and IAsp have the capability to produce mammary tumours in the Sprague-Dawley rat upon prolonged exposure at supraphysiological doses (approximately 100 times the human exposure). The relevance of results generated at such high doses/exposures as well as the ethics of conducting long-term studies at doses, which produce 50% mortality within one year, was questioned. Although the design of the 52-week studies with IAsp can be criticised, it was concluded that the results obtained in studies with a similar background incidence of benign and malignant mammary tumours did not indicate any significant or relevant difference in tumourigenic potential between insulin aspart and HI. The overall evidence from in vitro and in vivo data thus suggests that the mammary tumours observed are not relevant for the proposed therapeutic use of insulin aspart.

Genotoxicity

Studies have been conducted with NovoRapid/NovoLog. No specific studies have been conducted with Fiasp. The ability of insulin aspart to induce gene mutations in bacteria and mammalian cells and chromosomal aberrations in vitro and in vivo was investigated. Tests of primary DNA damage in vitro were also conducted. Insulin aspart showed no potential for mutagenicity or clastogenicity in the standard battery of genotoxicity tests in the presence and absence of rat liver S9 fraction.

Carcinogenicity

As stated in the ICH guideline S6, standard 2-year carcinogenicity bioassays are generally considered inappropriate for biotechnology-derived pharmaceuticals such as insulin aspart. The carcinogenic potential of insulin aspart (NovoRapid/NovoLog) was assessed based on two 52-week studies in rats. No specific studies have been performed with Fiasp.

Reproduction Toxicity

No specific studies have been conducted with Fiasp. This is acceptable as studies have been conducted with NovoRapid/NovoLog, where toxicity to reproduction was investigated with conventional designs in

Sprague-Dawley rats and rabbits following subcutaneous administration. Reference groups of animals treated with HI were included in all the three separate studies. In rats, insulin aspart had no direct effect on fertility or embryo-foetal development. Findings observed were secondary to treatment-induced hypoglycaemia and were similar to those observed with HI.

Toxicokinetic data

No toxicokinetic study was performed in the nonclinical development programme of Fiasp, and none were required by the CHMP.

Local Tolerance

Local tolerance studies in rats, rabbit and minipigs demonstrated no concern for local effects. Of most importance, the comparative study in rats showed that no difference in local tolerance was seen when comparing insulin aspart with NovoRapid.

2.3.5. Ecotoxicity / environmental risk assessment

Insulin aspart is a protein consisting of amino acids derived from a biological system and therefore expected to be readily biodegradable.

The use of faster-acting insulin aspart for treatment of diabetes is unlikely to result in significant risk to the environment.

2.3.6. Discussion on non-clinical aspects

The active substance, insulin aspart, is the active substance of the approved product NovoRapid. It is agreed that the nonclinical assessment of the current application for FIASP can be supported by the studies performed with Novorapid to a major extent.

For the current application, the Applicant has provided in addition data on PK-PD in pigs, demonstrating a more rapid absorption and glucose-lowering effect of faster-acting insulin aspart when compared to NovoRapid. The importance of this difference is discussed in the clinical section of the assessment report.

Local tolerance studies in rats, rabbits and minipigs showed no concern for local tolerability with this product.

Drug product related impurities and leachables have been addressed and shown to be of no toxicological concern.

No safety issues have been identified for the excipients nicotinamide or L-arginine. The daily exposure after dosing in highly insulin-resistant patient is >10-fold / 100-fold lower than what is acceptable for normal intake from food and dietary supplements.

2.3.7. Conclusion on the non-clinical aspects

Non clinical aspects have been sufficiently addressed.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2 Therapeutic confirmatory and exploratory trials with Fiasp

Trial ID	**Population**	**Treatment duration and regimen**	**Number of randomised subjects**	**Trial design**
Confirmatory efficacy and safety trials				
Trial 3852[a]	T1DM Adults	26 + 26 weeks Basal-bolus	Mealtime Fiasp: 381 Post-meal Fiasp: 382 NovoRapid: 380	A randomised (1:1:1), multicentre, multi-national, parallel-group trial evaluating efficacy and safety of Fiasp compared to NovoRapid both in a basal-bolus regimen with insulin detemir. The trial consisted of two double-blind Fiasp or NovoRapid mealtime dosing arms with 26 +26 weeks of treatment; and an open-label Fiasp post-meal arm with 26 weeks of treatment. The primary and secondary confirmatory endpoints were analysed after the initial 26-week treatment period. The additional 26-week treatment period was primarily for further collection of safety information.
Trial 3853	T2DM Adults	26 weeks Basal-bolus	Fiasp: 345 NovoRapid: 344	A randomised (1:1), double-blind, multicentre, multi-national, parallel-group trial evaluating efficacy and safety of mealtime Fiasp compared to mealtime NovoRapid , both in a basal-bolus regimen with insulin glargine and metformin.
Trial 4049	T2DM Adults	18 weeks Basal-bolus vs. basal	Fiasp + basal: 116 Basal: 120	A randomised (1:1), open-label, multicentre, multi-national, parallel-group trial evaluating efficacy and safety of mealtime Fiasp in a basal-bolus regimen with insulin glargine or NPH insulin or insulin detemir vs. basal insulin

Trial ID	Population	Treatment duration and regimen	Number of randomised subjects	Trial design
				therapy, both in combination with metformin.
CSII trials				
Trial 3931	T1DM Adults	6 weeks CSII by external pump	Fiasp: 25 NovoRapid: 12	A randomised (2:1), double-blind, multicentre, multi-national, parallel-group trial, evaluating pump compatibility and safety of Fiasp compared to NovoRapid when used for CSII by external pumps.
Trial 3930	T1DM Adults	3 x 2 weeks CSII by external pump	43	An exploratory, randomised, double-blind, 3x2weeks, crossover, single-centre trial assessing Fiasp, FIA(R)[b] and NovoRapid for CSII by external pumps.

[a] The application includes data from the initial 26-week treatment period. The additional 26-week treatment period was ongoing at the time of the cut-off date for the clinical trials (10 March 2015).

[b] In trial 3930, an earlier formulation of Fiasp (FIA(R)) was also evaluated. To keep the focus on the formulation of Fiasp intended for the market, efficacy data pertaining to the FIA(R) formulation is not included.

CSII: continuous subcutaneous insulin infusion. NPH: Neutral Protamine Hagedorn. T1DM: type 1 diabetes mellitus. T2DM: type 2 diabetes mellitus.

Table 3 Summary of clinical pharmacology trials

Trial ID	Trial Design	Randomised subjects	Trial Objectives	Treatment
3887	Randomised Double-blind Crossover	46 T1DM	PK and PD properties during euglycaemic clamp, including dose relationship, within-subject variability, relative bioavailability	Faster aspart: 0.1, 0.2, 0.4 U/kg (single dose) NovoRapid®: 0.1, 0.2, 0.4 U/kg (single dose)
3888	Randomised Double-blind Crossover	41 T1DM	PK and PD during meal test in children, adolescents and adults	Faster aspart: 0.2 U/kg (single dose) NovoRapid®: 0.2 U/kg (single dose)
3889	Randomised Double-blind Crossover	36 T1DM	PK and PD properties during meal test (at meal dosing)	Faster aspart: 0.2 U/kg (single dose) NovoRapid®: 0.2 U/kg (single dose)
3890	Randomised Double-blind Crossover	48 T1DM	PK and PD properties during euglycaemic clamp (CSII)	Faster aspart: 0.08 U/kg (priming dose), 0.02 U/kg/h (basal rate) and 0.15 U/kg (bolus dose) NovoRapid®: 0.08 U/kg (priming dose), 0.02 U/kg/h (basal rate) and 0.15 U/kg (bolus dose)
3891	Randomised Double-blind Crossover	67 T1DM	PK and PD properties during euglycaemic clamp in geriatric and younger adult subjects	Faster aspart: 0.2 U/kg (single dose) NovoRapid®: 0.2 U/kg(single dose)
3918	Randomised Double-blind Crossover	50 T1DM	PK and PD properties during euglycaemic clamp in Japanese subjects	Faster aspart: 0.2 U/kg (single dose) NovoRapid®: 0.2 U/kg (single dose)
3921	Randomised Open-label Crossover	33 T1DM	PK and PD properties during meal test (post-meal dosing)	Faster aspart: 0.2 U/kg (single dose 20 minutes after meal) NovoRapid®: 0.2 U/kg (single dose at meal)
3978	Randomised Double-blind Crossover	52 T1DM	PK and PD properties during euglycaemic clamp (single dose)	Faster aspart: 0.2 U/kg (single dose) FIA (R): 0.2 U/kg (single dose) NovoRapid®: 0.2 U/kg (single dose)
3949	Randomised Double-blind Crossover	22 Healthy	PK after s.c. administration at three different injection regions (abdomen, deltoid and thigh), and i.m. and i.v. administration	Faster aspart: 0.2 U/kg (single s.c. dose), 0.2 U/kg (single i.m. dose), 0.02 U/kg (single i.v. dose)

2.4.2. Pharmacokinetics

Faster-acting insulin aspart (Fiasp /Fiasp) is insulin aspart in a new formulation which contains two additional excipients compared to NovoRapid: addition of nicotinamide results in a faster initial absorption of insulin aspart following subcutaneous injection and addition of L-arginine hydrochloride supports the stabilisation in the Fiasp formulation.

The insulin aspart molecule in Fiasp and NovoRapid is identical and therefore, once systemically absorbed, the pharmacokinetic characteristics are assumed to be similar as that of NovoRapid. The characterisation of absorption and bioavailability of Fiasp comparing different administration routes and administration sites are

expected to be studied. The absorption rate and serum exposure of Fiasp in comparison with NovoRapid is also expected to be studied.

The clinical pharmacology programme included eight trials in subjects with type 1 diabetes mellitus (T1DM) and one trial in healthy subjects, all conducted with the final Fiasp formulation intended for the market .

Free insulin aspart was quantified by a specific sandwich enzyme-linked immunosorbent assay (ELISA) in human serum sampled over a period of 12 hours following administration of a single dose of Fiasp or NovoRapid. Blood sampling time, sampling frequency and sampling method were standardised across the clinical pharmacology trials.

In order to compare the pharmacokinetic properties of Fiasp and NovoRapid, the insulin aspart concentration-time profiles were characterised according to selected temporal components which describe the onset of exposure, early exposure, the late (tail) exposure and the total exposure and maximum concentration of insulin aspart (Table 9).

In addition to the reported pharmacokinetic results of all individual studies a pooled pharmacokinetic analyses was performed aimed at estimating one set of PK parameters corresponding to the dose (0.2 U/kg) administered to all subjects across trials and included all trials (3887, 3888, 3889, 3891, 3921, 3978) where white adult T1DM patients (18 to 64 years) were included and received a dose of 0.2 U/kg of Fiasp or NovoRapid administered in the abdomen.

Table 4 Overview of endpoints used to describe pharmacokinetic properties

Endpoint	Onset of insulin exposure	Early insulin exposure	Late insulin exposure	Total insulin exposure and maximum insulin concentration
Onset of appearance	✓			
Time to 50% C_{max}	✓			
$t_{max,IAsp,}$	✓			
$AUC_{IAsp,\ 0\text{-}15min,}$		✓		
$AUC_{IAsp,\ 0\text{-}30min}$		✓		
$AUC_{IAsp,\ 0\text{-}1hour}$		✓		
$AUC_{IAsp,\ 0\text{-}90min}$		✓		
$AUC_{IAsp,\ 0\text{-}2hour}$		✓		
Time to late 50% $C_{max,IAsp}$			✓	
$AUC_{IAsp,\ 2\text{-}12\ hours}$ [a]			✓	
$AUC_{IAsp,\ 0\text{-}12hours}$				✓
$C_{max,IAsp}$				✓

[a] In s.c trials $AUC_{IAsp,\ 2\text{-}12\ h}$ and in CSII trial 3890 $AUC_{IAsp,1\text{-}12h}$

In the therapeutic confirmatory trial 3852, pharmacokinetic samples were taken at 1 and 2 hours after the start of a standardised meal. A linear regression model was used for prediction of $AUC_{0\text{-}12}$.

Absorption

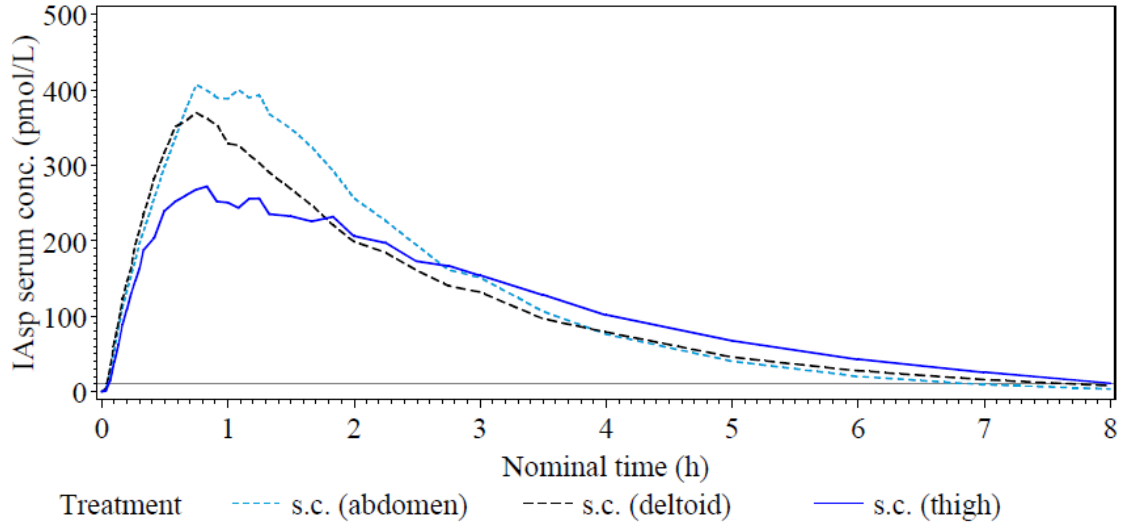
Study 3949 was conducted to evaluate the systemic extent of exposure of insulin aspart after administration of Fiasp in different injection regions and via different routes of administration. Fiasp was administered as a single dose subcutaneously (0.2 U/kg) in the abdomen, deltoid and thigh region, intramuscularly (0.2 U/kg) in the thigh, and intravenously (0.02 U/kg), on five different dosing visits in healthy subjects.

The absolute bioavailability of insulin aspart was approximately 80% after subcutaneous administration of Fiasp in the abdomen, deltoid and thigh and approximately 60 % after intramuscular injection.

Total exposure ($AUC_{IAsp,\ 0\text{-}12h}$) was comparable for Fiasp administered subcutaneously in the abdomen, the deltoid and the thigh (Figure 4). Maximum insulin aspart concentration ($C_{max,IAsp}$) was approximately 30 % lower following subcutaneous injection in the thigh compared to the abdomen.

Also the early insulin exposure ($AUC_{IAsp,0\text{-}1h}$ and $AUC_{IAsp,0\text{-}2h}$) was lower following subcutaneous injection in the thigh compared to the abdomen and the deltoid region.

Onset of exposure was assessed using the endpoints: onset of appearance, time to 50% $C_{max,IAsp}$ and $t_{max,IAsp}$. Median onset of appearance was around 3 minutes and median $t_{max,IAsp}$ was 50.0-57.5 minutes for Fiasp across the abdomen, deltoid and the thigh regions.



Horizontal grey line at 10 pmol/L indicates the LLOQ

Figure 2 Mean serum insulin aspart profiles (0-8 h) following subcutaneous administration of Fiasp in the abdomen, deltoid and thigh in healthy subjects in trial 3949.

Pooled pharmacokinetic analysis and individual trial results of Studies 3887, 3888, 3889, 3891, 3921 and 3978.

The pooled pharmacokinetic analysis included all six trials in which White adult subjects (18 to 64 years) with T1DM were included and received a single-dose of 0.2 U/kg of Fiasp or NovoRapid administered in the abdomen.

The total insulin exposure ($AUC_{IAsp,\ 0\text{-}12hours}$) and the maximum insulin concentration ($C_{max,IAsp}$) were comparable between Fiasp and NovoRapid, both in the individual trials and in the pooled analysis (Figure 5).

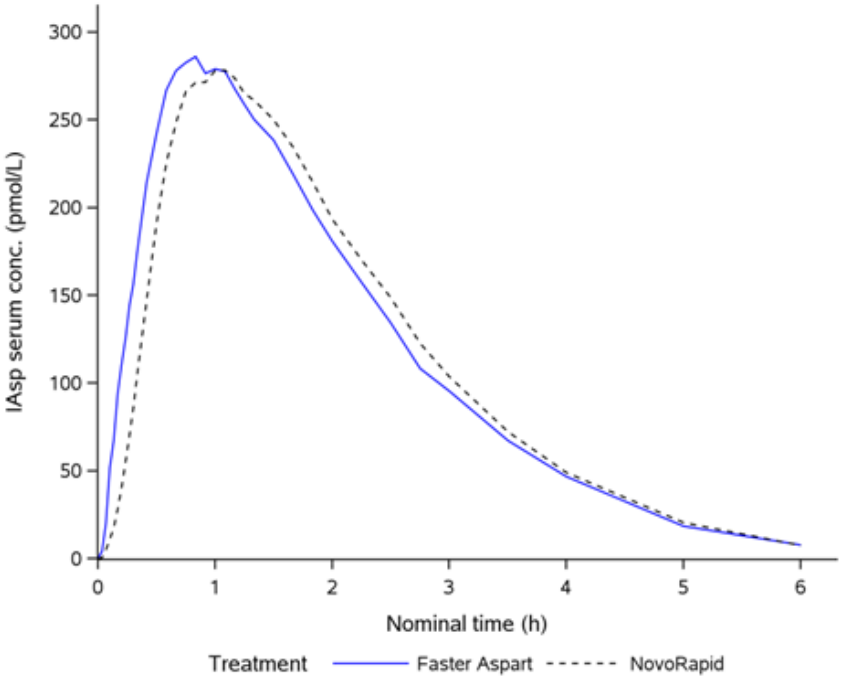


Figure 3 Mean insulin aspart profiles (0-6 hours) for adults with T1DM in the pooled analysis (0.2 U/kg, trials 3887, 3888, 3889, 3891, 3921 and 3978)

A consistent pattern was seen across all trials, with Fiasp resulting in a faster onset of appearance and earlier time to 50% $C_{max,IAsp}$ and $t_{max,IAsp}$ than NovoRapid (Figure 6). In the PK pool (trials 3887, 3888, 3889, 3891, 3921 and 3978), the mean onset of appearance was twice as fast with Fiasp (4.1 minutes) as with NovoRapid (8.9 minutes) and the time to 50% $C_{max,IAsp}$ was approximately 9.5 minutes earlier with Fiasp compared to NovoRapid.

Time to maximum insulin concentration (t_{max}) was between 54.2 and 67.9 minutes in the individual trials with Fiasp and between 59.1 and 75.0 in the individual trials with NovoRapid. In the PK pool, $t_{max,IAsp}$ was 62.4 minutes with Fiasp and 69.8 minutes with NovoRapid and the difference of 7.3 minutes was statistically significant.

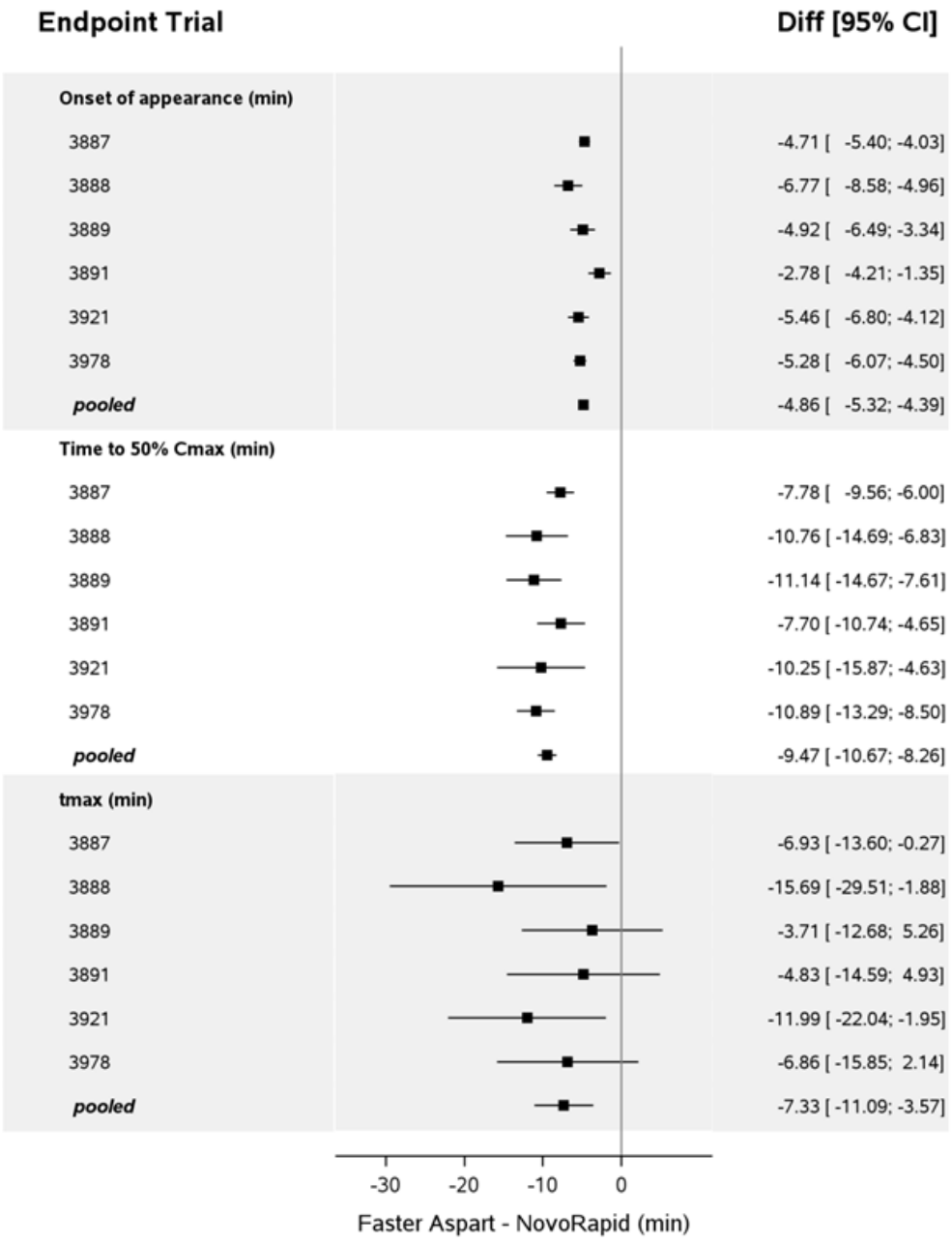


Figure 4 Mean treatment difference and 95 % CI for onset of insulin exposure in adults with T1DM in individual trials and in the pooled analysis (0.2 U/kg, trials 3887, 3888, 3889, 3891, 3921 and 3978).

Early insulin exposure has also been evaluated and the partial AUCs covering the first 90 minutes were consistently statistically significantly larger with Fiasp than NovoRapid in the individual trials (Figure 7). The largest differences were seen during the first 15 minutes, where the ratio ranged from 2.51 to 5.66. A similar pattern was seen in the PK pool where the difference was also statistically significant for the first two hours ($AUC_{IAsp,\ 0\text{-}2hour}$). The estimated treatment ratio for $AUC_{IAsp,\ 0\text{-}30min}$ was between 1.67 and 2.47 in the individual trials, and was 2.01 in the PK pool, showing that twice as much insulin was available during the first 30 minutes after administration with Fiasp than with NovoRapid.

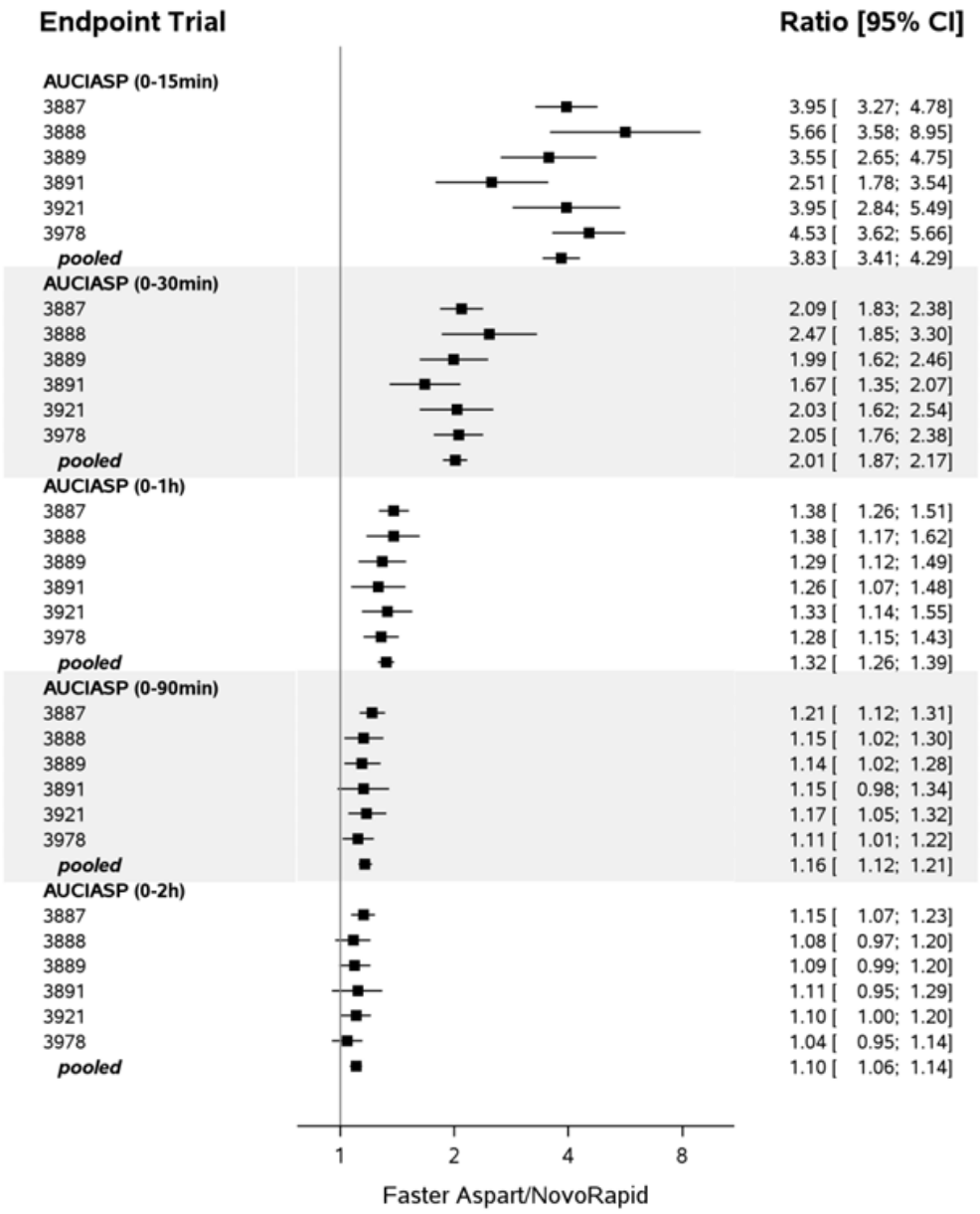


Figure 5 Mean treatment ratios and 95%CI for insulin aspart exposure (AUC_{IAsp}) in adults with T1DM in individual trials and in the pooled analysis (0.2 U/kg, trials 3887, 3888, 3889, 3891, 3921 and 3978)

Late insulin exposure and the duration of exposure was assessed using the estimated time taken for the serum insulin aspart concentration to fall to 50% of the maximum in the later part of the concentration-time curve (time to late 50% $C_{max,IAsp}$) and the area under the later part of the insulin aspart concentration-time curve ($AUC_{IAsp,\ 2\text{-}12\ hours}$). The pooled analyses supported the left shift of the whole pharmacokinetic profile of Fiasp compared to that of NovoRapid, including the tail. The estimated time to late 50% $C_{max,IAsp}$ was approximately 12 minutes shorter with Fiasp than with NovoRapid. Exposure during the later part of the pharmacokinetic profile ($AUC_{IAsp,\ 2\text{-}12\ hours}$) of Fiasp was approximately 11% lower than with NovoRapid. Thus, Fiasp has ~10%

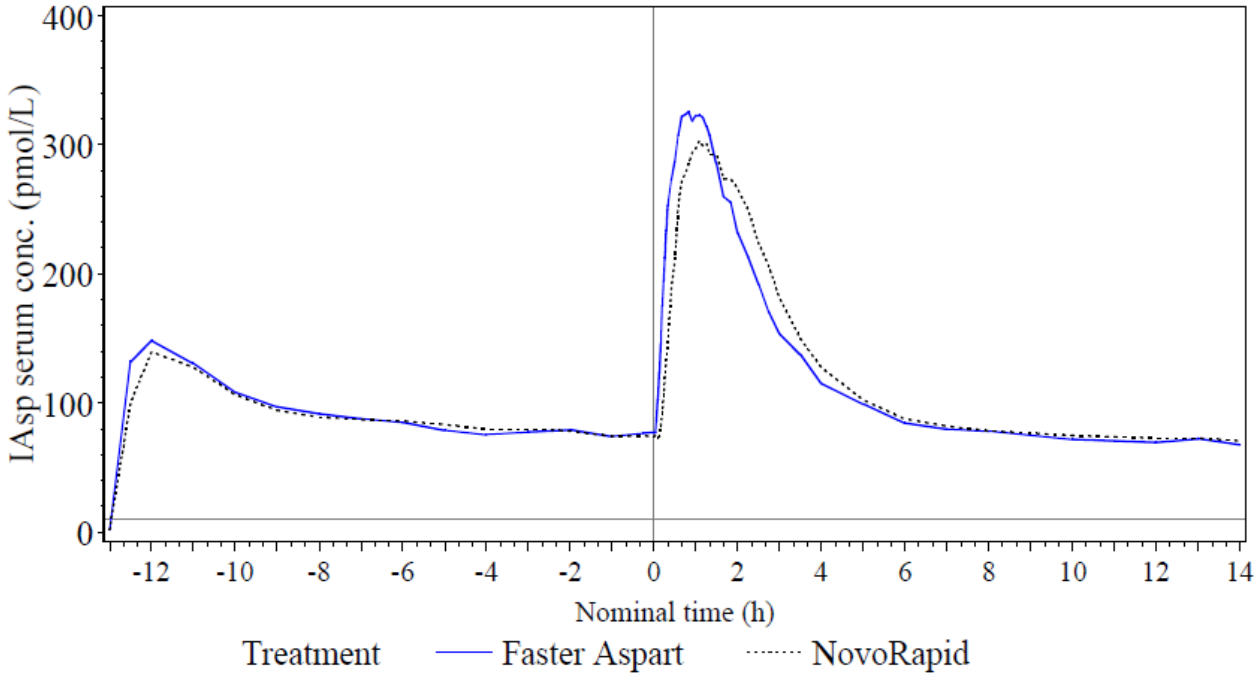
more insulin exposure in the first two hours and ~10% less in the late part, leading to similar overall total exposure as NovoRapid.

Study 3890 investigated the pharmacokinetic properties of Fiasp and NovoRapid when given as a bolus on top of a basal CSII by external pump in subjects with T1DM. The mean profiles for insulin aspart concentration after bolus administration of Fiasp and NovoRapid are shown in Figure 8.

The total insulin aspart exposure ($AUC_{IAsp, Total}$) was similar for faster-acting insulin aspart and NovoRapid and the maximum serum concentration was 11 % higher with Fiasp than NovoRapid.

Early insulin exposure: All of the bolus-related partial AUCs measured during the first 2 hours after administration of the bolus dose were statistically significantly greater with faster-acting insulin aspart than with NovoRapid (Table 10). $AUC_{IAsp, 0-30min}$ with faster-acting insulin aspart treatment was approximately 3 times as great as $AUC_{IAsp, 0-30min}$ with NovoRapid treatment.

Onset of insulin exposure: tmax was estimated to occur 31% earlier with faster-acting insulin aspart (56.6 minutes after administration) than with NovoRapid (82.3 minutes after administration). The difference in time to maximum concentration was 26 minutes between Fiasp and NovoRapid in the CSII setting compared to 7 minutes after subcutaneous injection in the pooled analysis.



Horizontal grey line at 10 pmol/L indicates the LLOQ

Figure 6 Mean insulin aspart serum concentration profiles (-13 to 14 hours) in adults with T1DM in CSII trial 3890

Table 5 Statistical analysis of endpoints assessing early insulin exposure - bolus-related AUCs during the first 2 hours after bolus administration in CSII trial 3890

Endpoint	Faster Aspart Estimated LSMean (pmol·h/L)	NovoRapid® Estimated LSMean (pmol·h/L)	Estimated Treatment Ratio Faster Aspart/NovoRapid® [95 % CI]
$AUC_{IAsp,0–15min}$*	12.54	1.78	7.05 [3.73;136.57]
$AUC_{IAsp,0–30min}$†	51.36	17.43	2.95 [2.32;3.73]
$AUC_{IAsp,0-1h}$†	162.98	107.25	1.52 [1.37;1.69]
$AUC_{IAsp,0-90min}$†	275.15	212.00	1.30 [1.20;1.41]
$AUC_{IAsp,0-2h}$†	362.98	308.84	1.18 [1.10;1.26]

CI: Confidence interval; LSMean: least squares mean

*Endpoint was analysed in a linear mixed model with treatment and period as fixed effects and subject as a random effect. Ratios and the corresponding CIs were estimated using Fieller's method.

†Endpoint was log-transformed and analysed in a linear mixed model with treatment and period as fixed effects and subject as a random effect.

In zinc-containing formulations of insulin aspart, the presence of nicotinamide gives rise to a slight increase in the trans-endothelial transport of insulin aspart.

Distribution

The volume of distribution of insulin aspart was 0.22 L/kg following an intravenous dose of 0.02 U/kg Fiasp.

The *in vitro* plasma protein binding of insulin aspart was 2-10% in human plasma (n=4) determined at concentrations ranging from 10 pM to 10 nM.

Elimination

Clearance of insulin aspart was 1.0 L/h/kg and elimination half-life was 10 minutes following an intravenous dose of 0.02 U/kg Fiasp. The terminal half-life of insulin aspart was 57 minutes following subcutaneous administration of Fiasp.

Insulin aspart is similar to human insulin and is rapidly and extensively degraded to smaller peptides and all metabolites formed are inactive

Dose proportionality and time dependencies

Total exposure ($AUC_{IAsp,0-12h}$) and maximum serum insulin aspart concentration ($C_{max,IAsp}$) increased nearly dose proportional with increasing dose after single dose administration of 0.1 U/kg, 0.2 U/kg and 0.4 U/kg.

The pharmacokinetic within subject variability was low for both Fiasp and NovoRapid. The between-subject (interindividual) variability was larger than the within-subject variability in study 3887. No statistically significant differences in between-subject variability were observed between Fiasp and NovoRapid.

Special populations

The effect of renal and hepatic impairment is expected to be similar to what has been observed for NovoRapid earlier. The pharmacokinetic properties of IAsp have previously been shown not to be affected by renal impairment or hepatic impairment. The lack of new data with Fiasp is acceptable.

The effect of gender, race/ethnicity and body weight was estimated using a linear mixed effects model using data from study 3852. For Fiasp, no differences in exposure was found between gender or between the racial and ethnic groups investigated. A lower early exposure was observed with larger BMI for both Fiasp and NovoRapid. The influence of BMI on the absorption was less pronounced for Fiasp leading to relatively higher initial exposure compared to NovoRapid.

When comparing elderly and younger adults, the AUC_{0-12} and C_{max} was higher in geriatric subjects compared to younger adult subjects (30 % and 28 %, respectively).

When comparing children with adults, the AUC_{0-12} and C_{max} was lower in children compared to adult subjects (41 % and 9 %, respectively). When comparing adolescents with adults, the AUC_{0-12} was 22 % lower in adolescents compared to adult subjects and C_{max} was similar between adolescents and adults.

In general, any observed differences in the pharmacokinetic exposure between different special populations are not believed to have any clinical implications considering the product is individually titrated.

The number of patients in the elderly age groups across the Fiasp clinical programme is shown in table 11 below.

Table 6 Number of patients in the Fiasp clinical programme treated with Fiasp

Controlled Trials	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
3852 (T1DM)	Fiasp mealtime: 31/381 Fiasp post-meal: 20/382 NovoRapid: 20/380	Fiasp mealtime: 4/381 Fiasp post-meal: 3/382 NovoRapid: 8/380	0
3853 (T2DM)	Fiasp: 91/345 NovoRapid: 84/344	Fiasp: 13/345 NovoRapid: 12/344	0
4049 (T2DM)	Fiasp: 26/116 Basal: 27/120	Fiasp: 4/116 Basal: 2/120	0
3930 (T1DM)	Fiasp: 6/43 NovoRapid: 6/43	Fiasp: 0/43 NovoRapid: 0/43	0
3931 (T1DM)	Fiasp: 6/25 NovoRapid: 0/12	Fiasp: 0/25 NovoRapid: 0/12	0
Clinical pharmacology trial (T1DM and healthy)	Fiasp: 29/382 NovoRapid: 30/359	Fiasp: 0/382 NovoRapid: 0/359	0

All trials	Fiasp: 209/1674 NovoRapid: 140/1138 Basal: 27/120	Fiasp: 24/1674 NovoRapid: 20/1138 Basal: 2/120	0

Pharmacokinetic interaction studies

Insulin is a large protein and no classic drug-drug interactions have been encountered between insulins and other marketed medications. Therefore, it is highly unlikely that co-administration with other drugs will interact with the principal enzymes of insulin aspart catabolism and thus cause a change in its elimination.

2.4.3. Pharmacodynamics

Mechanism of action

Fiasp is insulin aspart in a new formulation with two additional excipients. The addition of nicotinamide results in a faster initial absorption of insulin aspart following subcutaneous (s.c.) injection. The addition of L-arginine hydrochloride supports stabilisation of the Fiasp formulation.

The active substance in Fiasp is insulin aspart, which is a rapid-acting analogue of human insulin where the amino acid proline has been replaced with aspartic acid in position B28. The insulin aspart molecule in Fiasp and NovoRapid is identical and therefore, once systemically absorbed, it has the same biological action at the insulin receptor as that of NovoRapid.

The primary activity of Fiasp is the regulation of glucose metabolism. Insulins, including insulin aspart, the active ingredient in Fiasp, regulate glucose metabolism. Insulin and its analogues lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin also inhibits lipolysis and proteolysis and enhances protein synthesis.

In in vitro tests, including binding to insulin and IGF-1 receptor sites and effects on cell growth, insulin aspart behaved in a manner that closely resembled human insulin. Studies also demonstrate that the dissociation of binding to the insulin receptor of insulin aspart is equivalent to human insulin.

Primary and Secondary pharmacology

The clinical pharmacology programme included eight trials in subjects with type 1 diabetes mellitus (T1DM) and one trial in healthy subjects (Table 8). In addition to the nine clinical pharmacology trials, the therapeutic exploratory CSII trial 3930 included pharmacodynamic analyses during a standardised meal test. Pharmacodynamic analyses were also included in the therapeutic confirmatory trial 3852. These data are discussed in the efficacy part of this report.

Pharmacodynamic endpoints

In order to describe the pharmacodynamic properties of single dosing with Fiasp during the euglycaemic clamp, the pharmacodynamic profiles were characterised according to selected temporal components which describe the onset, early, late and total and maximum glucose-lowering effect (Table 12).

For the CSII trial 3890 all endpoints were based on the glucose infusion rate (GIR) adjusted for baseline. For this trial the endpoint $AUC_{GIR,2\text{-}12h}$ was not analysed due to the confounding of effects from the underlying basal insulin infusions.

Table 7 Overview of endpoints used to described pharmacodynamic properties

	Onset of glucose lowering effect	Early glucose lowering effect	Late glucose lowering effect	Total and maximum glucose lowering effect
Onset of action	✓			
Time to 50% $GIR_{max,IAsp,}$	✓			
$t_{GIRmax,IAsp,}$	✓			
$AUC_{GIR,\ 0\text{-}30min}$		✓		
$AUC_{GIR,\ 0\text{-}1hour}$		✓		
$AUC_{GIR,\ 0\text{-}90min}$		✓		
$AUC_{GIR,\ 0\text{-}2hour}$		✓		
Time to late 50% GIR_{max}			✓	
$AUC_{GIR,\ 2\text{-}12hours}$			✓	
$AUC_{GIR,\ 0\text{-}12hours}$				✓
GIR_{max}				✓

Pharmacodynamic pooled analysis

The overall design of the trials in the Fiasp clinical pharmacology programme was standardised in order to allow for comparison across studies and to allow for a pooled analysis of the results.

The pooled pharmacodynamic analyses aimed at estimating one set of PD parameters corresponding to the dose (0.2 U/kg) administered to all subjects across trials and included all trials where White adult T1DM patients (18 to 64 years) were included and received a dose of 0.2 U/kg of Fiasp or NovoRapid administered in the abdomen (Figure 9).

Pooled PD euglycaemic clamp trials
Trial 3978: Formulation selection trial, T1DM
[a] Trial 3887: Dose-response trial, T1DM
[b] Trial 3891: Elderly subjects, T1DM

[a] Only 0.2 U/kg dose level
[b] Only adult subjects (18-64 years) were included in the pooled analysis

Figure 7 Trials included in the pooled pharmacodynamic analysis

Pharmacodynamic treatment differences during a euglycaemic clamp

Pharmacodynamic profiles

In each of the three individual trials where the glucose infusion rate (GIR) was collected, and in the pooled analysis, the GIR profile of Fiasp shows a similar left shift compared to that of NovoRapid (Figure 10).

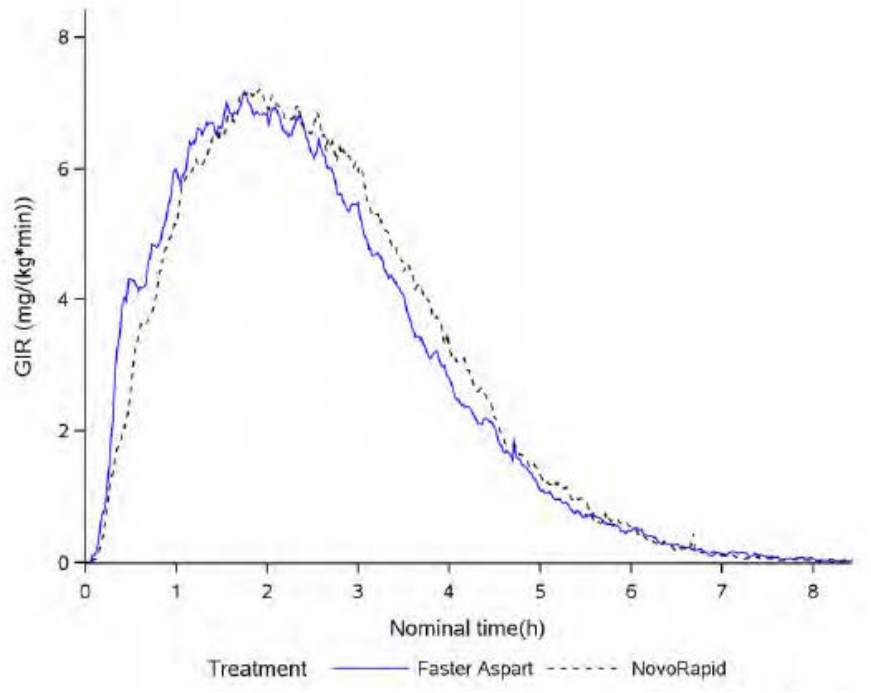


Figure 8 Mean GIR profiles (0-8 hours) in adults with T1DM in the pooled analysis (0.2 U/kg, trials 3887, 3891 and 3978)

Onset of glucose-lowering effect

The onset of the glucose-lowering effect was assessed using three endpoints (see Table 12).

A consistent pattern was seen across the trials, with Fiasp resulting in a faster onset of glucose-lowering effect and an earlier time to 50% GIR_{max} and $tGIR_{max}$ than NovoRapid. The onset of action was between 2.6 and 8.7 minutes earlier with Fiasp and time to 50%GIR_{max} was between 7.8 and 10.3 minutes shorter with Fiasp than with NovoRapid (Figure 11).

In the pooled analysis, the estimated onset of action was approximately 5 minutes faster for Fiasp than for NovoRapid. Time to 50% C_{max} was approximately 9.5 minutes earlier and $tGIR_{max}$ was approximately 10.5 minutes earlier, with Fiasp than with NovoRapid (Figure 11).

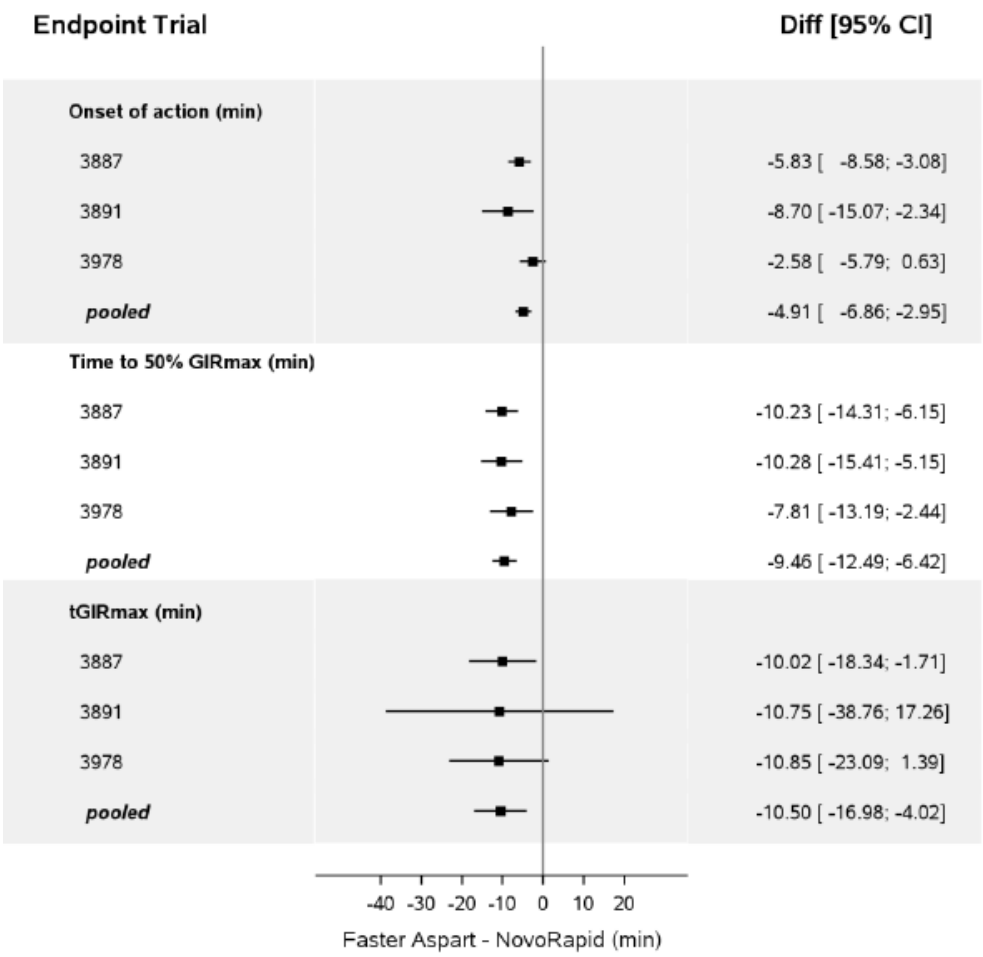


Figure 9 Mean treatment differences and 95% CI for onset of glucose-lowering effect in adults with T1DM in individual trials and in the pooled analysis (0.2 U/kg, trials 3887, 3891 and 3978)

Early glucose-lowering effect

Analysis of the early part of the area under the GIR profile shows that there is a consistent left shift of the glucose-lowering effect with Fiasp both in the individual trials and in the pooled analysis (Figure 12) with the largest difference seen during the first 30 minutes. Estimates of $AUC_{GIR,\ 0\text{-}30\ min}$ were between 48% and 109% larger with Fiasp than with NovoRapid.

In the pooled analysis, all partial AUCs covering the first 2 hours were statistically significantly larger with Fiasp. The area under the GIR curve was 74% larger during the first 30 minutes ($AUC_{GIR,\ 0\text{-}30\ min}$) with Fiasp than with NovoRapid (Figure 12).

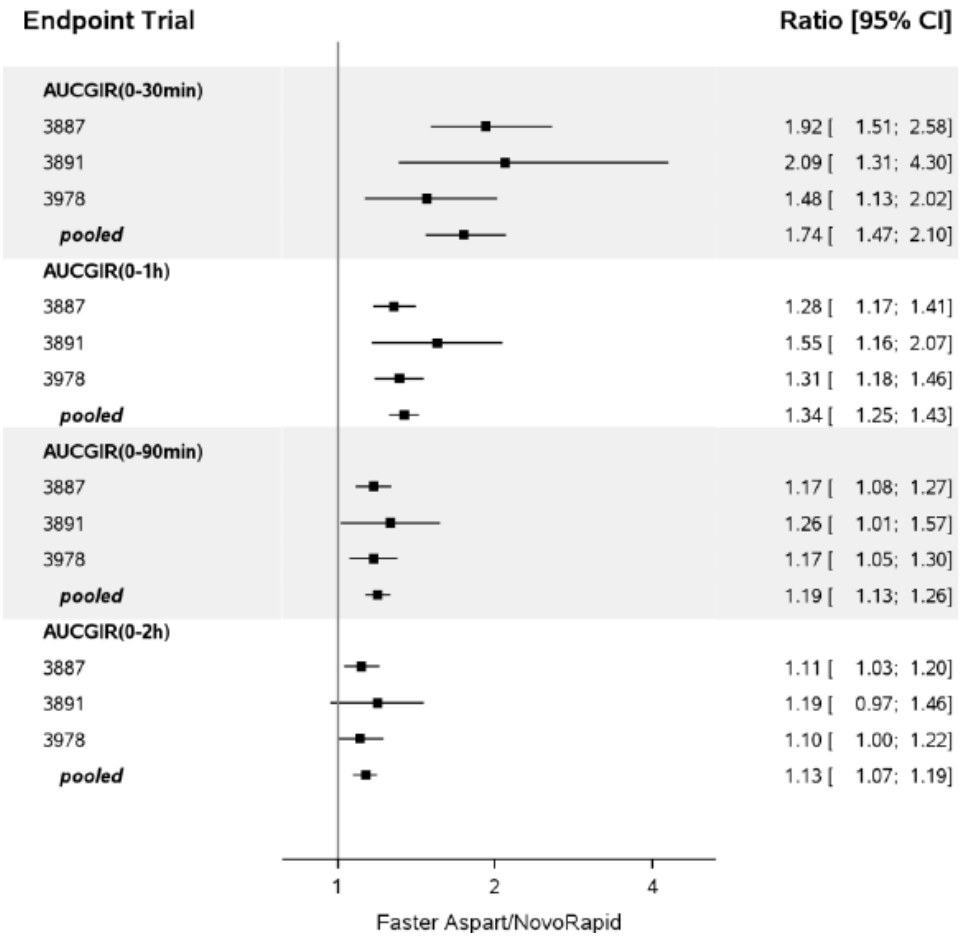


Figure 10 Mean treatment ratios and 95 % CI for early glucose-lowering effect (AUCGIR) in adults with T1DM in individual trials and in the pooled analysis (0.2 U/kg, trials 3887, 3891 and 3978)

Duration of glucose-lowering effect and late glucose-lowering effect

The duration of the glucose-lowering effect and late glucose-lowering effect was assessed using two endpoints (see Table 12). The estimated time to late 50%GIR_{max} and $AUC_{GIR,\ 2\text{-}12\ h}$ were both consistently smaller with Fiasp compared to NovoRapid in each of the individual trials (Table 13).

In the pooled analysis, the estimated time to late 50% GIR_{max} occurred approximately 14 minutes earlier with Fiasp than with NovoRapid (Table 13). The area under the later part of the GIR curve ($AUC_{GIR,\ 2\text{-}12\ h}$) was 10% smaller with Fiasp. Thus duration of action was shorter and the late glucose-lowering effect was smaller with Fiasp compared to NovoRapid.

Table 8 Late glucose-lowering effect and duration of glucose-lowering effect in adults with T1DM in individual trials and in the pooled analysis (0.2 U/kg, trials 3887, 3891 and 3978)

Endpoint	Number of subjects		Estimated mean		Treatment difference [95% CI]
	Faster aspart	NovoRapid®	Faster aspart	NovoRapid®	Faster aspart/NovoRapid®
Time to late 50%GIR_{max} (minutes)					
3887	90	88	230.59	243.19	-12.60 [-23.78; -1.42]
3891	22	21	219.15	239.31	-20.15 [-41.95; 1.65]
3978	51	51	233.48	246.80	-13.32 [-36.33; 9.69]
Pooled analysis	**163**	**160**	**229.85**	**244.14**	**-14.30 [-22.08; -6.52]**
			Estimated mean		**Treatment ratio[95% CI]**
	Faster aspart	NovoRapid®	Faster aspart	NovoRapid®	Faster aspart-NovoRapid®
$AUC_{GIR, 2\text{-}12\ h}$ (mg/kg)					
3887	90	88	754.94	840.53	0.90 [0.81;0.99]
3891	22	21	664.78	717.54	0.93 [0.81;1.06]
3978	51	51	773.68	873.15	0.89 [0.68;1.16]
Pooled analysis	**163**	**160**	**747.85**	**834.02**	**0.90 [0.85;0.95]**

Number of subjects: For trial 3887 and the pooled analysis, the number of subjects should be read as the number of profiles contributing to the analysis as subjects in trial 3887 received more than one dose at 0.2 U/kg

Total glucose-lowering effect and maximum glucose-lowering effect

The total ($AUC_{GIR, 0\text{-}12h}$) and maximum (GIR_{max}) glucose-lowering effect were comparable between Fiasp and NovoRapid, both in the individual trials and in the pooled analysis, supporting that 1 unit of Fiasp results in equivalent glucose-lowering effect as 1 unit of NovoRapid.

Across dose levels

In trial 3887, the estimated onset of action was 5.0−5.8 minutes faster, and time to 50% of GIR_{max} was 8.8−11.8 minutes earlier, with Fiasp than NovoRapid across the 3 dose levels (0.1, 0. 2 and 0.4 U/kg). Time to GIR_{max} was 8−22% shorter with Fiasp compared to NovoRapid across the 3 dose levels. The estimated mean time to GIR_{max} was 10.0 to 29.7 minutes shorter compared to NovoRapid across the 3 dose levels.

The early glucose-lowering effect was statistically significantly larger with Fiasp than with NovoRapid across all three dose levels, except for $AUC_{GIR,0\text{-}30min}$ and $AUC_{GIR,0\text{-}2h}$ for the 0.1 U/kg dose level.

The left shift of the later part glucose infusion rate profile of Fiasp seen in the individual trials and pooled analysis was maintained across the three dose levels. There was a trend for a shorter time to late 50%GIR_{max} across dose levels which was statistically significant at the 0.2 U/kg and 0.4 U/kg dose. $AUC_{GIR, 2\text{-}12\ hours}$ was between 10% and 13 % smaller with Fiasp than with NovoRapid across dose levels.

The total ($AUC_{GIR, 0\text{-}12h}$) and maximum (GIR_{max}) glucose-lowering effect were comparable between Fiasp and NovoRapid across the three dose levels as was also seen in the individual trials and pooled analysis.

Pharmacodynamic treatment differences during a meal test

During a standardised meal test in the clinical pharmacology trials and in the therapeutic exploratory CSII trial 3930, the average postprandial plasma glucose increment during time 0-t (t=1, 2 or 6 hours) and the plasma glucose concentrations at 1 and 2 hours after the start of meal were used to describe the early and total effect of Fiasp. The therapeutic trial 3852 did also include pharmacodynamic data during a meal test. These data are presented in the efficacy section of this report.

Mealtime dosing

Clinical pharmacology trials

Trials 3889 and 3888 compared the pharmacodynamic properties of Fiasp and NovoRapid administered as a single subcutaneous injection (0.2 U/kg) immediately before a standardised meal in adult subjects with T1DM.

In trial 3889, plasma glucose parameters were not statistically significantly different between Fiasp and NovoRapid. The estimated mean PPG increment over 2 hours following administration ($\Delta PG_{av,0-2h}$) was 3.55 mmol/L for Fiasp and 3.74 mmol/L for NovoRapid and the estimated treatment ratio was 0.95 [0.81; 1.11]95% CI]. $\Delta PG_{av,0-6h}$ was not statistically significantly different (treatment ratio 0.98 [0.77; 1.26]95% CI).

In trial 3888, the estimated mean PPG increment over 2 hours ($\Delta PG_{av,0-2h}$) with Fiasp in adults was 2.36 mmol/L with Fiasp and 2.93 mmol/L with NovoRapid . The estimated treatment difference between Fiasp and NovoRapid for $\Delta PG_{av,0-2h}$ was not statistically significantly different (-0.57 mmol/L $[-1.83;0.69]_{95\%\ CI}$). The treatment difference (Fiasp – NovoRapid) in mean PPG increment over 1 hour ($\Delta PG_{av,0-1h}$) (-0.31mmol/L $[-1.48;0.86]_{95\%\ CI}$) was smaller than at 2 hours.

Therapeutic exploratory trial

Similar improvement with respect to glycaemic control was observed for Fiasp compared to NovoRapid during a meal test in the therapeutic exploratory CSII trial 3930. A statistically significantly greater glucose-lowering effect was demonstrated in post prandial glucose with Fiasp as compared to NovoRapid during the first 2 hours of a standardised meal test. The estimated mean PPG increment over the first 2 hours after the meal ($\Delta PG_{av,0-2h}$) was -0.99 mmol/L $[-1.95; -0.03]_{95\%CI}$ smaller with Fiasp (3.03 mmol/L) than with NovoRapid (4.02 mmol/L). Similarly, the mean PPG increment over the first hour after the meal ($\Delta PG_{av,0-1h}$) was -0.50 $[-1.07; 0.07]_{95\%CI}$ lower with Fiasp than with NovoRapid.

Post-meal dosing

In trial 3921, Fiasp (0.2 U/kg) administered 20 minutes post-meal resulted in a smaller glucose-lowering effect ($PG_{av,0-6h}$ was 13% higher; treatment ratio 1.13 $[1.06; 1.21]_{90\%\ CI}$) compared to NovoRapid administered immediately before the meal.

Pharmacodynamic treatment differences during CSII by external pump

Euglycaemic clamp in a CSII setting

The mean glucose infusion rate profiles in trial 3890 were shifted to the left for Fiasp compared to NovoRapid (Figure 13).

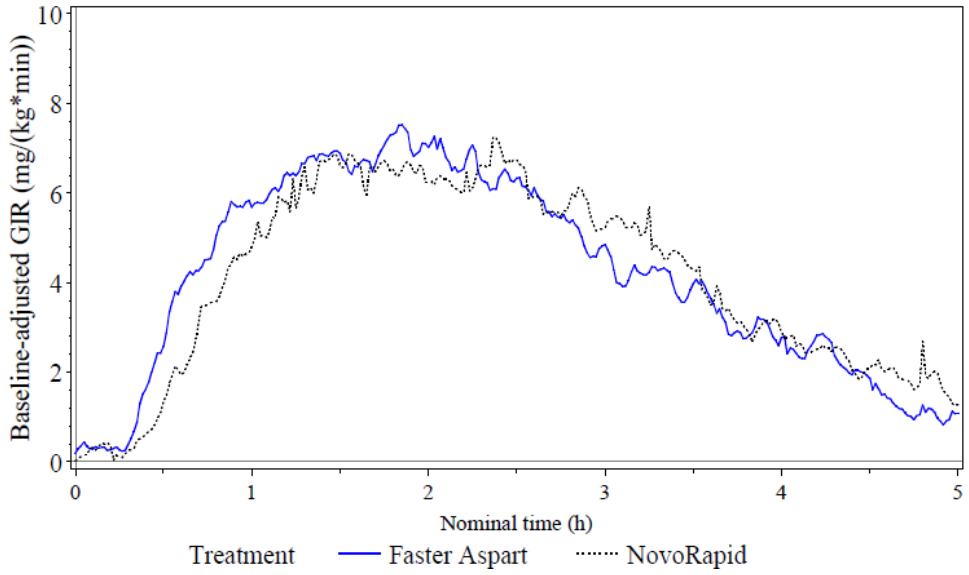


Figure 11 Mean GIR profiles (0-5 hours) corrected for basal-insulin infusion in adults with T1DM in CSII trial 3890

Onset of glucose-lowering effect and early glucose-lowering effect

In a CSII setting, Fiasp resulted in a faster onset of glucose-lowering effect (Table 14) and a greater early glucose-lowering effect) than NovoRapid. The difference in time to maximum glucose-lowering effect was 18.7 minutes between Fiasp and NovoRapid in the CSII setting compared to 10.5 minutes after subcutaneous injection (pooled analysis) (Table 14).

Table 9 Onset of glucose-lowering effect with CSII (trial 3890) and single s.c. injection (pooled trials 3887, 3891 and 3978)

Endpoints		CSII trial (3890)	Pooled analysis (single injection trials)
Time to 50% GIR_{max} (min)	Faster aspart	41.1	36.3
	NovoRapid®	52.3	45.7
	Treatment difference [95% CI]	**-11.13 [-15.36; -6.90]**	**-9.5 [-12.5;-6.4]**
tGIRmax (min)	Faster aspart	111.9	121.6
	NovoRapid®	130.6	132.1
	Treatment difference [95% CI]	**-18.69 [-34.43; -2.95]**	**-10.5 [-17.0;-4.0]**

Number of subjects: Trial 3890; Fiasp 44 subjects, NovoRapid 45 subjects. Pooled analysis; Fiasp 163 profiles; NovoRapid 160 profiles.

Table 10 Treatment ratios and 95 % CI for glucose-lowering effect (AUC_{GIR}) in CSII (trial 3890) and single s.c. injection (pooled trials 3887, 3891 and 3978)

Endpoints	CSII trial (3890) Faster aspart / NovoRapid®	Pooled analysis (single injection trials) Faster aspart / NovoRapid®
$AUC_{GIR, 0\text{-}30min}$	2.18 [1.33; 5.04]	1.74 [1.47; 2.10]
$AUC_{GIR, 0\text{-}1hour}$	1.52 [1.29; 1.83]	1.34 [1.25; 1.43]
$AUC_{GIR, 0\text{-}90min}$	1.34 [1.14; 1.57]	1.19 [1.13; 1.26]
$AUC_{GIR, 0\text{-}2hours}$	1.21 [1.07; 1.36]	1.13 [1.07; 1.19]

Number of subjects: Trial 3890; Fiasp 44 subjects, NovoRapid 46 subjects. Pooled analysis; Fiasp 163 profiles; NovoRapid 160 profiles.

Duration of glucose-lowering effect and late glucose-lowering effect

The larger left shift in onset of action and early glucose-lowering effect with Fiasp seen in a CSII setting was reflected in a time to late 50% GIR_{max} that was 24 minutes earlier with Fiasp than with NovoRapid in a CSII setting, compared to a treatment difference 14 minutes for single dose subcutaneous injection (Table 16). $AUC_{GIR, 2\text{-}12\ h}$ was similar for Fiasp and NovoRapid in a CSII setting.

Table 11 Duration of glucose-lowering effect in adults with T1DM in CSII (trial 3890) and single s.c. injection (pooled trials 3887, 3891 and 3978)

Endpoints		CSII trial (3890)	Pooled analysis (single injection trials)
Time to late 50% GIR_{max} (min)	Faster aspart	214.71	229.85
	NovoRapid®	238.71	244.14
	Treatment difference [95% CI]	**-24.00 [-38.88;-9.13]**	**-14.30 [-22.08; -6.52]**

Number of subjects: Trial 3890; Fiasp 44 subjects, NovoRapid 45 subjects. Pooled analysis; Fiasp 163 profiles; NovoRapid 160 profiles.

Total glucose-lowering effect and maximum glucose-lowering effect

Total ($AUC_{GIR, 0\text{-}12h}$) and maximum (GIRmax) glucose-lowering effect were both comparable between Fiasp and NovoRapid in a CSII setting.

Injection regions and routes of administration

In trial 3949, the glucose-lowering effect was assessed after administration of Fiasp using different injection regions and routes of administration. Fiasp was administered as a single dose (0.2 U/kg) subcutaneously in the abdomen, deltoid and thigh and intramuscularly in the thigh in healthy subjects.

The mean glucose infusion rate profiles showed that the glucose-lowering effect was within the same range following Fiasp administered subcutaneously in the abdomen, the deltoid and the thigh (Figure 14). Descriptive statistics for $AUC_{GIR,0\text{-}12h}$ and GIR_{max} supported these findings even though GIR_{max} was higher after abdominal dosing.

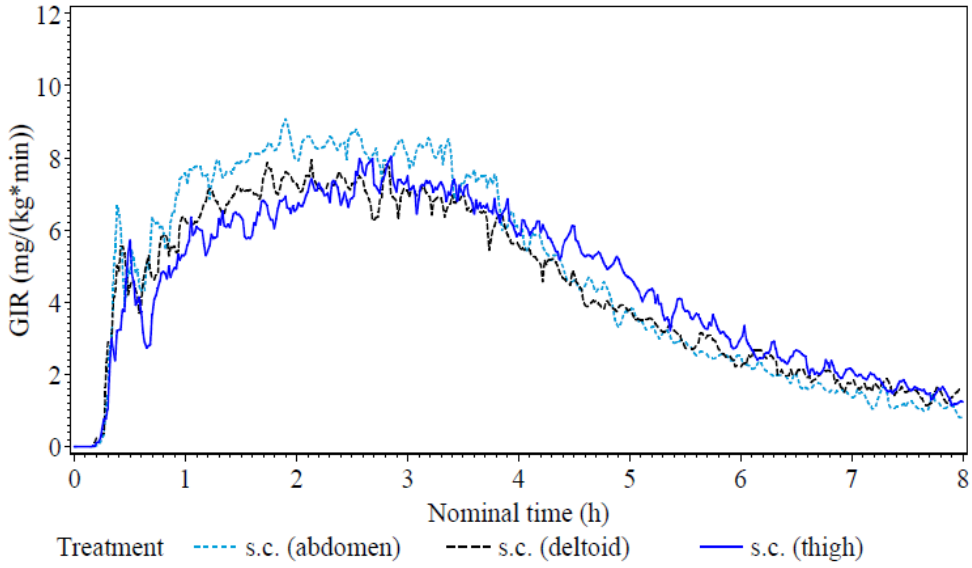


Figure 12 Mean glucose infusion rate profiles (0-8hours) for Fiasp administered subcutaneously (0.2 U/kg) in the abdomen, deltoid and thigh in healthy adults in trial 3949

Intramuscular versus subcutaneous administration

The mean glucose infusion rate in trial 3949 showed that the glucose-lowering effect of Fiasp was similar following intramuscular administration of Fiasp compared to subcutaneous administration in the thigh. Descriptive statistics for $AUC_{GIR,0-12h}$, GIR_{max} and $tGIR_{max}$ supported these finding.

Intrinsic factors

Body mass index

A greater early glucose-lowering effect was observed during the first 2 hours after administration with Fiasp compared to NovoRapid across the range of BMI. Total ($AUC_{GIR,\ 0\text{-}12\ hours}$) and maximum ($GIR_{max}$) glucose-lowering effect were comparable between Fiasp and NovoRapid at all three BMI levels. As expected, the early, total and maximum glucose-lowering effect decreased with increasing BMI for both Fiasp and NovoRapid in accordance with the well-known higher insulin resistance with increasing BMI.

Age

Children and adolescents

In trial 3888, Fiasp had a larger glucose-lowering effect than NovoRapid during a meal test in children. In adolescents, a larger glucose-lowering effect for Fiasp was not demonstrated during a meal test, despite a greater early insulin exposure. In adults, the glucose-lowering effect tended to be larger for Fiasp than for NovoRapid during a meal test. The treatment effect did not differ significantly between age groups.

For Fiasp, the mean PPG increment and the mean PG levels 1 and 2 hours post dosing during the meal test were similar between children and adults, and between adolescents and adults. A test for interaction between age group and treatment showed that the age group effect did not differ significantly between the treatments for the pharmacodynamic endpoints.

Elderly subjects with T1DM

The onset of action in elderly subjects was approximately 10 minutes faster (estimated difference Fiasp - NovoRapid: -10.17 $[-15.29;-5.06]_{95\% CI}$) with Fiasp than with NovoRapid, and time to 50% GIR_{max} was approximately 6 minutes faster (-5.58 $[-8.99;-2.17]_{95\% CI}$) with Fiasp than for NovoRapid (Trial 3891). The early glucose-lowering effect was also larger with Fiasp than NovoRapid. The total ($AUC_{GIR,0-12h}$) and maximum (GIR_{max}) glucose-lowering effect were both similar for Fiasp and NovoRapid in elderly subjects.

The total and maximum glucose-lowering effect of Fiasp was similar for elderly and younger adult subjects. The same was observed for NovoRapid and no statistically significant age-by-treatment interaction was observed (Trial 3891).

Sex

Both female and male adult subjects with T1DM had a greater early glucose-lowering effect with Fiasp compared to NovoRapid during the first 2 hours following administration and the treatment differences appeared comparable for males and females. Furthermore, the total and maximum glucose-lowering effects were both similar for Fiasp and NovoRapid for both sexes. Early, maximum and total glucose-lowering effect appeared overall to be similar in females and males for both Fiasp and NovoRapid.

Anti-insulin aspart antibodies

Across all quartiles of total anti-insulin aspart antibodies a greater early glucose-lowering effect was observed with Fiasp compared to NovoRapid during the first hour following administration. The size of the greater early glucose-lowering effect appeared to be comparable across the three total anti-insulin aspart antibody quartiles. Both total and maximum glucose-lowering effects were comparable for Fiasp and NovoRapid across all total anti-insulin aspart antibody quartiles.

Total glucose-lowering effect did not appear to be affected by the level of total anti-insulin aspart antibodies for either Fiasp or NovoRapid. However, GIR_{max} was slightly lower for the high total anti-insulin aspart antibody percentiles compared to the 25th percentile and this difference was significant for NovoRapid.

Pharmacodynamic within-subject variability

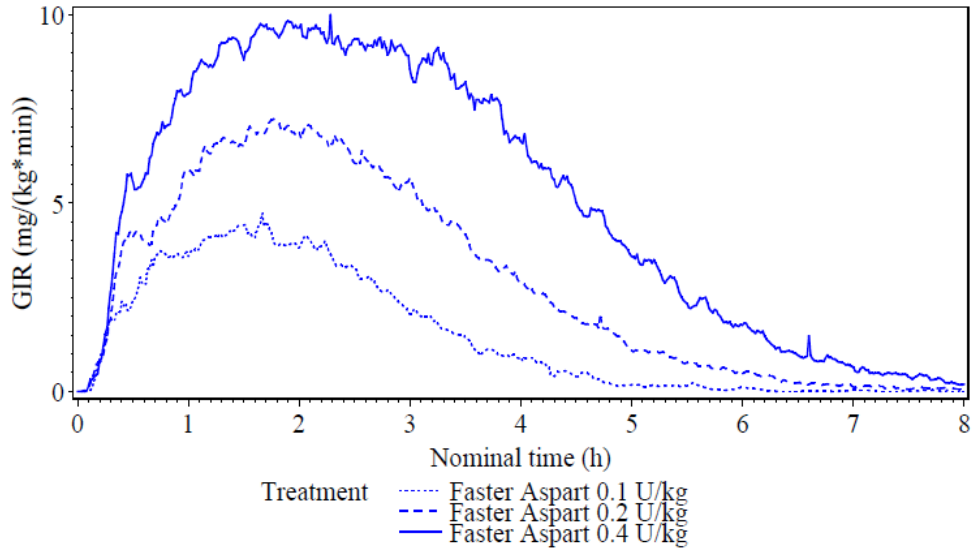
In trial 3887, the pharmacodynamic within-subject day-to-day variability of a single dose of Fiasp was investigated. The pharmacodynamic within-subject variability was determined by the coefficient of variation (CV%) calculated based on 3 single doses (0.2 U/kg) of Fiasp or NovoRapid.

The within-subject day-to-day variability in glucose-lowering-effect was low for Fiasp for early ($AUC_{GIR, 0-1h}$, CV~26 %), total ($AUC_{GIR, 0-12h}$, CV~18 %) and maximum glucose-lowering effect (GIR_{max}, CV ~19 %). The within-subject day-to-day variability in glucose-lowering effect for NovoRapid was similarly low.

Relationship between plasma concentration and effect

Dose-response relationship

In trial 3887, the pharmacodynamic dose-response relationship of Fiasp was investigated after single-dose administration of three clinically relevant doses (0.1, 0.2 and 0.4 U/kg). The mean glucose-lowering effect increased with increasing dose (Figure 15).



Repetitions of 0.2 U/kg have been replaced by their average

Figure 13 Mean GIR profiles (0-8 hours) at three Fiasp dose levels (0.1, 0.2 and 0.4 U/kg) in adults with T1DM in trial 3887

The total glucose-lowering effect ($AUC_{GIR,\ 0\text{-}12\ hours}$) of the 0.2 U/kg dose was approximately twice as high (~110%) than that of the 0.1 U/kg dose. The glucose-lowering effect of the 0.4 U/kg dose was only ~70% larger than that of the 0.2 U/kg dose level. This indicates that some subjects were no longer on the linear part of the s-shaped dose-response curve and had approached the plateau of insulin action expected at the higher insulin dose of 0.4 U/kg. This is supported by the estimates of GIR_{max} for Fiasp which were 4.18, 7.12 and 9.98 mg/(kg*min) for 0.1, 0.2 and 0.4 U/kg, respectively. Analysis of dose-linearity, where a second order coefficient equal to 0 corresponds to dose linearity, indicated that the increases in $AUC_{GIR,0\text{-}12h}$ and GIR_{max} after administration of Fiasp were slightly less than linear. Similar results were observed for NovoRapid.

Relationship between pharmacokinetic and pharmacodynamic properties

The pharmacokinetic and pharmacodynamic properties of Fiasp were characterised in a therapeutically relevant dose range (0.1, 0.2 and 0.4 U/kg) in trial 3887. The added excipients of Fiasp resulted in a left shift in the pharmacokinetic properties of Fiasp compared to NovoRapid which translated into a faster onset of glucose-lowering effect. As expected, there was a correlation between total exposure ($AUC_{IAsp,0\text{-}12h}$) and total glucose-lowering effect ($AUC_{GIR,0\text{-}12h}$) within the investigated dose range of Fiasp in subjects with T1DM (R^2=0.51). Correspondingly, GIR_{max} correlated with $C_{max,IAsp}$ (R^2=0.46). This was supported by the observation that both $AUCI_{Asp,0\text{-}12h}$ and $AUC_{GIR,0\text{-}12h}$ increased approximately proportionally with increasing dose.

The correlation between total exposure ($AUC_{IAsp,0\text{-}12h}$) and total glucose-lowering effect ($AUC_{GIR,0\text{-}12h}$) for Fiasp was comparable to that seen with NovoRapid.

Genetic differences in PD response

Japanese subjects with T1DM (trial 3918)

The design of trial 3918 replicated that of trial 3978 which compared the pharmacokinetic and pharmacodynamic properties of Fiasp and NovoRapid in White subjects. In general, the design and methodology used was comparable across the studies, including the clamp methodology.

A faster onset of action (assessed using time to 50%GIR_{max} and $tGIR_{max}$) was seen with Fiasp than with NovoRapid in Japanese subjects, as was also observed in White subjects. The estimated time to 50% GIR_{max} for Fiasp in Japanese subjects was significantly earlier (by 10 minutes) than for NovoRapid. Moreover, $tGIR_{max}$ in Japanese subjects was also significantly earlier for Fiasp than for NovoRapid. Early glucose-lowering effect was significantly greater for Fiasp than for NovoRapid in Japanese subjects with the largest difference occurring in the first 30 minutes, as was also seen in White subjects.

The total glucose lowering effect ($AUC_{GIR,0\text{-}12h}$) was slightly lower for Fiasp than for NovoRapid in Japanese subjects whereas the maximum glucose-lowering effect (GIR_{max}) was similar for Fiasp and NovoRapid in both Japanese subjects and in White subjects.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

In study 3949 comparing serum exposure of insulin aspart after administration of Fiasp in different injection regions and via different routes of administration in healthy volunteers, $C_{max,IAsp}$ was approximately 30 % lower following subcutaneous injection of Fiasp in the thigh compared to the abdomen in healthy subjects. Also the early exposure ($AUC_{IAsp,0–1h}$, $AUC_{IAsp,0–2h}$) was lower following subcutaneous injection in the thigh compared to the abdomen and the deltoid region. The total serum exposure ($AUC_{IAsp,0–12h}$) of insulin aspart was however comparable following subcutaneous administration of Fiasp in all three injection sites.

The results of the pooled pharmacokinetic analysis and individual trial results of studies 3887, 3888, 3889, 3891, 3921 and 3978 indicated a left shift of the serum concentration-time curve for Fiasp with a higher early exposure following administration of Fiasp compared to NovoRapid. All individual pharmacokinetic parameters were not statistically significant in all individual studies (for example t_{max} and $AUC_{IAsp,0–2h}$) but the point estimates showed a faster absorption for Fiasp in all studies. In the pooled PK analysis, all pharmacokinetic parameters were statistically significant and showed a faster absorption of Fiasp compared to NovoRapid. The magnitude of the left shift of the serum concentration-time curve could be described in the parameters of early exposure and the AUC following the first 15 minutes was 3.8 times larger for Fiasp compared to NovoRapid, $AUC_{IAsp,0–30min}$ was 2 times larger, $AUC_{IAsp,0–1h}$ was 1.3 times larger, $AUC_{IAsp,0\text{-}90min}$ was 1.16 times larger and $AUC_{IAsp,0–2h}$ was 1.10 times larger for Fiasp compared to NovoRapid. Another parameter describing the left shift of the concentration-time curve is the time to maximum serum concentration (t_{max}) which was observed 7 minutes earlier following Fiasp compared to NovoRapid.

Pharmacodynamics

The active substance, insulin aspart, is well characterised with regards to the mechanism of action. No additional data has been provided which is acceptable.

The clinical pharmacology program consists of 9 studies, designed to compare the pharmacodynamic properties of Fiasp and NovoRapid. Further to this, pharmacodynamic data was collected from the clinical trial and 3930 (T1DM, CSII). Pharmacodynamic data was also collected in the confirmatory trial 3852, these data are discussed in the efficacy part of this report. The program was conducted in line with the EMA Guideline (CHMP/EWP/1080/00 Rev.1) and covers all important aspects.

The choice of NovoRapid as comparator was adequate, as were the doses used. The use of the same dose of 0.2 U/kg in all clinical pharmacology trials (where administration was by subcutaneous injection), allowed for comparison across trials as well as pooling of data from trials 3978, 3887 and 3891. As the design and

methodology used was comparable across the studies (e.g., dose per kg body weight, inclusion and exclusion criteria) and the clamp studies were standardised across studies, the pooling strategy is acceptable.

Euglycaemic clamp studies

In six trials (trials 3887, 3890, 3891, 3918, 3949 and 3978), the pharmacodynamic properties of Fiasp were evaluated using a glucose clamp technique as recommended in the current EMA Guideline (CPMP/EWP/1080/00 Rev. 1). Adequate measures were taken to minimise the effect of factors that could interfere with the results.

In all three studies which were included in the pooled analysis (3978, 3887 and 3891), the point estimates for the endpoints describing the onset of glucose-lowering effect indicated a faster onset of action with Fiasp compared to NovoRapid. The findings were statistically significant not only in the pooled analysis but also in the individual studies with few exceptions, i.e. onset-of action in trial 3978 and $tGIR_{max}$ in trials 3891 and 3978. In the pooled analysis, the onset of appearance was observed 5 minutes earlier and time to 50% GIR_{max} was 9.5 minutes earlier with Fiasp compared to NovoRapid. Time to GIR_{max} occurred 10.5 minutes earlier with Fiasp than with NovoRapid.

In all three studies, the point estimates for the endpoints describing the early glucose-lowering effect indicated an earlier effect with Fiasp compared to NovoRapid, as reflected by a greater treatment difference in $AUC_{GIR,\ 0\text{-}30\ min}$ (74 %) than in AUC for longer time-periods ($AUC_{GIR,\ 0\text{-}1\ h}$, $AUC_{GIR,\ 0\text{-}90\ min}$ and $AUC_{GIR,\ 0\text{-}2\ h}$). The findings were statistically significantin the pooled analysis and in the individual studies with one exception, i.e. $AUC_{GIR,\ 0\text{-}2\ h}$ in trial 3891. Thus, the early glucose-lowering effect was more pronounced with Fiasp compared to NovoRapid and the difference was statistically significant.

The late glucose-lowering effect and duration of action, as reflected by time to late 50 % GIR_{max} and $AUC_{GIR,\ 2\text{-}12\ h}$, indicated a lower late glucose-lowering effect and shorter duration of action with Fiasp compared to NovoRapid. In the individual studies, statistically significant effects were only observed in study 3887. However, consistent findings were seen across studies as reflected by statistically significant differences observed in the pooled analysis. In the pooled analysis, time to late 50 % GIR_{max} occurred about 14 minutes earlier and the late glucose-lowering effect was about 10 % lower with Fiasp compared to NovoRapid.

No differences were observed in the total and maximum glucose-lowering effect between Fiasp and NovoRapid. Comparable results were also observed across the doses investigated.

The differences observed in the pharmacodynamic profiles between Fiasp for the 0.2 U/kg dose was maintained for the dose range investigated (0.1-0.4 U/kg).

In the CSII setting a similar shift of the curve to the left for Fiasp compared to NovoRapid as in the single injection trials was observed. The onset of the glucose-lowering effect showed a greater difference between Fiasp and NovoRapid in the CSII setting than in single injection trials (time to 50 % GIR_{max}, -11.1 min vs -9.5 min; $tGIR_{max}$, -18.7 min vs -10.5 min), in line with the pharmacokinetic observation of a faster onset of exposure. The duration of the glucose-lowering effect was shorter with Fiasp, whereas no difference in $AUC_{GIR,\ 2\text{-}12\ h}$ was observed. In spite of the more pronounced onset of action, the total glucose-lowering effect did not differ between treatments in the CSII setting.

Low and comparable within-subject variation in the glucose-lowering effect was observed for both Fiasp and NovoRapid.

A linear dose-response was observed in the dose range 0.1-0.2 U/kg, whereas this was not confirmed for the 0.4 U/kg dose. The same pattern was observed for NovoRapid. Thus the 0.4 U/kg dose is on the top of the dose-response curve for both products. There was a good correlation between exposure and effect for Fiasp.

Meal test

Standardised meal tests were performed in the pharmacological trials 3889 and 3888, in the clinical CSII trial 3930 in order to investigate the pharmacodynamic properties of Fiasp and NovoRapid in a clinically relevant but still standardised setting.

Both in trial 3889 and 3888, a numerically lower increment in PPG during the first 2 hours was observed with Fiasp compared to NovoRapid after a standardised meal but the difference was not statistically significant. In the CSII trial 3930, the estimated mean PPG increment over the first 2 hours after the meal ($\Delta PG_{av,0\text{-}2h}$) was -0.99 mmol/L [-1.95; -0.03]$_{95\%\ CI}$ smaller with Fiasp (3.03 mmol/L) than with NovoRapid (4.02 mmol/L). The mean PPG increment over the first hour after the meal ($\Delta PG_{av,0\text{-}1h}$) was also lower with Fiasp than with NovoRapid, however not statistically significant.

Post-meal dosing was investigated in the clinical pharmacological trial 3921. When compared to NovoRapid, the glucose lowering effect with Fiasp was statistically significantly smaller.

Impact of site of injection and type of injection on the pharmacodynamic profile

The pharmacodynamic profile after s.c. injection at different injection sites (abdomen, upper arm and thigh) was investigated. From the graphical presentation of data after injection of Fiasp at different sites it appears as if the onset of action is not affected by the injection site chosen. However, at 1 and 2 hours after the dose, the curves separate indicating a lower and longer duration of action after an injection in the thigh compared to injection in the abdomen. These differences appear to be of the same magnitude as those observed when comparing Fiasp with NovoRapid. The main objective of the study was to investigate the pharmacokinetics of Fiasp when administered at different sites. Information on the pharmacokinetic differences observed is included in section 5.2 of the SmPC, and section 4.2 recommends administration in the abdominal wall and upper arm only.

No difference in the time to onset of action or the maximum effect of Fiasp was observed when injected subcutaneously or intramuscularly. This is reassuring as accidental intramuscular injection may occur.

Intrinsic factors

The effect of intrinsic factors (BMI, age, sex and ethnicity) as well as the influence of anti-insulin antibodies on the pharmacodynamic properties of Fiasp after subcutaneous injection was evaluated in comparison with NovoRapid. Furthemore, the pharmacodynamic properties of Fiasp were investigated in Japanese subjects. No clinically relevant effects of the intrinsic factors investigated were observed.

2.4.5. Conclusions on clinical pharmacology

The total serum exposure ($AUC_{IAsp,0-12h}$) and $C_{max,IAsp}$ were similar for Fiasp and NovoRapid, both in the individual trials and in the pooled pharmacokinetic analysis. The results for parameters reflecting the rate of exposure are consistent in all studies (including adults, children, elderly, Japanese, CSII setting) indicating a left shift of the serum concentration-time curve for Fiasp with a higher early exposure following administration of Fiasp compared to NovoRapid.

The pharmacodynamic profile of Fiasp in relation to that of NovoRapid has been adequately characterised. The pharmacodynamic data show that Fiasp (given before a meal) has an earlier onset of action than NovoRapid, while the total glucose-lowering effect remains unchanged. This was also observed in the CSII setting. This difference in onset of action resulted in lower post-prandial glucose increments in meal tests. When Fiasp was given post-meal, this effect was no longer observed. As a lower and longer duration of action was observed when

Fiasp was injected in the thigh, the SmPC only recommends injection in the abdominal wall or upper arm. The pharmacodynamic profile was not affected by intrinsic factors.

2.5. Clinical efficacy

The efficacy evaluation of Fiasp (in the final formulation intended for the market) is based on three therapeutic confirmatory trials evaluating efficacy and safety of Fiasp in subjects with T1DM and T2DM. In addition, two CSII trials provide supportive data evaluating Fiasp for CSII by external pump.

More than 2500 subjects with T1DM or T2DM were included in the clinical development programme overall, including 2068 randomised subjects in the 3 therapeutic confirmatory trials, 80 randomised subjects in the CSII trials as well as 395 randomised subjects in the clinical pharmacology trials.

2.5.1. Dose response studies

For dose-response studies, please refer to the Clinical pharmacology section of this report.

Considering that the phase 3 trials were conducted with a treat-to-target principle, the frequent visits and close monitoring with careful insulin titration of FIASP and NovoRapid, it is considered acceptable to proceed directly from phase 1 to phase 3 trials.

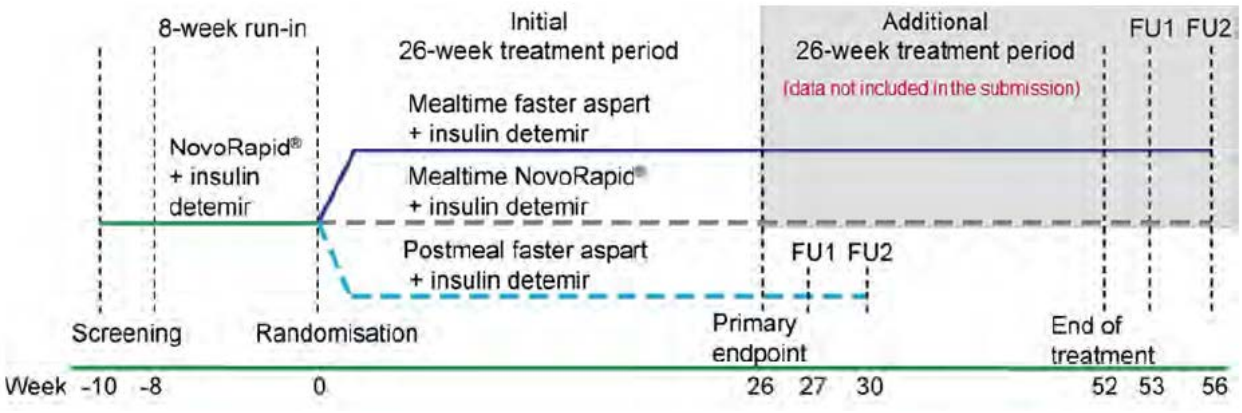
2.5.2. Main studies

Methods

Trial 3852 (26+26 weeks basal-bolus trial in subjects with T1DM)

This was a 26+26-week randomised (1:1:1), active-controlled, parallel-group, basal-bolus trial in 1143 subjects with T1DM on a pre-trial basal-bolus regimen for ≥12 months. The trial included a double-blind comparison of the efficacy and safety of mealtime Fiasp with mealtime NovoRapid, both administered 0-2 minutes prior to main meals. The trial also included a comparison of an open-label post-meal Fiasp arm (administered 20 minutes after start of the meal) with the mealtime NovoRapid arm. In all three treatment arms, the bolus insulin was given in combination with once or twice daily insulin detemir. After screening, subjects had their basal insulin switched to insulin detemir and their bolus insulin to NovoRapid, both on a unit-to-unit basis. During an 8 week run-in period, the basal insulin dose was then optimised using a treat-to-target approach. The primary and secondary confirmatory objectives were addressed based on results from the initial 26-week treatment period.

Subjects in the double-blind mealtime Fiasp and mealtime NovoRapid arms continued into an additional 26-week treatment period, primarily for further collection of safety information. The additional 26-week treatment period was ongoing at the time of the cut-off date for this application (10th March 2015).

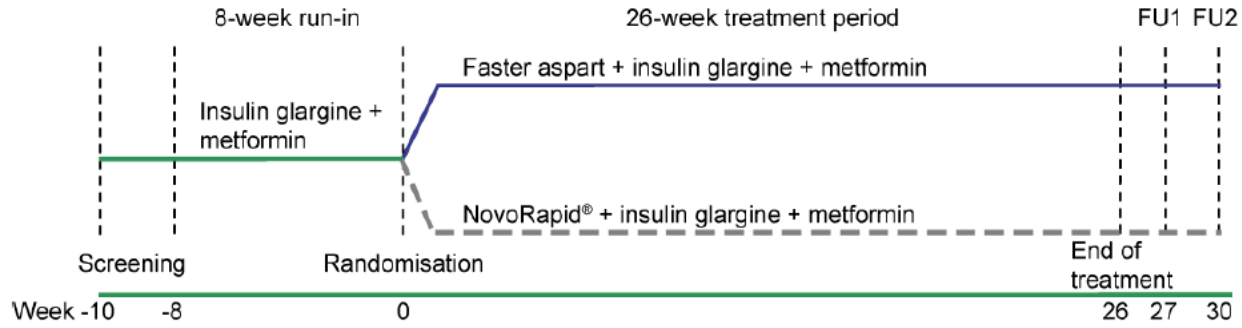


FU1: Follow-up 7 days after end of treatment for collection of treatment-emergent adverse events and new diabetes treatment. **FU2**: Follow-up 30 days after end of treatment for recording information on cardiovascular events requiring medical assistance and deaths.

Figure 14 Design of trial 3852

Trial 3853 (26-week basal-bolus trial in subjects with T2DM)

This was a 26-week randomised (1:1), double-blind, parallel-group, active-controlled basal-bolus trial in 689 subjects with T2DM on a pre-trial basal insulin + OAD regimen for ≥6 months. The trial compared the efficacy and safety of mealtime Fiasp with mealtime NovoRapid, both administered 0−2 minutes prior to main meals and both in combination with once-daily insulin glargine and metformin in a basal-bolus regimen. An 8-week run-in period was included at the start of which all OADs other than metformin were discontinued. During the run-in period the basal insulin treatment was optimised using a treat-to-target approach.



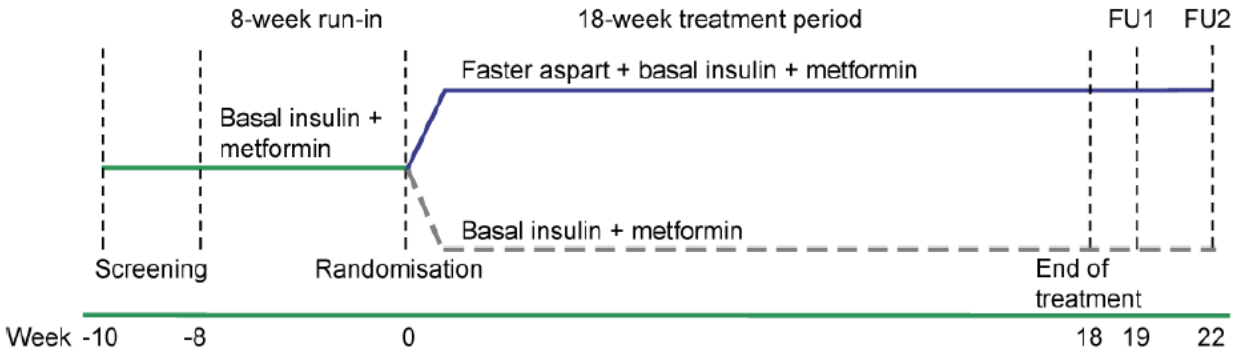
FU1: Follow-up 7 days after end of treatment for collection of treatment-emergent adverse events and new diabetes treatment. **FU2**: Follow-up 30 days after end of treatment for recording information on cardiovascular events requiring medical assistance and deaths.

Figure 15 Design of trial 3853

Trial 4049 (18-week basal-bolus vs. basal trial in subjects with T2DM)

This was an 18-week randomised (1:1), open-label, parallel-group, active-controlled basal-bolus vs. basal insulin therapy trial in 236 subjects with T2DM on a pre-trial basal insulin + OAD regimen for ≥6 months. The trial compared the efficacy and safety of mealtime Fiasp in a basal-bolus regimen with a basal insulin regimen. In both arms, the basal insulin was the subject's pre-trial basal insulin (once-daily insulin detemir, insulin glargine or human isophane insulin (Neutral Protamine Hagedorn (NPH) insulin). The subjects also continued

their pre-trial metformin regimen (dose and frequency), whereas all other OAD were discontinued at screening. During an 8 weeks run-in period, the once-daily basal insulin treatment was optimised using a treat-to-target approach.



FU1: Follow-up 7 days after end of treatment for collection of treatment-emergent adverse events and new diabetes treatment. **FU2**: Follow-up 30 days after end of treatment for recording information on cardiovascular events requiring medical assistance and deaths.

Figure 16 Design of trial 4049

Study Participants

Inclusion and exclusion criteria for the therapeutic confirmatory efficacy and safety trials (3852, 3853 and 4049) are presented in

Table 17 and Table 18, respectively. Subjects in the 3 therapeutic confirmatory trials had to fulfil an additional randomisation criterion related to their HbA1c levels measured a week prior to randomisation:

- HbA1c ≤9.5% (80 mmol/mol) (trial 3852, subjects with T1DM)
- HbA1c 7.0–9.5% (53–80 mmol/mol) (trial 3853, subjects with T2DM)
- HbA1c 7.0–9.0% (53–75 mmol/mol) (trial 4049, subjects with T2DM)

There were prespecified criteria for withdrawal in all the clinical trials.

Table 12 Inclusion criteria of the therapeutic confirmatory efficacy and safety trials: Trials 3852, 3853 and 4049

Inclusion criterion	Trial 3852 T1DM 26-week basal-bolus[f]	Trial 3853 T2DM 26-week basal-bolus	Trial 4049 T2DM 18-week basal-bolus vs. basal
Informed consent was obtained before any trial-related activities took place	X	X	X
Females and males aged ≥18 years at the time of screening	X	X	X
Clinical diagnosis of diabetes: T1DM for at least 12 months; T2DM for at least 6 months at time of screening	X	X	X
Treated with a basal-bolus insulin regimen for at least 12 months at the time of screening	X	–	–
Treated with a basal insulin	X[a]	X[b,c]	X[c]
Treated with unchanged dose of metformin, or metformin in combination with sulphonylurea, glinide, DPP-IV inhibitors and/or alpha-glucosidase inhibitors for at least 3 months	–	X	X
HbA_{1c} 7.0–9.5% (53–80 mmol/mol) (both inclusive)	X	X[d]	
HbA_{1c} 7.5–9.5% (58–80 mmol/mol) (both inclusive)			X[e]
Body mass index (BMI): ≤35.0 kg/m^2 (T1DM); ≤40 kg/m^2 (T2DM)	X	X	X
Ability and willingness to adhere to the protocol including SMPG profiles	X	X	X
Ability and willingness to eat at least 3 meals (breakfast, lunch and dinner) every day	X	X	X
Not currently using real time CGM system and/or willing not to use a real time CGM system during the trial other than the blinded one provided if selected to the CGM subgroup	X	X	–

CGM: continuous glucose monitoring. DPP-IV: dipeptidyl peptidase-IV. HbA1c: glycosylated haemoglobin A1c. NPH: neutral protamine hagedorn. OAD: oral antidiabetic drug. SMPG: self-measured plasma glucose. T1DM: type 1 diabetes mellitus. T2DM: type 2 diabetes mellitus.

[a]Treated with a basal insulin analogue (insulin detemir or insulin glargine) for at least 4 months

[b]Treated with basal insulin for at least 6 months

[c]Treated with once-daily insulin NPH, insulin detemir or insulin glargine for at least 3 months

[d]HbA1c 7.0-9.0% (53–75 mmol/mol) in the metformin plus other OADs group.

[e]HbA1c 7.5-9.0% (58–75 mmol/mol) in the metformin plus other OADs group.

[f]26+26 weeks trial. This application includes data only from the initial 26-week treatment period.

Table 13 Key exclusion criteria of the clinical trials included in the efficacy evaluation: Trials 3852, 3853, 4049, 3931 and 3930

Key exclusion criterion	Trial 3852 T1DM 26-week basal-bolus[b]	Trial 3853 T2DM 26-week basal-bolus	Trial 4049 T2DM 18-week basal-bolus vs. basal	Trial 3931 T1DM 6-week pump compatibility	Trial 3930 T1DM 3-way, 2-week period, crossover
CV disease in the last 6 months at screening, defined as stroke, decompensated heart failure New York Heart Association (NYHA) class III or IV, myocardial infarction, unstable angina pectoris, coronary arterial bypass graft or angioplasty	X	X	X	X	X
Recurrent severe hypoglycaemia (>1 severe hypoglycaemic event in the last 12 months[a]) or hypoglycaemic unawareness, or hospitalisation for diabetic ketoacidosis in the last 6 months	X	X	X	X	X
Use of any antidiabetic drug other than insulin in the previous 3 months	X	–	–	X	X
Any use of bolus insulin, except short-term use due to intermittent illness (no longer than 14 days' consecutive treatment) and not in the previous 3 months	–	X	X	–	–
Use of GLP-1 agonists and/or TZDs in the previous 3 months	–	X	X	–	–
History of abscess at the infusion site in the previous 6 months	–	–	–	X	X

GLP-1: glucagon-like peptide-1. T1DM: type 1 diabetes mellitus. T2DM: type 2 diabetes mellitus. TDZ: thiazolidinediones; CV: cardiovascular.

[a]Severe hypoglycaemia was defined as requiring hospitalisation in the last 6 months in trials 3931 and 3930.
[b]26+26 weeks trial. This application includes data only from the initial 26-week treatment period.

Treatments

Basal insulin titration during run-in and treatment period

In trials 3852 and 3853 (the basal-bolus trials), the basal insulin was titrated by the investigator on a weekly basis in the 8-week run-in period using a treat-to-target approach with a protocol specified pre-breakfast SMPG glycaemic target of 4.0–5.0 mmol/L. From randomisation and onwards, bolus titration was the focus of both trials 3852 and 3853.

In trial 4049, subjects continued on their once-daily basal insulin and metformin regimen at the same dose-level as before the trial. The basal insulin treatment was optimised using a treat-to-target approach, with a protocol specified pre-breakfast SMPG glycaemic target of 4.0–6.0 mmol/L. From randomisation and onwards, focus was placed on optimising the bolus insulin in the treatment arm with basal-bolus treatment.

Bolus insulin during run-in and treatment period

In trial 3852, in subjects with T1DM, subjects were switched from their pre-trial bolus insulin to mealtime NovoRapid at the start of the 8-week run-in period. NovoRapid was not to be titrated during the run-in period unless necessary for safety reasons. At randomisation, subjects were randomised to Fiasp (mealtime or post-meal) or NovoRapid for bolus insulin administration at each of the three main meals. Additional bolus doses were allowed if necessary. All subjects continued on the same bolus insulin dose (Fiasp or NovoRapid) after randomisation as at the end of the run-in period. The bolus dose was administered either 0–2 minutes before each main meal (mealtime dosing), which is in accordance with the approved label for NovoRapid, or 20 minutes after the start of the meal (post-meal dosing, Fiasp only).

Subjects who were by the investigator considered adequately trained during the run-in period to do flexible bolus adjustments based on the carbohydrate content of their meals were able to continue doing so after randomisation. The bolus insulin was titrated to pre-prandial or bedtime SMPG glycaemic target of 4.0–6.0 mmol/L at the subsequent meal or bedtime (for the dinner dose) in a treat-to-target fashion (Table 19).

In trial 3853, subjects were randomised to the addition of bolus insulin treatment with Fiasp or NovoRapid taken 0–2 minutes before each of the three main meals. Additional bolus doses were allowed if necessary. The bolus insulin start dose was 4 units at each main meal. Thereafter the bolus insulin dose was titrated daily to the prespecified pre-prandial or bedtime SMPG glycaemic target of 4.0–6.0 mmol/L at the subsequent meal or bedtime in a treat-to-target fashion (Table 19).

In trial 4049, in the basal-bolus arm, Fiasp was initiated with a start bolus dose of 4 units taken 0−2 minutes before each of the three main meals. Thereafter the bolus insulin was titrated daily to the pre-prandial or bedtime SMPG glycaemic target of 4.0–6.0 mmol/L at the subsequent meal or bedtime in a treat-to-target fashion (Table 19). Additional bolus doses were allowed if necessary.

Table 14 Fiasp and NovoRapid dose adjustment algorithm in trials 3852, 3853 and 4049

Preprandial or bedtime plasma glucose		Dose adjustment (U)
mmol/L	mg/dL	
<4.0	<71	-1
4.0–6.0	71–108	0
>6.0	>108	+1

SMPG: self-measured plasma glucose
In trial 3852, titration was done twice weekly based on SMPG values measured the previous 3-4 days (-1 unit if ≥1 SMPGs below target; no change if 0–1 SMPG above target or no SMPGs below target; +1 unit if ≥2 SMPGs above target or no SMPGs below target). In trials 3853 and 4049, titration was done daily based on the corresponding SMPG value measured the previous day.

Meal test

Trials 3852 (T1DM) and 3853 (T2DM) included a standardised meal test in a controlled setting at baseline and week 26 for measurement of parameters of PPG over 1, 2, 3 and 4 hours after meal ingestion.

Objectives

An overview of the assessments, primary and secondary confirmatory and supportive endpoints, is presented for the confirmatory therapeutic trials (trials 3852, 3853 and 4049) in Table 20.

Table 15 Prespecified assessments, primary and secondary efficacy endpoints in trials 3852, 3853 and 4049

Endpoint (change from baseline unless stated)	Trial 3852 26-week basal-bolus[d] T1DM	Trial 3853 26-week basal-bolus T2DM	Trial 4049 18-week basal-bolus vs. basal T2DM
Primary endpoint			
HbA_{1c}	X	X	X
Confirmatory secondary endpoints			
2-hour PPG increment (meal test)	X	X	N/A
Number of severe or BG confirmed hypoglycaemic episodes[a] (week 0 to 26)	X	X	
Body weight	X	X	
Other assessments and supportive secondary endpoints			
Glycaemic control parameters			
Subjects reaching HbA_{1c} targets and composite endpoints[e]	X	X	X
1-hour and 2-hour PPG (meal test)	X	X	–
1-hour PPG increment (meal test)	X	X	–
SMPG profiles[b] including:	X	X	X
PPG and PPG increments (SMPG)	X	X	X
PPG targets and composite endpoints (SMPG)	X	X	X
1,5-anhydroglucitol	X	X	X
Interstitial glucose[c]	X	X	–
Fasting plasma glucose	X	X	X
Fasting lipid profile			
Total cholesterol	X	X	X
HDL cholesterol	X	X	X
LDL cholesterol	X	X	X
Triglycerides	X	X	X
Insulin dose (total bolus and total basal)	X	X	X
Body weight	X	X	X
Patient reported outcomes[f]	X	X	–

BG: blood glucose. HbA1c: glycosylated haemoglobin A1c. HDL: high-density lipoprotein. LDL: low-density lipoprotein. PG: plasma glucose. PPG: postprandial glucose. SMPG: self-measured plasma glucose. T1DM: type 1 diabetes mellitus. T2DM: type 2 diabetes mellitus.
[a] Definition of Severe or BG confirmed: Subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56mg/dL), treatment emergent hypoglycaemic episodes.
[b] 7-9-7-point SMPG profiles in trials 3852 and 3853, 7-8-7-point SMPG profiles in trial 4049.
[c] Subgroup of individuals wearing a CGM device;
[d] 26+26 weeks trial. This application includes data only from the initial 26-week treatment period.
[e] Composite endpoints: number of subjects reaching HbA1c targets without severe hypoglycaemia or without severe hypoglycaemia and minimal weight gain.
[f] Patient reported outcome: Endpoints based on the Short-Form 36 Health Survey version 2 (SF-36v2)23 and treatment related impact measure – diabetes (TRIM-D)24 questionnaires.

Sample size

Studies 3852 and 3853

For study 3852, the sample size is determined based on the combined power to test the primary hypothesis (step 1), and step 2 and 3 in the hierarchical testing procedure. For sample size of study 3853, step 2 was considered in addition to the primary hypothesis. Consequently, number of treatment emergent hypoglycaemic

events was not considered in the sample size calculations, although it was advised by the EMA that this variable needed to be part of the primary evaluation (scientific advice from 2011). This was suboptimal, and seems to be intentional.

Study 4049

The minimum randomised sample size required to meet the primary objective with at least 90% power is 218 with an assumed SD of 1.2%. The expected difference between treatment used in the calculations were 0.53%. The assumptions are reasonable, the expected treatment difference is adjusted downwards to account for a less pronounced difference in withdrawn subjects compared to completers.

Randomisation

In **study 3852** the randomisation was carried out in a 1:1:1 manner to the 3 treatments using the IV/WRS:

- Mealtime Fiasp and insulin detemir
- Mealtime NovoRapid and insulin detemir
- Post meal Fiasp and insulin detemir.

The randomisation was stratified based on the following 3 factors:

- Method used by the subject for adjusting the bolus insulin (principles of flexible dosing based on the meal carbohydrate content (carbohydrate counting) or using pre-defined bolus dosing algorithm)
- Current basal treatment regimen (once or twice daily dosing)
- Whether the subject participates in the CGM and frequently sampled meal test subgroup (yes or no).

In study **3853** the randomisation was carried out in a 1:1 manner to two different treatments using the IV/WRS:

- Mealtime Fiasp in addition to insulin glargine and metformin
- Mealtime NovoRapid in addition to insulin glargine and metformin.

In order to aim for an equal number of subjects for the two treatment groups in the CGM-subgroup the trial was stratified according to CGM-subgroup participation (yes/no).

In **study 4049** the randomisation is 1:1 and stratified to ensure an equal distribution of Subjects on the three types of once daily basal insulin in the two treatment arms.

Blinding (masking)

For studies 3852 and 3853 the initial 26-week treatment with mealtime Fiasp and NovoRapid was double-blinded. Study 4049 was an open-label study, and this was considered reasonable.

Statistical methods

Trial 3852 and 3853

The evaluation of efficacy was based on the full analysis set (FAS). For the sensitivity analyses, a per protocol analysis set was defined, as well as a completer analysis set and a sensitivity analysis set for 1 to 4 hour PPG endpoints.

The primary endpoint, change from baseline in HbA1c after 26 weeks of randomised treatment, was analysed by similar methods in the two non-inferiority studies, using a mixed-effects model for repeated measurements (MMRM). The model included treatment, region and stratification as fixed effects, subject as random effect, HbA1c at baseline as covariate and interactions between all fixed effects and visit, and between the covariate and visit. In study 3852, stratification effect included eight strata, based on the combination of the three stratification variables. In study 3853, the stratification effect was only CGM. From the MMRM model, estimated treatment difference and 95% confidence interval (CI) was obtained.

The null-hypothesis (H_0) was that the mean treatment difference (Fiasp minus NovoRapid) for change in HbA1c at week 26 was greater than 0.4%. The null-hypothesis was to be rejected, and non-inferiority of Fiasp considered confirmed, if the upper bound of the two-sided 95% confidence interval for the mean HbA1c treatment difference was below or equal to 0.4%. If non-inferiority was confirmed for the primary endpoint, the trials also compared treatment arms for a number of confirmatory secondary endpoints in a stepwise hierarchical (fixed sequence) procedure in order to control the family-wise type I error rate in the strong sense. This was based on a priority ordering of the null hypotheses, and testing them in this order using the two-sided 95% confidence interval approach until an insignificant result appeared. The steps in the hierarchical testing procedure in study 3852 and study 3853 are presented in Figure 19, respectively. The rejection of the null hypothesis was only confirmed for the endpoints where all previous null-hypotheses had been rejected in favour of Fiasp.

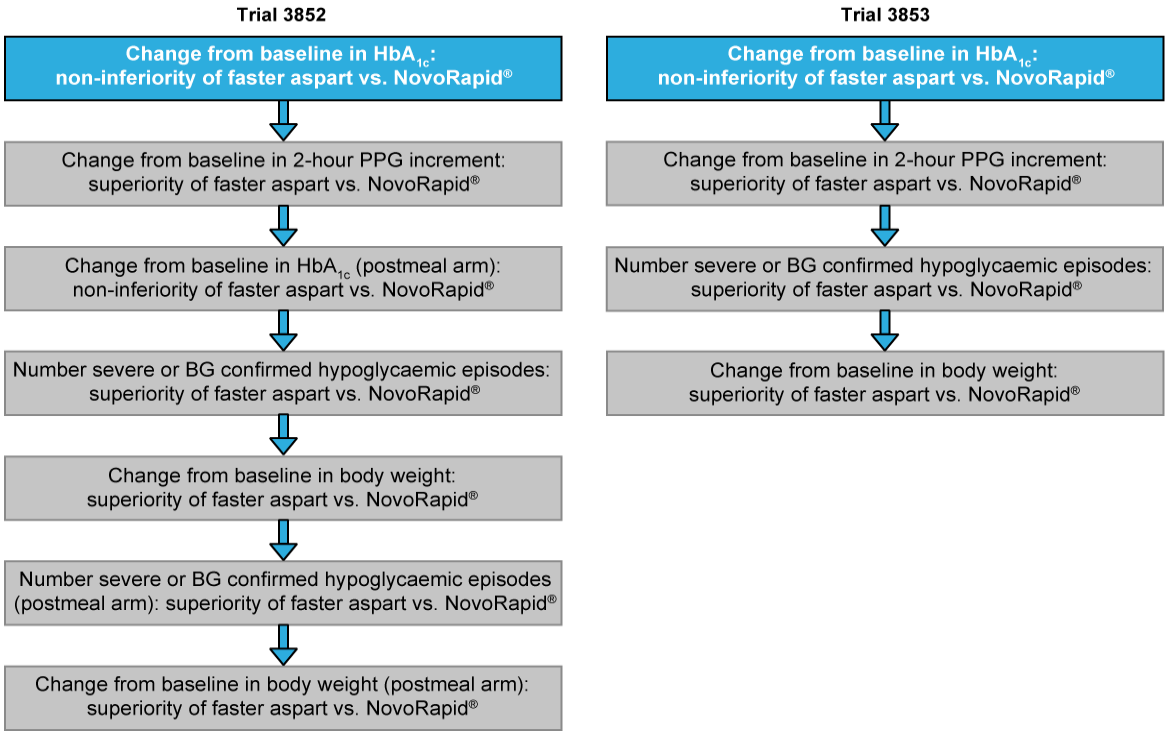


Figure 17 Testing hierarchy for the confirmatory statistical analyses: Trials 3852 and 3853

The main purpose of the sensitivity analyses was to investigate the impact of missing data on the primary analysis. A series of sensitivity analyses were pre-specified in the statistical analysis plans, including re-run of the primary MMRM analysis based on the per protocol analysis set and the completer analysis set, an analysis of variance (ANOVA) using the last observation carried forward (LOCF) imputation, and several multiple imputation

methods using a copy-reference approach. Also *post-hoc* sensitivity analyses were performed, with multiple imputation method using jump-to-reference approach and tipping point analysis.

Analysis methods of the confirmatory secondary endpoints are presented in Table 21.

Table 16 Statistical analyses of the confirmatory secondary endpoints

Endpoint	Statistical method
Change from baseline in 2-hour PPG increments after 26 weeks of treatment	ANOVA model including treatment, strata and region as factors and with 2-hour PPG increment at baseline as covariate.
Number of treatment-emergent severe or BG confirmed hypoglycaemic episodes from baseline until week 26	Negative binomial regression model with a log-link function, and the logarithm of the time period in which a hypoglycaemic episode was considered treatment-emergent as offset. The model included treatment, strata and region as factors.
Change from baseline in body weight after 26 weeks of treatment	MMRM model similar to the model used for analysis of the primary endpoint except with body weight as baseline covariate.

Across trial analysis was prospectively planned for study 3852 and study 3853, in order to add statistical power and confirm the potential findings of the individual studies. Superiority of Fiasp treatment over NovoRapid was tested on 1-hour (the primary endpoint) and 2-hour mealtime PPG increments (change from baseline to 26 weeks of treatment) based on the standardised meal test, using ANOVA model with treatment, type of diabetes, CGM-strata and region as factors and the corresponding PPG increment at baseline as a covariate. In addition, number of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes (in total, daytime, and nocturnal) from baseline until week 26, was analysed using negative binomial regression model with a log-link function, the logarithm of the exposure as offset, and with treatment, type of diabetes, CGM strata and region as factors.

Trial 4049

Analyses of efficacy endpoints will be based on the Full Analysis Set (FAS). Change from baseline in HbA1c after 18 weeks of treatment was analysed using a mixed-effect model for repeated measurements (MMRM) where all calculated changes in HbA1c from baseline at visits 16, 22 and 28 were included in the analysis. This model will include treatment, region, strata (type of once daily basal insulin (insulin detemir, insulin glargine or human isophane insulin, NPH)) as fixed effects, Subject as random effect, HbA1c at baseline as covariate and interactions between all fixed effects and visit and between covariate and visit. An unstructured covariance matrix was used to describe the variability for the repeated measurements for a subject. From this model contrasts were set up to estimate the relevant treatment difference together with a 95% confidence interval and associated p-value.

Superiority is considered confirmed if the upper bound of the two-sided 95% confidence interval for the estimated treatment difference (FIAsp+basal minus basal), which is calculated using the FAS, is below 0 %.

Results

Participant flow

Subject disposition of the subjects included in the therapeutic confirmatory trials (3852, 3853 and 4049) are presented by treatment in Table 22. Overall, a total of 1219 subjects with T1DM or T2DM were exposed to Fiasp: 763 subjects with T1DM and 456 subjects with T2DM in the therapeutic confirmatory trials.

Table 17 Subject disposition in the therapeutic confirmatory trials: 3852, 3853 and 4049

	Trial 3852 T1DM 26-week basal-bolus[a]			Trial 3853 T2DM 26-week basal-bolus		Trial 4049 T2DM 18-week basal-bolus vs. basal	
	Faster aspart (mealtime) N=381 (%)	NovoRapid (mealtime) N=380 (%)	Faster aspart (postmeal) N=382 (%)	Faster aspart N=345 (%)	NovoRapid N=344 (%)	Faster aspart basal-bolus N=116 (%)	Basal N=120 (%)
Randomised	381 (100.0)	380 (100.0)	382 (100.0)	345 (100.0)	344 (100.0)	116 (100.0)	120 (100.0)
Exposed	386*	380	377*	341 (98.8)	341 (99.1)	115 (99.1)	120 (100.0)
Withdrawn at/after randomisation	30 (7.9)	24 (6.3)	27 (7.1)	44 (12.8)	39 (11.3)	9 (7.8)	5 (4.2)
Due to adverse event	5 (1.3)	2 (0.5)	4 (1.0)	2 (0.6)	5 (1.5)	2 (1.7)	1 (0.8)
Withdrawal criteria	7 (1.8)	8 (2.1)	10 (2.6)	20 (5.8)	15 (4.4)	4 (3.4)	1 (0.8)
Pregnancy	0	2 (0.5)	1 (0.3)	0	0	0	0
Lost to follow up	0	2 (0.5)	3 (0.8)	5 (1.4)	2 (0.6)	0	1 (0.8)
Withdrawal by subject	17 (4.5)	10 (2.6)	7 (1.8)	15 (4.3)	15 (4.4)	3 (2.6)	1 (0.8)
Lack of efficacy	0	0	0	0	1 (0.3)	0	0
Other	1 (0.3)	0	2 (0.5)	2 (0.6)	1 (0.3)	0	1 (0.8)
Completed trial	351 (92.1)	356 (93.7)	355 (92.9)	301 (87.2)	305 (88.7)	107 (92.2)	115 (95.8)
Full analysis set	381 (100.0)	380 (100.0)	382 (100.0)	345 (100.0)	344 (100.0)	116 (100.0)	120 (100.0)
Safety analysis set	386*	380	377*	341 (98.8)	341 (99.1)	115 (99.1)	120 (100.0)

Recruitment

Trial 3852 (26+26 weeks basal-bolus trial in subjects with T1DM) : A total of 169 sites screened subjects and 163 sites randomised subjects in 9 countries across North America and Europe.

Trial 3853 (26-week basal-bolus trial in subjects with T2DM) : A total of 135 sites screened subjects and 123 sites randomised subjects in 9 countries across North America, Europe and Asia (India).

Trial 4049 (18-week basal-bolus vs. basal trial in subjects with T2DM): A total of 51 sites screened subjects and 45 sites randomised/assigned subjects in 6 countries across North and South America, Europe and Asia (India).

All studies were global, multicentre studies. All studies included a relevant proportion of patients from EU.

Conduct of the study

No protocol amendment was made after the initiation of any of the trials (or inclusion of first patient). The amendments made are not considered to affect the outcome or interpretation of the data.

With regards to trials 3852 and 3853, the Applicant submitted exhaustive data listings with protocol deviations. In the response to D120 LOQ the applicant explained that their use of strict definitions of important protocol deviations had resulted in a large number of registered protocol deviations; the Applicant performed the requested re-run of the non-inferiority analyses based on the restricted PP population. The results of this

analysis were almost identical to that of the original PP population and confirmed the results of the primary non-inferiority analysis of HbA1c.

In trial 4049, protocol deviations were rather few and evenly distributed between treatment groups. The data does not evoke any concerns on the conduct of the study.

Baseline data

The baseline characteristics for randomised subjects in trials 3852, 3853 and 4049 are summarised in Table 23.

Table 18 Baseline characteristics for randomised subjects in the therapeutic confirmatory trials: 3852, 3853 and 4049

	Trial 3852 T1DM 26-week basal-bolus[c]			Trial 3853 T2DM 26-week basal-bolus		Trial 4049 T2DM 18-week basal-bolus vs. basal	
	Faster aspart (mealtime) N=381	Faster aspart (postmeal) N=382	NovoRapid (mealtime) N=380	Faster aspart N=345	NovoRapid N=344	Faster aspart basal-bolus N=116	Basal N=120
Age (years)							
Mean (SD)	46.1 (13.8)	43.5 (13.7)	43.7 (14.0)	59.6 (9.3)	59.4 (9.6)	57.5 (9.9)	57.4 (8.5)
Min–max	18.0–83.0	18.0–77.0	19.0–78.0	33.0–82.0	21.0–83.0	27.0–77.0	36.0–77.0
Age group (years)							
18–64	346 (90.8)	359 (94.0)	352 (92.6)	241 (69.9)	248 (72.1)	86 (74.1)	91 (75.8)
≥65	35 (9.2)	23 (6.0)	28 (7.4)	104 (30.1)	96 (27.9)	30 (25.9)	29 (24.2)
≥75	4 (1.0)	3 (0.8)	8 (2.1)	13 (3.8)	12 (3.5)	4 (3.4)	2 (1.7)
Sex[d]							
Female	166 (43.6)	163 (42.7)	142 (37.4)	182 (52.8)	171 (49.7)	61 (52.6)	61 (50.8)
Male	215 (56.4)	219 (57.3)	238 (62.6)	163 (47.2)	173 (50.3)	55 (47.4)	59 (49.2)
Race[d]							
White	363 (95.3)	355 (92.9)	348 (91.6)	277 (80.3)	281 (81.7)	80 (69.0)	85 (70.8)
Black or African American	5 (1.3)	12 (3.1)	9 (2.4)	22 (6.4)	18 (5.2)	5 (4.3)	4 (3.3)
Asian	5 (1.3)	2 (0.5)	7 (1.8)	40 (11.6)	42 (12.2)	31 (26.7)	31 (25.8)
American Indian or Alaska Native	1 (0.3)	0	0	3 (0.9)	0	0	0
Native Hawaiian or other Pacific Islander	0	1 (0.3)	2 (0.5)	2 (0.6)	0	0	0
Other[a]	7 (1.8)	12 (3.2)	14 (3.7)	1 (0.3)	3 (0.9)	0	0
Ethnicity[d]							
Hispanic or Latino	33 (8.7)	30 (7.9)	16 (4.2)	26 (7.5)	18 (5.2)	40 (34.5)	48 (40.0)
Not Hispanic or Latino	348 (91.3)	352 (92.1)	364 (95.8)	319 (92.5)	326 (94.8)	76 (65.5)	72 (60.0)
Body weight (kg)							
Mean (SD)	78.6 (14.9)	80.5 (15.9)	80.2 (15.2)	89.0 (16.9)	88.3 (16.7)	82.2 (16.2)	85.1 (17.3)
Min–max	45.3–131.6	46.0–140.0	41.0–124.3	54.9–139.1	53.1–147.6	49.6–133.1	52.3–133.2
BMI (kg/m^2)							
Mean (SD)	26.4 (3.8)	26.9 (4.1)	26.7 (3.7)	31.5 (4.7)	31.0 (4.5)	30.4 (5.0)	31.1 (4.7)
Min–max	18.1–35.8	17.0–37.9	17.1–36.8	20.6–42.4	20.6–40.9	19.9–40.9	21.2–40.5
BMI category (kg/m^2)							
<18.5	1 (0.3)	7 (1.8)	1 (0.3)	0	0	0	0
18.5–24.9	143 (37.5)	123 (32.2)	128 (33.7)	32 (9.3)	36 (10.5)	19 (16.4)	10 (8.3)
25–29.9	168 (44.1)	156 (40.8)	174 (45.8)	109 (31.6)	108 (31.4)	36 (31.0)	46 (38.3)
30-34.9	67 (17.6)	87 (22.8)	72 (18.9)	123 (35.7)	131 (38.1)	35 (30.2)	34 (28.3)
≥35	2 (0.5)	9 (2.4)	5 (1.3)	81 (23.5)	69 (20.1)	26 (22.4)	30 (25.0)
Duration of diabetes (years)[d]							
Mean (SD)	20.9 (12.9)	19.5 (12.1)	19.3 (11.8)	13.2 (6.7)	12.3 (6.3)	10.9 (6.1)	11.8 (7.4)
Min–max	1.3–65.4	1.2–59.2	1.2–57.4	2.0–39.0	1.0–38.0	2.0–29.0	1.0–33.0
HbA_{1c} (%)							
Mean (SD)	7.62 (0.71)	7.63 (0.72)	7.58 (0.68)	7.96 (0.68)	7.89 (0.71)	7.93 (0.69)	7.92 (0.68)
Min–max[b]	6.0–9.8	6.1–9.8	5.6–9.6	6.7–10.6	5.3–10.0	6.4–11.4	6.4–10.2
HbA_{1c} (mmol/mol)							
Mean (SD)	59.73 (7.73)	59.94 (7.88)	59.31 (7.45)	63.53 (7.47)	62.70 (7.73)	63.20 (7.59)	63.07 (7.44)
Min–max	42.1–83.6	43.2–83.6	37.7–81.4	49.7–92.4	34.4–85.8	46.5–101.1	46.5–88.0
FPG (mg/dL)							
Mean (SD)	151.4 (55.8)	145.6 (56.9)	141.8 (50.2)	121.7 (32.7)	122.7 (35.1)	132.5 (43.5)	138.9 (51.4)
Min–max	41.4–400.0	18.0–454.1	52.3–324.4	45.1 ; 254.1	55.9 ; 293.7	66.7–304.5	48.7–324.4
FPG (mmol/L)							
Mean (SD)	8.4 (3.1)	8.1 (3.2)	7.9 (2.8)	6.8 (1.8)	6.8 (2.0)	7.4 (2.4)	7.7 (2.9)
Min–max	2.3–22.2	1.0–25.2	2.9–18.0	2.5–14.1	3.1–16.3	3.7–16.9	2.7–18.0
1,5-anhydroglucitol (µg/mL)							
Mean (SD)	4.18 (2.39)	4.08 (2.60)	3.80 (2.65)	7.24 (5.16)	7.18 (4.72)	8.16 (5.37)	7.70 (4.67)
Min–max	0.4–17.4	0.2–23.2	0.4–25.7	1.0–32.9	0.5–28.8	1.2–30.8	1.1–27.4

BMI: body mass index. FPG: fasting plasma glucose. HbA_{1c}: glycosylated haemoglobin A_{1c}. Max: maximum value. Min: minimum value. SD: standard deviation. T1DM: type 1 diabetes mellitus. T2DM: type 2 diabetes mellitus. Data are at

randomisation and are mean (SD) or number (%) for the full analysis set. [a]In trial 3852, race group 'other' includes subjects from Belgium who did not provide information about race. [b]Some baseline HbA_{1c} values are outside the HbA_{1c} randomisation criteria , which were assessed 1 week prior to randomisation. However, all subjects did fulfil the randomisation criteria.[c]26+26 weeks trial. This application includes data only from the initial 26-week treatment period. [d] Obtained at screening

Numbers analysed

The number of randomised subjects was somewhat larger than initially planned for study 3852. According to the analysis sets presented in study 3852, relatively high percentages of subjects complied with the protocol and completed the trial, which is indicative of a successfully conducted trial. The per protocol and trial completion numbers were lower for study 3853. As conventional, the per protocol analysis set was prospectively defined. Further to CHMP questions regarding reported protocol deviations (see above - conduct of the study), the requested re-run of the non-inferiority analyses based on the restricted PP population was submitted. The results of this analysis were almost identical to that of the original PP population and, thus, confirmed the results of the primary non-inferiority analysis of HbA1c.

In trial 4049 the drop-outs were few and evenly distributed between age groups.

Outcomes and estimation

Prespecified hierarchical testing in trials 3852 and 3853

In trials 3852 and 3853, the confirmatory endpoints were analysed using a hierarchical testing procedure to control the type I error rate. The results of the testing procedures are shown in Table 24 (trial 3852) and Table 25 (trial 3853).

Table 19 Confirmatory statistical analyses for trial 3852

Endpoint	Estimate [95% CI]	p-value	Conclusion
PRIMARY			
1) Change from baseline in HbA1c after 26 weeks of treatment			
Treatment difference			
Faster aspart (meal) - NovoRapid (meal) (%)	-0.15 [-0.23; -0.07]	<0.0001	Non-inferiority confirmed
Faster aspart (meal) - NovoRapid (meal) (mmol/mol)	-1.62 [-2.50; -0.73]		
CONFIRMATORY SECONDARY			
2) Change from baseline in 2-hour PPG increment after 26 weeks of treatment (meal test)			
Treatment difference			
Faster aspart (meal) - NovoRapid (meal) (mmol/L)	-0.67 [-1.29; -0.04]	0.0187	Superiority confirmed
Faster aspart (meal) - NovoRapid (meal) (mg/dL)	-12.01 [-23.33; -0.70]		
3) Change from baseline in HbA1c after 26 weeks of treatment			
Treatment difference			
Faster aspart (post) - NovoRapid (meal) (%)	0.04 [-0.04; 0.12]	<0.0001	Non-inferiority confirmed
Faster aspart (post) - NovoRapid (meal) (mmol/mol)	0.47 [-0.41; 1.36]		
4) Number of treatment emergent severe or BG confirmed hypoglycemic episodes			
Treatment ratio			
Faster aspart (meal) / NovoRapid (meal)	1.01 [0.88; 1.15]	0.5404	Superiority not confirmed
5) Change from baseline in body weight (kg) after 26 weeks of treatment			
Treatment difference			
Faster aspart (meal) - NovoRapid (meal)	0.12 [-0.30; 0.55]	0.7176	Testing procedure stopped
6) Number of treatment emergent severe or BG confirmed hypoglycemic episodes			
Treatment ratio			
Faster aspart (post) / NovoRapid (meal)	0.92 [0.81; 1.06]	0.1218	
7) Change from baseline in body weight (kg) after 26 weeks of treatment			
Treatment difference			
Faster aspart (post) - NovoRapid (meal)	0.16 [-0.27; 0.58]	0.7655	

BG:

Blood glucose. CI: Confidence interval. PPG: Postprandial glucose. P-values are from the 1-sided test for non-inferiority and superiority respectively evaluated at the 2.5% level. The conversion factor between mmol/L and mg/dL is 0.0555.

Table 20 Confirmatory statistical analyses: Trial 3853

Endpoint	Estimate [95% CI]	p-value	Conclusion
PRIMARY			
1) Change from baseline in HbA1c (%) after 26 weeks of treatment			
Treatment difference			
Faster aspart - NovoRapid (%)	-0.02 [-0.15; 0.10]	<0.0001	Non-inferiority confirmed
Faster aspart - NovoRapid (mmol/mol)	-0.24 [-1.60; 1.11]		
CONFIRMATORY SECONDARY			
2) Change from baseline in 2-hour PPG increment after 26 weeks of treatment			
Treatment difference			
Faster aspart - NovoRapid (mmol/L)	-0.36 [-0.81; 0.08]	0.0531	Superiority not confirmed
Faster aspart - NovoRapid (mg/dL)	-6.57 [-14.54; 1.41]		
3) Number of treatment emergent severe or BG confirmed hypoglycaemic episodes			
Treatment Ratio			
Faster aspart / NovoRapid	1.09 [0.88; 1.36]	0.7877	Testing Procedure Stopped
4) Change from baseline in body weight (kg) after 26 weeks of treatment			
Treatment difference			
Faster aspart - NovoRapid	0.00 [-0.60; 0.61]	0.5061	

BG: Blood glucose. CI: Confidence interval. PPG: Postprandial glucose. P-values are from the 1-sided test for non-inferiority and superiority respectively evaluated at the 2.5% level. The conversion factor between mmol/L and mg/dL is 0.0555.

Description of selected endpoints

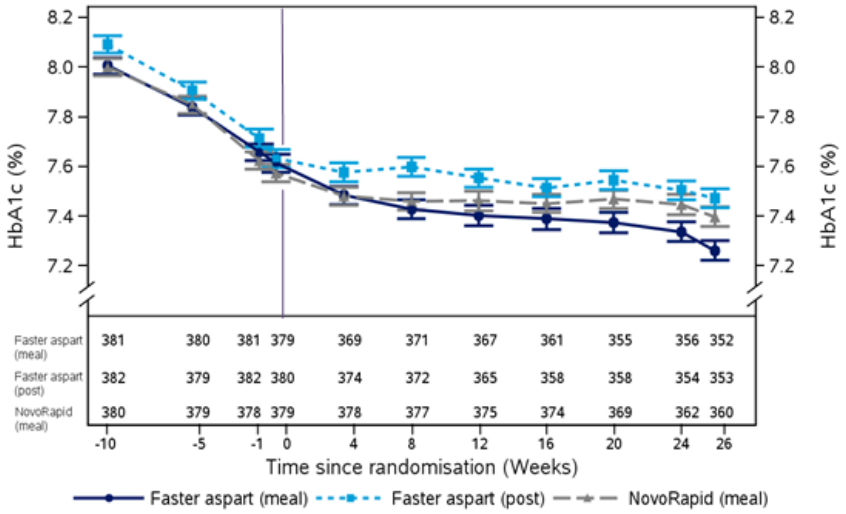
HbA1c over time

Change in HbA1c from baseline to end of treatment was the primary endpoint in each of the therapeutic confirmatory trials (3852, 3853 and 4049;

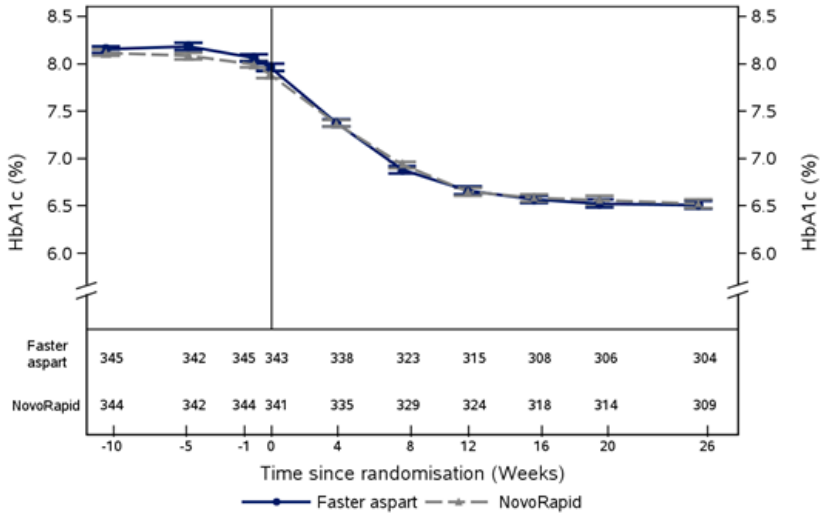
Table **26**). The change in HbA1c in the 3 trials is presented over time in Figure 20. Both the 8-week run-in period to optimise basal insulin treatment and the treatment period are displayed with a vertical line marking the baseline (randomisation). In trial 3852 in subjects with T1DM, all subjects received NovoRapid as bolus insulin during the run-in period. In trials 3853 and 4049 in subjects with T2DM, all OADs other than metformin were discontinued at the start of the run-in period, during which subjects were treated with basal insulin and metformin. Bolus insulin treatment was not initiated until at randomisation. The mean estimates and treatment differences for the primary endpoint are shown in

Table **26** for the 3 trials.

Trial 3852



Trial 3853



Trial 4049

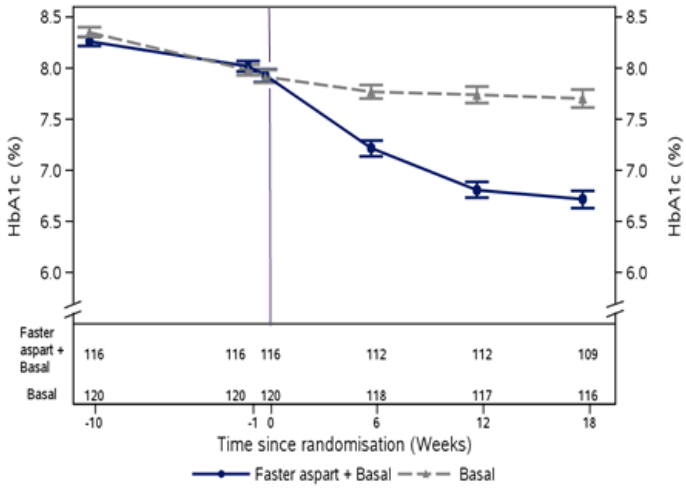


Figure 18 HbA1c by treatment week in trials 3852, 3853 and 4049

Data are observed means ± standard error bars. Vertical line marks randomisation.

Table 21 Change from baseline in HbA1c in trials 3852, 3853 and 4049

	Trial 3852 26-week basal-bolus[a] T1DM	**Trial 3853 26-week basal-bolus T2DM**	**Trial 4049 18-week basal-bolus vs. basal T2DM**
	Fiasp (meal), N=381/ Fiasp (post), N=382 / NovoRapid (meal), N=380	Fiasp, N=345 / NovoRapid , N=344	Fiasp + basal, N=116 / Basal, N=120
Baseline HbA_{1c}, observed means (%)	7.62 / 7.63 / 7.58	7.96 / 7.89	7.93 / 7.92
Change in HbA_{1c}, est. means (%-points)	-0.32 / -0.13 / -0.17	-1.38 / -1.36	-1.16 / -0.22
	Fiasp (meal) vs. NovoRapid (meal)	Fiasp vs. NovoRapid	Fiasp+ basal vs. basal
Treatment difference [95% CI]	-0.15 [-0.23; -0.07][b]	-0.02 [-0.15; 0.10][b]	-0.94 [-1.17; -0.72][b]
	Fiasp (post) vs. NovoRapid (meal)		
Treatment difference [95% CI]	0.04 [-0.04; 0.12][b]		

CI: confidence interval. HbA1c: glycosylated haemoglobin A1c. est.: estimated; N: number of subjects in full analysis set; T1DM: type 1 diabetes mellitus. T2DM: type 2 diabetes mellitus.
[a]Data based on initial 26-week treatment period.
[b]Result of confirmatory statistical analyses (trial 3852: Table 24, trial 3853: Table 25 and Trial 4049. Data are based on the full analysis set. The analysis is based on a mixed-effect model for repeated measures.

Subjects achieving HbA_{1c} targets

The proportion of subjects achieving the ADA HbA_{1c} target of <7.0% at the end of treatment and related composite endpoints were derived in all 3 therapeutic confirmatory trials. The observed mean percentages of subjects achieving HbA_{1c} <7.0% as well as the percentage of subjects with HbA_{1c} <7.0% without severe hypoglycaemia and the percentage of subjects with HbA_{1c} <7.0% without severe hypoglycaemia and with minimal weight gain are presented by trial and treatment in Figure 21.

In all 3 trials, the percentage of subjects achieving target HbA_{1c} <7% increased from baseline to end of treatment (Figure 21). The increase was most pronounced in trial 3853 and in the basal-bolus group in trial 4049 due to the intensification of insulin therapy.

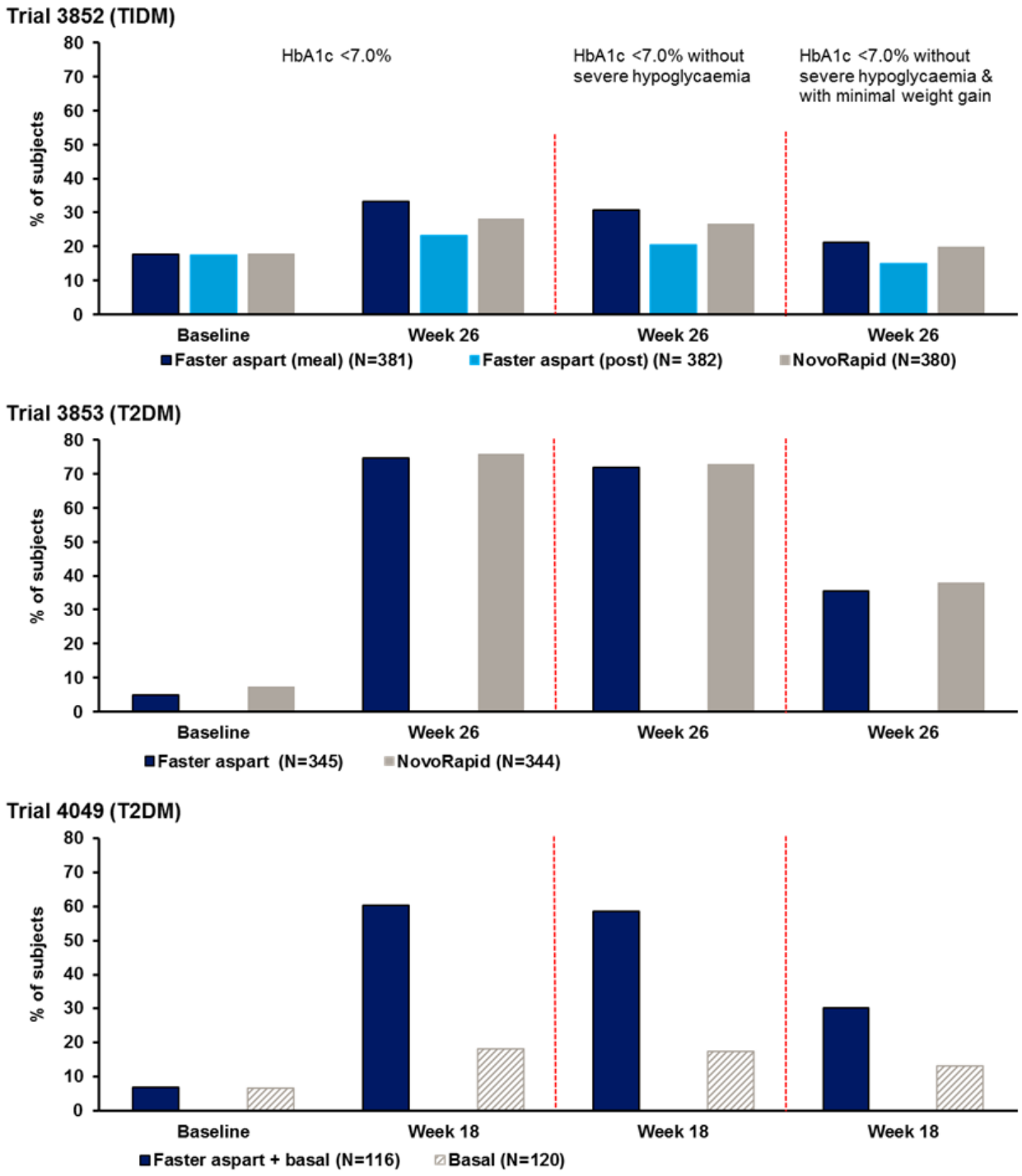


Figure 19 Subjects achieving HbA_{1c} targets in trials 3852, 3853 and 4049

Data are observed means for the full analysis set. HbA_{1c}: glycosylated haemoglobin A1c. N: number of subjects in full analysis set. Without severe hypoglycaemia: without severe hypoglycaemia during treatment period. Minimal weight gain is a weight gain of <3.0%.

Postprandial glucose in standardised meal test

In trials 3852 and 3853, standardised meal tests were included at baseline and after 26 weeks of treatment for the measurement of postprandial glucose (PPG) over 1, 2, 3 and 4 hours. The corresponding PPG increments were derived by subtracting the PPG measurement from the pre-prandial plasma glucose measurement.

Trial 3852 – postprandial glucose increments

Mean increments in plasma glucose during the meal test at baseline and after 26 weeks of treatment are presented in Figure 22 for trial 3852.

Mealtime Fiasp

The 2-hour PPG increment decreased from baseline to the end of treatment (estimated change: -0.29 mmol/L) with mealtime Fiasp, whereas it increased with mealtime NovoRapid (estimated change: 0.38 mmol/L). The estimated mean treatment difference of -0.67 mmol/L [-1.29; -0.04]$_{95\%CI}$ was statistically significant in favour of Fiasp.

The 1-hour PPG increment was reduced from baseline with mealtime Fiasp (estimated change: -0.84 mmol/L), and increased with mealtime NovoRapid (estimated change: 0.34 mmol/L) with the estimated mean treatment difference being -1.18 mmol/L [-1.65; -0.71]$_{95\%CI}$. The change from baseline was statistically significantly different for the two treatments in favour of mealtime Fiasp as also seen for the 2-hour PPG increment.

Post-meal Fiasp

The 1-hour PPG increment also increased from baseline with post-meal Fiasp (estimated change: 1.27 mmol/L), and the estimated increase was statistically significantly greater for post-meal Fiasp compared to mealtime NovoRapid. The estimated treatment difference (post-meal Fiasp – mealtime NovoRapid) was statistically significant in favour of mealtime NovoRapid (0.93 mmol/L [0.46; 1.40]$_{95\%CI}$). There were no statistically significant treatment differences (post-meal Fiasp – NovoRapid) in PPG increments at 2, 3 and 4 hours (120, 180 and 240 minutes) after start of the meal test.

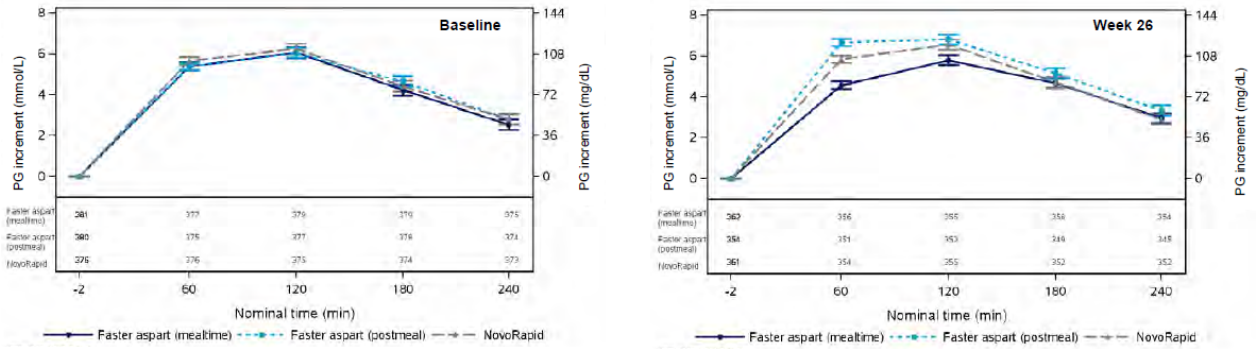


Figure 20 Plasma glucose increments at baseline and after 26 weeks of treatment based on meal test in trial 3852

PG: plasma glucose. Full analysis set. Error bars: ± standard error (mean). Observed data, except for the cases where glucose or glucagon is administered, in which case the last measurement before rescue intervention is carried forward. Numbers under graph are number of subjects at each time point. Conversion factor between mmol/L and mg/dL is 0.0555.

Trial 3853 – postprandial glucose increments

Mean plasma glucose increments calculated based on meal tests at baseline and after 26 weeks of treatment are presented in Figure 23.

Fiasp reduced the 2-hour PPG increment by 3.24 mmol/L (estimated change from baseline) and NovoRapid reduced the 2-hour PPG increment by 2.87 mmol/L (estimated change). The estimated treatment difference, -0.36 mmol/L [-0.81; 0.08]$_{95\%CI}$, was not statistically significant. The 1-hour PPG increment was also reduced with both treatments. For Fiasp, the estimated reduction in the 1-hour PPG increment (2.14 mmol/L) was statistically significantly greater compared to that of NovoRapid (1.55 mmol/L) and greater than the reduction seen at 2 hours (treatment difference -0.59 mmol/L [-1.09; -0.09]$_{95\%CI}$). The results of the prespecified and the post-hoc sensitivity analyses for the 2-hour PPG increment were comparable to that of the original analysis.

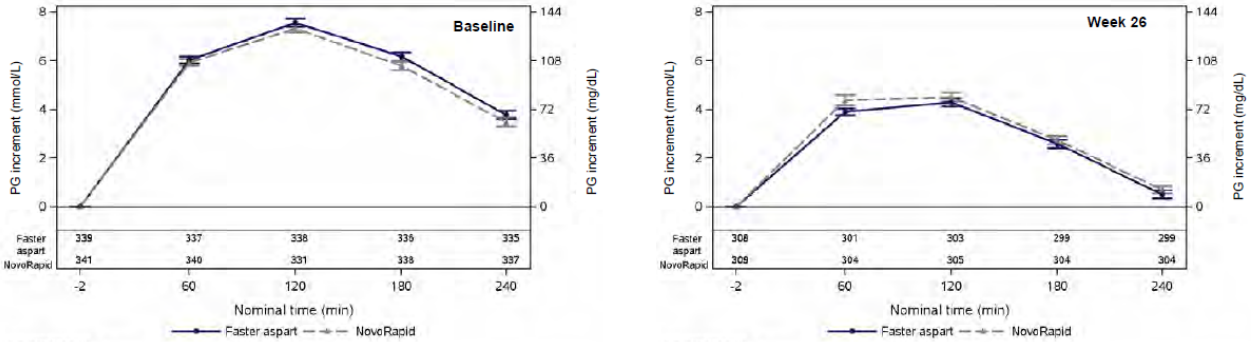


Figure 21 Plasma glucose increments at baseline and after 26 weeks of treatment based on meal test in trial 3853

Full analysis set. PG: plasma glucose. Error bars: ± standard error (mean). Observed data, except for the cases where glucose or glucagon is administered, in which case the last measurement before rescue intervention will be carried forward. Numbers under graph are number of subjects at each time point. The conversion factor between mmol/L and mg/dL is 0.0555. Subjects did not receive bolus insulin at the baseline meal test.

Comparison of plasma glucose during meal test in clinical pharmacology and therapeutic trials in subjects with T1DM

The data on mean PPG increment over 1 and 2 hours across the two clinical pharmacology and two therapeutic trials which included T1DM patients are summarised in (Table 27).

Table 22 Treatment difference for mean PPG increment over 1 and 2 hours in adults with T1DM during meal test in the clinical pharmacology trials 3888 and 3889 and in the therapeutic trials 3852 (s.c. injection) and 3930 (CSII)

Trial	Number of subjects		Mean PPG increment over 1 hour	Mean PPG increment over 2 hours
	Fiasp	NovoRapid	Fiasp – NovoRapid	Fiasp – NovoRapid
3888	15	13	-0.31 mmol/L [-1.48; 0.86]	-0.57 mmol/L [-1.83; 0.69]
			-5.60 mg/dL [-26.71;15.52]	-10.29 mg/dL [-33.03; 12.45]
3889	35	36	-0.19 mmol/L [-0.57; 0.20]	-0.19 mmol/L [-0.77; 0.39]

			-3.43 mg/dL	[-10.29;3.61]	-3.43 mg/dL	[-13.9; 7.04]
3930	39	35	-0.50 mmol/L	[-1.07; 0.07]	-0.99 mmol/L	[-1.95;-0.03]
			-9.03 mg/dL	[-19.31; 1.26]	-17.87 mg/dL	[-35.20;-0.54]
3852	353	350	-1.18 mmol/L	[-1.65; -0.71]	-0.67 mmol/L	[-1.29; -0.04]
			-21.3 mg/dL	[-29.78;-12.82]	-12.09 mg/dL	[-23.28; -0.72]

[a] For trial 3852, the change at 1 and 2 hours is the 1 and 2 hour PG increment

Post-meal glucose increments based on meal test in trials 3852 and 3853 and in across trial analysis

In an across trial analysis including both the T1DM and T2DM populations, the results supplemented those of the individual trials (Figure 24). The estimated treatment difference (Fiasp - NovoRapid) was -0.90 mmol/L $[-1.24; -0.56]_{95\%CI}$ for the change from baseline in 1-hour PPG increment and -0.52 mmol/L $[-0.93; -0.11]_{95\%CI}$ for the change in 2-hour PPG increment.

The results of the across trial analyses of 1-hour and 2-hour PPG increments against missing data were investigated in sensitivity analyses. The results of all the sensitivity analyses were comparable to the results of the original across trial analyses.

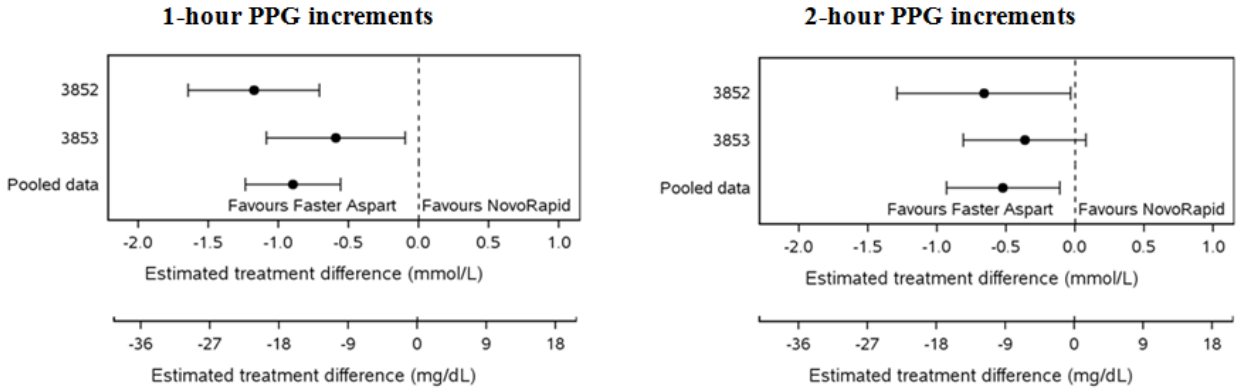


Figure 22 Change from baseline in 1-hour and 2-hour postprandial glucose (meal test) increments after 26 weeks of treatment in across trial analysis (trials 3852 and 3853)

Severe or BG confirmed symptomatic hypoglycaemic episodes in trials 3852 and 3853, and across trial analysis

Trial 3852

The observed rate of severe or BG confirmed hypoglycaemic episodes per 100 PYE was: 5899, 5443 and 5865 for mealtime Fiasp, post-meal Fiasp and NovoRapid, respectively. The estimated rate ratio for severe or BG confirmed hypoglycaemic episodes was 1.01 $[0.88; 1.15]_{95\%CI}$ (mealtime Fiasp versus NovoRapid) and 0.92 $[0.81; 1.06]_{95\%CI}$ (post-meal Fiasp versus NovoRapid), showing no statistically significant differences between the treatment groups after 26 weeks of treatment.

Trial 3853

The observed rate of episodes of severe or BG confirmed hypoglycaemia was 1787.8 episodes per 100 PYE in the Fiasp group and 1659.1 episodes per 100 PYE in the NovoRapid group. The estimated rate ratio (Fiasp vs.

NovoRapid) for severe or BG confirmed hypoglycaemic episodes was 1.09 [0.88; 1.36]$_{95\%CI}$ after 26 weeks of randomised treatment and no statistically significant difference was observed between the 2 treatment groups.

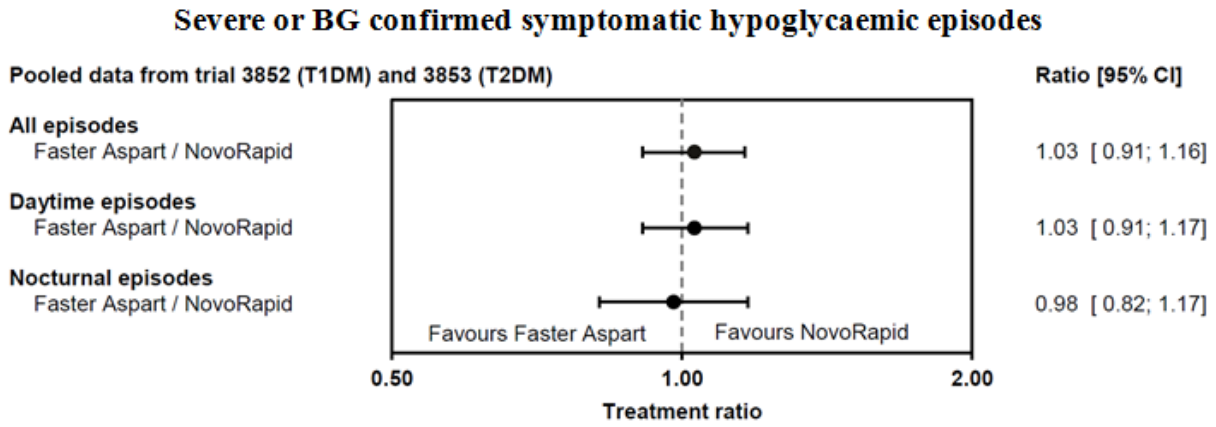


Figure 23 Treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes in across trial analysis (trials 3852 and 3853)

The across trial analyses of all, daytime and nocturnal treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes showed that the estimated event rates per 100 patient years of exposure (PYE) were similar for Fiasp and NovoRapid both during the full 26-week treatment period (Figure 25) and during the maintenance period. The sensitivity analyses supported the results of the original analyses, showing comparable results.

Self-measured plasma glucose (SMPG) profiles

Trial 3852

The mean 9-point SMPG profiles at baseline and after 26 weeks of treatment are presented in Figure 26. There were no statistically significant treatment differences.

For the endpoint 'change from baseline in mean of the SMPG profile', no statistically significant difference was seen between mealtime faster vs. mealtime NovoRapid or between post-meal Fiasp and mealtime NovoRapid.

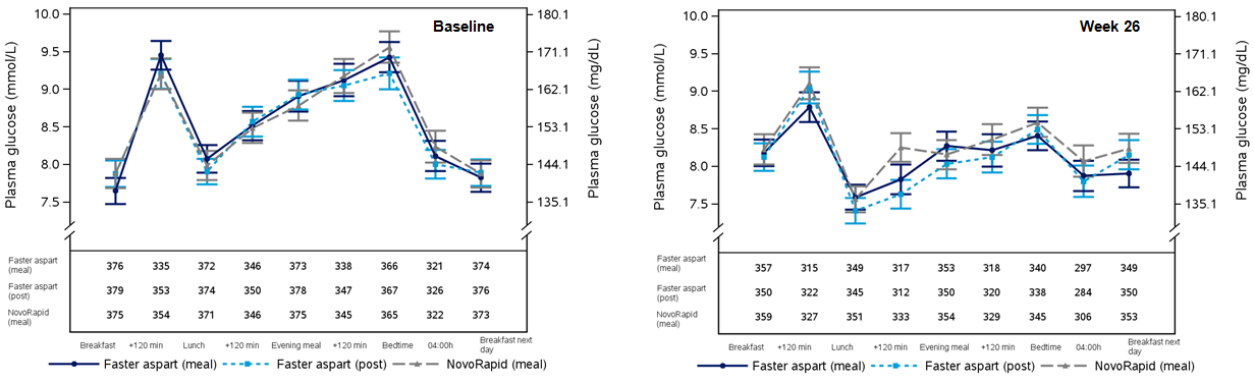


Figure 24 Mean 9-point self-measured plasma glucose profiles at baseline and after 26 weeks in trial 3852

Data are observed means ± standard error bars. Numbers under graph are number of subjects. Conversion factor between mmol/L and mg/dL is 0.0555.

Trial 3853

The mean 9-point SMPG profiles at baseline and at the end of the trial are shown in Figure 27. The estimated reductions for the change from baseline in PPG and change from baseline in PPG increment after 26 weeks of treatment based on the SMPG profiles were generally not statistically significantly different between treatments except for the lunch meal where the estimated reduction in the PPG increment was statistically significantly greater for the Fiasp group than for the NovoRapid group (-0.35 (mmol/L) [-0.65; -0.05]$_{95\%CI}$).

For the endpoint 'change from baseline in the mean of the SMPG profile', there was no statistically significant difference between Fiasp and NovoRapid.

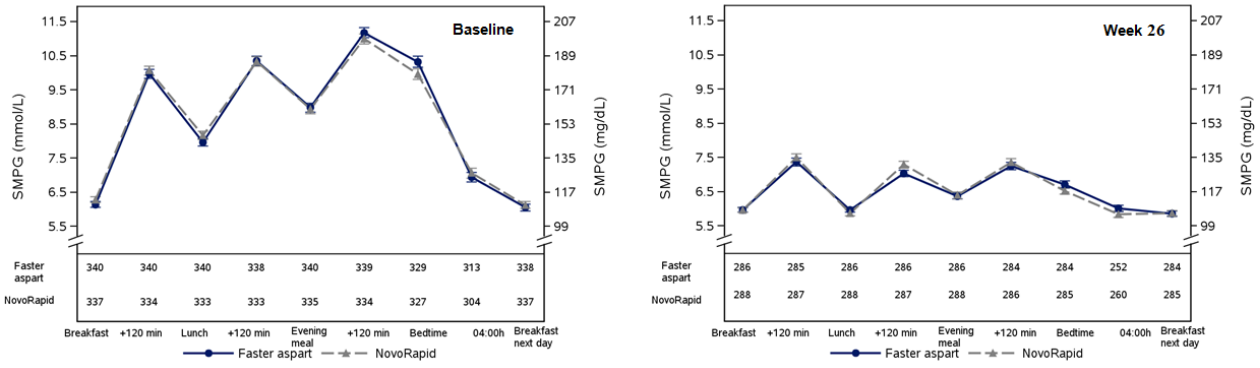


Figure 25 Mean 9-point self-measured plasma glucose profiles at baseline and after 26 weeks in trial 3853

SMPG: self-measured plasma glucose. Data are observed means ± standard error bars. Numbers under graph are number of subjects per treatment group. Conversion factor between mmol/L and mg/dL is 0.0555.

Trial 4049

Mean 8-point SMPG profiles at baseline and at the end of the trial are presented in Figure 28. For all main meals, and across all meals, the estimated reductions in terms of change from baseline in PPG and change from baseline in PPG increment were statistically significantly greater for the Fiasp + basal group as compared to the basal group.

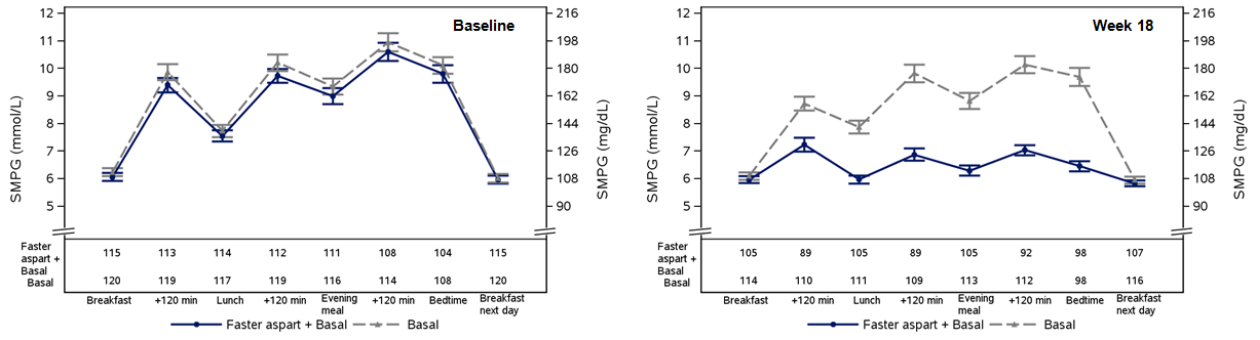


Figure 26 Mean 8-point self-measured plasma glucose profile at baseline and after 18 weeks in trial 4049

SMPG: self-measured plasma glucose. Data are observed means ± standard error bars. Numbers under graph are number of subjects per treatment group. Conversion factor between mmol/L and mg/dL is 0.0555.

1,5-anhydroglucitol (GlycoMark)

In trial 3852, in subjects with T1DM, mean 1,5-AG increased from baseline to week 26 in all 3 treatment groups (0.85 µg/mL, 0.19 µg/mL and 0.35 µg/mL for Fiasp (meal), Fiasp (post-meal) and NovoRapid, respectively). For mealtime Fiasp, the change from baseline in 1,5-AG was statistically significantly greater compared to mealtime NovoRapid after 26 weeks of treatment (estimated mean treatment difference: 0.50 µg/mL $[0.24; 0.76]_{95\%CI}$). For post-meal Fiasp as compared to mealtime NovoRapid, there was no statistically significant difference in 1,5-AG after 26 weeks.

In trial 3853, in subjects with T2DM, mean 1,5-AG increased from baseline to week 26 in both the Fiasp and the NovoRapid treatment groups, with no statistically significant difference between treatments (5.82 µg/mL vs 6.25 µg/mL, Fiasp and NovoRapid, respectively).

In trial 4049, the addition of Fiasp to basal insulin (in combination with metformin) led to a marked increase in the estimated mean 1,5-AG after 18 weeks of treatment in the Fiasp + basal group (5.28 µg/mL) , which was statistically significantly greater than the increase obtained in the basal group (1.04 µg/mL; estimated mean treatment difference: 4.24 µg/mL $[3.04; 5.44]_{95\%CI}$).

Fasting plasma glucose

In trial 3852, the change from baseline in FPG was -0.17 mmol/L for Fiasp (meal), -0.15 mmol/L for Fiasp (post-meal) and 0.08 mmol/L for NovoRapid. There was no statistically significant difference in FPG for mealtime Fiasp compared to mealtime NovoRapid or for post-meal Fiasp compared to mealtime NovoRapid after 26 weeks of treatment.

In trial 3853, the change from baseline in FPG was 0.02 mmol/L for Fiasp and -0.24 mmol/L for NovoRapid and in trial 4049, the change from baseline in FPG was -0.89 mmol/L for Fiasp + basal and -0.77 mmol/L for basal. No statistically significant treatment difference with respect to FPG was observed in trial 3853 after 26 weeks or in trial 4049 after 18 weeks of treatment.

Fasting lipid profile

In trial 3852, there were no statistically significant treatment differences in change from baseline for any of the fasting lipids after 26 weeks of treatment, except with respect to HDL cholesterol, for which a statistically significant increase in HDL cholesterol was observed for the post-meal Fiasp treatment arm as compared to the NovoRapid arm. Given the size of the change and the fact that no other statistically significant treatment differences with respect to fasting lipids were observed either in trial 3853 after 26 weeks or in trial 4049 after 18 weeks of treatment, the treatment difference is not considered clinically meaningful.

Insulin dose

Trial 3852

In trial 3852, the median daily bolus insulin doses were similar in the 3 treatment arms after 26 weeks of treatment: 29.7 U (0.39 U/kg) in the mealtime Fiasp arm, 31.0 U (0.39 U/kg) in the post-meal Fiasp arm and 30.0 U (0.38 U/kg) in the NovoRapid arm.

The median daily basal insulin dose was slightly lower in the mealtime Fiasp arm (30.0 U (0.39 U/kg)) as compared to the post-meal Fiasp arm (34.0 U (0.42 U/kg)) and the NovoRapid arm (32.0 U (0.43 U/kg)) after 26 weeks of treatment. The median basal dose was stable and similar at start and end of treatment in each of the 3 treatment arms.

Approximately 50% of the total daily insulin dose after 26 weeks treatment was provided by bolus insulin for each of mealtime Fiasp (51%), post-meal Fiasp (48%) and NovoRapid (49%).

Trial 3853

A similar pattern of bolus dose results as described above was observed in trial 3853, with similar median daily bolus insulin doses in the 2 treatment arms after 26 weeks of treatment: 43.0 U (0.49 U/kg) in the Fiasp arm and 45.5 U (0.51 U/kg) in the NovoRapid arm. The median daily basal insulin dose was slightly higher in the Fiasp arm (48.0 U (0.53 U/kg)) as compared to the NovoRapid arm (42.0 U (0.48 U/kg)) after 26 weeks of treatment, mirroring the pattern seen at baseline.

For both treatment groups, 56% of the total daily insulin dose after 26 weeks treatment was provided by bolus insulin.

Trial 4049

As expected, the median daily bolus insulin dose increased during the treatment period, from a median starting dose of 18.0 U (0.23 U/kg) at week 1 to 39.3 U (0.48 U/kg) after 18 weeks of treatment in the Fiasp + basal group, due to the addition and titration of Fiasp as the mealtime insulin. By contrast, in the basal group, in which insulin was not titrated after week 1, the median daily basal dose was 48.0 U (0.6 U/kg) at week 1 and 52.0 U (0.6 U/kg) at the end of treatment.

In the Fiasp + basal group, 55% of the total daily insulin dose after 26 weeks treatment was provided as bolus insulin.

Body weight

In trial 3852 in subjects with T1DM, mean body weight increased slightly from baseline to week 26 in all 3 treatment groups (0.67 kg for Fiasp (meal), 0.70 kg for Fiasp (post-meal) and 0.55 kg NovoRapid, respectively). There was no statistically significant treatment difference after 26 weeks of treatment.

In trial 3853, in subjects with T2DM, mean body weight increased from baseline in both treatment groups to a similar extent, with no statistically significant difference between treatments after 26 weeks (2.67kg for Fiasp and 2.68 kg for NovoRapid).

In trial 4049, in subjects with T2DM, a statistically significantly greater mean body weight increase was observed in the Fiasp + basal treatment group as compared to the basal group after 18 weeks of treatment (1.83 kg for Fiasp and 0.17 kg for basal insulin). The mean weight gain in the Fiasp + basal group was still below 2 kg.

Patient reported outcomes

In the therapeutic confirmatory basal-bolus trials, 3852 and 3853, aspects of health-related quality of life were assessed by two PRO questionnaires; one generic (the Short-Form 36 Health Survey version 2; SF-36v2) and one specific for diabetes (treatment related impact measure – diabetes; TRIM-D).

Short-Form 36 health survey version 2

At baseline in trial 3852 in subjects with T1DM, the scores in all domains were close to 50 (i.e., the U.S. population average), which indicated a relatively good health status of the subjects at baseline. The observed

mean scores changed marginally in all 3 treatment groups after 26 weeks of treatment, and the changes were not considered clinically meaningful.

A similar pattern was observed in trial 3853 in subjects with T2DM, with mean scores changing marginally from baseline in both groups after 26 weeks of treatment. None of the estimated changes were considered clinically meaningful.

Treatment Related Impact Measure - Diabetes (TRIM-D)

At baseline in trial 3852, there were no marked differences in the observed mean dimension scores between treatment groups. The mean scores changed marginally in all 3 treatment groups after 26 weeks of treatment. There was no consistent pattern in the magnitude and direction of the estimated changes from baseline in the different domains or between treatment groups.

In trial 3853, scores were lower for all domains in both treatment groups after 26 weeks of randomised treatment, except for the domain 'diabetes management'. There was a general trend that scores were lower for the Fiasp group compared to NovoRapid group, and the treatment differences were statistically significantly different for the domains 'treatment burden', 'diabetes management' and 'TRIM-D total score'.

Ancillary analyses

Subgroup analyses of efficacy

The intrinsic factors investigated were demographic factors (age, sex, race and ethnicity) and disease factors (duration of diabetes, HbA_{1c}, BMI and concomitant illness such as renal or hepatic impairment, at baseline or screening). The extrinsic factors were treatment related factors and region. The treatment related factors included concomitant medication having glucose increasing or decreasing effect (other than antidiabetic drugs), basal insulin regimen at randomisation (T1DM), and method of insulin dose adjustment (T1DM).

Comparisons were made between Fiasp and NovoRapid for trial 3852 in subjects with T1DM and trial 3853 in subjects with T2DM. The evaluation was made for each trial separately, and in trial 3852, for mealtime Fiasp and post-meal Fiasp separately. Pooling of the two trials was not done to prevent the possibility that heterogeneity in the trial populations (T1DM and T2DM) might mask potential subgroup differences or complicate the interpretation of the results since the two trials would contribute differently to the different subgroups.

The subgroup analyses were performed for primary endpoint (change from baseline in HbA_{1c}) and selected secondary endpoints (change in 1-hour and 2-hour PPG increments (meal test) and 1,5-AG).

The subgroup analysis did not indicate any consistent overall impact of the investigated intrinsic or extrinsic factors on the efficacy of Fiasp vs. NovoRapid.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 23 Summary of efficacy for trial NN1218-3852

Title: Efficacy and safety of FIAsp[a] compared to insulin aspart both in combination with insulin detemir in adults with type 1 diabetes (onset 1) [a] FIAsp is an earlier abbreviation for faster-acting insulin aspart used in the protocol		
Study identifier	Protocol number: NN1218-3852; EudraCT number: 2010-024049-53; Study identifier: NCT01831765. See Trial 3852 report body (M 5.3.5.1)	
Design	This trial was a 26+26-week, randomised (1:1:1), multicentre, multinational, active-controlled, parallel-group trial in adult subjects with type 1 diabetes. The aim of the trial was to compare the efficacy and safety of mealtime Fiasp with mealtime NovoRapid, both in combination with once- or twice-daily insulin detemir in a double-blind basal–bolus regimen. An 8-week run-in period was included during which the basal insulin treatment was optimised using a treat-to-target approach. The trial also included a 26-week open-label post-meal Fiasp arm in combination with once- or twice-daily insulin detemir. This arm did not include the additional 26-week treatment period. The initial 26-week partly double-blind treatment period with the three parallel treatment arms was for the primary analysis of efficacy and safety. The additional 26-week double-blind treatment with the two mealtime dosing arms was for further evaluation of long-term safety and efficacy. Results from the initial 26-week trial period are described in this clinical trial report synopsis. Subjects with a glycated haemoglobin A_{1c} (HbA_{1c}) ≤9.5% (80 mmol/mol) measured at week 7 of the 8-week run-in period were randomised to continue using double-blinded mealtime NovoRapid (administered 0–2 minutes prior to main meals), or to receive either double-blinded mealtime Fiasp (administered 0–2 minutes prior to main meals), or open-label post-meal Fiasp (administered 20 minutes after the start of eating main meals), all in addition to insulin detemir. Extra bolus dosing was allowed at the investigator's recommendation.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	26 weeks 8 weeks 26 weeks (not included in this table)
Hypothesis	**Primary objective** To confirm efficacy of treatment with mealtime Fiasp in terms of glycaemic control as measured by change from baseline in HbA_{1c} after 26 weeks of randomised treatment by comparing it to mealtime NovoRapid both in combination with insulin detemir using a noninferiority approach. **Confirmatory secondary objectives** To confirm superiority of mealtime Fiasp compared to mealtime NovoRapid both in combination with insulin detemir after 26 weeks of randomised treatment in terms of: Postprandial glucose (PPG) regulation	

	Number of hypoglycaemic episodes Body weight regulation To confirm efficacy of treatment with post-meal Fiasp in terms of glycaemic control measured by changes from baseline in HbA_{1c} after 26 weeks of randomised treatment by comparing it to mealtime NovoRapid both in combination with insulin detemir using a non-inferiority approach. To confirm superiority of post-meal Fiasp compared to mealtime NovoRapid both in combination with insulin detemir after 26 weeks of randomised treatment in terms of: Number of hypoglycaemic episodes Body weight regulation To compare other efficacy and safety endpoints after treatment with mealtime Fiasp, post-meal Fiasp and mealtime NovoRapid , all in combination with insulin detemir after 26 weeks of randomised treatment.		
Treatments groups	Fiasp (mealtime)		A total of 381 subjects were randomised to the Fiasp mealtime treatment group. The total treatment duration was 26 weeks.
	Fiasp (post-meal)		A total of 382 subjects were randomised to the Fiasp post-meal treatment group. The total treatment duration was 26 weeks.
	NovoRapid (mealtime)		A total of 380 subjects were randomised to the NovoRapid mealtime treatment group. The total treatment duration was 26 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} after 26 weeks of randomised treatment. (step 1)	Analysed using a mixed-effect model for repeated measurements (MMRM). This model included treatment, region, the strata variable (including eight strata, based on the combination of method of insulin dose adjustment from randomisation and onwards (principles of flexible dosing based on the carbohydrate content of the meal or using bolus dosing algorithms), continuous glucose monitoring (CGM) inclusion (yes or no) and basal dosing regimen (once or twice daily dosing)) as fixed effects, subject as random effect, HbA_{1c} at baseline as covariate and interactions between all fixed effects and visit, and between the covariate and visit.
	Confirmatory secondary Endpoint	Change from baseline in 2-hour PPG increment after 26 weeks of	Tested for superiority of mealtime Fiasp compared to mealtime NovoRapid , using an analysis of variance (ANOVA) model including treatment, the strata variable and region as factors and with

		randomised treatment (meal test) (step 2)	2-hour PPG increment at baseline as covariate
	Confirmatory secondary Endpoint	Change from baseline in HbA_{1c} after 26 weeks of randomised treatment (step 3)	Tested for noninferiority of post-meal Fiasp to NovoRapid in exactly the same way as for the primary analysis
	Confirmatory secondary Endpoint	Number of treatment-emergent severe or blood glucose (BG) confirmed hypoglycaemic episodes from baseline until week 26 (steps 4 and 6):	In step 4, mealtime Fiasp was tested for superiority compared to mealtime NovoRapid , and in step 6, post-meal Fiasp was tested for superiority compared to mealtime NovoRapid . The analyses were 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 was considered treatment-emergent as offset. The model included treatment, the strata variable and region as factors
	Confirmatory secondary Endpoint	Change from baseline in body weight after 26 weeks of randomised treatment (steps 5 and 7):	In step 5 mealtime Fiasp was tested for superiority compared to mealtime NovoRapid , and in step 7, post-meal Fiasp was tested for superiority compared to mealtime NovoRapid , using an MMRM for repeated measurements similar to the model used for analysis of the primary endpoint except with body weight as baseline covariate
	Supportive secondary endpoint	Change from baseline in 1,5-anhydroglucitol after 26 weeks of randomised treatment	Analysed based on all planned post-baseline measurements until 26 weeks using an MMRM for repeated measurements, similar to the model used for analysis of the primary endpoint, except with baseline 1,5-anhydroglucitol as covariate.
Database lock	10 March 2015		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and description	Analyses of efficacy endpoints were based on the full analysis set (FAS). If efficacy of mealtime Fiasp was confirmed, as assessed by comparing the change from baseline in HbA_{1c} after 26 weeks treatment difference to a noninferiority limit of 0.4%, the trial also aimed to compare treatment arms for a number of confirmatory secondary endpoints. The family-wise type I error rate was controlled in the strong sense using a		

<table>
<tr><td></td><td colspan="4">hierarchical (fixed sequence) testing procedure. This was based on a priority ordering of the null-hypotheses, and testing them in this order using the two-sided 95% confidence interval approach until an insignificant result appeared. The effect was that rejection of the null hypothesis only was confirmed for endpoints where all previous null-hypotheses had been rejected in favour of Fiasp.

The steps in the hierarchical testing procedure were:

Step 1. Primary analysis: Change from baseline in HbA_{1c} after 26 weeks of randomised treatment (noninferiority of mealtime Fiasp versus NovoRapid)

Step 2. Change from baseline in 2-hour PPG increments after 26 weeks of randomised treatment (meal test) (superiority of mealtime Fiasp versus NovoRapid)

Step 3. Change from baseline in HbA_{1c} after 26 weeks of randomised treatment (noninferiority of post-meal Fiasp versus NovoRapid)

Step 4. Number of treatment-emergent severe or BG confirmed hypoglycaemic episodes from baseline until week 26 (superiority of mealtime Fiasp versus NovoRapid)

Step 5. Change from baseline in body weight after 26 weeks of randomised treatment (superiority of mealtime Fiasp versus NovoRapid)

Step 6. Number of treatment-emergent severe or BG confirmed hypoglycaemic episodes from baseline until week 26 (superiority of post-meal Fiasp versus NovoRapid).

Step 7. Change from baseline in body weight after 26 weeks of randomised treatment (superiority of post-meal Fiasp versus NovoRapid)</td></tr>
<tr><td>Results</td><td>Treatment group</td><td>Fiasp (mealtime)</td><td>Fiasp (post-meal)</td><td>NovoRapid (mealtime)</td></tr>
<tr><td></td><td>Number of subject (FAS)</td><td>381</td><td>382</td><td>380</td></tr>
<tr><td></td><td>Change from baseline in HbA_{1c} after 26 weeks of randomised treatment %-points</td><td>-0.32</td><td>-0.13</td><td>-0.17</td></tr>
<tr><td></td><td>Change from baseline in 2-hour PPG increment after 26 weeks of randomised treatment (meal test) mmol/L</td><td>-0.44</td><td>0.55</td><td>0.49</td></tr>
</table>

	Number of treatment-emergent severe or BG confirmed hypoglycaemic episodes from baseline until week 26 (100 PYE)	5899	5443	5865
	Change from baseline in body weight after 26 weeks of randomised treatment (kg)	0.67	0.70	0.55
	Change from baseline in 1,5-anhydroglucitol after 26 weeks of randomised treatment (µg/mL)	0.85	0.19	0.35
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} after 26 weeks of randomised treatment %-points	**Comparison groups**	Fiasp (mealtime) – NovoRapid (mealtime)	Fiasp (post-meal) – NovoRapid (mealtime)
		Estimated treatment difference (%-points)	-0.15	0.04
		95% CI	-0.23; -0.07	-0.04; 0.12
	Change from baseline in 2-hour PPG increment after 26 weeks of randomised treatment (meal test) mmol/L	**Comparison groups**	Fiasp (mealtime) – NovoRapid (mealtime)	*Not part of the hierarchical testing*
		Estimated treatment difference (mmol/L)	-0.93	
		95% CI	-1.62; -0.23	
	Number of treatment-emergent severe or BG confirmed hypoglycaemic episodes from baseline until week	**Comparison groups**	Fiasp (mealtime) / NovoRapid (mealtime)	Fiasp (post-meal) / NovoRapid (mealtime)
		Estimated treatment ratio	1.01	0.92

	26 (100 PYE)	95% CI	0.88; 1.15	0.81; 1.06
	Change from baseline in body weight after 26 weeks of randomised treatment (kg)	**Comparison groups**	Fiasp (mealtime) – NovoRapid (mealtime)	Fiasp (post-meal) – NovoRapid (mealtime)
		Estimated treatment difference (kg)	0.12	0.16
		95%CI	-0.30; 0.55	-0.27; 0.58
	Change from baseline in 1,5-anhydroglucitol after 26 weeks of randomised treatment	**Comparison groups**	Fiasp (mealtime) – NovoRapid (mealtime)	Fiasp (post-meal) – NovoRapid (mealtime)
		Estimated treatment difference (µg/mL)	0.50	-0.16
		95%CI	0.24; 0.76	-0.42; 0.10
Notes	In total, 81 (7.1%) subjects were withdrawn from the trial at or after randomisation: 30 (7.9%) subjects in the mealtime Fiasp group, 27 (7.1%) subjects in the post-meal Fiasp group and 24 (6.3%) subjects in the NovoRapid group. The most frequent reason for withdrawal was 'withdrawal by subject': 17 subjects in the mealtime Fiasp group, 7 subjects in the post-meal Fiasp group and 10 subjects in the NovoRapid group. Eleven (11) subjects were withdrawn due to AEs: 5 subjects in the mealtime Fiasp group, 4 subjects in the post-meal Fiasp group and 5 subjects in the NovoRapid group. Subjects in the NovoRapid group generally discontinued later in the trial (mainly after week 14) compared to the two Fiasp treatment groups in which subjects discontinued on a more on-going basis throughout the trial.			

Table 24 Summary of efficacy for trial NN1218-3853

Title: Efficacy and safety of FIAsp[a] compared to insulin aspart in combination with insulin glargine and metformin in adults with type 2 diabetes (onset 2) [a] FIAsp is an earlier abbreviation for faster-acting insulin aspart used in the protocol		
Study identifier	Protocol number: NN1218-3853; EudraCT number: 2010-024051-93; Study identifier: NCT01819129. See Trial 3853 report body (M 5.3.5.1)	
Design	This was a 26-week, multicentre, multinational, 1:1 randomised, double-blind, active controlled, treat-to-target, parallel group trial comparing the efficacy and safety of mealtime Fiasp vs. mealtime NovoRapid , both in combination with once-daily insulin glargine and metformin in a basal-bolus regimen. The total duration of the trial was approximately 40 weeks: 2 weeks for screening, an 8-week run-in period (basal insulin titration), a 26-week double-blind treatment period (bolus insulin titration), a follow-up contact 1 week after end-of-treatment and an additional follow-up contact 30 days after end-of-treatment. The trial included a screening visit to assess the subject's eligibility and additional weekly visits/phone contacts during the 8-week run-in and the 26-week double-blind treatment period. At run-in, subjects eligible to enter the trial were switched from their previous basal insulin to once-daily insulin glargine at their pre-trial dose and had all their current oral antidiabetic drug (OAD) treatments discontinued, with the exception of metformin treatment which was continued without changing the frequency or dose throughout the trial. Subjects on a metformin combination product had to stop the combination product at run-in continuing on metformin only, at the same dose as in the combination product. At randomisation (visit 10, week 0), mealtime bolus insulin either Fiasp or NovoRapid was initiated.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	26 weeks 8 weeks Not applicable

Hypothesis	**Primary objective** To confirm efficacy of treatment with mealtime Fiasp in terms of glycaemic control measured by HbA_{1c} after 26 weeks of randomised treatment, by comparing to mealtime NovoRapid , both in combination with once-daily insulin glargine and metformin, using a non-inferiority approach. **Secondary objectives** To confirm superiority of mealtime Fiasp vs. mealtime NovoRapid , both in combination with once-daily insulin glargine and metformin after 26 weeks of randomised treatment in terms of: Post prandial glucose (PPG) regulation Number of hypoglycaemic episodes Body weight regulation To compare other efficacy and safety endpoints of mealtime Fiasp with mealtime NovoRapid, both in combination with once-daily insulin glargine and metformin, after 26 weeks of randomised treatment.		
Treatments groups	Fiasp		345 subjects were randomised to the Fiasp group. The total treatment duration was 26 weeks.
	NovoRapid		344 subjects were randomised to the NovoRapid group. The total treatment duration was 26 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} after 26 weeks of randomised treatment (Step 1)	Analysed using a mixed-effect model for repeated measurements (MMRM). This model included treatment, CGM strata yes/no and region as fixed effects, subject as random effect, HbA_{1c} at baseline as covariate and interactions between all fixed effects and visit, and between the covariate and visit. From this model, estimated treatment difference and 95% confidence interval (CI) was obtained.
	Confirmatory secondary endpoint	Change from baseline in 2-hour PPG increment after 26 weeks of randomised treatment (meal test) (step 2)	Superiority of mealtime Fiasp compared to mealtime NovoRapid was tested using an analysis of variance (ANOVA) model including treatment, CGM strata and region as factors and with 2-hour PPG increment at baseline as covariate.

	Confirmatory secondary endpoint	Number of treatment-emergent severe or blood glucose (BG) confirmed hypoglycaemic episodes from baseline to week 26 (step 3).	Superiority of Fiasp compared to NovoRapid was tested using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode was considered treatment-emergent as offset. The model included treatment, CGM strata and region.
	Confirmatory secondary endpoint	Change from baseline in body weight after 26 weeks of randomised treatment (step 4)	Superiority of mealtime Fiasp compared to mealtime NovoRapid was tested using a MMRM similar to the model used for analysis of the primary endpoint but with body weight at baseline as covariate.
Database lock	12 February 2015		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and description	Analyses of efficacy endpoints were based on the full analysis set (FAS). If efficacy of Fiasp could be confirmed, as assessed by comparing the difference vs. NovoRapid in change from baseline in HbA_{1c} after 26 weeks of treatment to a non-inferiority limit of 0.4%, then the trial also aimed to show superiority of Fiasp over NovoRapid for a number of confirmatory secondary endpoints. The family-wise type I error rate was controlled in the strong sense using a hierarchical (fixed sequence) testing procedure. This was based on an a priori ordering of the null-hypotheses and testing them in this order using the two sided 95% CI approach until an insignificant result appeared. The effect was that superiority only would be confirmed for endpoints where all previous null-hypotheses had been rejected in favour of Fiasp. The steps in the hierarchical testing procedure were: Step 1. Primary analysis: Change from baseline in HbA_{1c} after 26 weeks of randomised treatment (non-inferiority of mealtime Fiasp vs. NovoRapid) Step 2. Change from baseline in 2-hour PPG increment after 26 weeks of randomised treatment (meal test) Step 3. Number of severe or BG confirmed hypoglycaemic episodes from baseline to week 26 Step 4. Change from baseline in body weight after 26 weeks of randomised treatment		

Results	Treatment group	Fiasp	NovoRapid
	Number of subjects (FAS)	345	344
	Change from baseline in HbA_{1c} (%) after 26 weeks of randomised treatment	-1.38	-1.36
	Change from baseline in 2-hour PPG (mmol/L) increment after 26 weeks of randomised treatment (meal test)	-3.24	-2.87
	Number (events per 100 PYE) of treatment-emergent severe or blood glucose (BG) confirmed hypoglycaemic episodes from baseline to week 26	1787.8	1659.1
	Change from baseline in body weight (kg) after 26 weeks of randomised treatment	2.68	2.67
Effect estimate per comparison	Primary endpoint Change from baseline in HbA_{1c} after 26 weeks of randomised treatment	**Comparison groups**	Fiasp - NovoRapid
		Estimated treatment difference (%-points)	-0.02
		95% CI	-0.15; 0.10
	Change from baseline in 2-hour PPG increment after 26 weeks of randomised treatment (meal test)	**Comparison groups**	Fiasp – NovoRapid
		Estimated treatment difference (mmol/L)	-0.36
		95% CI	-0.81; 0.08
	Number of treatment-emergent severe or blood glucose (BG) confirmed hypoglycaemic episodes from baseline to week 26	**Comparison groups**	Fiasp / NovoRapid
		Estimated treatment ratio	1.09
		(95% CI)	0.88; 1.36

	Change from baseline in body weight after 26 weeks of randomised treatment	**Comparison groups**	Fiasp – NovoRapid
		Estimated treatment difference (kg)	0.00
		(95% CI)	-0.60; 0.61
Notes	In total, 83 subjects withdrew or were withdrawn from the trial at or after randomisation; 44 subjects from the Fiasp group and 39 subjects from the NovoRapid group. For both treatment groups, the main reason for being withdrawn was criterion #10, non-compliance with trial procedures (11 subjects in the Fiasp group and 6 subjects in the NovoRapid group). In total 30 subjects withdrew at their own will from the trial; 15 subjects from each treatment group. Seven (7) subjects were withdrawn due to AEs (2 subjects in the Fiasp group and 5 subjects in the NovoRapid group). Three (3) subjects were withdrawn due to reason 'other'. One of these subjects was in fact withdrawn due to AEs.		

Table 25 Summary of efficacy for trial NN1218-4049

Title Efficacy and safety of FIAsp[a] in a basal-bolus regimen versus basal insulin therapy, both in combination with metformin in adult subjects with type 2 diabetes (onset 3) [a] FIAsp is an earlier abbreviation for Fiasp used in the protocol		
Study identifier	Protocol number: NN1218-4049; EudraCT number: 2012-005583-10; Study identifier: NCT01850615. See Trial 4049 report body (M 5.3.5.1)	
Design	This was a multicentre, multinational, randomised (1:1), open-label, parallel group trial comparing the efficacy and safety of mealtime Fiasp in a basal-bolus regimen with once daily insulin detemir, insulin glargine or human isophane insulin, Neutral Protamine Hagedorn (NPH), versus once daily insulin detemir or insulin glargine or human isophane insulin, NPH, in combination with metformin. Subjects were patients with type 2 diabetes mellitus, 18 years of age or older, who were being treated with once-daily insulin detemir, insulin glargine or human isophane insulin, NPH, in addition to metformin ± other oral antidiabetic drugs (OADs) (sulfonylurea (SU) or glinide or dipeptidyl peptidase-IV (DPP-IV) inhibitors and/or alpha-glucosidase inhibitors (AGI)) prior to the screening visit. At the start of the 8-week run-in period, subjects continued on the once-daily basal insulin (insulin detemir, insulin glargine or human isophane insulin, NPH) and metformin at the same dose-level as before the trial. Any OADs except metformin were to be discontinued when the run-in period started; no anti-diabetic treatment other than metformin was allowed during the trial. At randomisation, subjects were randomised to either the basal arm or the basal-bolus arm, both in combination with metformin. Subjects in the basal-bolus treatment arm started to inject Fiasp before each main meal, in addition to their basal insulin and metformin treatment. Subjects in the basal insulin treatment arm continued on the basal insulin and metformin treatment. The total duration of the trial was approximately 32 weeks and consisted of a 2-week screening period, 8-week run-in period, 18-week treatment period and 7-day and 30-day follow-up periods.	
	Duration of main phase:	18 weeks
	Duration of Run-in phase:	8 weeks
	Duration of Extension phase:	Not applicable

Hypothesis	**Primary objective** To confirm the superiority of mealtime Fiasp in a full basal-bolus regimen versus basal insulin therapy, both in combination with metformin, in terms of glycaemic control after 18-weeks of randomised treatment. In this trial there were no confirmatory secondary endpoints.			
Treatments groups	Fiasp + Basal		116 subjects were randomised to the Fiasp + basal group. The total treatment duration was 18 weeks.	
	Basal		120 subjects were randomised to the basal group. The total treatment duration was 18 weeks.	
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} after 18 weeks of randomised treatment	Change from baseline in HbA_{1c} after 18 weeks of treatment was analysed using a mixed-effect model for repeated measurements (MMRM) , including treatment, region, strata (type of basal insulin) as fixed effects, subject as random effect, HbA_{1c} at baseline as covariate, and interactions between all fixed effects and visit and between covariate and visit. Superiority was considered confirmed if the upper bound of the two-sided 95% confidence interval (CI) for the estimated treatment difference (Fiasp+basal minus basal), using the FAS, was below 0%.	
Database lock	10 December 2014			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and description	Analyses of efficacy endpoints were based on the full analysis set (FAS).			
Descriptive statistics and estimate variability	Treatment group		Fiasp + basal	Basal
	Number of subject		116	120
	Change from baseline in HbA_{1c} (%) after 18 weeks of randomised treatment		-1.16	-0.22
Effect estimate per comparison	Primary endpoint Change from baseline in HbA_{1c} after 18 weeks of randomised treatment		Comparison groups	Fiasp + basal vs. basal
			Estimated treatment difference (%-points)	-0.94
			95% CI	-1.17; -0.72

Notes	In total, 14 subjects were withdrawn from the trial at or after randomisation. Nine subjects were withdrawn from the Fiasp + basal arm due to protocol violation (4 subjects), withdrawal by subject (3 subjects) and AE (2 subjects). Five subjects were withdrawn from the basal arm due to protocol violation (1 subject), withdrawal by subject (1 subject), AE (1 subject), loss to follow-up (1 subject) and other reason (1 subject who was incarcerated and unable to attend study visits).

Analysis performed across trials (pooled analyses and meta-analysis)

Please see the section on Post-meal glucose and hypoglycaemic episodes in trials 3852 and 3853 (under Outcomes and endpoints).

Clinical studies in special populations

No dedicated studies were performed in special populations. The table below shows that 12.5% of patients treated with Fiasp were aged 65-74 years and 1.5% of patients were aged 75-84 years. The majority of older patients were included in the main clinical trials.

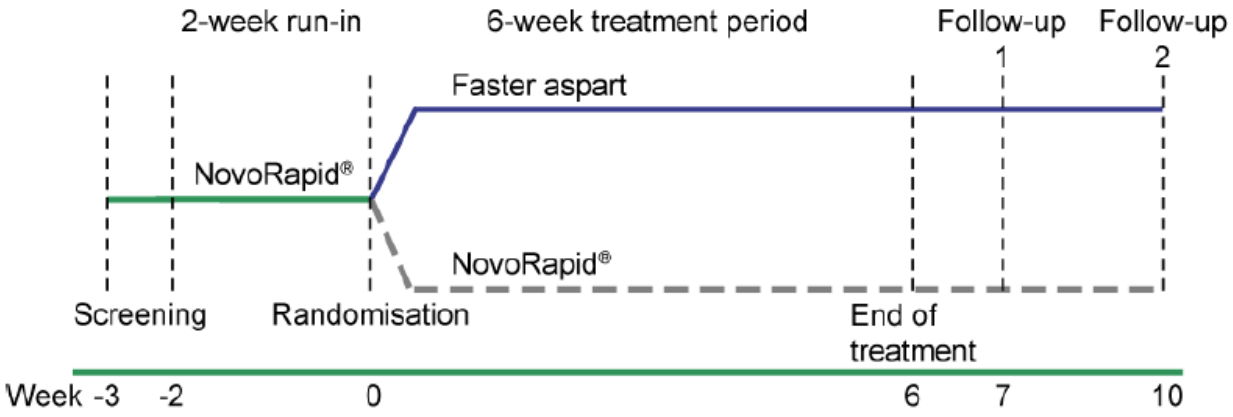
Controlled Trials	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
3852 (T1DM)	Fiasp meal: 31/381 Fiasp post-meal: 20/382 NovoRapid: 20/380	Fiasp meal: 4/381 Fiasp post-meal: 3/382 NovoRapid: 8/380	0
3853 (T2DM)	Fiasp: 91/345 NovoRapid: 84/344	Fiasp: 13/345 NovoRapid: 12/344	0
4049 (T2DM)	Fiasp: 26/116 Basal: 27/120	Fiasp: 4/116 Basal: 2/120	0
3930 (T1DM)	Fiasp: 6/43 NovoRapid: 6/43	Fiasp: 0/43 NovoRapid: 0/43	0
3931 (T1DM)	Fiasp: 6/25 NovoRapid: 0/12	Fiasp: 0/25 NovoRapid: 0/12	0
Clinical pharma-cology trial (T1DM and healthy)	Fiasp: 29/382 NovoRapid: 30/359	Fiasp: 0/382 NovoRapid: 0/359	0
All trials	Fiasp: 209/1674 NovoRapid: 140/1138 Basal: 27/120	Fiasp: 24/1674 NovoRapid: 20/1138 Basal: 2/120	0

Supportive studies

Trial 3931 (6-week pump compatibility trial in subjects with T1DM)

Trial 3931 was a 6-week randomised (2:1), double-blind, active-controlled pump trial in 37 subjects with T1DM on a pre-trial CSII regimen for ≥6 months with an insulin analogue for ≥3 months. The trial compared the pump compatibility and safety of Fiasp and NovoRapid using CSII by external pump with the secondary aim of evaluating short-term efficacy and safety. Subjects had their insulin in the CSII switched to NovoRapid, which

was used during a 2 week run-in period prior to randomisation to reinforce correct use of the device. Two sites screened and randomised subjects; 1 in the U.S. and 1 in Germany.

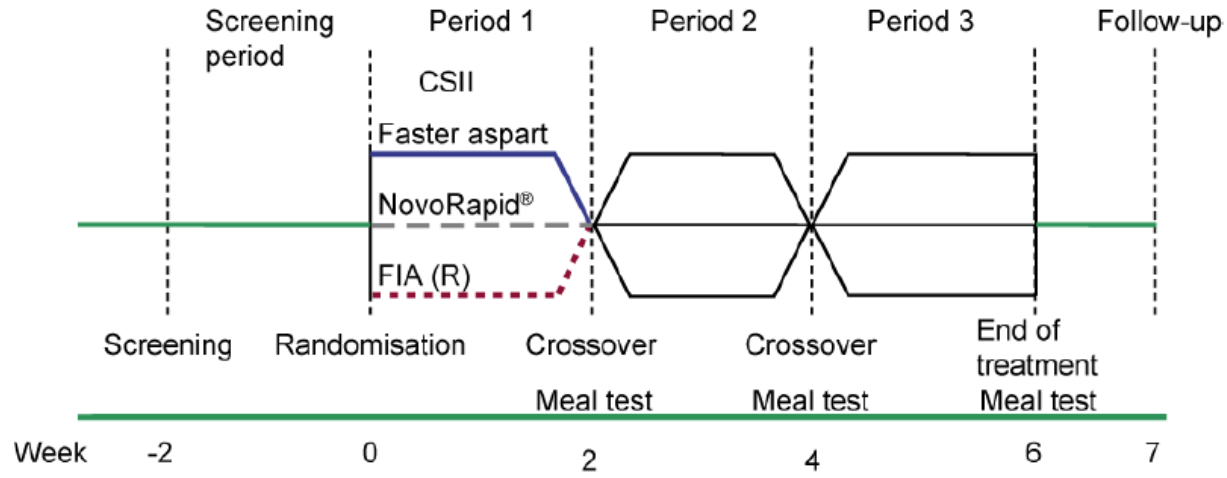


Follow-up 1: 7 days after end of treatment for collection of treatment-emergent adverse events and new diabetes treatment.
Follow-up 2: 30 days after end of treatment for recording information on cardiovascular events requiring medical assistance and deaths.

Figure 27 Design of trial 3931

Trial 3930 (3-way, 2-week period, crossover CSII trial in subjects with T1DM)

Trial 3930 was a randomised (1:1:1), double-blind, active-controlled, 3-way crossover CSII trial in 43 subjects with T1DM on a pre-trial CSII regimen for ≥6 months with an insulin analogue for ≥3 months. The trials compared 3 different formulations of insulin aspart after 2 weeks of treatment with each, using CSII by external pump, with regard to 2-hour post-meal glucose response after a standardised meal and other efficacy, safety and pump related endpoints. Subjects were randomised to receive the trial products (Fiasp, NovoRapid and FIA(R); an earlier formulation of Fiasp not pursued for further development) in one of six treatment sequences in this crossover trial. The trial was conducted at a single site in the U.S.



CSII: continuous subcutaneous insulin infusion. FIA (R): earlier exploratory formulation of Fiasp.

Figure 28 Design of trial 3930

Study participants

Inclusion criteria for the CSII trials (3931 and 3930), which included additional pump-related criteria, are shown in Table 31. Key exclusion criteria were similar for all the 5 clinical trials and are presented in Table 18.

Table 26 Inclusion criteria of the CSII trials: Trials 3931 and 3930

Inclusion criterion	Trial 3931 T1DM 6-week pump compatibility	Trial 3930 T1DM 3-way, 2-week period, crossover
Informed consent was obtained before any trial-related activities took place	X	X
Females and males aged ≥18 years	X	X
Clinical diagnosis of T1DM for at least 12 months at screening	X	X
Treated with insulin for at least 3 months at screening	X[a]	X[b]
Using an external CSII system for the previous 6 months at screening	X	X[c]
Using a MiniMed Paradigm® approved pump for the previous 6 months	X	X
Has used Quick-Set® or Silhouette® infusion set in the previous 6 months (and willing to use for trial duration)	X[d]	X
HbA_{1c} ≤9.0%	X	X
Body mass index (BMI): 3931 20–35 kg/m^2 ; 3930 ≤35 kg/m^2	X	X
Ability to use the insulin pump, calculate bolus manually or using the pump bolus calculator and willingness to eat regular meals and do carbohydrate counting and SMPG profiles	X	X
Not currently using real time CGM system and/or willing not to use a real time CGM system during the trial other than the one provided	–	X

CGM: continuous glucose monitoring. CSII: continuous subcutaneous insulin infusion. HbA1c: glycosylated haemoglobin A1c. SMPG: self-measured plasma glucose. T1DM: type 1 diabetes mellitus.
[a]Treated with insulin aspart, lispro or gluisine
[b]Treated with the same insulin analogue
[c]For three months at screening in trial 3930
[d]Used Quick-Set or Silhouette infusion set for at least 1 month in the previous 6 months

Endpoints

The primary and supportive secondary efficacy endpoints for the CSII trials, 3931 and 3930, are presented in Table 32.

Table 27 Prespecified assessments, primary and secondary efficacy endpoints in Trials 3931 and 3930

Endpoint	Trial 3931 6-week pump compatibility T1DM	Trial 3930 2-week crossover CSII T1DM
Primary endpoints		
Number of confirmed episodes of infusion set occlusions	X	–
$\Delta PG_{av,0\text{-}2h}$[a] (meal test)	–	X
Supportive secondary endpoints		
Pump-related parameters (number of occurrences)		
Episodes of possible infusion set occlusions	X	X
Premature infusion set changes	X	–
Days since insertion of infusion set until possible episode of infusion set occlusion	X	–
Laboratory findings	X	–
Subject/investigator findings[b]	X	X
Infusion sets used / week	X	X
Glycaemic control parameters (change from baseline unless stated)		
HbA_{1c}	X	–
Fructosamine	X	X
PPG and PPG increments[c]	X	X
1,5-anhydroglucitol	X	–
SMPG profiles[d]	X	X
Interstitial glucose	–	X
Fasting plasma glucose	X	X
Insulin dose (total bolus and total basal)	X	X
Body weight	X	X[e]

HbA1c: glycosylated haemoglobin A1c. PPG: postprandial glucose. SMPG: self-measured plasma glucose. T1DM: type 1 diabetes mellitus. T2DM: type 2 diabetes mellitus.
[a] Change in plasma glucose concentration over the first 2 hours after a standardised meal (after each 14-day treatmentperiod);
[b] In trial 3931, subject's findings were recorded. In trial 3930, the investigator findings were recorded;
[c] Measured in meal test in trial 3930, SMPG in trial 3931;
[d] 7-9-7-point SMPG profiles in trial 3931 and 7-7-9-point SMPG profiles in trial 3930.
[e] Only at screening in trial 3930

Results

Compatibility and pump-related parameters

In trial 3931, the 6-week pump compatibility trial, no microscopically confirmed episodes of infusion set occlusions (primary endpoint) were observed with treatment with either Fiasp or NovoRapid. None of the premature infusion set changes reported in trials 3931 and 3930 were associated with formation of a plug.

Exploratory efficacy parameters

In trial 3931, Fiasp appeared to be effective in controlling blood glucose levels as assessed by several measures of intermediate and long-term glycaemic control, such as HbA_{1c}, serum fructosamine, and 1,5-AG, and measures related to postprandial glucose control, such as 2-hour PPG increment (SMPG) and mean of 9-point SMPG profile. There were no statistically significant differences observed between treatments. With the exception of FPG (where a larger decrease was observed with NovoRapid than with Fiasp in trial 3931), the results obtained in trial 3931 for the glycaemic control parameters were in line with those obtained for subjects with T1DM in the therapeutic confirmatory trial 3852.

In trial 3930, a statistically significantly greater glucose-lowering effect was demonstrated with Fiasp compared to NovoRapid in terms of mean change in the plasma glucose concentration during the first 2 hours of a standardised meal test ($\Delta PG_{av,0-2h}$) (estimated treatment difference: -0.99 mmol/L $[-1.95; -0.03]_{95\%CI}$). The mean change over the first hour after the meal ($\Delta PG_{av,0-1h}$) pointed in the same direction. Fiasp was comparable to NovoRapid across most other endpoints related to overall glucose control.

The finding of a lower post-meal glucose increment with Fiasp as compared to NovoRapid was supported by mean prandial IG increments during 14 days of CGM that were statistically significantly lower for Fiasp at 1 hour and 2 hours after all meals.

Insulin dose

In trial 3931, the median daily bolus insulin dose at end of treatment (Week 6) was similar for Fiasp (26 U (0.28 U/kg) and NovoRapid (27 U (0.34 U/kg). The median daily basal insulin dose at end of treatment (Week 6) was slightly lower with Fiasp (21U (0.25 U/kg)) than NovoRapid (24 U (0.30 U/kg).

Approximately 50% of the total daily dose after 6 weeks treatment was provided by bolus insulin for both Fiasp (53%) and NovoRapid (52%).

In trial 3930, the median daily bolus insulin dose at end of treatment (Day 14) was similar for Fiasp (0.22 U/kg) and NovoRapid (0.21 U/kg). The median daily basal insulin dose at end of treatment (Day 14) was 0.29 U/kg for both of Fiasp and NovoRapid.

Body weight

In trial 3931, mean body weight remained stable from baseline to end of treatment in both groups, and there was no clinically relevant difference in body weight between the Fiasp treatment group and the NovoRapid group at end of treatment.

Trial 3852 – 26 week extension phase

For the description of the design of the study, please see the main study. The additional 26 week period of the trial was conducted in order to gather longer-time safety data such as antibodies development. Only meal-time arms were included in the additional 26 weeks of the trial.

During the extension phase of the study, visit intervals were extended from 4 to 6 weeks. Only results of the two mealtime groups (entire 52-week treatment period) are presented since the post-meal group was ended at week 26. The term 'baseline' refers to randomisation.

Of a total of 761 subjects randomised to one of the two mealtime groups, 675 (88.7%) subjects completed the 52-week treatment period (mealtime Fiasp: 337 (88.5%) subjects and NovoRapid: 338 (88.9%) subjects). Thus there was no imbalance between treatments with regards to discontinuations.

The primary outcome of the study was the change in HbA1c from baseline at week 26. Thus only a brief summary of the outcome of secondary endpoints is provided in the following.

HbA1c mean changes

In the run-in and basal optimisation period, all subjects were treated with insulin detemir and NovoRapid. During run-in, mean observed HbA1c was reduced from 8.01% to 7.62% in the group subsequently randomised to mealtime Fiasp and from 8.00% to 7.58% in the group subsequently randomised to NovoRapid. During the first 26 weeks of treatment, the observed mean HbA1c was further reduced to 7.26% with mealtime Fiasp and to 7.40% with NovoRapid, but then increased to 7.51% with mealtime Fiasp and 7.58% with NovoRapid after 52 weeks of treatment (**Error! Reference source not found.**).

The estimated change from baseline in HbA1c after 52 weeks of randomised treatment was -0.08%-points with mealtime Fiasp and 0.01%-points with NovoRapid. The estimated treatment difference (mealtime Fiasp versus NovoRapid) after 52 weeks of randomised treatment was -0.10%-points [-0.19; -0.00]95%CI and was statistically significant.

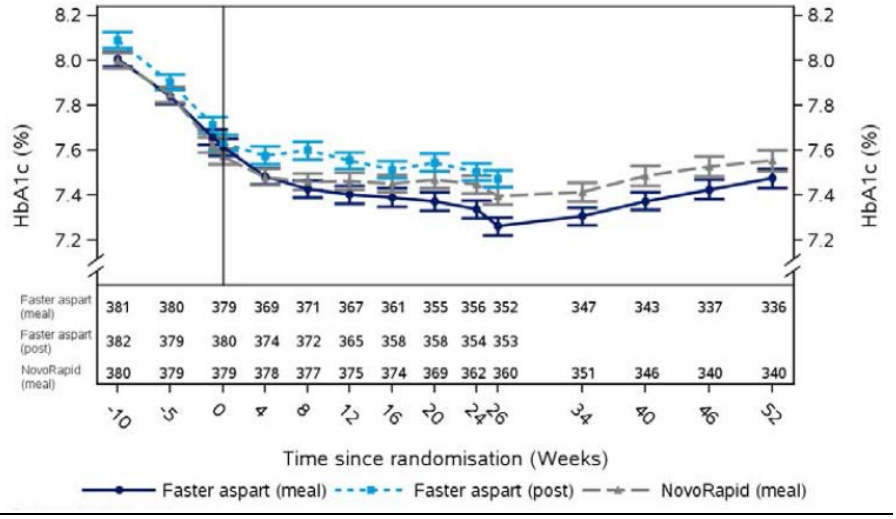


Figure 29 HbA1c by treatment week

Full analysis set. Observed data. Error bars: ± standard error (mean). Subjects in the post-meal faster aspart group did not continue in the extension phase of the study.

HbA1c responders

The proportion of subjects who achieved the HbA1c targets of <7.0% and ≤6.5% increased from baseline to 52 weeks of treatment both with mealtime Fiasp and with NovoRapid.

With mealtime Fiasp, the estimated odds of achieving HbA1c <7.0% after 52 weeks were not statistically different from the estimated odds of achieving HbA1c <7.0% with NovoRapid after 52 weeks of treatment. None of the other HbA1c responder endpoints were statistically significantly different between mealtime Fiasp and NovoRapid.

Postprandial glucose (PPG)

In both treatment groups, mean PPG increased up to 120 minutes after meal consumption and then started to decrease. Estimated treatment differences after 52 weeks of treatment for PPG at 1 and 2 hours after start of the meal test both favoured mealtime Fiasp, but only reached statistical significance at 1 hour (Table 33).

Table 28 Postprandial glucose (meal test) – treatment differences after 52 weeks

	Estimate	95% CI
PPG at 60 min (mmol/L)		
Treatment difference at week 52		
Faster aspart (meal) - NovoRapid (meal)	-0.93	[-1.58; -0.27]
PPG at 120 min (mmol/L)		
Treatment difference at week 52		
Faster aspart (meal) - NovoRapid (meal)	-0.40	[-1.19; 0.40]
PPG at 180 min (mmol/L)		
Treatment difference at week 52		
Faster aspart (meal) - NovoRapid (meal)	0.19	[-0.61; 0.99]
PPG at 240 min (mmol/L)		
Treatment difference at week 52		
Faster aspart (meal) - NovoRapid (meal)	0.27	[-0.47; 1.01]

Full analysis set. N: Number of subjects, CI: Confidence interval, PPG: Postprandial glucose
CGM: Continuous glucose monitoring
Change from baseline in postprandial glucose (meal test) is analysed using a mixed-effect model for repeated measurements including visit 36 and 62. The model includes treatment, region and strata (combination of bolus adjusting method, basal treatment regimen and CGM and frequently sampled meal test sub-group) as fixed effects, subject as random effect, baseline postprandial glucose (meal test) as covariate and interaction between all fixed effects and visit, and between the covariate and visit.
Subjects in the Faster aspart (post) arm are included in the statistical analysis.

Postprandial glucose increments

After 52 weeks of randomised treatment, the observed mean PPG increment at 1 hour (60 minutes) was reduced from 5.39 mmol/L to 4.50 mmol/L (97.17 to 81.16 mg/dL) with mealtime Fiasp and from 5.65 mmol/L to 5.44 mmol/L (101.87 to 98.10 mg/dL) with NovoRapid. The estimated change from baseline in 1-hour PPG increment was -1.05 mmol/L with mealtime Fiasp and -0.14 mmol/L with NovoRapid. The estimated treatment difference (mealtime Fiasp versus NovoRapid) was statistically significant in favour of mealtime Fiasp (-0.91 mmol/L [-1.40; -0.43] 95%CI; -16.48 mg/dL [-25.17; -7.80] 95%CI).

There were no statistically significant treatment differences (mealtime Fiasp versus NovoRapid) after 52 weeks of treatment in PPG increment at 2, 3 and 4 hours (120, 180 and 240 minutes) after start of the meal test.

Self-measured plasma glucose: 7-9-7-point profiles

Subjects recorded SMPG as 7-9-7-point profiles on 3 consecutive days before the visits at baseline, week 12, week 26, week 40 and week 52 (Figure 32).

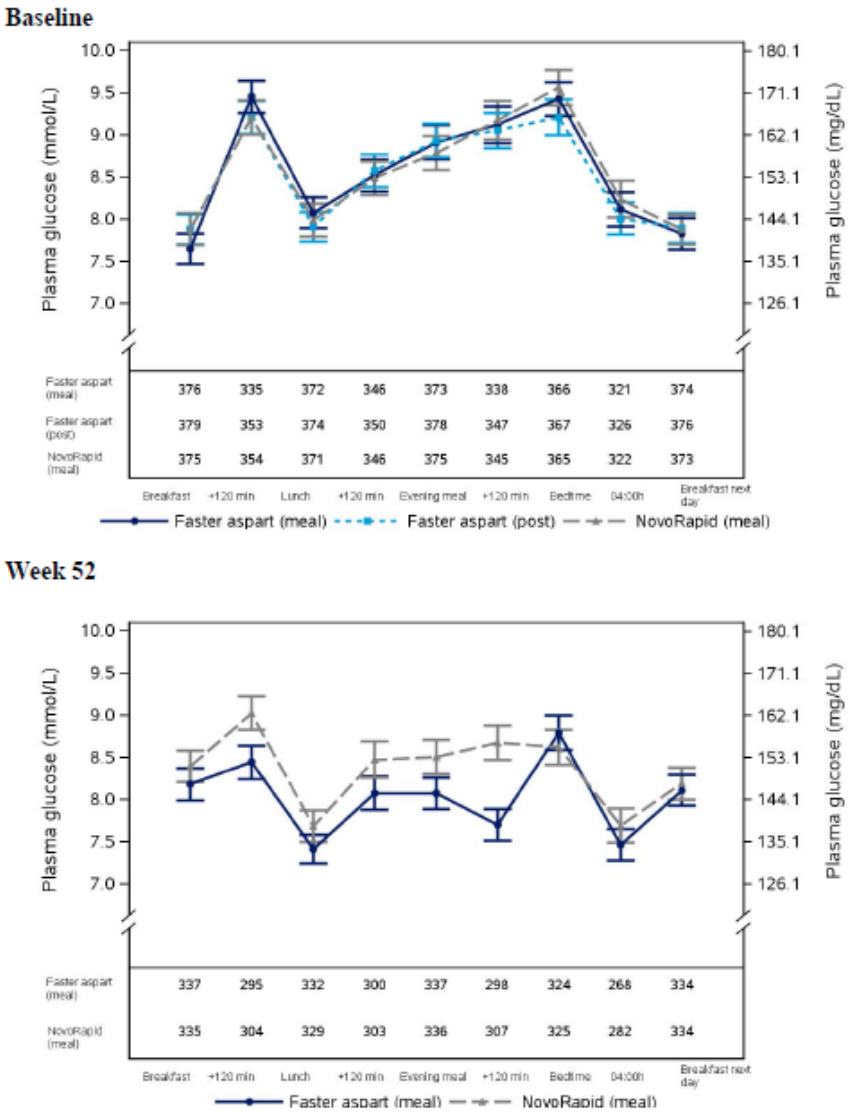


Figure 30 9-point self-measured plasma glucose profile at baseline and week 52

Full analysis set. Observed data. Error bars: ± standard error (mean). Numbers under graph are number of subjects. Subjects in the post-meal Fiasp group did not continue in the extension phase of the study.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The application is supported by three therapeutic confirmatory trials, including 2068 randomised subjects, evaluating efficacy and safety of Fiasp in subjects with T1DM and T2DM. Further to this, two CSII trials, which include 80 randomised subjects, provide supportive data.

No dose-finding study has been performed which is acceptable, considering that the pharmacology program show that the glucose-lowering effect of Fiasp is comparable to that of NovoRapid. Furthermore, the insulin dose is titrated based on blood glucose levels.

Trial 3852 was of 26-weeks duration and provide data on a double blind comparison of Fiasp with NovoRapid in subjects with T1DM; in addition post-meal dosing with Fiasp was investigated. The data from the extension was submitted with the responses to the Day 120 LoQ.

Two studies in T2DM patients were conducted, both with metformin as background treatment. Trial 3853 was a double blind study of 26-weeks duration, in which Fiasp was compared to NovoRapid. Trial 4049 was an open label study of 18-weeks duration which compared Fiasp in a basal-bolus regimen vs an optimised basal insulin regimen. The shorter duration of trial 4049 is acceptable, considering that only intensification of basal therapy was allowed in the comparator arm. The open label design is acceptable, considering the difference in therapy (basal-bolus regimen vs basal regimen).

Inclusion criteria were adequate in order to enrol a population representative for the target population and exclusion criteria were relevant and acceptable. Patients with recent CV disease were excluded as the intensive treat-to-target approach with ambitious glycaemic goals must be applied with caution in these individuals. This is acceptable as the major aim of the studies were to compare Fiasp with NovoRapid applying a treat-to-target approach. In addition to standard withdrawal criteria, prespecified withdrawal criteria were in place.

The choice of NovoRapid as the active comparator in trials 3852 and 3853 is adequate, especially considering that Fiasp is a new formulation with insulin aspart.

In trial 4049, intensification of pre-trial basal insulin therapy was the active comparator, after stopping any additional OAD other than metformin. This provides would information on the effect of a bolus-basal versus basal insulin therapy. However, the outcome could possibly be affected by the discontinuation of OADs used prior to inclusion in the study if the metabolic control deteriorates.

Titration of the basal insulin dose was done according to pre-set targets. Bolus doses were titrated according to prespecified titration algorithms, or using carbohydrate counting (trial 3852). In the three confirmatory studies, bolus insulin was only to be administered in the abdomen, whereas basal insulin could be administered in the upper arm or thigh.

Standardised meal tests were performed in trials 3852 and 3853. The test methods applied were adequate.

The objectives and endpoints were adequate and in line with both scientific advice given by the CHMP and current guidelines. However, with respect to the confirmatory secondary endpoint of hypoglycaemia, it is noticed that the PG confirmed hypoglycaemic episodes are not according to the latest ADA classification specified in the current Diabetes guideline. Furthermore, updating of the ADA classification of hypoglycaemia to reflect the latest ADA classification was one important amendment to the final protocol prior to randomisation for all trials. The measured plasma glucose concentration are specified to be less than or equal to 3.9 mmol/L in the ADA classification criteria, but a lower limit value of 3.1 mmol/L was used for the secondary confirmatory endpoint in the trials (**3852** and **3853**). A statistical analysis of hypoglycaemic episodes using the ADA classification for trials **3853** and **3853** has been provided; the outcome of this analysis did not change the assessment of the primary analysis.

In general, statistical methods are acceptable. Confidence interval approach for the non-inferiority analysis in trials 3852 and 3853 was applied versus a non-inferiority margin of 0.4% (absolute) which was considered adequate by EMA (scientific advice from 2011).

The chosen stratification procedure in studies 3852, 3853 and 4049, ensured an equal distribution of the treatment arms within each stratum, but not within a combination of strata, which may explain the fact that several centres in study 3852 included subjects who were randomized to 2 treatment groups instead of to 3 treatment groups.

The Applicant has submitted long and exhaustive appendices containing data listings with important protocol deviations. Overall the important protocol deviations were judged by the Applicant not to affect the outcome of the trials. Among others, there were issues of noncompliance with the GCP principle regarding informed consent, and also poor compliance with study assessments and violations of entry criteria, which are usually identified as relevant protocol violations according to the ICH E9. It was unclear if these GCP/ICH principles were strictly followed in the current definitions of the analysis populations; however acceptable reassurance with regards to adherence to the GCP/ICH principles has been provided. However, a restricted PP analysis set has been defined, with additional requirements and after a re-evaluation of deviations related to informed consent, as well as violations of entry and withdrawal criteria. Exclusions from this new per protocol population were summarized per category and treatment group, and a re-run of the non-inferiority analyses was submitted. The results almost identical to that of the original PP population and, thus, confirmed the results of the primary non-inferiority analysis of HbA1c.

Efficacy data and additional analyses

In all studies, the study populations were representative for the target population and well balanced between study groups with regards to demographic and disease characteristics. Across the study program, about 30 % of subjects were recruited from the EU (47 % of T1DM subjects and 26 % of T2DM subjects). It is noted, though, that the baseline values for HbA1c are outside the range that was pre-specified in the inclusion criteria for all the trials. The Applicant has clarified that only a limited numbers of subjects had HbA1c values outside the inclusion criteria at visit 10, and this is therefore not considered to have had any significant impact on the results.

In general, drop-out rates were low and balanced between groups. In trial 3852, the highest withdrawal rates were due to withdrawal by subject (4.5 % in the Fiasp meal group and 2.6 % the NovoRapid group). The highest overall drop-out rate was observed in trial 3853 (T2DM). In this study, between 4.4 and 5.8 % were withdrawn due to withdrawal criteria whereas withdrawal by subject was made by a similar proportion (4.3 and 4.4 %). In trial 4049 (T2DM), the reasons for discontinuations in the test arm may be related to treatment in at least some of the cases, i.e. missing at random not really valid. However the events are few and it is not expected to change the results very much.

During the run-in period in study 3852, the optimising of ongoing treatment leads to a slight decrease in HbA1c. In trials 3853 and 4049, there was no change in HbA1c during the run-in period in spite of the fact that all other OADs than metformin were discontinued. Thus life-style counselling and optimising basal insulin treatment was sufficient to balance the reduction in OAD treatment in these trials.

Non-inferiority was confirmed for the primary endpoint (mean change in HbA1c from baseline) in both T1DM (trial 3852: -0.15 % $[-0.23; -0.07]_{95\%CI}$) and T2DM (trial 3853, -0.02 % $[-0.15; 0.10]_{95\%CI}$) and the 95 % CI was well within the non-inferiority margin of 0.4 %. Furthermore, in T1DM patients the upper 95 % CI was below zero, indicating superiority of Fiasp (mealtime) over NovoRapid, although the mean treatment difference was small. However, it should be noted that testing for superiority was not included in the confirmatory hierarchical testing procedure to control for multiplicity. In trial 4049, a statistically significant and clinically relevant effect of Fiasp, when compared to optimised basal insulin treatment, was observed (treatment difference -0.94 % $[-1.17; -0.72]_{95\%CI}$).

In trial 3852, more patients achieved the target of HbA1c <7.0% in the Fiasp meal group (33.3 %) than in the NovoRapid group (28.2 %), whereas there was no difference in the proportion of patients reaching the HbA1c targets between treatment groups in trial 3853. As expected, in trial 4049, more patients achieved the HbA1c targets in the bolus-basal treated group.

In trial 3852, a statistically significant effect onthe 1-hour PPG and the 2-hour PPG increment was observed in the Fiasp (meal) treated group compared to NovoRapid, with 2-hour PPG increment being a confirmatory secondary endpoint. The magnitude of the difference in post-prandial glucose-lowering effect in trial 3852 (-0.67 mmol/L) was comparable to that observed in the clinical pharmacology trial 3888 (-0.57 mmol/L) and higher than observed in trial 3889 (0.19 mmol/L). The observed differences between trials could be due to the comparatively small number of subjects in the clinical pharmacology trials. In trial 3853 there was no statistically significant effect on the 2-hour PPG increment, whereas a statistically significant difference was observed in favour of Fiasp on the 1-hour PPG increment. In the pooled analysis, including both T1DM and T2DM subjects (trials 3852 and 3853), a statistically significant difference in treatment effect on both 1-hour and 2-hour PPG increment was observed.

In trial 3852, the overall rate of severe or BG confirmed hypoglycaemia episodes was comparable for Fiasp (meal) and NovoRapid. In trial 3853, the overall rate of severe or BG confirmed hypoglycaemia episodes was higher for Fiasp than for NovoRapid, although not statistically significant. In the pooled analysis, numerically slightly more BG confirmed daytime episodes were observed in the Fiasp treated groups, although not statistically significant. Nocturnal BG confirmed episodes were numerically slightly less frequent, although again not statistically significant. Thus no clinically relevant differences in the overall number of BG confirmed episodes were observed.

Across the trials, comparable effects on the 9-point SMPG profiles were observed for both Fiasp and NovoRapid and there were no statistically significant differences between treatments. In trial 4049, the 9-point SMPG curve in the basal-bolus treated group showed great resemblance with the curves observed in trial 3853, whereas no apparent change in the profile was observed in the basal treated group.

Plasma 1,5-anhydroglucitol (1,5-AG), has been proposed as a marker for post-meal hyperglycaemia. However there are no outcome studies using this measure of glycaemic control. Change in 1,5-anhydroglucitol was included as a secondary endpoint in all confirmatory trials. The results reflect the data from the meal test and the SMPG profiles. A statistically significant treatment differences was observed between Fiasp meal and NovoRapid (trial 3852; 0.50 µg/mL $[0.24; 0.76]_{95\%CI}$), whereas no significant difference was observed in trial 3853. In trial 4049, the estimated mean treatment difference was statistically significant and in favour of Fiasp (4.24 µg/mL $[3.04; 5.44]_{95\%CI}$).

No relevant difference in FPG was observed between treatment arms in any of the three studies. The largest decrease in FPG was observed in trial 4049. Nor were any clinically relevant differences in lipid profile observed in either of the studies. Weight gain is expected with intensified insulin treatment. No relevant differences between Fiasp and NovoRapid were observed in the studies.

In trials 3852 or 3853, there were no apparent differences in the bolus or basal insulin doses between treatment arms. In trial 4049, the bolus and basal doses in the Fiasp treated group, were rather similar to the doses in trial 3853. In trial 3852, about 50 % of the total dose was provided by bolus insulin, whereas the bolus insulin dose constituted about 55 % in the T2DM studies.

The PROs did not show any clinically meaningful changes.

Data from the long-term extension of trial 3852 show that in both treatment groups, HbA1c increased again after the initial decline during the first 26 weeks of treatment. The estimated treatment difference (mealtime Fiasp versus NovoRapid) after 52 weeks of randomised treatment was -0.10%-points [-0.19; -0.00]95%CI and although statistically significant, the difference was smaller than after 26 weeks. No difference in the HbA1c responder endpoints was observed between mealtime Fiasp and NovoRapid. After 52 weeks of treatment, the estimated treatment differences for PPG at 1 and 2 hours after start of the meal testt only reached statistical

significance at 1 hour. The effect on post-prandial glucose control was also reflected in the self-monitored glucose profiles at 52 weeks, where the post-prandial increase in blood glucose appeared less pronounced after break-fast and lunch in the Fiasp group.

The 52 week data provided by the Applicant thus indicate that the difference in effect between Fiasp and NovoRapid observed in the main study was less pronounced.

In study 3852, post-meal dosing of Fiasp was compared to NovoRapid in order to support this posology in the SmPC. With regards to the mean change from baseline in HbA1c, Fiasp post-meal was non-inferior to NovoRapid with the point estimate slightly above zero (0.04 % $[-0.04; 0.12]_{95\%CI}$). The proportion of patients achieving HbA1c targets were lower in the Fiasp post-meal group compared to NovoRapid. Furthermore, numerically higher 1-hour and 2-hour PPG increment was observed with Fiasp post-meal compared to NovoRapid, with the difference at 1-hour being statistically significant in favour of NovoRapid.. Thus the data indicate that a comparable effect of Fiasp to that of NovoRapid is achieved when given post-meal, however, the effects on 1-hour and 2-hour PPG observed with meal Fiasp are not preserved. The data are considered sufficient to support the posology.

No dedicated studies in special populations were performed. Considering the long experience with insulin aspart, and the available data on Fiasp, this is acceptable. The clinical trials included almost 200 patients above the age of 65 and the experience in this age group is considered adequate whereas the experience in patients above the age of 75 is still limited.

Two supportive studies, trials 3931 and 3930 were submitted in order to provide data on compatibility and safety with the use of Fiasp in CSII by external pump. Trial 3930 also provide data on 2-hour PPG after a standardised meal. The trials were of adequate design. Notably, compatibility was only tested for the MiniMed Paradigm external pump. Although some imbalances with regards to age and sex was observed in trial 3931, the studies included a representative, adult T1DM population.

There was no microscopically confirmed episodes of infusion set occlusions in trial 3931, thus supporting compatibility for Fiasp with the pump system. A more extensive assessment of pump compatibility data is made in the section of clinical safety of this report.

In both trials, most glycaemic control parameters were comparable between Fiasp and NovoRapid. The data from the standardised meal test in trial 3930 showed statistically significantly lower 2-hour PPG levels for Fiasp compared to NovoRapid, supporting the meal test data obtained from trial 3852 (see also the section on “Primary pharmacology” of this report). Interstitial glucose (IG) data obtained by CGM measurements provide further support showing lower IG increments post-meal. There were no relevant differences in insulin doses between treatment groups in any of the two studies. Body weight remained stable in both treatment groups in trial 3931.

2.5.4. Conclusions on the clinical efficacy

The data from the clinical trials show a clinically relevant glucose lowering effect associated with treatment with Fiasp as expected considering that the active component is insulin aspart.

Compared to Novorapid, a small difference in reduction of HbA1c and a statistically significant difference in PPG increment in patients with T1DM was documented. HbA1c and PPG outcomes in patients with T2DM were very similar in the two treatment groups and no statistically significant differences were shown.

The clinical relevance of the effect on PPG and the resulting small decrease in HbA1c observed at week 26 in T1DM is unclear. The 52 week data in T1DM indicate that the difference in effect between Fiasp and NovoRapid observed in the main study was less pronounced.

Post-meal dosing was also investigated in patients with T1DM and showed a comparable effect to that of NovoRapid given *before* a meal; a direct comparison of post-meal dosing was not studied.

The data are considered sufficient to support the posology.

Comparable effects to those of NovoRapid were observed when Fiasp was used for CSII.

2.6. Clinical safety

Patient exposure

The safety evaluation of Fiasp primarily focused on data from the 2 completed therapeutic confirmatory basal-bolus trials in subjects with T1DM and T2DM (trials 3852 and 3853; 26 weeks) as these trials covered the intended target populations and enabled a focus on the comparison of the safety profile of Fiasp to NovoRapid. The other 3 completed therapeutic confirmatory and exploratory trials 4049 (18 weeks in T2DM), 3931 (6 weeks in T1DM) and 3930 (T1DM) were used to support the safety evaluations from the 2 pivotal basal-bolus trials. Trials 3930 and 3931 assessed the use of Fiasp in CSII with pumps, with trial 3931 focusing on the compatibility of Fiasp with the CSII system. Exposure by treatment groups in the therapeutic confirmatory and exploratory trials are presented in Table 34. The **"diabetes pool"** consisted of trials 3852, 3853, 4049 and 3931 and exposure by duration of treatment in the diabetes pool is presented in Table 35.

Table 29 Exposure by treatment group in the therapeutic confirmatory and exploratory trials

	Faster aspart (mealtime)		Faster aspart (postmeal)		Faster aspart (total)		NovoRapid		Basal		Comparator		Total	
	N	(PYE)	N	(PYE)	N	(PYE)	N	(PYE)	N	(PYE)	N	(PYE)	N	(PYE)
Diabetes pool	386	(186.4)	377	(183.0)	1244	(570.5)	733	(352.5)	120	(40.8)	853	(393.3)	2097	(963.8)
T1DM														
3852	386	(186.4)	377	(183.0)	763	(369.4)	380	(188.9)			380	(188.9)	1143	(558.2)
T2DM														
3853					341	(159.8)	341	(162.3)			341	(162.3)	682	(322.1)
4049					115	(38.4)			120	(40.8)	120	(40.8)	235	(79.2)
CSII trials														
3931					25	(2.9)	12	(1.4)			12	(1.4)	37	(4.3)
3930					43	(1.7)	42	(1.6)			42	(1.6)	43	(1.7)

N: Number of subjects, PYE: Patient years of exposure. One patient year of exposure = 365.25 days. Exposure during run-in is excluded. The 'Diabetes pool' consists of trials 3852, 3853, 4049 and 3931. NovoRapid is known as NovoLog in the U.S. 'Comparator' consists of NovoRapid plus basal insulin.

Table 30 Exposure by duration of treatment in the diabetes pool

	Any exposure N	>= 6 months N
Diabetes pool		
Faster aspart	1244	967
NovoRapid	733	646
Basal	120	NA

NA: Not applicable. N: Number of subjects. Completers in 6 months trials and subjects exposed for at least 6 months in trials with duration > 6 months, where a month is set to 30 days. Exposure during run-in is excluded. The 'Diabetes pool' consists of trials 3852, 3853, 4049 and 3931. NovoRapid is known as NovoLog in the U.S.

In the diabetes pool the two pivotal trials 3852 and 3853 accounted for the vast majority (93%) of the exposure to Fiasp. Insulin aspart with the new formulation do not have safety results beyond 26 weeks. Safety data from study 3852 (T1DM) will in an ongoing extension of the study later be provided up to 52 weeks of exposure. In addition long-term safety of insulin aspart is available from results in clinical trials and post-marketing experience with other formulations of the product.

Overall, the safety database seems be sufficient to cover the populations of the planned indications. The main limitation is the lack of long-term experience with the new formulation. In addition, off-label use in subjects below 18 years is anticipated. There were no subjects included below 18 years in the present studies. Treatment of children and adolescents < 18 years of age is classified as missing information in the RMP of Fiasp. A phase 3b efficacy and safety trial in children is planned.

In addition, the number of subjects exposed to Fiasp in the age ≥ 65 years (elderly) was 196 (84.2 PYE) and in subjects ≥ 75 years (very elderly) 24 (2%) corresponding to 11.2 PYE Table 36. The low exposure of Fiasp in the group of patients above 75 years should be reflected in the SmPC.

Table 31 Exposure by age groups in the diabetes pool

	Fiasp	**Comparator**
Age groups (Years)	**N (PYE)**	**N (PYE)**
Total number (all ages)	1244	853
18-64	1048 (486.3)	703 (325.6)
65-<75	172 (73.0)	128 (57.3)
>= 65	196 (84.2)	150 (67.7)
>= 75	24 (11.2)	22 (10.4)
> 85	0* (0)	0* (0)

Adverse events

Common adverse events

The percentage of subjects reporting AEs in the diabetes pool was 61% for Fiasp and 65% for the comparator and with the corresponding rates 394 and 387 events per 100 PYE, respectively. There were no difference of clinical importance for Fiasp and the comparator group respectively regarding frequency of adverse events as well as severity, relation to study drug and outcome of the events (Table 37).

The most frequently reported PTs (occurring in ≥5% of subjects in any treatment group) were *nasopharyngitis* (37.1 and 33.9 events per 100 PYE for Fiasp and comparator, respectively), *upper respiratory tract infection* (14.9 and 17.8 events per 100 PYE for the two groups, respectively) and *headache* (14.8 and 17.2 events per 100 PYE, respectively).

When summarizing differences in the diabetes pool between the two formulations regarding AE pattern on a PT level, most of the PTs had a rate difference close to 0. For some PTs, the confidence interval did not span 0 with *influenza* and *sinusitis* favouring Fiasp and *back pain, abdominal pain upper, dizziness* and *fall* favouring the comparator. The clinical relevance for these differences were considered to be low (Figure 33).

The Applicant looked further into cases with fall and dizziness in relation to hypoglycaemia. In total 30 events of fall occurred in 21 subjects in the diabetes pool. This corresponded to a total rate of 3.1 per100 PYE (4.2 per 100 PYE in the Fiasp group and 1.7 per 100 PYE in the comparator group, respectively). Based on this analyse no possible relationship between the hypoglycaemic episodes and the events of fall (or dizziness) could be concluded (five of the events of fall took place on the same day as a hypoglycaemic episode). No other underlying factors could be identified.

Adverse events in general were more common in T1DM (73%) compared to patients with T2DM (53%) with no apparent difference between Fiasp and NovoRapid. However, most frequent PT:s were similar between the different types of diabetes.

Table 32 All adverse events in diabetes pool

	Faster aspart				Comparator				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	1244				853				2097			
Total exposure (yrs)	570.48				393.30				963.78			
Events	784	(60.7)	2332	394	539	(64.7)	1475	387	1323	(63.1)	3807	395
Serious												
Yes	68	(5.3)	89	15.4	51	(5.9)	62	15.3	119	(5.7)	151	15.7
No	762	(59.0)	2243	378	526	(63.3)	1413	372	1288	(61.4)	3656	379
Missing	0				0				0			
Severity												
Severe	66	(4.9)	82	13.4	39	(4.6)	45	11.5	105	(5.0)	127	13.2
Moderate	297	(23.4)	584	101	192	(23.3)	342	90.6	489	(23.3)	926	96.1
Mild	665	(51.1)	1666	279	464	(55.5)	1087	285	1129	(53.8)	2753	286
Missing	0				1	(0.1)	1	0.3	1	(0.0)	1	0.1
Related to investigational products												
Probable	58	(4.4)	67	11.3	33	(4.1)	40	10.7	91	(4.3)	107	11.1
Possible	33	(2.8)	44	8.5	27	(3.1)	35	8.6	60	(2.9)	79	8.2
Unlikely	758	(58.6)	2179	366	458	(56.4)	1248	335	1216	(58.0)	3427	356
Missing	34	(2.9)	42	8.1	88	(9.0)	152	33.1	122	(5.8)	194	20.1
Outcome												

N: Number of subjects, %: Percentage of subjects, E: Number of event, R: Event rate per 100 patient years of exposure, yrs: Years. Treatment emergent adverse events in the safety summary are those events that were treatment emergent and belonged to the main treatment period of each of the individual trials. Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigator's assessment. The 'Diabetes pool' consists of trials 3852, 3853, 4049 and 3931. 'Comparator' consists of NovoRapid plus basal insulin. Proportions and event rates were calculated using the Cochran-Mantel-Haenszel method to account for different exposures in the trials. If no events are experienced for the subjects in a trial, the subjects contribute with exposure.

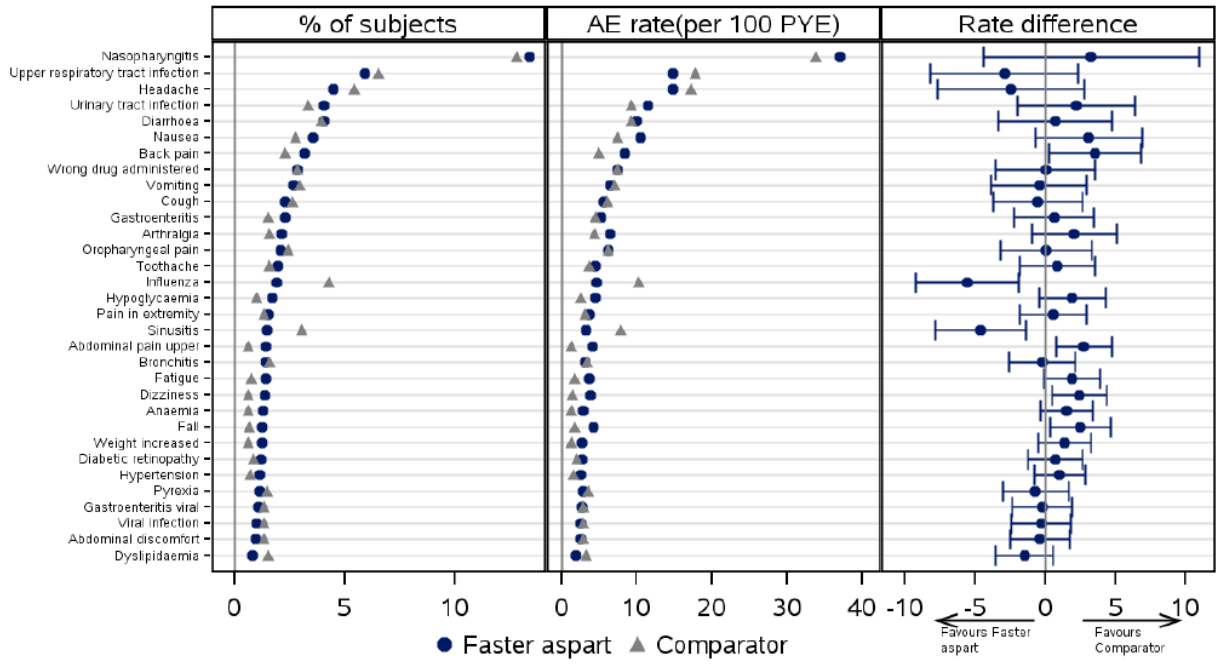


Figure 31 Adverse events occurring in ≥ 1% of subjects in any of the treatments groups by PT (sorted by frequency in the Fiasp group) in the diabetes pool.

Other significant adverse events

The rates of Cardiovascular events, Peripheral oedema, Eye disorders (diabetic retinopathy and refraction disorders), Peripheral neuropathy and Rare events were seen without any difference of clinical importance between Fiasp and the comparator.

Injection or infusion site reactions

Overall in a pool of the trials 3852, 3853 and 4049, the rates of injection site reactions were higher for Fiasp (23 events) than for the comparators (10 events) (3.8 and 2.4 events per 100 PYE, respectively). The total numbers of injection site reactions in the pooled data set were 23 events in the Fiasp group and 10 events in the comparator group. None of these injection site reactions were serious or severe (Table 38 and Figure 34)

However, when also including study 3930 and 3931 the total number of events of injection site reactions increases to 40 events of injection site reactions of which, 30 occurred in the Fiasp group and 10 in the comparator groups.

Twenty-nine of the 40 events with injection site reactions occurred in T1DM trials. In trial 3852 there were 22 events of injection site reactions of which 19 occurred in the Fiasp groups without any difference between the two groups (mealtime or post-meal Fiasp). In the CSII studies (3930 and 3931) 7 events of injection site reactions occurred. All occurred in the Fiasp groups.

In the T2DM population there was an equally distributed frequency between the two formulations.

Even if other possible explanations have been suggested for some of the events by the sponsor there is an apparent difference both in total frequency of injection site reactions and also injection site reactions judged as possible or probably related to study drug between the two formulations, especially in T1DM.

The sponsor has suggested Injection/infusion site reactions to be labelled in SmPC section 4.8 as common adverse reaction which is endorsed.

Table 33 Injection site reaction adverse event- summary trials 3852, 3853 and 4049.

	Faster aspart N	(%)	E	R	Comparator N	(%)	E	R	Total N	(%)	E	R
Number of subjects	1219				841				2060			
Total exposure (yrs)	567.57				391.89				959.46			
Events	20	(1.5)	23	3.8	6	(0.7)	10	2.4	26	(1.3)	33	3.4
Serious												
Yes	0				0				0			
No	20	(1.5)	23	3.8	6	(0.7)	10	2.4	26	(1.3)	33	3.4
Missing	0				0				0			
Severity												
Severe	0				0				0			
Moderate	2	(0.1)	2	0.3	0				2	(0.1)	2	0.2
Mild	18	(1.4)	21	3.5	6	(0.7)	10	2.4	24	(1.2)	31	3.2
Missing	0				0				0			
Related to investigational products												
Probable	6	(0.4)	6	0.9	0				6	(0.3)	6	0.6
Possible	1	(0.1)	1	0.2	1	(0.1)	2	0.4	2	(0.1)	3	0.3
Unlikely	13	(1.0)	16	2.7	5	(0.6)	5	1.3	18	(0.9)	21	2.2
Missing	0				1	(0.1)	3	0.6	1	(0.0)	3	0.3

N: Number of subjects, %: Percentage of subjects, E: Number of event, R: Event rate per 100 patient years of exposure, yrs: Y
Treatment emergent adverse events in the safety summary are those events that were treatment emergent and belonged to the main treatment period of each of the individual trials.
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigator's assessment.
MedDRA version 17.0
The 'Diabetes pool' consists of trials 3852, 3853, 4049 and 3931.
'Comparator' consists of NovoRapid plus basal insulin. Proportions and event rates with associated 95% confidence intervals w

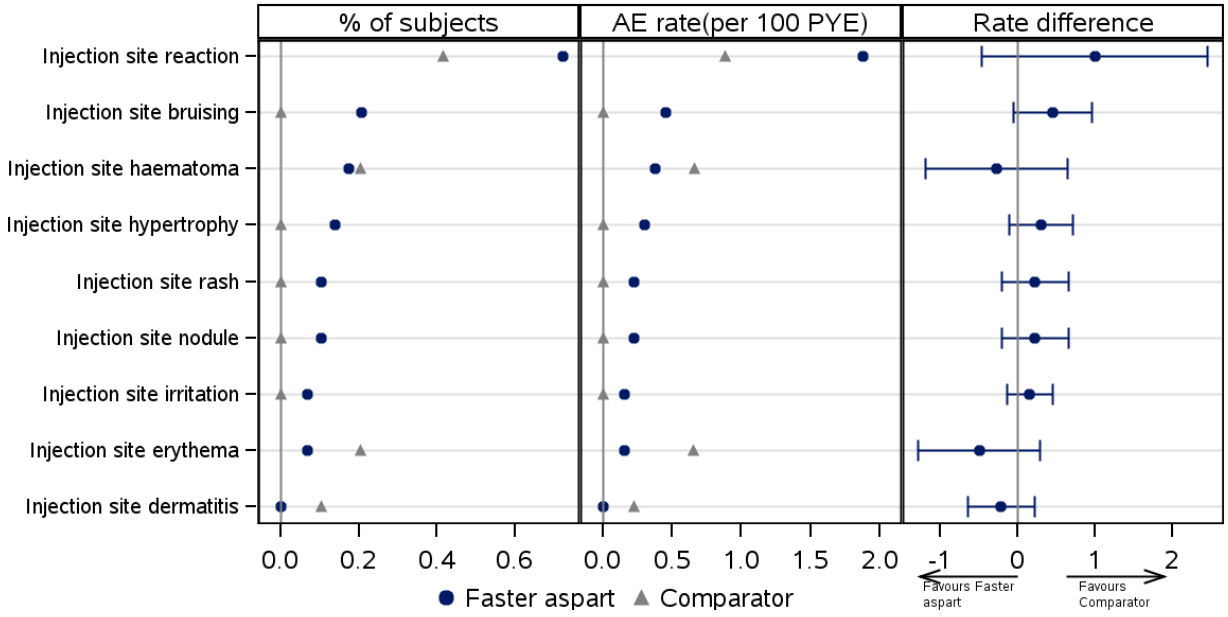


Figure 32 Injection site reactions in trials 3852, 3853, 4049.

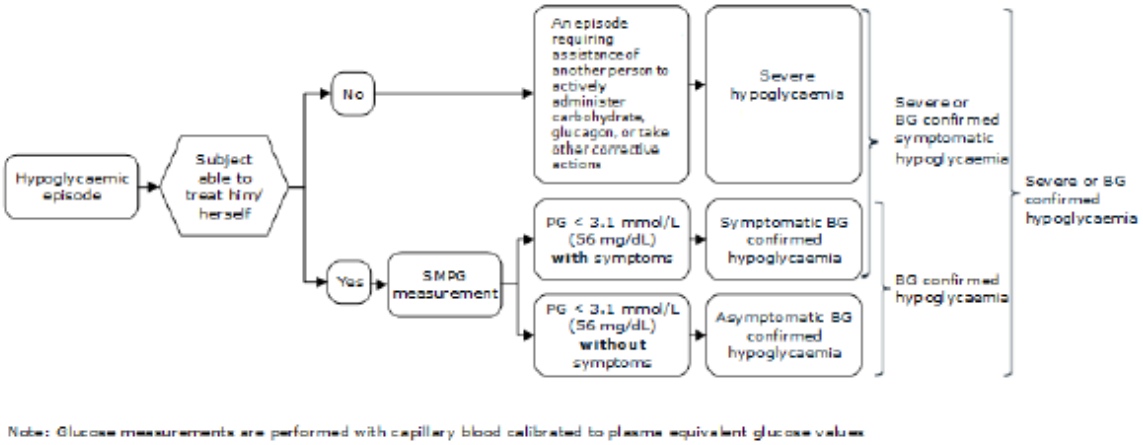
Medication errors

In total 65 events of *"wrong drug administered"* occurred in 55 (5%) of the subjects. The number of medication errors due to *wrong drug administered* were higher in study 3852 (T1DM) compared to study 3853 (T2DM). The possible explanation given is that the blinded pen PDS290 prefilled pen-injector used for Fiasp and NovoRapid and the FlexPen injector used for insulin detemir were reported to have certain similarities. The blinded version of the PDS290 prefilled pen-injector differs from the version that will be the used for the marketed product. According to information in the RMP a summary usability test has been performed in 87 subjects including 21 subjects with colour blindness. The aim was to validate that PDS290 Fiasp pen-injector could be differentiated from other relevant products. All the participants in this study performed, according to the Applicant, the differentiation tasks without any usage error or encountering any operational difficulties.

Medication errors including *wrong drug administered* is characterised as an important potential risk in the RMP.

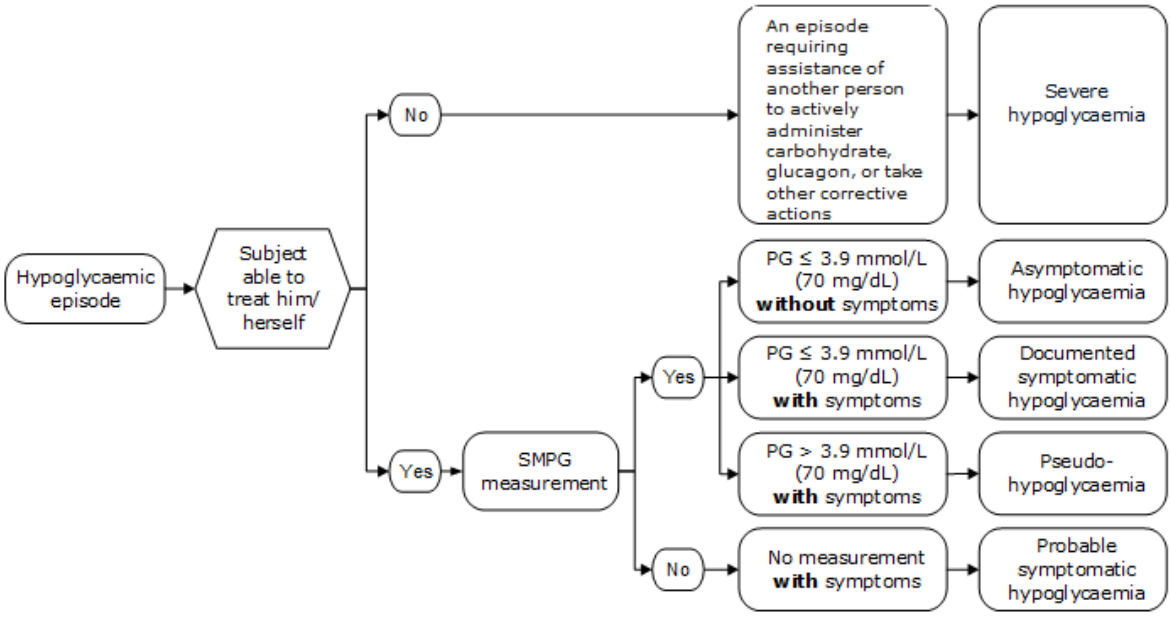
Hypoglycaemia

In the trials, subjects were to always measure and record PG when a hypoglycaemic episode was suspected. PG was also measured for 7-point and 4-point self-measured PG (SMPG) profiles, as according to the trial protocols. All PG values equal to or below 3.9 mmol/L (70 mg/dL) or higher than 3.9 mmol/L (70 mg/dL) in conjunction with symptoms of hypoglycaemia were to be recorded by the subject in their diary, and subsequently transferred by the investigator to a hypoglycaemic episode form in the eCRF at the next visit to site. The ADA definition of hypoglycaemia is presented in Figure 35.



BG: blood glucose; PG: plasma glucose; SMPG: self-measured plasma glucose

Episodes that were non-severe with blood glucose (BG) between 3.1 mmol/L (56 mg/dL) and 3.9 mmol/L (70 mg/dL), not BG confirmed, or that could not be classified due to missing data were included in the category 'Novo Nordisk unclassifiable'.



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 33 ADA (top) and Novo Nordisk classification (bottom) of hypoglycaemia

In total approximately 98% of the subjects in study 3852 and approximately 94% of the subject in study 3853 experienced any event of hypoglycaemia. Severe or BG confirmed hypoglycaemic episodes were reported in 8% of the subjects with T1DM (study 3852) during the trial compared to 3.5% in the patients with T2DM (study 3853). Thus, a higher rate and frequency of both hypoglycaemic events in total as well as severe and BG confirmed hypoglycaemic events were, as expected, more common in patients with T1DM compared to T2DM. There was no significant difference between the two formulations in either of the trials. There were no differences between the two formulations regarding hypoglycaemia over time of day (daytime and nocturnal hypoglycaemia) or accumulation rate of hypoglycaemia over the trial duration.

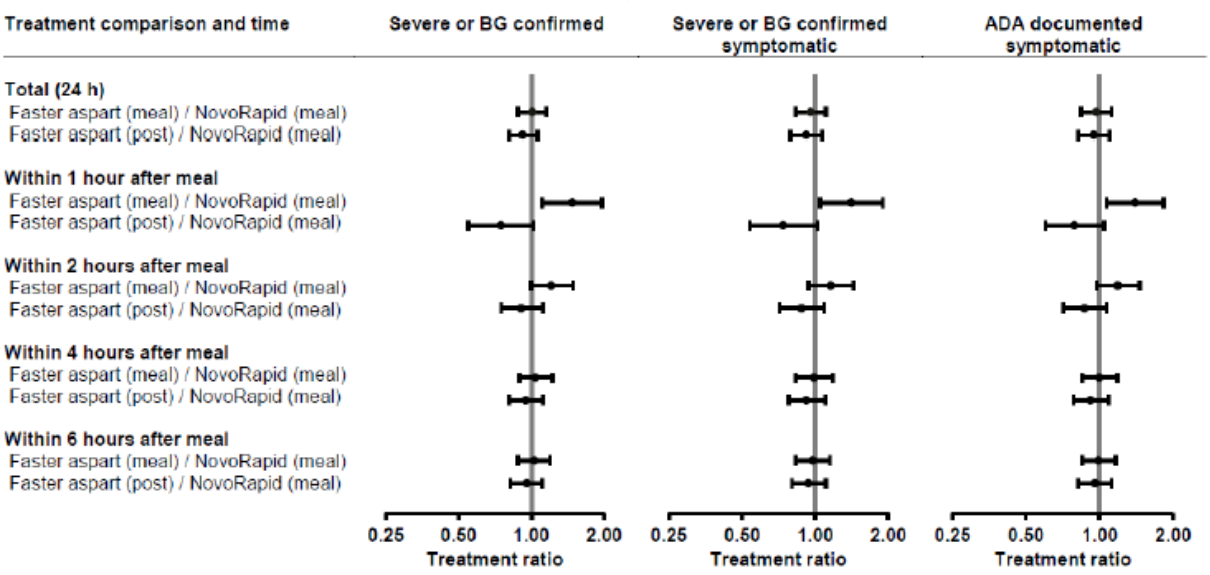
Hypoglycaemia in relation to mealtime

Study 3852 (T1DM)

A statistical significant difference in rate of severe or BG confirmed hypoglycaemia episodes was noted between the Fiasp mealtime (but not post-meal) and NovoRapid group the first hour after meal. The frequency of subjects experiencing severe or BG confirmed hypoglycaemia one hour after meal was 33.9% in the Fiasp group, 22.5% in Fiasp post-meal and 28.4% in subjects using NovoRapid. The corresponding rates were 147.6, 71.6 and 96.4 per 100 PYE respectively. After two hours there was still a difference but no longer significant. The difference in the rate of hypoglycaemic episodes dilutes over time and 6 hours after meal the frequency of events are equally distributed between the groups (Table 39 and Figure 36)

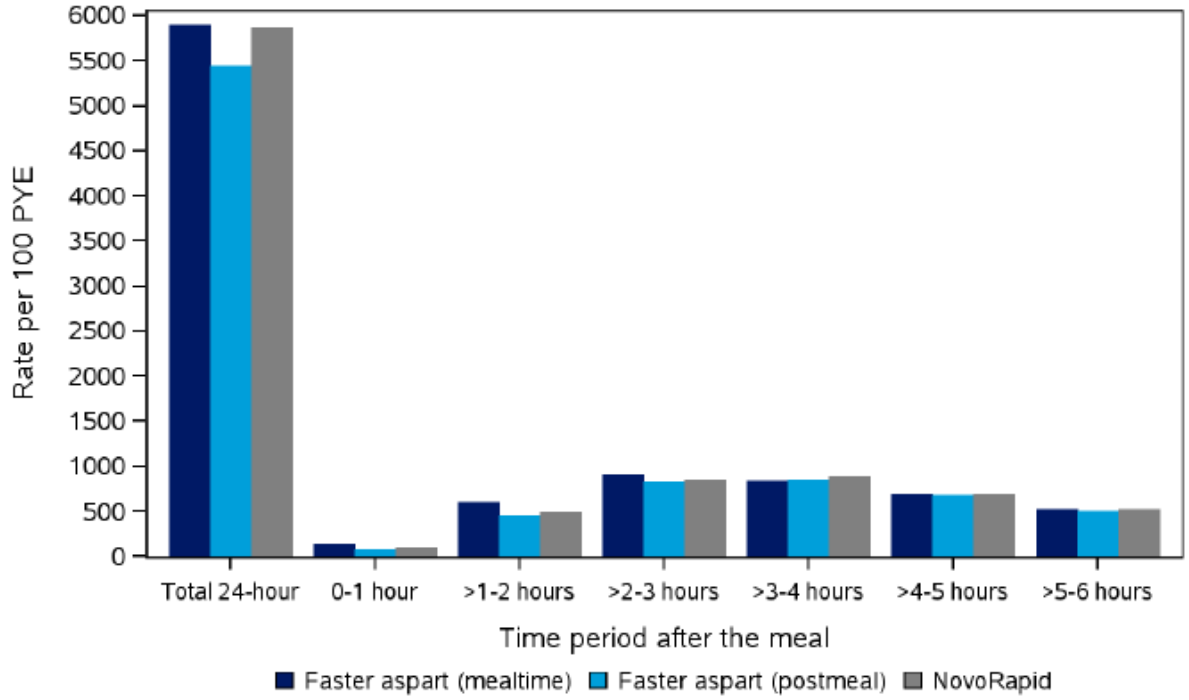
Table 34 Statistical analysis of hypoglycaemic episodes related to meal in trial 3852

	Severe or BG confirmed		Severe or BG confirmed symptomatic		ADA documented symptomatic	
	Mealtime faster aspart/NovoRapid® (estimate; [95% CI])					
Total (24 h)	1.01	[0.88; 1.15]	0.96	[0.83; 1.11]	0.97	[0.84; 1.12]
Within 1 hour after meal	1.48	[1.11; 1.96]	1.41	[1.05; 1.90]	1.40	[1.07; 1.83]
Within 2 hours after meal	1.21	[0.99; 1.48]	1.16	[0.94; 1.44]	1.19	[0.97; 1.46]
Within 4 hours after meal	1.04	[0.89; 1.22]	0.99	[0.83; 1.18]	1.00	[0.85; 1.19]
Within 6 hours after meal	1.03	[0.88; 1.19]	0.98	[0.83; 1.15]	0.99	[0.85; 1.16]
	Postmeal faster aspart/NovoRapid® (estimate; [95% CI])					
Total (24 h)	0.92	[0.81; 1.06]	0.92	[0.79; 1.07]	0.95	[0.82; 1.10]
Within 1 hour after meal	0.75	[0.55; 1.02]	0.74	[0.54; 1.02]	0.79	[0.60; 1.04]
Within 2 hours after meal	0.91	[0.75; 1.12]	0.88	[0.71; 1.09]	0.87	[0.71; 1.07]
Within 4 hours after meal	0.95	[0.81; 1.12]	0.92	[0.78; 1.10]	0.92	[0.78; 1.09]
Within 6 hours after meal	0.96	[0.82; 1.11]	0.94	[0.80; 1.11]	0.96	[0.82; 1.12]



Treatment ratios are presented on a logarithmic scale.

ADA: American Diabetes Association, BG: blood glucose



Treatment emergent episodes occur after trial product administration after randomisation and no later than 1 day after last trial product administration.
Episodes with missing time stamps or missing last meal time are excluded. PYE: Patient years of exposure.
NovoRapid is known as NovoLog in the U.S.

Figure 34 Rates of severe or BG confirmed hypoglycaemic episodes 0-6 hours after the start of meal in study 3852

A post-hoc stratified analysis compared subjects who dosed the bolus insulin according to a flexible dosing regimen based on meal carbohydrate content to subjects using an algorithm. Within 1 hour after the start of meal, the rates of severe or BG confirmed hypoglycaemia was statistically significantly higher for mealtime Fiasp than for NovoRapid for those subjects dosing according to the algorithm. For the first 2 hours after the start of a meal, the rates were still higher but not statistical significant, for mealtime Fiasp than for NovoRapid for those subjects dosing according to the algorithm.

There were no statistically significant differences in the rates of severe or BG confirmed hypoglycaemia between mealtime Fiasp and NovoRapid for the subjects following the flexible dosing method of counting carbohydrates, although the rates were slightly higher for mealtime Fiasp for the first 2 hours after the start of a meal (Table 40).

Table 35 Statistical analysis of severe or BG confirmed hypoglycaemic episodes related to a meal in subjects following either carbohydrate or bolus dosing algorithm in trial 3852.

Bolus dosing approach	Time period	Mealtime faster aspart/NovoRapid®		Postmeal faster aspart/NovoRapid®	
		Estimates	Ratio [95% CI]	Estimates	Ratio [95% CI]
Carbohydrate counting	**Overall**		1.01 [0.85;1.18]		0.98 [0.83;1.15]
	Within 1 hour after a meal	96.56/83.98	1.15 [0.80; 1.65]	59.94/83.98	0.71 [0.48; 1.05]
	Within 2 hours after a meal	545.41/471.31	1.16 [0.89; 1.50]	484.92/471.31	1.03 [0.79;1.34]
	Within 4 hours after a meal	2010.06/1982.42	1.01 [0.83; 1.24]	2079.33/1982.42	1.05 [0.86;1.28]
	Within 6 hours after a meal	3113.66/3084.03	1.01 [0.84; 1.22]	3192.56/3084.03	1.04 [0.86; 1.25]
Bolus dosing algorithm	**Overall**		1.00 [0.80; 1.25]		0.84 [0.68; 1.06]
	Within 1 hour after a meal	206.49/107.87	1.91 [1.23; 2.99]	85.59/107.87	0.79 [0.49; 1.29]
	Within 2 hours after a meal	941.17/739.29	1.27 [0.93; 1.75]	573.55/739.29	0.78 [0.56; 1.07]
	Within 4 hours after a meal	2961.30/2787.41	1.06 [0.81; 1.39]	2313.42/2787.41	0.83 [0.64; 1.08]
	Within 6 hours after a meal	4307.72/4173.32	1.03 [0.80; 1.33]	3556.58/4173.32	0.85 [0.66; 1.10]

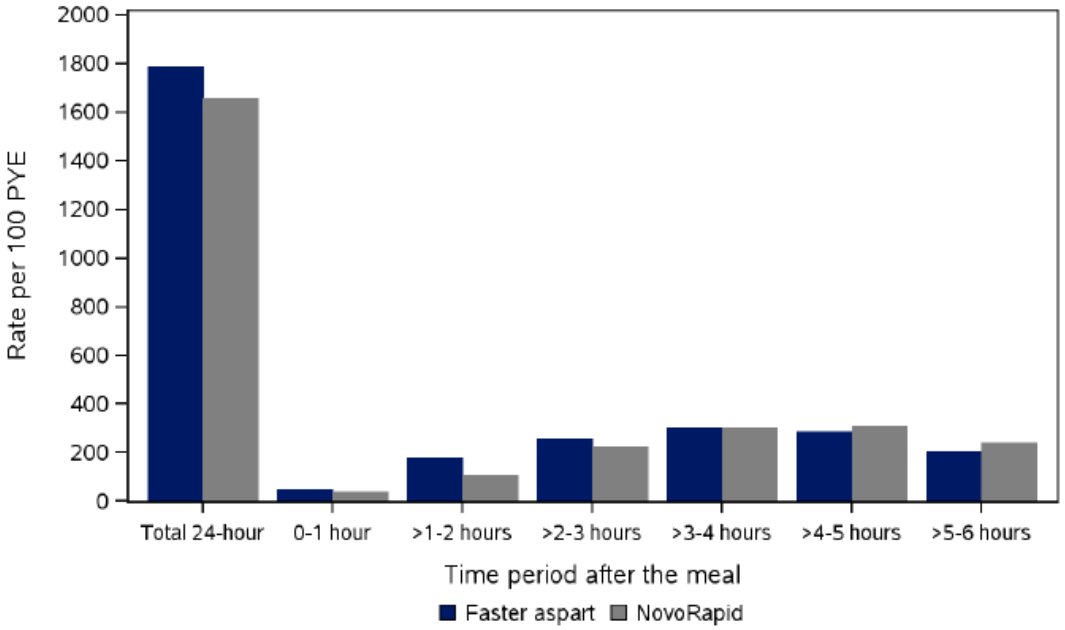
N: Number of subjects, CI: Confidence interval, BG: Blood glucose, PYE: Patient years of exposure
CGM: Continuous glucose monitoring
For analysis related to meals, episodes with missing time stamps or with missing main meal time are not included.
Severe or BG confirmed: Subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56 mg/dL)
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.
Number of hypoglycaemic episodes is analysed using a negative binomial regression model with a log-link function and the logarithm of the time in which the hypoglycaemic episode is considered treatment emergent as offset. The model includes treatment, region and strata (combination of basal treatment regimen and CGM and frequently sampled meal test sub-group) as factors.
NovoRapid is known as NovoLog in the U.S.

Study 3853

Rates were higher for Fiasp compared to NovoRapid within 1 hour after the start of a meal, and were statistically significantly higher for Fiasp compared to NovoRapid for episodes occurring within 2 hours of the start of a meal (Table 41 and Figure 37). Up to two hours after meal the frequency of subjects experience Severe or BG confirmed hypoglycaemia was 32.8% in subjects using Fiasp and 28.2% in patients using NovoRapid. The corresponding rates were 226.5 per 100 PYE and 148.5 per 100 PYE, respectively.

Table 36 Statistical analysis of hypoglycaemic episodes related to a meal by classification in trial 3853.

	Mealtime faster aspart/NovoRapid® (estimate; [95% CI])					
	Severe or BG confirmed		Severe or BG confirmed symptomatic		ADA documented symptomatic	
Total (24 h)	1.09	[0.88; 1.36]	1.13	[0.89; 1.43]	1.06	[0.86; 1.30]
Within 1 hour after meal	1.29	[0.78; 2.15]	1.48	[0.87; 2.53]	1.25	[0.83; 1.89]
Within 2 hours after meal	1.60	[1.13; 2.27]	1.72	[1.19; 2.48]	1.47	[1.08; 2.01]
Within 4 hours after meal	1.18	[0.91; 1.53]	1.22	[0.93; 1.61]	1.22	[0.96; 1.54]
Within 6 hours after meal	1.07	[0.84; 1.36]	1.12	[0.87; 1.45]	1.09	[0.87; 1.36]



Treatment emergent episodes occur after trial product administration after randomisation and no later than 1 day after last trial product administration.
Episodes with missing time stamps or missing last meal time are excluded. PYE: Patient years of exposure.
NovoRapid is known as NovoLog in the U.S.

Figure 35 Rates of severe and BG confirmed hypoglycemic episodes 0-6 hours after the start of a meal in trial 3853

In summary, the overall frequencies of hypoglycaemic episodes did not differ between the two formulations. However, the mealtime Fiasp had a statistical significant higher rate of hypoglycaemic episodes (severe or BG confirmed, severe or BG confirmed symptomatic and ADA documented) the first hour after meal compared to NovoRapid in patients with T1DM. Two hour after meal a difference was still present but this was not significant. The group randomised to post-meal Fiasp had rates of hypoglycaemia events similar to the subjects using NovoRapid. For patient with T2DM there was a statistical significant difference with higher rate of corresponding definitions of hypoglycaemic episodes two hours after meal (a difference was seen also the first hour after meal but this was not statistical significant). This difference probably reflects the PK/PD differences in the two formulations.

Serious adverse event / deaths / other significant events

Deaths

In total 5 deaths were reported after randomisation in the completed clinical trials: 2 in the Fiasp group, 2 in the comparator group (of which 1 occurred during the 30-day follow-up period and 1 in the additional part of trial 3852 which was blinded) (Table 42). In addition two deaths occurred during the run-in phase one in trial 3852 (self-injurious behaviour) and 1 in trial 4049 (acute myocardial infarction). The numbers of deaths were similar for Fiasp and NovoRapid.

Three of the patients with events leading to fatal outcomes were diagnosed with T2DM and two with T1DM. All deaths occurring in patients with T2DM were adjudicated and confirmed by the EAC as cardiovascular deaths. Four of the five deaths were judged as unlikely related to the study drug. One event of pulmonary embolism (Subject 502003 in trial 3853) was judged by the investigator as possibly related to trial drug (Fiasp). However, this event was confounded by cardiovascular disease in medical history. Further, in the total diabetes pool two events of pulmonary embolism were noted. One was noted in the Fiasp group and one in the comparator group. In summery the risk of deaths seemed not to reflect a difference between Fiasp and comparator. There was no apparent association between insulin aspart and mortality risk.

Table 37 Adverse event with fatal outcome

Treatment	Subject ID	Trial	Age (years)/ Sex (M/F)/	Trial day	Preferred term	Serious/ Relation/ Severity
Deaths occurring after randomisation:						
Faster aspart	704006	3852	39/M	96	Arrhythmia	Y/Unlikely/Severe
Faster aspart	502003	3853	63/M	204	Pulmonary embolism	Y/Possible/Severe
NovoRapid	302007	3853	52/M	20	Myocardial infarction	Y/Unlikely/Severe
NovoRapid	605002[a]	3853	66/M	205	Cardiac arrest	Y/Unlikely/Severe
Blinded	801001	3852	57/M	219	Myocardial infarction	Y/Unlikely/Severe
Deaths occurring before randomisation:						
NA (run-in)	206008	4049	60/M	NA	Acute myocardial infarction	Y/Unlikely/Severe
NA (run-in)	713018	3852	55/M	NA	Self-injurious behaviour	Y/unlikely/Severe

Y: Yes, N: No, yrs: years, F: Female, M: Male, NA: not applicable. Relationship is based on investigator assessment. NovoRapid is known as NovoLog in the U.S. [a]This event of cardiac arrest occurred during the 30-day follow-up period of trial 3853.

Serious adverse events

Overall in the diabetes pool, the rates of SAEs were similar for Fiasp and comparator (15.4 and 15.3 events per 100 PYE, respectively). The frequency of SAEs was approximately 6% of the subjects with no difference between type 1 or type 2 diabetes (Table 43). The most comment SAEs was hypoglycaemia and related events. Despite these there was no apparent clustering of events in the individual trial. The rates of SAEs were in the individual trials similar between the Fiasp and comparator without any apparent difference in SAE pattern on a PT level. However, a difference in SAE pattern was noted between Type 1 and Type 2 diabetes.

A summary of all SAEs in the diabetes pool has been submitted. The major difference is observed for the PT hypoglycaemia and hypoglycaemic unconsciousness where the reporting was higher for Fiasp (27 and 8 events, respectively) than for the comparator (10 and 3 events, respectively).

Excluding hypoglycaemia, the sponsor reported no SAEs occurring in ≥1% of subjects and no SAEs were reported in ≥2% of subjects in any treatment group in the diabetes pool. The rates of SAEs, in the diabetes pool, possibly or probably related to trial product were 4.8 per 100 PYE for Fiasp and 3.4 per 100 PYE for the comparator.

SAEs judged as related to the study drug were besides *hypoglycaemia* and related events 2 events of *wrong drug administered*, 1 event of *DKA* and the events with *cardiac myxoma* and *pulmonary embolism* described section "Deaths" above.

Table 38 All serious adverse events – summary –diabetes pool

	Faster aspart				Comparator				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	1244				853				2097			
Total exposure (yrs)	570.48				393.30				963.78			
Events	68	(5.3)	89	15.4	51	(5.9)	62	15.3	119	(5.7)	151	15.7
Serious												
Yes	68	(5.3)	89	15.4	51	(5.9)	62	15.3	119	(5.7)	151	15.7
No	0				0				0			
Missing	0				0				0			
Severity												
Severe	46	(3.4)	58	9.5	27	(3.3)	31	8.0	73	(3.5)	89	9.2
Moderate	23	(1.9)	27	5.2	20	(2.2)	25	5.9	43	(2.1)	52	5.4
Mild	4	(0.3)	4	0.7	6	(0.6)	6	1.4	10	(0.5)	10	1.0
Missing	0				0				0			
Related to investigational products												
Probable	14	(1.0)	18	3.0	5	(0.6)	6	1.5	19	(0.9)	24	2.5
Possible	8	(0.6)	10	1.8	7	(0.9)	7	1.9	15	(0.7)	17	1.8
Unlikely	46	(3.7)	60	10.4	36	(4.2)	42	10.4	82	(3.9)	102	10.6
Missing	1	(0.1)	1	0.2	5	(0.5)	7	1.5	6	(0.3)	8	0.8
Outcome												

N: Number of subjects, %: Percentage of subjects, E: Number of event, R: Event rate per 100 patient years of exposure, yrs: Y belonged to the main treatment period of each of the individual trials. Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigator's assessment. The 'Diabetes pool' consists of trials 3852, 3853, 4049 and 3931. 'Comparator' consists of NovoRapid plus basal insulin. Proportions and event rates were calculated using the Cochran-Mantel-Haenszel method to account for different exposures in the trials. If no events are experienced for the subjects in a trial, the subjects contribute with exposure.

Immunological events

Immunogenicity-related events (allergic reactions)

Overall in the diabetes pool, the rates of allergic reactions were similar for Fiasp and comparator (6.2 and 7.0 events per 100 PYE, respectively). None were serious (Table 44).

Rash was the most frequently reported PT for allergic reactions with a rate of 2.0 events per 100 PYE in the Fiasp group and 1.3 events per 100 PYE in the comparator group. *Eczema* was reported with a rate of 0.4 per 100 PYE events in the Fiasp group and 1.1 events per 100 PYE in the comparator group. The remaining PTs reported for allergic reactions were reported by few or single subjects with no apparent clustering in any group (

Figure 38).

The numbers of allergic reactions considered possibly or probably related to trial product by the investigator were 2 events of *hypersensitivity* in 1 subject for Fiasp and 1 event of *rash* for the comparator. A possible association with Fiasp was assessed by the sponsor for the events reported with the PTs *dermatitis*, *eczema, rash, rash pruritic* and *urticaria*. Hence, these PTs were suggested for inclusion in the Fiasp label by the sponsor.

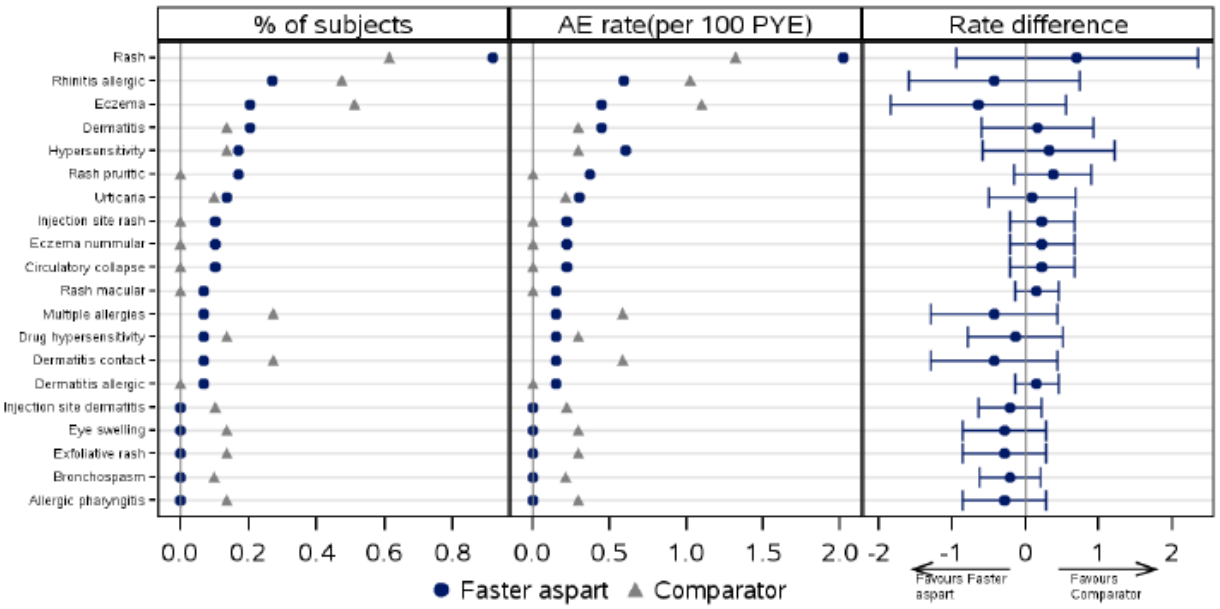
All PTs identified in the search for allergic reactions in the diabetes pool had similar rates for Fiasp and NovoRapid. Thus, the available data do not suggest a greater risk of allergic reactions for Fiasp than for comparators.

Allergic skin reactions were reported in 1.5% of subjects on Fiasp and 1.4% in the comparator group. *Systemic allergic reactions* have been suggested as an important identified risk in the RMP for Fiasp. However, even if several of the events could be related to a systemic allergic reaction there were only two subjects who experienced *hypersensitivity* events in the Fiasp group (0.2%) and one in the comparator group (0.1%) and no event of *anaphylactic reaction* were reported. Thus, it could be discussed if *Systemic allergic reactions* should be defined as an identified or potential risk. But the Rapporteur believes it is reasonable to extrapolate data from insulin aspart with other formulations in this case and remain *Systemic allergic reactions* as an important identified risk.

Table 39 Systemic allergic reactions adverse events – diabetes pool

	Faster aspart N (%)	E	R	Comparator N (%)	E	R	Total N (%)	E	R
Number of subjects	1244			853			2097		
Total exposure (yrs)	570.48			393.30			963.78		
Events	34 (2.5)	37	6.2	25 (3.1)	26	7.0	59 (2.8)	63	6.5
Serious									
Yes	0			0			0		
No	34 (2.5)	37	6.2	25 (3.1)	26	7.0	59 (2.8)	63	6.5
Missing	0			0			0		
Severity									
Severe	1 (0.1)	1	0.1	0			1 (0.0)	1	0.1
Moderate	5 (0.4)	6	1.1	4 (0.5)	4	1.1	9 (0.4)	10	1.0
Mild	28 (2.1)	30	5.0	22 (2.7)	22	5.9	50 (2.4)	52	5.4
Missing	0			0			0		
Related to investigational products									
Probable	0			0			0		
Possible	1 (0.1)	2	0.5	1 (0.1)	1	0.3	2 (0.1)	3	0.3
Unlikely	32 (2.4)	34	5.6	21 (2.7)	22	6.0	53 (2.5)	56	5.8
Missing	1 (0.1)	1	0.1	3 (0.3)	3	0.7	4 (0.2)	4	0.4

N: Number of subjects, %: Percentage of subjects, E: Number of event, R: Event rate per 100 patient years of exposure, yrs: Y
Treatment emergent adverse events in the safety summary are those events that were treatment emergent and belonged to the main treatment period of each of the individual trials.
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigator's assessment.
MedDRA version 17.0
The 'Diabetes pool' consists of trials 3852, 3853, 4049 and 3931.
'Comparator' consists of NovoRapid plus basal insulin. Proportions and event rates with associated 95% confidence intervals w



%: Percentage of subjects experiencing at least one event, PYE: Patient years of exposure
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigator's assessment.
MedDRA version 17.0. The 'Diabetes pool' consists of trials 3852, 3853, 4049 and 3931.
'Comparator' consists of NovoRapid plus basal insulin. NovoRapid is known as NovoLog in the U.S.
Proportions, event rates and rate differences with associated 95% confidence intervals were calculated using the Cochran-Mantel-Haenszel method to account for different exposures in the trials. If no events are experienced for the subjects in a trial, the subjects contribute with exposure.

Figure 36 Allergic reactions in the diabetes pool

Insulin antibodies

Anti-insulin antibodies (insulin aspart specific antibodies, antibodies cross-reacting with human insulin and the total level of antibodies) were assessed in trial 3852 at baseline, week 12 and week 26.

The presence of antibodies (insulin aspart specific antibodies and antibodies cross-reacting with human insulin as well as the total level of antibodies (comprised of the two types of antibodies) was on a group level presented as the percent of bound radioactivity (B) out of the total amount of radioactivity (T) (% B/T) on the 3 sampling days during the span of the trial.

According to the Applicant, most of the subjects had insulin antibodies at baseline in all 3 treatment groups due to previous insulin treatment. On a group level there seemed to be a slight increase over time (26 weeks) of the total anti-insulin antibodies, driven by an increase in cross-reacting antibodies to human insulin (and not insulin aspart specific antibodies). This increase was noted in all groups without any difference between the groups (Table 45 and Figure 39). There were no association between higher antibody levels and higher or increased HbA1c levels. Neutralizing antibody formation is suggested by the Applicant to insert as an important potential risk in the RMP.

Table 40 Total anti-insulin antibodies (%B/T) at baseline and end of treatment

	Faster aspart (meal) Mean (SD)	Faster aspart (post) Mean (SD)	NovoRapid® Mean (SD)	Total Mean (SD)
Visit 10 (Week 0)	14.0 (16.8)	13.7 (17.3)	13.7 (14.6)	13.8 (16.3)
Visit 22 (Week 12)	17.1 (17.5)	16.8 (17.4)	17.8 (15.1)	17.2 (16.7)
End of treatment	18.2 (16.9)	17.3 (17.4)	18.5 (15.4)	18.0 (16.6)

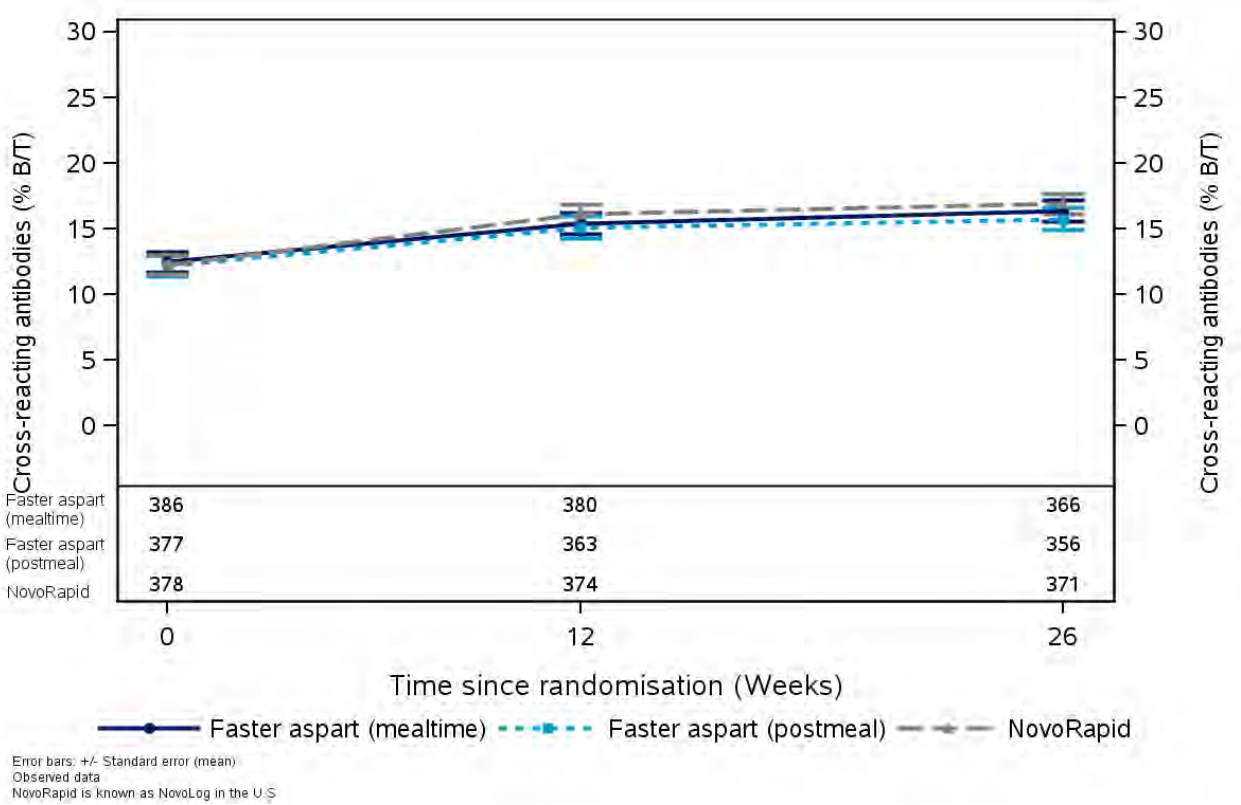


Figure 37 Cross-reacting antibodies to human insulin

Data from the 26 week extension phase of trial 3852 (T1DM) was submitted with the responses to the Day 120 LoQ. It is concluded that no significant differences were observed between the two formulations. A rather high proportion of patients (27% in both groups) were positive for specific antibodies at any time during the study and 97-98% of patients were positive to cross-reactive antibodies at any time during the study. However, only 0.9% and 0.6% of subjects showed a significant change from baseline ≥10 (%B/T) in the Fiasp and NovoRapid group, respectively. Analyses of antibody positivity in relation to allergic reaction, injection site reactions and change in HbA1c did not reveal any signs of apparent associations.

Laboratory findings

There were no indications of a significant difference between the two formulations regarding parameters such as Biochemistry and haematology laboratory values, Lipids, Cardiovascular risk markers (hsCRP and NT-proBNP), Urine analysis, Vital signs, Physical examination, Body weight and Fundoscopy/fundus photography.

Pump compatibility and related issues

The primary objective of trial 3931 was to evaluate the compatibility of Fiasp and NovoRapid with the external CSII system over a 6-week treatment period.

A higher frequency of possible infusion-set occlusions was reported for Fiasp compared to NovoRapid (7 vs 0). However, in none of the cases the macroscopic or microscopic event was found to be due to formation of a plug.

No microscopically confirmed episodes of infusion-set occlusions were observed with either Fiasp treatment or NovoRapid.

Thus, even if events of possible infusion-set occlusions leading to prematurely changed infusion sets were higher with the Fiasp formulation, no formations of plugs could be verified in any of the formulations.

Safety in special populations

The Applicant has presented safety in special populations by intrinsic (demographic) and extrinsic (environment) factors and compared subjects on Fiasp with the comparator. AE, SAE and most frequent $\geq$ 1% AE tables for different groups within the subpopulations divided by treatment groups has been submitted for study 3852 and 3853. In total 164 tables have been submitted in this appendix.

Overall no difference of clinical relevance was noted between Fiasp and NovoRapid regarding AE, SAE and most frequent $\geq$ 1% AE in the subpopulations of Sex, Age, Race, Ethnicity, BMI, Renal impairment and Hepatic impairment at baseline.

Moderate renal impairment (CLCR ≥30−<60 mL/min) was present in 3% (n=31) of the subjects in study 3852, 3853 and 4049. As expected no patient was presented with severe renal impairment (CLCR<30 mL/min) since impaired renal function was an exclusion criterion in all the therapeutic confirmatory and exploratory trials.

Among subjects with moderate renal impairment at baseline: subjects in the Fiasp group had a lower rate of AEs compared to those in the NovoRapid group for T1DM (401 vs. 625 events per 100 PYE). Corresponding results for subjects with T2DM showed comparable rates (595 vs. 553 events per 100 PYE).

Overall, the rates of AEs for subjects with moderate renal impairment, patients with hepatic impairment and very elderly (> 75 years) were small and the amounts of AEs were low. Therefore data in these groups should be analysed with caution. Exposure of Fiasp in the different age subgroups is presented in Table 36.

Safety related to drug-drug interactions and other interactions

In study 3852 (T1DM), the frequency of subjects on potential glucose lowering concomitant treatment was 46.5%. Concomitant treatment with glucose increasing drugs was used in 39% in this study.

The frequency of subjects on potential glucose-lowering concomitant treatment was higher in study 3853 (T2DM), 84% in the Fiasp group compared to 88% in the NovoRapid group. Potential glucose-increasing drugs were used in 38% in both groups.

In total, rates and frequency of AEs were similar between the two formulations in the subgroups of patients on or not on potential glucose-lowering or increasing drugs. When comparing the AE profile between these with or without respective concomitant glucose-increasing or glucose-decreasing treatment there was a tendency of higher rate of AEs in the groups using potentially glucose-lowering or glucose-increasing treatments compared to the patients without such treatment. This seem however logical since there is a potential increase comorbidity in these groups.

In the group of subjects, in study 3852 and 3853, with experience of severe or BG confirmed hypoglycaemic episodes, the four subgroups of patients with and without glucose-lowering drug as well as with and without glucose-increasing drugs were studied regarding differences in rate and frequency of severe or BG confirmed hypoglycaemic episodes. No difference in these subgroups between the two formulations regarding this parameter could be noted.

Discontinuation due to adverse events

Overall in the diabetes pool, the rates of *AEs leading to withdrawal* were 2.8 events per 100 PYE for Fiasp and 1.5 events per 100 PYE for the comparator. The total numbers of events leading to withdrawal were higher in the Fiasp group (n=17) compared to the comparator (n=6). The most commonly SOC was "Injury, poisoning and procedural complications" with 4 events, "Nervous system disorders" with 4 events followed by "Cardiac disorders" and "Metabolism and Nutritional disorders" with 3 events each. The most commonly reported AEs leading to withdrawal were *hypoglycaemic unconsciousness* (1 event in each group) and *hypoglycaemia* (2 events for Fiasp, none for comparator). No apparent difference in clustering of events on a SOC, HLGT or PT level explaining the difference in rate between the two formulations could be noted.

2.6.1. Discussion on clinical safety

The safety information for Fiasp was based on two 26-weeks completed basal-bolus trials in subjects with T1DM and T2DM (trials 3852 and 3853). Three other completed therapeutic confirmatory and exploratory trials 4049 (18 weeks in T2DM), 3931 (6 weeks in T1DM) and 3930 (T1DM) were used to support the safety evaluations from the 2 basal-bolus trials. In addition, the use of Fiasp in CSII with pumps was based in another two trials (3930 and 3931).

Common AE

After 26 weeks of treatment, 73% of the subjects with T1DM (trial 3852) and 53% of the subjects with T2DM (trial 3853) experienced adverse events. Besides hypoglycaemia, the overall most common adverse events in the pooled analysis were *nasopharyngitis* (14%)*, upper respiratory tract infections* (6%*)* and *headache* (5%). Excluding hypoglycaemia, the most frequently reported AEs with possible or probable relation to trial products in both groups were *wrong drug administered, weight increased* and *accidental overdose.* Increased weight could be explained by improved metabolic control.

Overall, in the individual studies and in the pooled analysis there was no apparent difference of clinical importance between Fiasp and the NovoRapid or comparator (including NovoRapid in 93%) respectively. This conclusion is based on frequency of adverse events as well as severity, relationship to study drug, and outcome of the events. Differences were however noted between type 1 and type 2 diabetes regarding frequency of AEs (73% in T1DM vs 53% in T2DM).

Serious adverse events and deaths

Serious adverse events occurred in approximately 6% of the subjects with no difference between type 1 and Type 2 diabetes. Overall in the diabetes-pool, the rate of SAEs was similar between the two formulations (Fiasp 15.4 and comparator 15.3 events per 100 PYE). The most comment SAEs was hypoglycaemia and related events. Despite these there was no apparent clustering of events in the individual trials. A summary of all SAEs in the diabetes pool has not been submitted by the Applicant and is requested. The five cases of deaths, which occurred after randomisation to trial drug, seemed not reflect a difference between Fiasp and comparator and do not suggest an association to insulin aspart.

Other significant adverse events

Events of *Wrong drug administered* or "mix-ups" of pens were noted in ≥5% in subjects with T1DM (study 3852). This was also after hypoglycaemia together with accidental overdose the most frequent SAE judged as possibly or probably related to trial product in this study. As commented by the Applicant, the possibly explanation is that the blinded pen PDS290 prefilled pen-injector used for Fiasp and NovoRapid and the FlexPen injector used for insulin detemir had certain similarities. *Medication errors* including *wrong drug administered* is characterised as an important potential risk in the RMP. According to information in the RMP a summary usability test has been performed in 87 subjects including 21 subjects with colour blindness. The aim was to evaluate if the PDS290 Fiasp pen-injector could be differentiated from other relevant products. All the participants in this study performed the differentiation tasks without committing any use error or encountering any operational difficulties.

In study including T1DM (study 3852) *injection site reactions* were noted with a rate of 4.8 and 5.5 per 100 PYE in the mealtime and postmeal Fiasp groups compared to 1.6 per 100 PYE in subjects using NovoRapid. This provides some support for a causal relation between Fiasp and increased risk for *injection site reaction*s. The components of the new formulation might have an increased risk of *injection site reaction*s and also the pooled analysis suggests an increased risk of *injection site reactions* with the new formulation. *Injection/infusion site reactions* are labelled in SmPC section 4.8 as common.

Analyses of *insulin antibodies* were performed in patients with T1DM in study 3852. On a group level there seemed to be a slight increase of the total anti-insulin antibodies from a mean of 13.8 %B/T at week 0 to 18.0 %B/T at week 26 over time. This increase was driven by an increase in cross-reacting antibodies to human insulin (and not insulin aspart specific antibodies). The increase was noted in all groups without any difference between the groups of different formulations. There were no association between higher antibody levels and higher or increased HbA1c levels. Neutralizing antibody formation is included as an important potential risk in the RMP. Data from the extension of trial 3852 (T1DM) confirmed these findings.

Overall, there were no clinical difference regarding *Systemic allergic reactions* between Fiasp and comparator. *Allergic skin reactions* were reported in 1.5% of subjects on Fiasp and 1.4% in the comparator group. *Hypersensitivity reactions* was reported in 0.2% and 0.1%, respectively. No anaphylactic reactions were reported in the clinical trials in either the Fiasp or comparator group.

Hypoglycaemia

A statistical significant difference of the hypoglycaemic rates was seen between NovoRapid and Fiasp mealtime groups during the first hour after meal in T1DM (study 3852; estimated treatment ratios: severe or BG confirmed 1.48 [1.11; 1.96]95% CI; severe or BG confirmed symptomatic 1.41 [1.05; 1.90]95% CI and ADA documented symptomatic 1.40 [1.07; 1.83]95% CI) and during two hours after meal between Fiasp and NovoRapid in T2DM (study 3853; estimated treatment ratios: severe or BG confirmed 1.60 [1.13; 2.27]95% CI; severe or BG confirmed symptomatic 1.72 [1.19; 2.48]95% CI and ADA documented symptomatic 1.47 [1.08; 2.01). Over time the difference between the two groups were diluted and after 4-6 hour after meal there were no longer any difference between the different formulations.

A post-hoc analysis demonstrated that the statistical difference in rates of severe of BG confirmed hypoglycaemic episodes 2 h after meal between the two formulations in trial 3852 (T1DM) was in the group of patients dosing according to the pre-defined bolus algorithm (estimated rate ratio 1.91 [1.23;2.99]95% CI). In the group of patients following the flexible dosing method of counting carbohydrates there was no statistical difference noted the first 2 hours after meal.

Other hypoglycaemic parameters such as accumulation over time and differences in frequency of daytime and nocturnal episodes did not differ between the two formulations within subjects with T1DM and T2DM, respectively.

Safety in special populations

In general there were no differences in AE and SAE rates within the different subgroups analysed within age, gender, BMI, race and ethnicity. The rates of AEs for subjects with moderate renal impairment, patients with hepatic impairment and very elderly (>75 years) should be analysed with caution since these were small groups of patients and the amount of AEs were low. In general, safety in special populations were analysed between the two formulations within a certain subgroup.

2.6.2. Conclusions on the clinical safety

The Applicant has provided a detailed and careful assessment of hypoglycaemic episodes. Overall, there were no significant differences in the frequency or rate of hypoglycaemic episodes between the two formulations in either Type 1 or Type 2 diabetes. However, a statistically significant difference was noticed in the rate of mealtime hypoglycaemic episodes one hour after meal in T1DM and 2 hours after meal in T2DM with higher rates in the Fiasp mealtime group compared to the group using NovoRapid. This likely reflects the PD/PK findings with faster action of Fiasp with the new formulation compared to NovoRapid and supports a significant difference of the safety profile between the two formulations.

Apart from differences in the timing of the hypoglycaemic episodes, the data provided did not reveal any significant differences of clinical importance in the pattern, proportions and rates of adverse events between Fiasp and NovoRapid in either type 1 or type 2 diabetes mellitus.

Regarding immunogenicity no differences in development of insulin antibodies were detected between the two formulations. Further, in contrast to the Applicant the CHMP considers, that a clinically relevant increase of the frequency of injection site reactions was noted in T1DM subjects using Fiasp (4.8 and 5.5 per 100 PYE in the mealtime and postmeal Fiasp groups) compared to NovoRapid (1.6 per 100 PYE).

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Hypoglycaemia Systemic allergic reactions
Important potential risks	Medication errors (mainly wrong drug administered) Neutralising antibody formation
Missing information	Children and adolescents <18 years of age

Pharmacovigilance plan

Not applicable.

Routine pharmacovigilance is sufficient to identify and characterise the safety concerns of the product.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Hypoglycaemia	**SmPC** Warning about the timing of and factors leading to hypoglycaemia in Section 4.4 Potential drug interactions with insulins listed in Section 4.5 Listed in Section 4.8 as an undesirable effect with additional description of related symptoms and potential consequences Warning in Section 4.9 and instruction on what to do in case of overdose	None proposed
Systemic allergic reactions	**SmPC** Contraindications for use in Section 4.3 Listed in Section 4.8 as an undesirable effect with additional description of related symptoms and potential consequences	None proposed
Important potential risks		
Medication errors (mainly wrong drug administered)	**Patient information (Package leaflet)** The patient information includes warnings with regard to medication errors due to storage of injection devices with the needle inserted and instructions for use to avoid wrong dosing. Coloured cartons and injection devices to prevent wrong drug administration due to mix-up of different insulin products **SmPC** Warning in Section 4.4 to verify insulin and dose prior to injection	None proposed
Neutralising antibody formation	**SmPC** Warning in Section 4.4	None proposed
Missing information		
Use in children and adolescents <18 years of age	**Addressed in the SmPC** The safety and efficacy of Fiasp® have not been established in children and adolescents <18 years, as described in Section 4.2. Pharmacokinetic properties in paediatric population are described in Section 5.2.	None proposed

Abbreviations: SmPC = Summary of Product Characteristics.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Fiasp (insulin aspart) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

2.10. Assessment for the purpose of Art 82(1) of Reg 726/2006 (duplicates)

The Applicant believes that there are distinct and clinically relevant differences between the two formulations which mandate different prescribing information and trade name for Fiasp, and that these differences include:

Faster absorption translates into an increased early glucose-lowering effect which in turn results in:

- lower meal-time glucose increments (improved postprandial glucose control)
- greater reduction in HbA1c in T1DM, without increasing dose and without increasing the incidence of overall hypoglycaemia
- distinct differences in early hypoglycaemia with an increase in the risk of hypoglycaemia 1-2 hours postmeal

CHMP assessment of the claim

Clinical relevance of differences in PPG increments between Fiasp and NovoRapid

The Applicant has provided epidemiological and clinical data aiming to support that PPG is of importance in the development of CV complications. Most of these data were generated in the T2DM population. Data has also been presented that show that therapy with impact on PPG (i.e. prandial insulin) could have effects on myocardial perfusion. Data from the DCCT study in patients with T1DM indicate that an increase in PPG of about 1 mmol/l may result in an 8 % increased risk for CV events. The changes observed in 1-hour PPG increment was of this magnitude for T1DM (-1.18 mmol/l), but less in T2DM (-0.59 mmol/l).

However, there is still scarce direct evidence from long-term randomised clinical trials that correcting postmeal hyperglycaemia directly improves clinical outcomes.

Clinical relevance of differences in HbA1c reduction between Fiasp and NovoRapid

It is agreed that with the currently available therapies there is no fixed glycaemic threshold for improvements in either microvascular or macrovascular complications. It is also agreed that there is a strong relationship between lower HbA1c and a higher risk for hypoglycaemia which limits the possibility to normalise HbA1c. However, there is no data to support that an extra reduction of HbA1c of 0.15% (which was even less pronounced after 52 weeks treatment) would result in a reduced risk of diabetic micro- or macrovascular complications.

It is acknowledged that the treatment difference is comparable to that observed between insulin analogues and human insulin. However, the approval of the analogues was not based on superiority vs human insulin with regards to metabolic control and the clinical relevance of this difference was questioned (see NovoRapid SmPC).

Differences in temporal distribution of hypoglycaemia

The difference in hypoglycaemia pattern is noted with a higher risk during the first 2 hours with Fiasp compared to Novorapid. The CHMP considered that this constitutes a clinically relevant difference between the products. This should be clearly reflected in the PI to inform patients and prescribers about the differences in the timing of hypoglycaemia.

CHMP Conclusion regarding the claim

There is a difference in the PK/PD profile between Fiasp and Novorapid with a ≈5 minute earlier onset of action. In the pivotal trials, there was a statistically significant difference in 2 hour PPG increments in favour of Fiasp in patients with T1DM; no statistically significant differences were observed in patients with T2DM. The Applicant has provided literature references aiming to support that increased PPG may be of importance in the development of CV complications. Further, treatment guidelines from learned societies recommend lowering of PPG. However, there is still scarce direct evidence from long-term randomised clinical trials that correcting postmeal hyperglycaemia directly improves clinical outcomes, and therefore it is difficult to conclude that the documented difference would translate into a clinically relevant benefit.The small difference in reduction of HbA1c between Fiasp and NovoRapid observed in patients with T1DM (trial 3852) is not considered to be of clinical relevance and no statistically significant difference in HbA1c was shown in patients with T2DM (trial 3538).

The difference in hypoglycaemia pattern is noted with a higher incidence during the first 2 hours associated with Fiasp compared to Novorapid.

In conclusion, regarding the applicant's claim of significant differences in safety or efficacy vs NovoRapid for the

purpose of Art 82(1) of Reg (EC) No 726/2004 and in view of the EC note on Handling of Duplicate Marketing Authorisation Applications Ares(2011)1044649, the CHMP concluded that Fiasp shows significant differences in terms of safety due to different excipients versus NovoRapid in view of the difference in the timing of hypoglycaemias (associated with differences in PK/PD).

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Fiasp is indicated in the treatment of diabetes mellitus in adults

3.1.2. Main clinical studies

Table 41 Therapeutic confirmatory trials with Fiasp

Trial ID	Population	Treatment duration and regimen	Number of randomised subjects	Trial design
Trial 3852[a]	T1DM Adults	26 + 26 weeks Basal-bolus	Mealtime Fiasp: 381 Post-meal Fiasp: 382 NovoRapid: 380	A randomised (1:1:1), multicentre, multi-national, parallel-group trial evaluating efficacy and safety of Fiasp compared to NovoRapid both in a basal-bolus regimen with insulin detemir. The trial consisted of two double-blind Fiasp or NovoRapid mealtime dosing arms with 26 +26 weeks of treatment; and an open-label Fiasp post-meal arm with 26 weeks of treatment. The primary and secondary confirmatory endpoints were analysed after the initial 26-week treatment period. The additional 26-week treatment period was primarily for further collection of safety information.
Trial 3853	T2DM Adults	26 weeks Basal-bolus	Fiasp: 345 NovoRapid: 344	A randomised (1:1), double-blind, multicentre, multi-national, parallel-group trial evaluating efficacy and safety of mealtime Fiasp compared to mealtime NovoRapid , both in a basal-bolus regimen with insulin glargine and metformin.
Trial 4049	T2DM Adults	18 weeks Basal-bolus vs. basal	Fiasp + basal: 116 Basal: 120	A randomised (1:1), open-label, multicentre, multi-national, parallel-group trial evaluating efficacy and safety of mealtime Fiasp in a basal-bolus regimen with insulin glargine or NPH

Trial ID	Population	Treatment duration and regimen	Number of randomised subjects	Trial design
				insulin or insulin detemir vs. basal insulin therapy, both in combination with metformin.

[a] The application includes data from the initial 26-week treatment period. The additional 26-week treatment period was ongoing at the time of the cut-off date for the clinical trials (10 March 2015).

[b] In trial 3930, an earlier formulation of Fiasp (FIA(R)) was also evaluated. To keep the focus on the formulation of Fiasp intended for the market, efficacy data pertaining to the FIA(R) formulation is not included.

3.2. Favourable effects

Fiasp is insulin aspart in a new formulation of insulin aspart with two additional excipients. The addition of nicotinamide is intended to result in a faster initial absorption following subcutaneous (s.c.) injection. The addition of L-arginine hydrochloride should support stabilisation of the Fiasp formulation.

The pharmacodynamic profile was characterised in a program consisting of 9 clinical pharmacology studies, out of which 8 were conducted in subjects with T1DM. The studies included 395 randomised subjects and in all studies, NovoRapid (insulin aspart) was chosen as comparator. The efficacy of Fiasp was investigated in three confirmatory trials including a total of 2068 randomised subjects. Two of the trials were of 26 weeks duration and included NovoRapid as the active comparator (trials 3852 (T1DM) and 3853 (T2DM)). The third trial was of 18 weeks duration and in this trial Fiasp was compared to intensified basal insulin therapy in subjects with T2DM (trial 4049). The study program was adequate and well designed. The 26 week extension of trial 3852 has been concluded and the results submitted.

Pharmacodynamic data showed an earlier onset of action with Fiasp compared to NovoRapid. In a pooled analysis the mean treatment difference was -4.91 min $[-6.86; -2.95]_{95\%CI}$ and time to GIRmax occurred 10.5 min $[-16.98; -4.02]_{95\%CI}$ earlier with Fiasp. The glucose-lowering effect during the first 30 minutes (AUC_{GIR}, 0-30 min) was 51 mg/kg with Fiasp and 29 mg/kg with NovoRapid(Fiasp/NovoRapid, ratio: 1.74 $[1.47; 2.10]_{95\% CI}$). The total glucose-lowering effect, as reflected by $AUC_{GIR, 0\text{-}12\ h}$, was however comparable between Fiasp and NovoRapid in patients with T1DM. The findings were consistent in all the three studies included in the pooled analysis. The differences observed in the pharmacodynamic profiles between Fiasp for the 0.2 U/kg dose was maintained for the dose range investigated (0.1-0.4 U/kg).

No difference in the time to onset of action or the maximum effect of Fiasp was observed when injected subcutaneously or intramuscularly.

In the confirmatory trials, non-inferiority was shown for Fiasp compared to NovoRapid for the primary endpoint, mean change from baseline in HbA1c, in T1DM (trial 3852: -0.15 % $[-0.23; -0.07]_{95\%CI}$) and T2DM subjects (trial 3853, -0.02 % $[-0.15; 0.10]_{95\%CI}$). The 95% CI was well within the non-inferiority margin of 0.4%. In trial 4049, a statistically significant effect of Fiasp, when compared to optimised basal insulin treatment, was observed (treatment difference -0.94 % $[-1.17; -0.72]_{95\%CI}$). These findings were supported by the responder analysis where more patients achieved the target of HbA1c <7.0% in the Fiasp meal group (33.3 %) than in the NovoRapid group (28.2 %) in trial 3852, whereas there was no difference in the proportion

of patients reaching the HbA1c targets between treatment groups in trial 3853. As expected, in trial 4049, more patients achieved the HbA1c targets in the bolus-basal treated group.

The effect of Fiasp on post-prandial glucose (PPG) increment measured after a standardised meal (meal test) and compared to NovoRapid, was a confirmatory secondary endpoint in trials 3852 (T1DM) and 3853 (T2DM). There was a statistically significant treatment difference in mean 2-hour PPG increment in subjects with T1DM (-0.67 mmol/L [-1.29; -0.04]$_{95\%CI}$). A statistically significant treatment difference was also observed for the mean 1-hour PPG increment in T1DM subjects (-1.18 mmol/L [-1.65; -0.71]$_{95\%CI}$). In T2DM, the estimated treatment difference in mean 2-hour PPG increment compared to placebo was Fiaspnot statistically significant (-0.36 mmol/L [-0.81; 0.08]$_{95\%CI}$), whereas a statistically significant treatment difference was observed for the mean 1-hour PPG increment (-0.59 mmol/L [-1.09; -0.09]$_{95\%CI}$).

In trial 3852, the overall rate of severe or BG confirmed hypoglycaemia episodes were comparable for Fiasp (meal) and NovoRapid (estimated rate ratio 1.01 [0.88; 1.15]$_{95\%CI}$). In trial 3853, the overall number of severe or BG confirmed hypoglycaemia episodes were higher for Fiasp than for NovoRapid (estimated rate ratio 1.09 [0.88; 1.36]$_{95\%CI}$). No statistically significant differences were observed. In the pooled analysis, numerically slightly more BG confirmed daytime episodes were observed in the Fiasp treated groups and nocturnal BG confirmed episodes were numerically slightly less frequent. None of these differences were statistically significant.

As increase in body weight is a known effect of intensified insulin treatment, change in body weight was included as a confirmatory secondary endpoint in trials 3852 and 3853. In trial 3852 (T1DM), mean body weight increased slightly from baseline to week 26 in all 3 treatment groups (0.55 kg to 0.70 kg). In trial 3853 (T2DM), mean body weight increased with 2.7 kg in both treatment groups.

In both trials 3852 or 3853, the bolus or basal insulin doses increased during titration-to-target, with no apparent difference between treatment arms.

Data from the long-term extension of trial 3852 (T1DM) show that in both treatment groups, HbA1c increased again after the initial decline during the first 26 weeks of treatment. The estimated treatment difference (mealtime Fiasp versus NovoRapid) after 52 weeks of randomised treatment was -0.10%-points [-0.19; -0.00]95%CI and although statistically significant, the difference was smaller than after 26 weeks. No difference in the HbA1c responder endpoints was observed between mealtime Fiasp and NovoRapid. After 52 weeks of treatment, the estimated treatment differences for PPG at 1 and 2 hours after start of the meal test only reached statistical significance at 1 hour.

In trial 3852, the effect of post-meal dosing with Fiasp compared to NovoRapid taken before the meal was investigated. Non-inferiority to mealtime NovoRapid with regards to mean change from baseline in HbA1c was confirmed. The estimated treatment difference was 0.04% [-0.04; 0.12]$_{95\%CI}$. With regards to the mean 2-hour PPG increment, a treatment difference of 0.39 [-0.34; 0.93]$_{95\%CI}$ in favour of NovoRapid was observed. This was also observed for the mean 1-hour PPG increment, where the treatment difference was statistically significant and in favour of NovoRapid (0.93 mmol/L [0.46; 1.40]$_{95\%CI}$).

Two supportive studies were performed using Fiasp in external pump (CSII) in order to support recommendations on such use in the SmPC. The effect of Fiasp on 2-hour PPG increment compared to NovoRapid was estimated to a treatment difference, -0.99 mmol/L [-1.95; -0.03]$_{95\%CI}$). With regards to other parameters for glycaemic control, the two treatments showed comparable results. In the studies, compatibility of Fiasp with the pump system was evaluated as the number of confirmed episodes of infusion set occlusions. There were no microscopically confirmed episodes of infusion set occlusions in trial 3931, thus supporting compatibility for Fiasp with the pump system.

3.3. Uncertainties and limitations about favourable effects

An adequate number of subjects above the age of 65 (209) were included in the clinical trials; however, the experience in patients above the age of 75 (24 patients included in clinical trials) is still limited. There is no indication that the effect is dependent on age. The limitation in the data is however reflected in the SmPC.

3.4. Unfavourable effects

There was no difference in overall rate of hypoglycaemic events between the two formulations in either of the pivotal trials (see “Beneficial effects” in section above). However, a statistical significant difference was seen between NovoRapid and the Fiasp mealtime groups regarding the hypoglycaemic event rates the first hour after meal in T1DM (study 3852; estimated treatment ratios: severe or BG confirmed 1.48 [1.11; 1.96]95% CI; severe or BG confirmed symptomatic 1.41 [1.05; 1.90]95% CI and ADA documented symptomatic 1.40 [1.07; 1.83]95% CI) hypoglycaemic event rates during two hours after meal in T2DM,respectively (study 3853; estimated treatment ratios: severe or BG confirmed 1.60 [1.13; 2.27]95% CI; severe or BG confirmed symptomatic 1.72 [1.19; 2.48]95% CI and ADA documented symptomatic 1.47 [1.08; 2.01). Over time the difference between the two groups were diluted and after 4-6 hour after meal there were no longer any difference between the different formulations.

Analysis of *insulin antibodies* was performed in patients with T1DM in study 3852. An increase of the total anti-insulin antibodies occurred from a mean of 13.8 %B/T at week 0 to 18.0 %B/T at week 26. This increase was driven by an increase in cross-reacting antibodies to human insulin (increased from 12.3%/B/T to 16.2%/B/T) and not insulin aspart specific antibodies (increased from 1.5%/B/T to 1.8%/B/T). The increases were noted in all groups without any difference between the groups or different formulations. In study 3852 there were no association between higher antibody levels and higher or increased HbA1c levels. The data from the extension phase of study 3852 confirms the findings.

Injection/infusion site reactions associated with Fiasp treatment was noted in 2.0% in subjects with type 1 diabetes (study 3852) and 1% in subjects with Type 2 diabetes (study 3853 and 4049). In the pump studies (3930 and 3931) higher frequencies of infusion site reactions was noticed (13% and 8% respectively) however, these studies were small and the frequencies corresponded to only two subjects in each study.

Allergic skin reactions are included among unfavourable effects with Fiasp and were reported in 1.5% of the subjects on Fiasp compared to 1.4% in subjects on comparator. These reactions included eczema, rash, rash pruritic, urticaria and dermatitis. *Hypersensitivity reactions* occurred in 0.2% with Fiasp and 0.1% in subjects using the comparator. No anaphylactic reactions were reported in the clinical trials in either the Fiasp or comparator group.

3.5. Effects Table

Table 42 Effects Table for Fiasp (data cut-off: 10th March 2015).

Effect	Short Description	Unit	Fiasp	NovoRapid	Uncertainties/ Strength of evidence	References
Favourable Effects						
HbA1c T1DM	Change in HbA1c from BL	%	-0.32	-0.17	Primary endpoint, treatment difference: -0.15 [-0.23; -0.07]$_{95\%CI}$. Non-inferiority confirmed	**Table 26** Study 3852, 3853,4049
HbA1c T2DM	Change in HbA1c from BL	%	-1.38	-1.36	Primary endpoint, treatment difference: -0.02 [-0.15; 0.10]$_{95\%CI}$. Non-inferiority confirmed	**Table 26** Study 3852, 3853,4049
2-hour PPG increment T1DM	Change in 2-hour PPG increment from BL after meal test	mmol/L	-0.29	0.38	Secondary endpoint, treatment difference of -0.67 mmol/L [-1.29; -0.04]$_{95\%CI}$. Superiority confirmed	Table 24 Study 3852
2-hour PPG increment T2DM	Change in 2-hour PPG increment from BL after meal test	mmol/L	3.24	2.87	Secondary endpoint, treatment difference, -0.36 mmol/L [-0.81; 0.08]$_{95\%CI}$. Superiority **not** confirmed	Table 25 Study 3853
Unfavourable Effects						
Hypoglycaemia T1DM	Number of BG confirmed episodes (week 0 to 26)	Episodes per 100 PYE	5899	5865	Secondary endpoint, treatment difference, 1.01 [0.88; 1.15]$_{95\%CI}$. Superiority **not** confirmed Difference in timing of hypoglycemia	Table 24 Study 3852
Hypoglycaemia T1DM	Number of BG confirmed episodes (week 0 to 26)	Episodes per 100 PYE	1788	1659	Secondary endpoint, treatment difference, 1.09 [0.88; 1.36]$_{95\%CI}$. Superiority **not** confirmed	Table 25 Study 3853

Effect	Short Description	Unit	Fiasp	NovoRapid	Uncertainties/ Strength of evidence	References
					Difference in timing of hypoglycaemia	
Anti-insulin antibody formation	Values at BL and EOT (w26)	Mean (SD) % B/T	Mealtime Fiaspt: BL: 14.0 (16.8) EOT: 18.2 (16.9) Postmeal Fiasp: BL: 13.7 (17.3) EOT: 17.3 (17.4)	BL: 13.7 (14.6) EOT: 18.5 (15.4)	None presented	Table 45 Study 3852
Injection/infusion site reactions	Reported AEs	Rate per 100 PYE	3.8	2.4	None presented	Table 38 Study 3852, 3853,4049
Allergic skin reactions	Reported AEs	Rate per 100 PYE	3.6	2.9 (NovoRapid or basal insulin)	None presented	**Figure 38** Study 3853

Abbreviations: T1DM – type 1 diabetes mellitus; T2DM – type 2 diabetes mellitus; PYE – person years of exposure; BL-baseline; EOT – End Of Treatment

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

In order to, not only avoid symptoms of hyperglycaemia, but also avoid long-term complications of diabetes there is consensus that good metabolic control as reflected by HbA1c at least <7% is desirable.

The data from the pivotal clinical trials show a clinically relevant glucose lowering effect associated with treatment with Fiasp as expected considering that the active component is insulin aspart.

The data provided on Fiasp show that, compared to NovoRapid, there is a shift in the PK/PD profile resulting in an earlier onset of the glucose-lowering effect while the total glucose-lowering effect is similar. With respect to results in the pivotal phase III studies, statistically significant lowering of the post-prandial glucose (PPG) increment with Fiasp compared to NovoRapid in patients with T1DM was documented, as well as a modest decrease in HbA1c (mean treatment difference -0.15%) after 26 weeks . The 52 week data indicate that the difference in effect between Fiasp and NovoRapid was less pronounced compared to week 26.

In patients with T2DM, there was no difference in HbA1c at weeks 26, but a statistically significant reduction in 1-hour PPG increment was observed.

There is no consistent data to support that the small differences in HbA1c documented in patients with type 1 diabetes would translate into a reduced risk in diabetic complications. The differences in PPG could possibly be

of clinical relevance, but it is uncertain if the effect on PPG is an independent marker of risk considering the limited effect on HbA1c. Further, the effect decreased over time.

With respect to safety, there was a difference in the pattern of hypoglycaemic episodes with a significantly higher rate of hypoglycaemia within the first 2 hours after the meal for Fiasp compared to Novorapid. However, the overall rate and severity of events was comparable between treatments.

3.6.2. Balance of benefits and risks

With the data provided, Fiasp has been well characterised with regards to PK/PD-profile, efficacy and safety and the benefit risk balance is considered positive.

Conclusions

The overall B/R of Fiasp is positive.

Regarding the applicant's claim of significant differences in safety or efficacy vs NovoRapid for the purpose of Art 82(1) of Reg (EC) No 726/2004 and in view of the EC note on Handling of Duplicate Marketing Authorisation Applications Ares(2011)1044649, the CHMP concluded by majority that Fiasp shows significant differences in terms of safety due to different excipients versus NovoRapid in view of the difference in the timing of hypoglycaemias (associated with differences in PK/PD).

Divergent position regarding the additional claim is appended to this report.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Fiasp is favourable in the following indication:

Treatment of diabetes mellitus in adults.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Other conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Appendix

1. Divergent position to the majority recommendation

APPENDIX 1

DIVERGENT POSITION DATED 10 NOVEMBER

DIVERGENT POSITION DATED 10 NOVEMBER 2016

Product name EMEA/H/C/004046/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion for the purpose of Art 82(1) of Reg (EC) No 726/2004, that Fiasp shows significant differences in terms of safety due to different excipients versus NovoRapid, as claimed by the applicant.

The reason for divergent opinion was the following:

Fiasp is submitted as a stand-alone application under Article 8 (3) of Directive 2001/83/EC. This application concerns a new formulation of insulin aspart denoted as faster aspart (Fiasp), which contains the same active substance and the same strength and pharmaceutical form as NovoRapid, but differs compared to NovoRapid in the addition of two excipients (nicotinamide and L-arginine hydrochloride).

According to the Article 82(1) of Regulation No 726/2004, for medicinal products which contain the same active substance and the same strength and pharmaceutical form but differ in the quantity/quality of excipients, significant differences in efficacy or safety with the already authorised product (NovoRapid in this case) which result from the difference in excipients between the two products need to be demonstrated in order to grant an opinion as a stand-alone application. Some differences have been observed in the PK/PD profile between these two medicinal products. However, the undersigned Members consider that the documented differences in efficacy or safety (i.e. Changes in glycemic control and/or the timing of hypoglycemias) between Fiasp and NovoRapid are not of sufficient clinical relevance to consider Fiasp a different medicinal product.

Sol Ruiz _____

David Lyons _____

Johann Lodewijk Hillege _____

Nikola Moravcova _____

Aranzazu Sancho-Lopez _____