Assessment report

Insulin aspart Sanofi

International non-proprietary name: insulin aspart

Procedure No. EMEA/H/C/005033/0000

Note

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

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List of abbreviations

ADA:	anti-drug antibodies
AE:	adverse event
AIA:	anti-insulin aspart antibody
ANCOVA:	analysis of covariance
AUC:	area under the concentration versus time curve extrapolated to infinity
AUC_{last}:	area under the concentration versus time curve from 0 to the corresponding to the last concentration above the limit of quantification
BG:	blood glucose
BMI:	body mass index
CHMP:	Committee for Medicinal Products for Human Use
CI:	confidence interval
C_{max}:	maximum observed concentration
CSR:	clinical study report
CV:	coefficient of variation
eGFR:	estimated glomerular filtration rate
EMA:	European Medicines Agency
EU:	European Union
FPG:	fasting plasma glucose
G6PC	gene regulation of glucose 6-phosphatase
GCP:	good clinical practice
GIR:	glucose infusion rate
HbA1c:	glycated hemoglobin
HLT:	high level term
IM:	intramuscular
IMP:	investigational medicinal product
IR-A:	insulin receptor A
IR-B:	insulin receptor B
ITT:	intent-to-treat
MDI:	multiple daily injection
MDRD:	modification of diet in renal disease
MedDRA:	medical dictionary for medical activities
NIMP:	non-investigational medicinal product

OAD: oral antidiabetic drug

PD: pharmacodynamic

PK: pharmacokinetic

PT: preferred term

PV: paravenous

qPCR :   quantitative polymerase chain reaction

RIPA: radioimmunoprecipitation assay

SAE: serious adverse event

SC: subcutaneous

SD: standard deviation

SMPG: self-monitored plasma glucose

SPR: surface plasmon resonance

T1DM: type 1 diabetes mellitus

T2DM: type 2 diabetes mellitus

TEAE: treatment-emergent adverse event

TK: toxicokinetic

US: United States

1. Background information on the procedure

1.1. Submission of the dossier

The applicant sanofi-aventis groupe submitted on 29 May 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Insulin aspart Sanofi, 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:

Insulin aspart Sanofi is indicated for the treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for biosimilar medicinal products.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: NovoRapid 100 Units/ml Solution for injection
- Marketing authorisation holder: Novo Nordisk A/S
- Date of authorisation: 07-09-1999
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EMEA/H/C/000258

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: NovoRapid 100 Units/ml Solution for injection
- Marketing authorisation holder: Novo Nordisk A/S
- Date of authorisation: 07-09-1999
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EMEA/H/C/000258

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: NovoRapid 100 Units/ml Solution for injection
- Marketing authorisation holder: Novo Nordisk A/S
- Date of authorisation: 07-09-1999
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EMEA/H/C/000258

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 submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
24 May 2012	EMEA/H/SA/2316/1/2012/III	*Kolbeinn Gudmundsson, Christophe Unkrig*
9 July 2012	EMEA/H/SA/2316/1/2012/III	*Kolbeinn Gudmundsson, Christophe Unkrig*
23 March 2017	EMEA/H/SA/2316/1/FU/1/2017/III	*Amany N. El-Gazayerly, Armin Koch*
18 October 2018	EMEA/H/SA/2316/1/FU/2/2018/I	*Juha Kolehmainen, Stephan Lehr*

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Adequacy of the planned physico-chemical comparability exercise to demonstrate biosimilarity

- Adequacy of the plans for isolating insulin aspart drug substance from the reference product in order to perform the physico-chemical comparison

- Adequacy of the plans for demonstration of drug product comparability (structure, impurity profile)

- Acceptability of the proposed disposable pen concept and the choice of comparator pens to be used in the pen differentiation study

- Acceptability of the proposed strategy to demonstrate drug substance and drug product stability

- Acceptability of the proposed number of batches to be used for demonstration of similarity

- Acceptability to use one batch of reference product per market in one presentation and one batch of the investigational product according to the presented study protocol to demonstrate similar degradation pathways

- Acceptability of the studies planned to support a plunger stopper as commercial plunger stopper for 3 mL cartridges in pen injector

- Adequacy of the proposed in-vitro nonclinical pharmacology programme

- Adequacy of the proposed in-vitro nonclinical toxicology programme to also support minor late changes to the commercial formulation without the need for repeat studies

- Adequacy of the proposed anti-insulin aspart antibody assay to be used in clinical studies

- Acceptability of the proposal to employ a PK/PD hyperinsulinemic euglycemic clamp study in subjects with Type 1 diabetes mellitus to demonstrate bioequivalence

- Acceptability of the proposed comparative efficacy and safety studies, in particular with a view to: characterisation of immunogenicity, patient population, endpoints, statistical analysis

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege   Co-Rapporteur: Agnes Gyurasics

The application was received by the EMA on	29 May 2019
The procedure started on	20 June 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	10 September 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	9 September 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	23 September 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 October 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 December 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	4 February 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 February 2020
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	27 February 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	30 March 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 and 23 April 2020
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 Insulin aspart Sanofi on	30 April 2020
The CHMP adopted a report on similarity of Insulin aspart Sanofi with Amglidia on (Appendix 1)	30 April 2020

2. Scientific discussion

2.1. Introduction

Problem statement

Insulin aspart Sanofi (also referred to in this report as SAR341402) has been developed as an insulin aspart biosimilar. The EU reference medicinal product is NovoRapid solution for injection 100 U/mL, which was authorised through the centralised procedure on 07 September 1999. NovoRapid is indicated to improve glycemic control in adults and children with diabetes mellitus. The Applicant is seeking approval for the same indication as NovoRapid.

About the product

SAR341402 (insulin aspart) is a rapid-acting insulin produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of Escherichia coli as the production organism. Insulin aspart is homologous to human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28. This modification renders the insulin molecule less prone to self-associate into hexamers and accounts for faster absorption and activity as compared to human insulin given subcutaneously.

Insulin aspart, like human insulin, acts via the human insulin receptor system. The primary activity of insulin, including insulin aspart, is the regulation of glucose metabolism by binding to a specific cell receptor. Insulin and its analogs lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

The finished product is presented as a solution for injection containing 100 units/ml of insulin aspart as the active substance. Other ingredients are metacresol, phenol, sodium chloride, zinc chloride, polysorbate 20, water for injections, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

SAR341402 solution for injection is a sterile, aqueous, clear, and colourless solution. Each milliliter of SAR341402 solution for injection contains 100 units (equivalent to 3.50 mg) insulin aspart. Two drug product presentations, 3 mL cartridge for use in a re-usable pen and 3 mL disposable pre-filled pen (SoloStar®), have been applied for. SAR341402 solution is to be administered subcutaneously by injection, at individualized doses.

Type of Application and aspects on development

This Marketing Authorisation Application is an abridged application for a similar biological medicinal product under Article 10 (4) of Directive 2001/83/EC as amended by Directive 2004/27/EC.

The clinical development programme of Insulin aspart Sanofi has specifically considered the following EU guidelines:

- "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)" (EMA/CHMP/BWP/247713/2012)

- "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" (EMEA/CHMP/BMWP/42832/2005 Rev. 1)

- "Annex to guideline on similar biological medicinal products containing Biotechnology-derived proteins as active substance: Non-clinical and clinical issues Guidance on similar medicinal products containing recombinant human soluble Insulin" (EMEA/CHMP/BMWP/32775/2005 Rev.1).

2.2. Quality aspects

2.2.1. Introduction

Insulin aspart, the active substance (AS), is a rapid-acting insulin with faster absorption and activity as compared to human insulin given subcutaneously. Insulin aspart is homologous to human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28.

Insulin aspart Sanofi has been developed in the EU as a similar biological medicinal product to the reference product, NovoRapid (insulin aspart 100 U/ml).

The finished product (FP), also referred to as SAR341402, is presented as a solution for injection containing 100 units/ml of insulin aspart as the active substance. Other ingredients are metacresol, phenol, sodium chloride, zinc chloride, polysorbate 20, water for injections, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

The product will be available in a 3 ml cartridge for use in re-usable pens (JuniorSTAR, Tactipen, AllStar or AllStar PRO) and a 3 ml disposable pre-filled pen injector (3 ml cartridge irreversibly integrated in a disposable pen injector SoloStar). Insulin aspart solution pen injector is a fully mechanical device, containing no electronic components. The pen injector is designed to deliver multiple doses of variable volume.

2.2.2. Active Substance

General information

The active substance is a two-chain peptide consisting of 51 amino acids. The international non-proprietary name (INN) is insulin aspart. It is identical in primary structure to human insulin, only differing in amino acid sequence at position 28 of the B-chain. Human insulin is 28B-L-Proline-, whereas insulin aspart is 28B-L-aspartic acid-. As human insulin, insulin aspart contains 2 interchain disulfide bonds and 1 intrachain disulfide bond. The structure, including the change in comparison to human insulin, is outlined in Figure 1 below.

Figure 1 - Schematic amino acid sequence

Figure 1

Manufacture, process controls and characterisation

- Manufacture

Description of manufacturing process and process controls

The manufacturing, quality control testing and release of insulin aspart active substance are carried out in accordance with Good Manufacturing Practices.

Insulin aspart is produced by recombinant DNA technology using an *Escherichia coli* strain as host cell for the expression plasmid. One vial of the working cell bank of the production strain is amplified in a seed culture and a pre-fermentation step prior to the main fermentation in a fermenter. Product formation is initiated in the main fermentation stage. During the expression phase, the insulin aspart fusion protein is produced as insoluble intracellular inclusion bodies. The culture is ended after induction when a specified optical density is reached.

The culture is inactivated. E. coli cells are separated by centrifugation and subsequently subjected to disruption by high-pressure homogenisation to liberate the inclusion bodies. The fusion protein is dissolved and the insulin aspart precursor pre-pro insulin aspart is formed by a folding reaction. The refolded molecule is digested by enzymatic cleavage.

After purification by chromatography, insulin aspart is isolated by precipitation, washed and dried. The active substance is filled into containers for storage.

The process for insulin aspart production was established for direct processing of intermediate solutions and suspensions. Only in-process holding of suspensions and solutions as required by the processing occurs. No long-term storage of isolated intermediates is intended.

The active substance manufacturing process is described in sufficient detail. Appropriate description of each step is provided, covering fermentation, recovery, chromatographic purification and including ranges of process parameters and in process-controls. Composition, preparation, sterilization, and storage of culture media are detailed. The active substance manufacturing process is considered acceptable.

- Control of materials

No materials of human or animal origin are used in the manufacturing process of insulin aspart. The raw materials used in the manufacturing have been adequately described in the dossier.

The cell bank system is characterized in line with ICH Q5B and ICH Q5D guidance. The characterisation and testing of the cell banks confirm the identity, purity and suitability of the cell banks for manufacturing use. Stability of the production cell line has been demonstrated. The tests confirmed the expected genetic characteristics of the cell line and demonstrate genetic stability.

Adequate protocols for stability monitoring of the MCB and the current WCB have been provided. Results were satisfactory. Specifications for release and stability monitoring of new WCBs are considered adequate. During the procedure a protocol for replacement of new WCB was requested and provided.

- Control of critical steps and intermediates

During the insulin aspart manufacturing process, the quality of the product is ensured by maintaining certain conditions within predetermined ranges and by in-process controls. The criticality of parameters

is based on the Company´s risk assessment of the process in order to ensure adequate process performance and product quality attributes falling within the established ranges. The classification is transparent and comprehensive. The set of in-process controls are logical and adequately justified.

- Process validation

The process verification studies of the commercial manufacturing process were performed by successfully manufacturing three active substance batches using normal processing parameter set points and conditions. Results of critical process parameters, in-process controls and final active substance are reported with pre-defined ranges/limits. In addition, a large range of additional tests (such as yield, product-related impurities, process-related impurities) were performed to monitor process performance. The data provided are satisfactory and consistent and indicates that each step has been appropriately designed.

Hold time studies are provided for all intermediates intended to be held for a certain processing time. The Company proposes a concurrent column lifetime validation approach. The provided criteria and frequency of evaluation are satisfactory. Column lifetime validation is considered addressed in an acceptable manner.

- Manufacturing process development

The active substance manufacturing process was developed and validated using a combination of traditional and enhanced approaches as described in ICH Q11. The Quality Target Product Profile (QTPP) is based on the reference medicinal product and other insulins and analogues. Based on the QTTP, critical quality attributes (CQA) were identified. Most of the identified CQAs coincide with the quality attributes indicated in Ph. Eur. monograph for insulin aspart (2084), which is at least, to a great extent, based on the reference product. The choice of the CQAs seems logical for manufacturing process development and can be endorsed.

The critical process parameters to be monitored during routine production and proven acceptable ranges were defined. Overall the manufacturing process development is considered comprehensive and satisfactory, supporting the proposed control strategy.

The first process stage at pilot scale was used to manufacture a batch that was used in early tox studies. Production scale batches were used in clinical studies. All batches included in the analytical similarity exercise and the non-clinical in vitro similarity studies with the reference product were also manufactured using active substance from production scale. Comparability of the active substance was demonstrated from laboratory scale to production scale.

Characterisation

The structural elucidation and confirmation of insulin aspart has been carried out on insulin aspart manufactured by Sanofi. The batch investigated has been manufactured at production scale and, as shown in comparability studies, can be considered representative for the commercial active substance.

Characterisation was performed using the following orthogonal techniques with the following analytical techniques: Mass spectrometry (MS), Amino acid sequencing, Peptide mapping, Isoelectric point determination by capillary isoelectric focusing, Ultraviolet (UV) / visible absorption spectrophotometry, Circular dichroism (CD) spectroscopy, Fourier transform infrared (FT-IR) absorption spectrophotometry, Nuclear magnetic resonance (NMR) spectrometry and Reversed phase chromatography. The studies cover primary, secondary, tertiary and higher order structural aspects. In

the studies, comparisons were made with compendial (PhEur, USP and JP) reference preparations. All studies supported the proposed structure. Biological methods do not form part of the characterisation section. In vivo and in vitro biological testing is reported in the biosimilarity studies (3.2.R) and Sanofi batches showed similar activities as EU NovoRapid and USA NovoLog batches. Biological activity is also investigated in Module 4.

Characterisation of active substance purity has been applied on many batches representing active substance process development. Process and product-related impurities including degradation products have been described and presented. The level of related substances/impurities in the active substance is low and complies with the Ph. Eur. monograph. The grouping of substances in a quantitative RP-HPLC assay used throughout module 3 sections has been appropriately justified.

Process impurities as HCP, DNA, residual enzymes, residual solvents and elemental impurities have been addressed and the low levels found do not raise any concern.

Viral contamination of the host cells is not likely because no mammalian host cells are used.
In addition, no material of animal or human origin is used in the manufacture of insulin aspart active substance.

Specification

The specification of insulin aspart active substance has been established based on its respective Ph. Eur. monograph and relevant ICH guidelines, quality of the active substance used in clinical testing, active substance stability, and analytical method variability.

The specification for the active substance includes appearance, identity, potency (HPLC assay), purity. The proposed tests and acceptance criteria for routine active substance release are acceptable.

- **Analytical procedures**

The limits for assay, related proteins, HMWP, endotoxins and sulphated ash are mainly based on the Ph. Eur. monograph for insulin aspart.

The applicant has provided acceptable justification for tests on residual impurities which are not included in the specification.

The analytical procedures applied to control the insulin aspart active substance are essentially those described in the published European Pharmacopoeia Monograph for insulin aspart. Where applicable, full method descriptions are provided.

Analytical results for batches manufactured for toxicological, clinical and supportive- and primary stability studies as well as analytical results for process evaluation batches are presented.

- Batch analysis

All batch results comply with specifications for the commercial active substance. Overall consistent quality characteristics can be seen from the data provided.

- Reference standards

No in house primary reference standard had been established since official standards have been issued by Pharmacopoeias. Working standards are developed. The establishment procedure of the working standard has been reported in sufficient detail.

- Container closure system

Insulin aspart active substance is packaged in stainless steel lidded drums which are sealed by silicone elastomers. Sufficiently detailed information on the container closure system of the AS is provided.

Stability

The stability studies of the active substance are designed in line with ICH guidelines and do not raise any concerns. All test results are presented. A photosensitivity study demonstrated that the active substances is sensitive to light degradation.

The primary stability study and the supportive study provide support for the claimed 5 years shelf life at the proposed storage condition of -20°C±5°C, protected from light. Each year, if manufactured, at least one commercial production batch will be placed on stability.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is available as sterile, clear and colourless solution for injection containing 3.50 mg/mL insulin aspart [equivalent to 100 U (units) of insulin per millilitre].

The product is packaged in colourless type I glass cartridges of 3 ml closed on one end with plunger stoppers and on the opposite end with flanged caps (with sealing disks). The cartridge is either packaged in a cardboard box to be used with pen-injectors referenced in the SmPC or included in a disposable pen injector (SoloStar). The user is able to select the dose by dialling numbers (units) of insulin aspart using the dose selector (dosage range 1-80 U, dose increments 1 U).

The excipients (metacresol, phenol, sodium chloride, zinc chloride, polysorbate 20 (stabilizing), sodium hydroxide and hydrochloric acid and water for injections) comply with the requirements of the Ph. Eur.

Manufacture of the product and process controls

- Pharmaceutical Development

The composition of the FP formulation was selected based on qualitative and quantitative information available on the reference product. After defining the QTPP, the CQAs of the FP were identified. In order to confirm the quantities of the formulation components in combination with the used active substance and to gain formulation understanding, the Applicant performed an appropriate formulation study with varying quantities of the formulation excipients. The outcome of the study finally confirmed the target composition and stability details on studied formulations have been provided. Differences between the FP formulation and that of the reference product NovoRapid/NovoLog have been discussed by the applicant.

The FP manufacturing process was adequately developed. Adequate comparability studies were conducted to study a potential impact of the modifications on FP quality. The development studies resulted in several Critical Process Parameters (CPP) and Critical Material Attributes (CMA), which have been implemented in the description of the manufacturing process and specifications of the excipients. An overview of the proven acceptable ranges of the CPPs have been presented.

In order to demonstrate the suitability of the selected container closure systems, different tests and studies were conducted. Extractables and leachables studies were adequately designed. A toxicological

assessment on the quantities of the leachables found in the FP came to the conclusion that these leachables do not present a toxicological concern.

Functional performance of the insulin aspart disposable pen (SoloStar) but also of the re-usable pen injectors (AllStar pen injector, JuniorSTAR pen injector and TactiPen pen injector) after assembly with insulin aspart cartridges was investigated according to the relevant ISO standards. All parameters tested were within the acceptance criteria required by the ISO standards. Dose accuracy for the reusable pens has been shown. Suitability of the selected disposable pen for insulin aspart 3 mL glass cartridges was confirmed in terms of dose accuracy and functionality.

The integrity of the container closure systems was confirmed by using an adequate container closure integrity evaluation study.

Finally, the optimum concentration of the preservative metacresol and phenol in insulin aspart FP solution was adequately evaluated.Sufficient antimicrobial efficacy up to the end of shelf life has been ensured.

- Process controls

The FP manufacturing process is adequately described and depicted in a flow chart. Process controls are indicated and are based on those identified in the development studies.

The operating parameters for sterilising the packaging components (rubber stopper, sealing disks and cartridges) are specified in the dossier and they are stated to comply with Ph. Eur. requirements.

A description of the disposable pen injector assembly process has been provided.

- Process validation

In order to demonstrate that the manufacturing process is capable of consistently producing the intended quality of insulin aspart solution in cartridges, process verification studies were conducted on a sufficient number of batches at commercial scale. All critical in-process controls were monitored. The impact of different manufacturing activities on the degradation of insulin aspart have been adequately evaluated during pharmaceutical development. Overall, the results of all process tests and the release data of the validation batches met their acceptance criteria.

The disposable pen injector assembly process has been validated.

Filter validation was adequately summarised and results of these studies have been provided.

Product specification

The specifications are considered appropriate for the finished product control at release. Justifications for all specification limits have been provided. The limits for most of the specification parameters are in compliance with Ph. Eur.and USP monographs for insulin preparations. In addition, an appropriate specification for the pre-filled Insulin aspart Sanofi pen injector has been established.

- **Analytical procedures**

The test parameters can be considered appropriate for the FP control at release. In general, analytical methods have been laid down in sufficient detail. The compendial methods have been verified or validated. All non-compendial analytical procedures were validated in line with ICH guidelines. The suitability of the methods for FP control was sufficiently shown.

- Batch analysis

Sufficient results of pilot-scale and production scale batches have been provided.

- Container Closure

The insulin aspart solution for injection 100 U/mL is packaged in a multidose container (3 mL colourless type I glass cartridge) closed with a flanged cap with sealing disk and a plunger stopper. The cartridge can be packaged in an outer carton (for use with re-usable pen injectors e.g. Allstar, not included in the pack but referred to in the SmPC) or integrated in a disposable pen injector (SoloStar). The disposable pen injector has been demonstrated to comply with relevant ISO norms and compliance to Directive 93/42/EEC.

Stability of the product

The current shelf life of 24 months for the finished product is proposed based on available stability data. Insulin aspart Sanofi finished product should be stored in a refrigerator between +2 °C and +8 °C, protected from light. After first use, it can be stored at room temperature protected from light for up to 28 days.

Stability testing in accordance with the ICH guideline has been initiated with commercial scale batches.

Disposable pen injection device assembled with the cartridge was demonstrated to accurately deliver multiple doses after storage.

The in-use stability of the finished product was shown to comply with the proposed shelf-life specification after 28 days.

Finally, light protection of the secondary packaging was confirmed. Based on the results of the stability studies, all storage instructions given in the SmPC are supported.

Biosimilarity

Insulin aspart is a relatively small and less complex protein molecule enabling thorough and reliable comparison of quality attributes covering the structure and impurity pattern. The finished product and the reference product NovoRapid are highly similar.

FP is presented in cartridges and prefilled pens, which are also the common presentations of the reference product.

A comprehensive analytical comparability study was performed to evaluate the similarity between solution for injection and the reference product Novorapid.

The applicant's strategy to establish similarity of solution for injection with the reference product is endorsed.

For several attributes, compliance to the reference product label claim is shown as well as similarity in analytical studies. In analytical studies, SAR341402 solution for injection batches have been tested side by side to EU sourced NovoRapid batches. The number of FP batches chosen for each test is appropriate to accommodate the expected variability of the analytical method

Similarity in primary, secondary, tertiary structure as well as higher-order structure between SAR341402 solution for injection, NovoRapid and NovoLog as well as between NovoRapid and NovoLog has been clearly established. The study design is considered sufficient to detect any possible difference

in the structure of a relatively less complex protein molecule as insulin aspart. Results of comparative in-vitro and in vivo biological activity assays further confirm the similarity in structure.

The primary/secondary/tertiary structure studies have been applied to two SAR341402 solution for injection batches derived from P02 and P03 AS process, three batches Novorapid and three batches of Novolog.

The SAR341402 solution for injection batches included in the analytical studies are considered sufficiently representative for the commercial product. - The comparative stability and degradation studies indicate that only minor effects on quality attributes could have occurred upon storage of SAR341402 solution for injection and reference products.

Quantitative results have been presented in clear graphs. This graphical presentation enables a satisfactory comparison of results. The latter is feasible due to the fact that values of different batches are in relatively good agreement with each other. In addition to presentation of the actual results, the applicant applies a statistical evaluation of the data.

No major qualitative and quantitative differences in purity are reported between SAR341402 solution for injection and the reference product.

The comparative in-use stability study is considered sufficiently well designed to demonstrate the similarity of the biosimilar with the reference product under the in-use conditions. No major qualitative or quantitative differences in impurity profiles are observed. Similar degradation profiles are also revealed in comparative side-by-side stability studies and thermal, hydrolytic and light stress studies.

The analytical studies in 3.2R, detailed in the table below, present strong support on the similarity of SAR341402 solution for injection and Novorapid.

Table: Analytical tests used in biosimilarity exercise

Analytical tests to compare the physio-chemical characteristics of SAR341402 and NovoRapid/NovoLog

Quality attribute	Test item	Purpose	Acceptance criteria for similarity
Protein structure			
Identity/primary structure	Intact mass (MALDI MS)	Additional characterization	Identical masses for SAR341402 and reference product
Primary structure, A- and B- chain	Reduced mass (MALDI MS)	Additional characterization	Identical masses of A- and B- chain
Primary structure, disulfide bonds	MALDI MS peptide map	Additional characterization	Identical masses of fragments

Quality attribute	Test item	Purpose	Acceptance criteria for similarity
Primary structure, IsoAsp	ESI MS/MS ETD	Additional characterization	Identical masses in MS/MS spectra
Primary structure	N-terminal Edman degradation	Additional characterization	Identical amino acid sequence
Secondary structure	Fourier transform infrared spectroscopy (FT-IR)	Additional characterization	Equivalent spectra
Secondary structure	Far UV CD spectroscopy	Additional characterization	Equivalent spectra
Tertiary structure	Near UV CD spectroscopy	Additional characterization	Equivalent spectra
Tertiary structure	NMR spectrometry (1H15N HSQC NMR)	Additional characterization	Equivalent spectra
Higher order structure	Dynamic light scattering (DLS)	Additional characterization	Equivalent size distribution
Higher order structure	Analytical ultracentrifugation (AUC)	Additional characterization	Distribution of sedimentation coefficients
Biological activity	In-vitro assay (iLITE)	Additional characterization	Equivalent biological activity
Biological activity	Rabbit blood sugar test (USP)	Additional characterization	Equivalent biological activity

Drug product quality attributes			
Potency	Assay Insulin aspart by drug product release method (RP-HPLC)	Release Test DP	Statistical evaluation
Content preservative	Content m-cresol by drug product release method (RP-HPLC)	Release Test DP	Statistical evaluation
Content preservative	Content phenol by drug product release method (RP-HPLC)	Release Test DP	Statistical evaluation
Purity	Purity by drug product release method (RP-HPLC)	Release Test DP	Statistical evaluation
Purity	Purity and pI by cIEF	Additional characterization	Equivalent electropherograms
High-molecular weight proteins, aggregates	HMWP by Size-exclusion chromatography	Release Test DP	Statistical evaluation
pH	Potentiometry	Release Test DP	Statistical evaluation
Content of Zinc	Atomic Absorption Spectroscopy (AAS)	Release Test DP	Statistical evaluation
Impurity profile	Impurity profile by HPLC-MS	Additional characterization	Equivalent impurity profile

Post approval change management protocol(s)

Not applicable

Adventitious agents

The production cell line is E. coli and no material of human or animal origin are used in the manufacturing process of insulin aspart.

GMO

Not applicable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Insulin aspart Sanofi is presented as 100 IU/m solution for injection in 3 ml cartridges for use with reusable or disposable injector devices. The development, characterisation, manufacture and control of insulin aspart active substance and finished product were well described and minor issues resolved during the assessment. In addition, biosimilarity versus the reference product, NovoRapid has been adequately described.

No major objections were identified during the assessment. There is a good control strategy in place to guarantee consistent quality of the finished product. The overall quality is considered acceptable when used in accordance with the conditions defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

From a quality perspective, the marketing authorisation application of Insulin aspart Sanofi can be recommended for approval.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The limit for Total '21A-Asp insulin aspart, 3B-Asp insulin aspart/28B-succinimide insulin aspart and 3B-isoAsp insulin aspart' in the finished product should be reconsidered when sufficient experience with commercial manufacturing has been gained.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical development of SAR341402 was done in accordance with the 'Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues' (EMEA/CHMP/BMWP/32775/2005 Rev. 1) and the 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues' (EMEA/CHMP/BMWP/42832/2005 Rev. 1).

Comparative *in vitro* nonclinical pharmacology studies were focused on insulin receptor (IR-A and IR-B) binding and binding kinetics and their activation, metabolic responses, insulin-like growth factor-1 receptor (IGF-1R) binding and activation, and mitogenic activities.

The toxicological development program consisted of two 1-month repeat-dose toxicity studies in rats and a local tolerability study in rabbits.

Specific studies on safety pharmacology, pharmacodynamic drug interactions, pharmacokinetic, genotoxicity, carcinogenicity, reproductive and developmental toxicity were not submitted in accordance with the relevant guidelines.

2.3.2. Pharmacology

Primary pharmacodynamic studies

A series of in vitro studies were conducted to demonstrate similarity between Sanofi-produced and competitor-produced insulin aspart batches in accordance with EU and US guidelines. Four batches of SAR341402 and three batches each of NovoLog and NovoRapid were assessed in a side-by-side biological similarity characterization using an extensive set of in vitro activity assays: determination of the binding affinity to insulin receptor A (IR-A) and insulin receptor B (IR-B), analysis of the binding kinetics to IR-A, IR-B and IGF-1R, measurement of the auto phosphorylation of IR-A, IR-B and IGF-1R, determination of the metabolic activity by i) inhibition of lipolysis in human primary adipocytes, ii) stimulation of glucose uptake in rat L6 myocytes and iii) gene regulation of glucose 6-phosphatase (G6PC) in human primary liver cells, and determination of the mitogenic potency by stimulation of radiolabelled thymidine incorporation into DNA in the mammary carcinoma cell line MCF7.

For each *in vitro* activity assay, weighted geometric means of the respective assay parameters (EC50, IC50, ka1, kd1, ka2, kd2) and their 95% confidence intervals were calculated first per batch and second per compound. An equivalence approach was used to quantify the differences for each *in vitro* assay between SAR341402, NovoLog and NovoRapid. The ratios of the weighted geometric means of each assay parameter with their 90% confidence intervals were calculated for SAR341402 batches / NovoLog batches, SAR341402 batches / NovoRapid batches and NovoLog batches / NovoRapid batches. The acceptance criteria on the ratio for each assay were defined based on the coefficient of variation (CV) % of the individual assay parameters as well as the number of determinations per batch. SAR341402 is considered similar to NovoLog and NovoRapid, if the 90% confidence interval of the ratio is totally within the acceptance region.

Determination of binding affinity to insulin receptor A (study DIVT0110):

IR-A binding affinity was measured with a competitive radio ligand binding assay using plasma membranes of CHO cells overexpressing human IR-A and scintillation proximity assay (SPA) technology. Four batches of SAR341402 and three batches each of NovoLog and NovoRapid were analysed for their potency to inhibit the binding of $A14[^{125}I]$-labelled human insulin to the human IR-A. IC50 values were generated and the weighted geometric mean per compound was calculated as a measure of the binding affinity. The IC50 of the affinity of SAR341402 to IR-A was 0.763 nmol/l [0.723; 0.806] (n=6 per batch). NovoLog and NovoRapid exhibited an IC50 value of 0.801 nmol/l [0.747; 0.858] (n=6 per batch) and 0.790 nmol/l [0.738; 0.846] (n=6 per batch), respectively.

Table 1 Ratios of mean normalized IC50 values with 90% confidence intervals for IR-A

Contrast	Ratio	90% CI
NovoRapid vs. NovoLog	1.01	[0.94;1.09]
SAR341402 vs. NovoLog	0.96	[0.90;1.02]
SAR341402 vs. NovoRapid	0.95	[0.89;1.01]

The ratio of mean normalized IC50 values between the products are shown in the table above. For binding affinity to IR-A, the confidence interval of the ratios of mean normalized IC50 values is well within the acceptance interval of 0.80 - 1.25 for the comparison of SAR341402 to NovoLog and NovoRapid, respectively, as well as for the comparison between NovoRapid and NovoLog. SAR341402, NovoLog and NovoRapid can therefore be considered as similar in the binding affinity to human IR-A.

Determination of binding affinity to insulin receptor B (study DIVT0111):

Insulin receptor B binding affinity was measured in the same way with the same number of batches as for IR-A (study DIVT0110), using plasma membranes of CHO cells overexpressing IR-B. IC50 values were generated and the weighted geometric mean per compound was calculated as a measure of the binding affinity to the human IR-B. The affinity of SAR341402 to the human IR-B was 0.657 nmol/l [0.621; 0.694] (n=6). NovoLog and NovoRapid exhibited an IC50 value on the human IR-B of 0.667 nmol/l [0.625; 0.711] (n=6) and 0.686 nmol/l [0.638; 0.738] (n=6), respectively. The ratio of mean normalized IC50 values between the products are shown in the below table.

Table 2 Ratios of mean normalized IC50 values with 90% confidence intervals for IR-B

Contrast	Ratio	90% CI
NovoRapid vs. NovoLog	1.03	[0.95;1.11]
SAR341402 vs. NovoLog	1.00	[0.93;1.07]
SAR341402 vs. NovoRapid	0.97	[0.90;1.04]

For binding affinity to the human IR-B, the confidence interval of the ratios of mean normalized IC50 values is well within the 0.80 - 1.25 acceptance interval for the comparison of SAR341402 to NovoLog and NovoRapid, respectively, as well as for the comparison between NovoRapid and NovoLog. They can therefore be considered as similar.

Analysis of binding kinetics to insulin receptor A and B (studies DIVT0112 and DIVT0113):

The binding kinetics to IR-A and to IR-B were assessed using a rapid, real-time, direct interaction assay measuring the binding of insulin to an immobilized IR-A via surface plasmon resonance (SPR) assessment. The SPR-sensor chip with immobilized IR-A or IR-B was perfused with SAR341402 (four batches) or reference compounds (three batches each of NovoLog and NovoRapid) in specified concentrations till reaching a stable association maximum (6 experiments per batch). Dissociation was measured by switching back to compound-free buffer. Four kinetic constants (ka1, kd1, ka2, and kd2) were determined and the weighted geometric means per compound were calculated (see below table).

Table 3 Weighted geometric means of binding constants, CV and 95% confidence intervals by compound for IR-A (left) and IR-B (right)

Compound	Geometric Mean	CV [%]	95% CI	Geometric Mean	CV [%]	95% CI
ka1 (1/Ms)						
NovoLog	1.77E+06	2.76	[1.67E+06;1.88E+06]	1.52E+06	1.73	[1.46E+06;1.57E+06]
NovoRapid	1.71E+06	1.62	[1.65E+06;1.77E+06]	1.42E+06	1.71	[1.37E+06;1.48E+06]
SAR341402	1.83E+06	1.46	[1.78E+06;1.89E+06]	1.50E+06	1.28	[1.46E+06;1.54E+06]
kd1 (1/s)						
NovoLog	1.13E-02	1.90	[1.09E-02;1.18E-02]	8.41E-03	0.67	[8.29E-03;8.53E-03]
NovoRapid	1.15E-02	1.09	[1.12E-02;1.17E-02]	8.26E-03	0.99	[8.09E-03;8.44E-03]
SAR341402	1.19E-02	0.67	[1.17E-02;1.20E-02]	8.60E-03	0.72	[8.47E-03;8.73E-03]
ka2 (1/Ms)						
NovoLog	6.92E+05	2.46	[6.57E+05;7.29E+05]	5.54E+05	2.78	[5.22E+05;5.88E+05]
NovoRapid	6.65E+05	1.56	[6.43E+05;6.87E+05]	5.50E+05	2.25	[5.25E+05;5.77E+05]
SAR341402	7.19E+05	1.73	[6.94E+05;7.46E+05]	5.72E+05	2.89	[5.39E+05;6.07E+05]
kd2 (1/s)						
NovoLog	2.44E-01	2.05	[2.34E-01;2.55E-01]	1.26E-01	1.56	[1.22E-01;1.30E-01]
NovoRapid	2.54E-01	1.94	[2.44E-01;2.65E-01]	1.27E-01	2.79	[1.20E-01;1.35E-01]
SAR341402	2.74E-01	1.71	[2.64E-01;2.83E-01]	1.32E-01	1.23	[1.29E-01;1.36E-01]

For the association and dissociation constants ka1, ka2, kd1, and kd2 the confidence intervals of the ratios of the mean association and dissociation constants are well within the 0.70 - 1.43 acceptance interval for the comparison of SAR341402 to NovoLog and NovoRapid, respectively, as well as for the comparison between NovoRapid and NovoLog. SAR341402, NovoLog and NovoRapid can therefore be considered as similar in the IR-A and IR-B binding kinetics (see table below).

Table 4 Ratios of mean normalized binding constants with 90% confidence intervals for IR-A (left) and IR-B (right)

Contrast	Ratio	90% CI	Ratio	90% CI
ka1 (1/Ms)				
NovoRapid vs. NovoLog	0.97	[0.93;1.01]	0.94	[0.91;0.97]
SAR341402 vs. NovoLog	1.05	[1.01;1.09]	1.00	[0.97;1.02]
SAR341402 vs. NovoRapid	1.08	[1.05;1.12]	1.06	[1.03;1.09]
kd1 (1/s)				
NovoRapid vs. NovoLog	1.02	[0.98;1.05]	0.99	[0.97;1.01]
SAR341402 vs. NovoLog	1.05	[1.01;1.08]	1.03	[1.01;1.05]
SAR341402 vs. NovoRapid	1.03	[1.01;1.05]	1.04	[1.02;1.06]
ka2 (1/Ms)				
NovoRapid vs. NovoLog	0.96	[0.92;1.01]	1.02	[0.97;1.06]
SAR341402 vs. NovoLog	1.05	[1.01;1.09]	1.05	[0.99;1.11]
SAR341402 vs. NovoRapid	1.09	[1.05;1.13]	1.04	[0.99;1.09]
kd2 (1/s)				
NovoRapid vs. NovoLog	1.03	[1.00;1.07]	1.01	[0.96;1.06]
SAR341402 vs. NovoLog	1.12	[1.08;1.16]	1.05	[1.02;1.08]
SAR341402 vs. NovoRapid	1.08	[1.04;1.12]	1.05	[1.00;1.09]

Analysis of binding kinetics to IGF-1 receptor (study DIVT0114):

The binding kinetics to IGF-1R was also assessed by using the surface plasmon resonance (SPR) assay. Four kinetic constants (ka1, kd1, ka2, and kd2) were determined and the weighted geometric means per compound were calculated (Table 11). The overlay of concentration response curves averaged over all experiments for the binding kinetics to the human IGF-1R of SAR341402, NovoLog and NovoRapid batches and shows that independent of the origin all batches display a similar dynamic range. The ratios of mean normalized binding constants are shown in Table 12.

For the association and dissociation constants ka1, ka2, kd1, and kd2 the confidence intervals of the ratios of the mean association and dissociation constants are well within the 0.70 - 1.43 acceptance interval for the comparison of SAR341402 to NovoLog and NovoRapid, respectively, as well as for the comparison between NovoRapid and NovoLog. SAR341402, NovoLog and NovoRapid can therefore be considered as similar in the IGF-1R binding kinetics.

Table 5 Weighted geometric means of binding constants, CV and 95% confidence intervals for the IGF-1 receptor

Compound	Geometric Mean	CV [%]	95% CI
ka1 (1/Ms)			
NovoLog	2.18E+05	4.06	[2.00E+05;2.38E+05]
NovoRapid	2.29E+05	2.58	[2.16E+05;2.41E+05]
SAR341402	2.19E+05	2.47	[2.08E+05;2.30E+05]
kd1 (1/s)			
NovoLog	3.94E-02	0.94	[3.86E-02;4.02E-02]
NovoRapid	4.11E-02	1.05	[4.02E-02;4.20E-02]
SAR341402	4.08E-02	0.68	[4.02E-02;4.14E-02]
ka2 (1/Ms)			
NovoLog	2.00E+04	2.56	[1.89E+04;2.11E+04]
NovoRapid	2.07E+04	2.51	[1.96E+04;2.18E+04]
SAR341402	1.99E+04	2.41	[1.89E+04;2.09E+04]
kd2 (1/s)			
NovoLog	2.99E-01	0.69	[2.95E-01;3.03E-01]
NovoRapid	3.06E-01	0.92	[3.00E-01;3.12E-01]
SAR341402	3.10E-01	0.89	[3.04E-01;3.15E-01]

Table 6 Ratios of mean normalized binding constants with 90% confidence intervals for the IGF-1 receptor

Contrast	Ratio	90% CI
ka1 (1/Ms)		
NovoRapid vs. NovoLog	1.05	[0.97;1.14]
SAR341402 vs. NovoLog	1.01	[0.93;1.09]
SAR341402 vs. NovoRapid	0.95	[0.90;1.01]
kd1 (1/s)		
NovoRapid vs. NovoLog	1.04	[1.02;1.06]
SAR341402 vs. NovoLog	1.03	[1.02;1.05]
SAR341402 vs. NovoRapid	0.99	[0.98;1.01]
ka2 (1/Ms)		
NovoRapid vs. NovoLog	1.04	[0.98;1.10]
SAR341402 vs. NovoLog	1.00	[0.94;1.05]
SAR341402 vs. NovoRapid	0.96	[0.90;1.02]
kd2 (1/s)		
NovoRapid vs. NovoLog	1.02	[1.01;1.04]
SAR341402 vs. NovoLog	1.04	[1.02;1.06]
SAR341402 vs. NovoRapid	1.01	[0.99;1.03]

<u>Measurement of autophosphorylation of insulin receptor A (study DIVT0115):</u>

Insulin receptor A autophosphorylation was studied using CHO cells overexpressing IR-A. For detection an immunocytochemical microplate assay (In-Cell Western) based on two-colour fluorescence was applied. The EC50 value was obtained from a dose response curve of ten concentrations for the insulin analogue from each batch. Assays were performed in six experiments in quadruplicates for each dilution. Four batches of SAR341402 and three batches each of NovoLog and NovoRapid were measured and the weighted geometric mean EC50 per compound was calculated (see below table).

Table 7 Weighted geometric means of EC50 values with 95% confidence intervals, by compound

Compound	Geometric Mean (nmol/l)	CV [%]	95% CI
NovoLog	4.73E+00	4.95	[4.26E+00;5.24E+00]
NovoRapid	5.27E+00	3.33	[4.92E+00;5.65E+00]
SAR341402	5.24E+00	4.51	[4.77E+00;5.74E+00]

The overlay of the concentration-response curves averaged over all experiments for the autophosphorylation(provided in relative fluorescence units, RFU) of the human IR-A of SAR341402, NovoLog and NovoRapid batches is shown in the figure below.
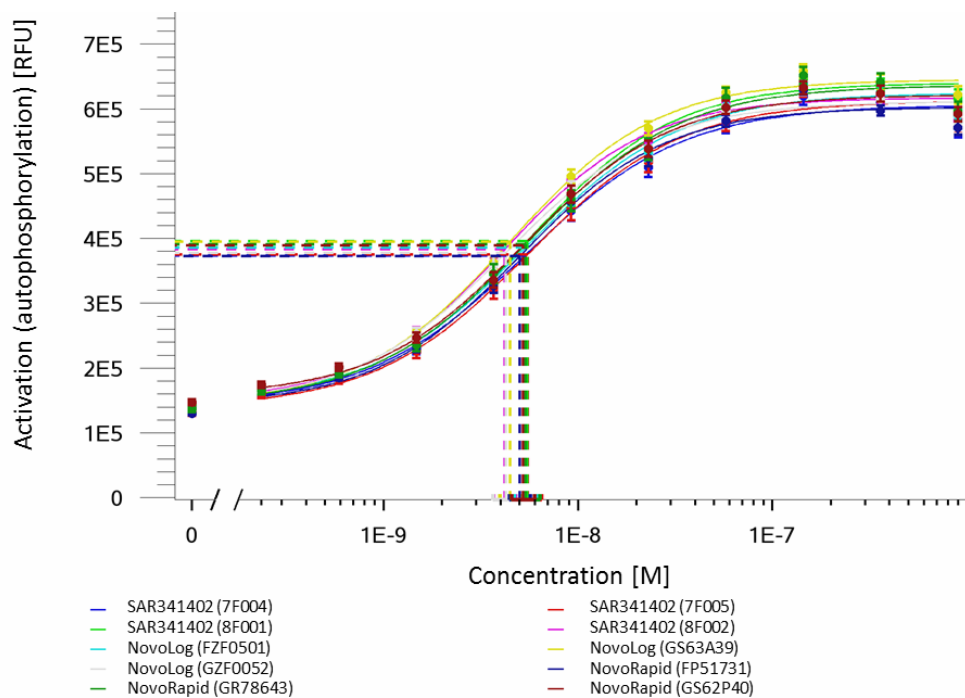

SAR341402 (7F004)   SAR341402 (7F005)
SAR341402 (8F001)   SAR341402 (8F002)
NovoLog (FZF0501)   NovoLog (GS63A39)
NovoLog (GZF0052)   NovoRapid (FP51731)
NovoRapid (GR78643)   NovoRapid (GS62P40)

Figure 2 Overlay of concentration-response curves averaged over all experiments for autophos-phorylation of human IR-A of SAR341402, NovoLog and NovoRapid batches

The ratios of mean normalized EC50 values are shown in the below table. For autophosphorylation of the human IR-A, the confidence interval of the ratios of mean normalized EC50 values is well within the 0.80 - 1.25 acceptance interval for the comparison of SAR341402 to NovoLog and NovoRapid,

respectively. SAR341402, NovoLog and NovoRapid can therefore be considered as similar in stimulating human IR-A autophosphorylation.

Table 8 Ratios of mean normalized EC50 values with 90% confidence intervals for IR-A

Contrast	Ratio	90% CI
NovoRapid vs. NovoLog	1.13	[1.01;1.26]
SAR341402 vs. NovoLog	1.10	[0.98;1.24]
SAR341402 vs. NovoRapid	0.98	[0.89;1.07]

Measurement of autophosphorylation of insulin receptor B (study DIVT0116):

Insulin receptor B autophosphorylation was studied using CHO cells overexpressing IR-B. The ratio of mean normalized EC50 values are shown in the below table. The confidence interval of the ratios of mean normalized EC50 values is well within the 0.80 - 1.25 acceptance interval for the comparison of SAR341402 to NovoLog and NovoRapid, respectively, as well as for the comparison between NovoRapid and NovoLog. They can therefore be considered as similar in this assay.

Table 9 Ratios of mean normalized EC50 values with 90% confidence intervals for IR-B

Contrast	Ratio	90% CI
NovoRapid vs. NovoLog	1.00	[0.91;1.09]
SAR341402 vs. NovoLog	1.01	[0.92;1.12]
SAR341402 vs. NovoRapid	1.02	[0.93;1.12]

Measurement of autophosphorylation of IGF-1 receptor (study DIVT0117):

IGF-1 receptor autophosphorylation was studied using mouse embryonic fibroblast (MEF) cells overexpressing IGF-1R. For detection an immunocytochemical microplate assay (In-Cell Western) based on two-colour fluorescence was applied. Four batches of SAR341402 and three batches each of NovoLog and NovoRapid were measured and the weighted geometric mean EC50 per compound was calculated and normalised (see table below). The confidence intervals of the ratios of mean normalized EC50 values are well within the 0.80 - 1.25 acceptance interval, and SAR341402, NovoLog and NovoRapid can therefore be considered as similar.

Table 10 Weighted geometric means of EC50 values with 95% confidence intervals, by compound and ratios of mean normalized EC50 values with 90% confidence intervals for the IGF-1 receptor

Compound	Geometric Mean (nmol/l)	CV [%]	95% CI	Contrast	Ratio	90% CI
NovoLog	4.77E+02	3.52	[4.44E+02;5.14E+02]	NovoRapid vs. NovoLog	0.96	[0.87;1.05]
NovoRapid	4.38E+02	5.09	[3.94E+02;4.87E+02]	SAR341402 vs. NovoLog	0.94	[0.88;1.00]
SAR341402	4.39E+02	2.88	[4.14E+02;4.66E+02]	SAR341402 vs. NovoRapid	0.98	[0.89;1.07]

Determination of metabolic activity: inhibition of lipolysis (DIVT0118):

The inhibition of lipolysis as a metabolic activity of insulin and insulin analogues was measured by estimation of glycerol release from in vitro differentiated human adipocytes. Four batches of SAR341402 and three batches each of NovoLog and NovoRapid were analyzed (n = 7) and the weighted geometric mean IC50 per compound was calculated as a measure of metabolic activity and

normalised (Table 17). For metabolic activity as assessed by inhibition of lipolysis, the confidence interval of the ratios of mean normalized IC50 values is well within the 0.75 - 1.33 acceptance interval for the comparison of SAR341402 to NovoLog and NovoRapid, respectively, as well as for the comparison between NovoRapid and NovoLog. SAR341402, NovoLog and NovoRapid can therefore be considered to have similar lipolysis inhibition activities.

Table 11 Weighted geometric means of IC50 values with 95% confidence intervals by compound and ratios of mean normalized IC50 values with 90% confidence intervals for inhibition of lipolysis

Compound	Geometric Mean (pmol/l)	CV [%]	95% CI	Contrast	Ratio	90% CI
NovoLog	4.36E+01	4.38	[3.98E+01;4.78E+01]	NovoRapid vs. NovoLog	0.85	[0.79;0.92]
NovoRapid	3.73E+01	4.71	[3.38E+01;4.12E+01]	SAR341402 vs. NovoLog	0.84	[0.78;0.91]
SAR341402	3.72E+01	3.83	[3.44E+01;4.02E+01]	SAR341402 vs. NovoRapid	0.99	[0.91;1.07]

Determination of metabolic activity: stimulation of glucose uptake (DIVT0119):

The stimulation of glucose uptake as a metabolic activity of insulin and insulin analogues was measured by uptake of [14C]-labelled glucose in rat L6 myocytes. Four batches of SAR331402 and three batches each of NovoLog and NovoRapid were studied (n = 7) and the weighted geometric mean EC50 per compound was calculated as a measure of metabolic activity and normalised (see table below). The confidence interval of the ratios of mean normalized IC50 values is well within the 0.80 – 1.25 acceptance interval for the comparison of SAR341402 to NovoLog and NovoRapid, respectively, as well as for the comparison between NovoRapid and NovoLog. They can therefore be considered to have similar stimulatory activities for glucose uptake.

Table 12 Weighted geometric means of EC50 values with 95% confidence intervals by compound and the ratios of mean normalized EC50 values with 90% confidence intervals for stimulation of glucose uptake

Compound	Geometric Mean (nmol/l)	CV [%]	95% CI	Contrast	Ratio	90% CI
NovoLog	6.73E+00	2.66	[6.36E+00;7.12E+00]	NovoRapid vs. NovoLog	0.98	[0.92;1.05]
NovoRapid	6.61E+00	3.09	[6.19E+00;7.05E+00]	SAR341402 vs. NovoLog	1.04	[0.98;1.11]
SAR341402	7.03E+00	2.34	[6.70E+00;7.38E+00]	SAR341402 vs. NovoRapid	1.06	[1.00;1.14]

Determination of metabolic activity: gene regulation of glucose 6-phosphatase (DIVT0120):

The attenuation of gluconeogenesis gene expression in liver as metabolic activity of insulin and insulin analogues was measured using real-time quantitative polymerase chain reaction (qPCR) assay. Four batches of SAR341402 and three batches each of NovoLog and NovoRapid were analyzed for their potency to inhibit the G6PC expression in in vitro primary human hepatocytes. IC50 values for each batch were generated and the weighted geometric mean per compound was calculated as a measure of G6PC expression, and were normalised (see below table). The confidence interval of the ratios of mean normalized IC50 values is well within the 0.80 - 1.25 interval for the comparison of SAR341402 to NovoLog and NovoRapid, respectively, as well as for the comparison between NovoRapid and NovoLog. SAR341402, NovoLog and NovoRapid can therefore be considered as similar in inhibiting G6PC gene expression.

Table 13 Weighted geometric means of IC50 values with 95% confidence intervals by compound and ratios of mean normalized IC50 values with 90% confidence intervals for gene regulation of glucose 6-phosphatase

Compound	Geometric Mean (pmol/l)	CV [%]	95% CI	Contrast	Ratio	90% CI
NovoLog	3.38E+02	9.07	[2.79E+02;4.09E+02]	NovoRapid vs. NovoLog	0.96	[0.85;1.10]
NovoRapid	3.24E+02	5.03	[2.92E+02;3.61E+02]	SAR341402 vs. NovoLog	1.06	[0.93;1.21]
SAR341402	3.57E+02	7.11	[3.08E+02;4.13E+02]	SAR341402 vs. NovoRapid	1.10	[0.98;1.23]

Determination of mitogenic potency: stimulation of radiolabelled thymidine incorporation into DNA (study DIVT0121):

The stimulation of [14C]-thymidine incorporation into DNA as a mitogenic potency of insulin and insulin analogues was measured using human MCF-7 cells. Four batches of SAR341402 and three batches each of NovoLog and NovoRapid were analyzed and the weighted geometric mean EC50 per compound was calculated as a measure of mitogenic potency and normalised (see table below). For mitogenic potency as assessed by [14C]-thymidine incorporation into DNA, the confidence interval of the ratios of mean normalized EC50 values is well within the acceptance interval for the comparison of SAR341402 to NovoLog and NovoRapid, respectively, as well as for the comparison between NovoRapid and NovoLog. SAR341402, NovoLog and NovoRapid can therefore be considered as similar in stimulating [14C]-thymidine incorporation into DNA.

Table 14 Weighted geometric means of EC50 values with 95% confidence intervals, by compound and ratios of mean normalized EC50 values with 90% confidence intervals for stimulation of [14C]-thymidine incorporation into DNA

Compound	Geometric Mean [nmol/l]	CV [%]	95% CI	Contrast	Ratio	90% CI
NovoLog	2.48E+01	6.79	[2.15E+01;2.85E+01]	NovoRapid vs. NovoLog	0.99	[0.89;1.11]
NovoRapid	2.49E+01	5.25	[2.23E+01;2.78E+01]	SAR341402 vs. NovoLog	0.92	[0.83;1.01]
SAR341402	2.21E+01	5.00	[2.00E+01;2.45E+01]	SAR341402 vs. NovoRapid	0.92	[0.85;0.99]

Measurement of autophosphorylation of insulin receptor B by the isolated product related substance 28B-succinimide insulin aspart (study DIVT0109):

SAR341402 contains the distinct impurity 28B-succinimide insulin aspart that is considered to contribute to the test item "assay", as determined by an RP-HPLC method used for drug product release testing. 28B-succinimide insulin aspart is formed upon drug product storage. The aim of this study was to compare the *in vitro* activity of the isolated impurity on the human insulin receptor expressed in a CHO cell line. As a reference compound served SAR341402 (batch 7F004). The insulin receptor B autophosphorylation was studied using CHO cells overexpressing human IR-B. For detection an immunocytochemical microplate assay (In-Cell Western) based on two-colour fluorescence was applied. The weighted geometric mean EC50 value obtained for SAR341402 was 7.72 nmol/l (6.90 - 8.63 nmol/l, n=12); that for 28B-succinimide insulin aspart (batch FFKRO-000096.01) was 20.7 nmol/l (18.8 - 22.7 nmol/l, n=12).

The ratio of mean EC50 values between 28B-succinimide insulin aspart and SAR341402 is 2.68 and the 90% confidence interval of this ratio, (2.43 - 2.95), is completely above 2.4. Thus, 28B-succinimide insulin aspart is considered 2.7-fold less potent than SAR341402.

Secondary pharmacodynamic studies

No studies regarding Secondary Pharmacodynamics were performed.

Safety pharmacology programme

No studies regarding Secondary Pharmacodynamics were performed.

Pharmacodynamic drug interactions

No comparative studies assessing pharmacodynamic drug interactions were submitted in line with relevant guidelines including the CHMP guidance on similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005 Rev. 1).

2.3.3. Pharmacokinetics

For SAR341402, no studies on non-clinical pharmacokinetics were performed.

Bioanalytical methods for the quantitation of SAR341402 and assessment of antidrug antibodies in rat plasma were developed in support of toxicokinetic evaluations in the 1-month repeat dose toxicity studies in rats. A validated specific LC-MS/MS method using immunoaffinity purification was applied for the analysis of SAR341402 in rat plasma with a dynamic range of 1 – 500 ng/ml. The accuracy for the quantitation of SAR341402 ranged from 97.6 to 107% of nominal values and the total precision ranged from 7.40 to 15.9%. At all concentration levels of SAR341402, the ranges of accuracy and precision were within established acceptance criteria. For the detection of anti-drug antibodies (ADA) against SAR341402 in rat plasma in the 1-month repeat dose toxicokinetic studies, a validated radioimmunoprecipitation assay (RIPA) was applied. The sensitivity was estimated as 26.0 ng/ml. At all tested concentration levels of the positive control, the assay is at least tolerant to 5 ng/ml SAR341402 or NovoRapid/NovoLog. The responses of positive control samples at 250 ng/ml level stayed positive at drug concentrations up to 100 ng/ml.

2.3.4. Toxicology

Single dose toxicity

No single dose toxicity studies were performed with SAR341402.

Repeat dose toxicity

The toxicological development program (see table below) consists of two 1-month repeat-dose toxicity studies in rats and a local tolerability study in rabbits. One 1-month repeat-dose toxicity study was performed to compare the proposed product SAR341402 to the reference product NovoRapid marketed in the EU, the other study to compare to NovoLog marketed in the US, and a local tolerance study to compare the proposed product SAR341402 to the reference product NovoRapid marketed in the EU.

The route of administration followed the clinical, subcutaneous route; the local tolerance study covered also possible incidental injections via the intravenous, paravenous and intramuscular routes.

Table 15 Toxicology program / Batches of SAR341402, NovoRapid EU and NovoLog US tested

Study	SAR341402 batches	NovoRapid EU batches	NovoLog US batches
TSA1504 - 1-month rat study	SAR341402_11_0046	AS63788	
TSA1518 - 1-month rat study	SAR341402_12_0150*		BZF0125
TOL1161 - local tolerance rabbit study	SAR341402_12_0150*	YS63847	

*this batch is analogous to clinical batches

The SAR341402 formulation used in the toxicology studies described below was either equal to the marketed product NovoLog or equal to the new formulation developed by Sanofi for the intended to be marketed biosimilar product and used in clinical trials (Table 22). All toxicology studies required to be conducted according to Good Laboratory Practice regulations were conducted in compliance with GLPs. An overview of the two repeat dose-toxicity studies in rats is presented in Table 23.

Table 16 NovoRapid or NovoLog and SAR341402 formulation excipients

Excipient	Quantity [mg/mL]	
	NovoRapid / NovoLog	SAR341402
$Na_2HPO_4 * 7(H_2O)$	1.88	-
Glycerol 85%	18.82	-
Polysorbate 20	-	0.02
Sodium chloride	0.58	6.8
Metacresol	1.72	1.72
Phenol	1.5	1.5
Zinc*	0.0196	0.0196
1N/ 0.03 N Hydrochloric acid	q.s. (ad pH 7.4)	q.s. (ad pH 7.4)
1N/ 0.02 N Sodium hydroxide	q.s. (ad pH 7.4)	q.s. (ad pH 7.4)
Water for injection	ad 1.0 mL	ad 1.0 mL

* only together with SAR341402, not in placebo formulation

Table 17 Subcutaneous Repeat-Dose Toxicity Studies

Species (Number/ Sex/group)	Duration	Dose levels [U/kg/day]	NOAEL [U/kg]	$C_{max, 1}$ at NOAEL (ng/mL)		AUC_{0-8} at NOAEL (ng*h/mL)		Study reference
Rat (10M / 10F)	1 month	SAR341402 10, 50, 200	200	Day 29: 2630 M 5150 F		Day 29: 13800 M 18300 F		TSA1504 (Section 3.1.1)
Rat (10M / 10F)	1 month	NovoRapid EU 10, 50, 200	NA	Day 29[a]: 3090 M 3850 F		Day 29: 13000 M 13900 F		TSA1504 (Section 3.1.1)
Rat (10M / 10F)	1 month	SAR341402 10, 50, 200	200	Day 29: 9040 M 7580 F		Day 29: 24600 M 30300 F		TSA1518 (Section 3.1.2)
Rat (10M / 10F)	1 month	NovoLog US 10, 50, 200	NA	Day 29[a]: 7240 M 10800 F		Day 29: 21000 M 44300 F		TSA1518 (Section 3.1.2)

F = female, M = male
a = NovoRapid or NovoLog exposure at the same level as NOAEL of SAR341402

To show similarity of SAR341402 to insulin aspart (NovoRapid EU (study TSA1504) or NovoLog US-marketed (study TSA1518)) regarding toxicity profile and exposure, Sprague-Dawley rats (7 to 9 weeks of age) received either solutions of insulin aspart (NovoRapid, NovoLog) or SAR341402 (formulation equal to NovoLog (study TSA1504) or new Sanofi formulation (study TSA1518)) at 0, 5, 25 or 100 U/kg/administration by subcutaneous injection twice daily for 1 month, using dose volumes of 1.0, 0.05, 0.25 and 1.0 mL/kg, respectively. Control groups received placebo solutions. Rats were designated as toxicity or toxicokinetic (TK) phase animals. For the toxicity phase, there were 10 rats/sex/group. For the TK phase, 6 rats per sex in the control groups and 18 rats per sex in the treated groups received the same dosages as the toxicity phase animals.

Parameters evaluated were mortality, clinical signs, body weight, food consumption, ophthalmology, blood glucose, haematology, coagulation, clinical chemistry and urinalysis. Plasma samples were obtained for anti-insulin aspart antibody (AIA) assessment and toxicokinetic determinations. Weights of selected organs were recorded, tissues were examined macroscopically and representative tissue samples were examined microscopically from rats in both control groups and in the 200 U/kg/day groups for both test compounds. Tissues with potential treatment-related findings were also evaluated microscopically for rats in the low- and mid-dose groups. Ki-67 staining of the mammary glands was done as a parameter for a mitogenic potential of the test compounds.

<u>One month subcutaneous toxicity study in rats with comparator NovoRapid EU (study TSA1504):</u>

After subcutaneous administration of either SAR341402 (equal to NovoLog formulation, batch SAR341402_11_0046) or NovoRapid EU, rats were systemically exposed to insulin aspart concentrations above 1 ng/mL (LLOQ) for up to 4 hours after each administration (see table below).

Table 18 Summary of toxicokinetic parameters for SAR341402 and NovoRapid EU in rats, SC

Sex	Dose (mg/kg)	SAR341402				NovoRapid EU			
		$C_{max, 1}$ (ng/mL)[a]		AUC_{0-8} (ng*h/mL)[a]		$C_{max, 1}$ (ng/mL)[a]		AUC_{0-8} (ng*h/mL)[a]	
		Day 1	Day 29	Day 1	Day 29	Day 1	Day 29	Day 1	Day 29
Male	10	186	229	525	694	319	196	537	441
	50	1170	1060	2150	2760	986	1450	2330	5150
	200	3760	2630	7800	13800	3060	3090	9100	13000
Female	10	929	519	876	727	827	534	919	1080
	50	1260	1650	2070	4790	1300	2010	3080	4850
	200	2510	5150	8820	18300	2830	3850	7200	13900

[a] Values are rounded to 3 significant figures.

No plasma samples of the control group animals tested AIA-positive on Day 29. In the dosed groups, however, between 0.0% and 22.2% (mean 13.0%) of all animals were confirmed AIA -negative, and between 0.0% and 50.0% (mean 25.0%) were confirmed AIA – positive (see table below). Between 27.8% and 88.9% (mean 62.0%) of all results were inconclusive due to high insulin aspart plasma concentration compared to the drug tolerance level of 5 ng/mL of the AIA assay. Therefore, no distinct evaluation about dose- or gender-dependency of the AIA-status could be made.

Table 19 Summary of percentage of AIA-positive animals for SAR341402 and NovoRapid EU in rats, SC

Sex	Dose U/kg/day	SAR341402 % AIA			NovoRapid EU % AIA		
		negative	positive	inconclusive [a]	negative	positive	inconclusive [a]
male	10	22.2	50.0	27.8	22.2	38.9	38.9
	50	5.6	38.9	55.6	11.1	22.2	66.7
	200	16.7	0.0	83.3	16.7	5.6	77.8
female	10	22.2	38.9	38.9	22.2	22.2	55.6
	50	0.0	50.0	50.0	5.6	16.7	77.8
	200	0.0	11.1	88.9	11.1	5.6	83.3

[a] Since the drug tolerance of the AIA assay was 5 ng/mL, all AIA results that were reported as negative in the AIA Sample Analysis phase report but had corresponding plasma concentration values > 5ng/mL, were set to "inconclusive"

The twice daily subcutaneous administration of NovoRapid and SAR341402 formulation for 1 month to rats at doses of 10, 50 and 200 U/kg/day resulted in hunched posture and mild lethargy. The observed increases in body weight, body weight gain, food consumption, glucose and phosphorous are all linked to either the direct or indirect pharmacological reactions to the administration of insulin. There were no systemic toxic effects related to either NovoRapid or SAR341402 formulation administration. However, red skin discoloration was observed in the injection sites and was increased at 200 U/kg/day in both sexes with NovoRapid and males only with SAR341402 formulation. Microscopically, both compounds induced an increase in the incidence and/or severity of subcutaneous changes associated with the route of administration (haemorrhage and/or inflammation) at 200 U/kg/day.

Therefore, under these study conditions, the NOAEL was considered to be 200 U/kg/day for both sexes and for both compounds. Based on the results of this study, SAR341402 and NovoRapid showed similar pharmacological activity. The toxicokinetic profile also demonstrated similarity between SAR341402 and NovoRapid.

<u>One month subcutaneous toxicity study in rats with comparator NovoLog US (study TSA1518):</u>

After administration of either SAR341402 or NovoLog US, rats were systemically exposed to insulin aspart concentrations above 1 ng/mL (LLOQ) for up to 4 hours after each administration, except at Day 1 for males given 50 U SAR341402 /kg/day (until 7 hours), and males and females given 10 U NovoLog /kg/day (until 6 hours), and for females given 50 U NovoLog /kg/day (until 7 hours). Additionally, on Day 1, plasma levels of NovoLog were only quantifiable until 2 or 3 hours post dose for some animals given 10 and 50 U/kg/day. Following repeated administration of SAR341402 for 4-weeks (Day 29), exposure patterns were similar, though firm conclusions could not be made for males and females given 10 U/kg/day and males given 200 U/kg/day, as much of the analytical data was not reportable due to technical constrains. Overall, there did not appear to be any significant differences in the toxicokinetic parameters between the two compounds dosed (see table below).

Table 20 Summary of toxicokinetic parameters for SAR341402 and NovoLog US in rats, SC

Sex	Dose (mg/kg)	SAR341402						NovoLog US					
		$C_{max,1}$ (ng/mL)[a]		$C_{max,2}$ (ng/mL)[a]		AUC_{0-8} (ng*h/mL)[a]		$C_{max,1}$ (ng/mL)[a]		$C_{max,2}$ (ng/mL)[a]		AUC_{0-8} (ng*h/mL)[a]	
		Day		Day		Day		Day		Day		Day	
		1	29	1	29	1	29	1	29	1	29	1	29
Male	10	379	NC	377	NC	544	NC	247	299	247	301	371	747
	50	1370	1970	1170	1650	2990	5560	1380	1560	971	1250	2990	4720
	200	4500	9040	3030	2690	14700	24600	3460	7240	2990	3130	11200	21000
Female	10	310	NC	453	715	486	2060	347	889	266	1010	446	1680
	50	3520	1860	1280	1780	4890	4470	1060	2160	1230	3080	2480	8740
	200	3050	7580	3910	8320	9850	30300	3220	10800	2540	11300	9920	44300

[a] Values are rounded to 3 significant figures.

No plasma samples of the control group animals were reported as AIA-positive on Day 29. In the SAR341402 dosed groups, between 27.8% and 66.7% (mean 45.4%) of all animals were confirmed as AIA positive (see table below). Specifically, six, twelve and five of eighteen (33.3%, 66.7% and 27.8%) male rats, and twelve, nine and five of eighteen (66.7%, 50.0% and 27.8%) female rats, in the 10, 50 and 200 U/kg/day dose groups respectively, were AIA-positive on Day 29. In the NovoLog dosed groups, between 11.1% and 55.6% (mean 27.8%) of all animals were confirmed as AIA positive. Specifically, seven, four and two of eighteen (38.9%, 22.2% and 11.1%) male rats, and ten, four and three of eighteen (55.6%, 22.2% and 16.7%) female rats, in the 10, 50 and 200 U/kg/day dose groups respectively, were AIA-positive on Day 29. Between 16.7% and 88.9% (mean 56.9%) of all results were inconclusive due to high SAR341402/Insulin Aspart plasma concentration compared to the drug tolerance level of 5 ng/mL of the AIA assay. Therefore, no distinct evaluation about dose- or gender-dependency of the AIA-status can be made.

Table 21 Summary of percentage of AIA-positive animals for SAR341402 and NovoLog US in rats

Sex	Dose U/kg/day	SAR341402 % AIA			NovoLog EU % AIA		
		negative	positive	inconclusive [a]	negative	positive	inconclusive [a]
male	10	0	33.3	66.7	22.2	38.9	38.9
	50	16.7	66.7	16.7	11.1	22.2	66.7
	200	0	27.8	72.2	0	11.1	88.9
female	10	0	66.7	33.3	11.1	55.6	33.3
	50	5.6	50.0	44.4	11.8	23.5	64.7
	200	0	27.8	72.2	0	16.7	83.3

[a] Since the drug tolerance of the AIA assay was 5 ng/mL, all AIA results that were reported as negative in the AIA Sample Analysis phase report but had corresponding plasma concentration values > 5ng/mL, were set to "inconclusive"

There were two premature deaths out of 336 treated animals during the study; one TK phase female at 50 U/kg/day NovoLog was found dead on Day 20 and one toxicity phase female at 200 U/k/day SAR341402 was found dead on Day 30. It was suspected that these deaths resulted from test compound-induced hypoglycaemia. All remaining animals survived to scheduled termination.

The exposed rats showed mild hunched posture, raised fur and lethargy, and also increases in body weight, body weight gain, food consumption, glucose and phosphorous, which are linked to either the direct or indirect pharmacological reactions to the administration of insulin. Mean liver weight was significantly lower in males at 10, 50, 200 U/kg/day NovoLog and in females at 50 U/kg/day SAR341402 and significantly higher mean kidney weight in males at 50 and 200 U/kg/day NovoLog and 50 U/kg/day SAR341402. Microscopic examination at 200 U/kg/day showed reduced glycogenic vacuolation in the liver (correlating with decreased liver weight) in both sexes with both compounds compared to controls. This effect, and the higher kidney weight, were judged to have a physiological and not a toxicological basis. Neither compound was found to exacerbate the effects of mechanical damage at the injection site. Therefore, under these study conditions, the NOAEL was considered to be 200 U/kg/day for both sexes and for both compounds. Based on the results of this study, SAR341402 and NovoLog showed similar pharmacological activity. The toxicokinetic profile also demonstrated similarity between SAR341402 and NovoLog.

Genotoxicity

No genotoxicity studies were performed with SAR341402.

Carcinogenicity

No carcinogenicity studies were performed with SAR341402.

Reproduction Toxicity

No reproductive and developmental toxicity studies were performed with SAR341402.

Local Tolerance

Local subcutaneous, intravenous, paravenous and intramuscular tolerance study in male rabbits (study TOL1161):

SAR341402 Sanofi formulation (100 U/mL, batch SAR341402_12_0150) was injected as single subcutaneous (SC, 0.1 mL), intravenous (IV, 0.5 mL), paravenous (PV, 0.1 mL) or intramuscular (IM, 0.5 mL) dose, respectively to 4 groups of 3 New Zealand White male rabbits. Each rabbit was dosed either by the combination of the IM and the PV routes or the IV and the SC routes. In the same conditions, four other groups of 3 animals received a marketed NovoRapid formulation (100 U/mL) and served as reference groups. As a control, 0.9% NaCl was injected contra-laterally for the SC and IM routes in all these groups, and two distinct groups of 3 animals received 0.9% NaCl on both ears, by IV or PV routes.

Local tolerance (at the injection site), mortality and clinical signs were assessed before administration and several times after administration. Body weight was evaluated on Day-1 and on the scheduled day of euthanasia. At necropsy (performed 24 h or 120 h after administration), the injection sites of all rabbits were dissected, examined and fixed for histological assessment.

No general toxicity, as assessed through absence of clinical signs, mortality and body weight changes, was reported during the study.

Local tolerance evaluation (erythema, edema, hematoma and eschar/ulcer) showed that NovoRapid and control were very well tolerated when administered by the SC, IM, IV and PV routes. SAR341402 was also very well tolerated when administered by the SC and IM routes, however, it was less tolerated than 0.9% NaCl or NovoRapid when administered by the IV and PV routes. When administered IV or PV, SAR341402 mildly increased severity, incidence and/or distribution of acute to subacute changes (oedema, fibrin deposits, haemorrhages and inflammation) 24 hours after administration. After 120 hours, SAR341402 slightly increased severity of chronic inflammation compared to NaCl 0.9%, but similar to that observed with NovoRapid. Consequently, SAR341402 was considered as well tolerated following intravenous and paravenous administration, with a possible slight local irritation.

Overall SAR341402 and NovoRapid were considered to be similar regarding local tolerability because no significant difference was observed.

Other toxicity studies

No additional immunotoxicology testing is required based on a weight of evidence review for compound NovoRapid. The weight of evidence review is based on the absence of immunotoxic findings in standard toxicity studies, lack of demonstrated pharmacologic activity affecting the immune system, no demonstrated structural similarities to known immunomodulatory compounds, the absence of elevated distribution of compound and/or its metabolites to organs/cells of the immune system.

No photosafety testing is considered necessary since insulins/insulin analogues are not described in the literature to have phototoxic potential and photosafety testing is not required in the current ICHS6 guideline for biopharmaceuticals.

No studies have been performed on SAR341402 metabolites and impurities.

2.3.5. Ecotoxicity/environmental risk assessment

In accordance with the Guideline on the environmental risk assessment of 5 medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev.1), the applicant did not submit any ERA studies as the active substance of SAR341402 (insulin aspart) is a natural substance (insulin analogue), the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, SAR341402 is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacology

According to the Guideline on the non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues, sufficient different biological assays have been performed for demonstrating the biosimilarity of Insulin aspart Sanofi for *in vitro* receptor binding, receptor autophosphorylation and metabolic activity assays with the reference product NovoRapid.

However, after a request of statistical reports on biosimilarity studies, which were not submitted with the initial MAA, it appeared that the *in vitro* biosimilar studies DIVT0112 and DIVT0113 were originally negative in biosimilarity outcome, and have been re-examined, without notification and discussion in the studies and in the Non-clinical Summary. The Applicant was requested to provide a thorough explanation of the handling of data, why studies DIVT0112 and DIVT0113 have been re-examined, why different batches have been used and why this has not been discussed in the originally submitted dossier. The Applicant provided during the evaluation additional information on the *in vitro* binding studies for the insulin receptor A and B, and IGF-1R. These binding kinetic studies (reports DIVT0112, DIVT0113 and DIVT0114) were outsourced to a CRO. After measurement on IRA and IRB, it was noted by the CRO that "not enough volume was left of three of the samples to finish all replicates", and the "volume remaining in the tubes varied although they had used essentially the same amount of each sample". Unfortunately, the cause of these deviations is not known. The CRO requested new samples, apparently only for measurement of IGF-1R. The statistical results of all measurements were reported in Report 1, with the conclusion that the binding kinetics to IRA and IRB showed insufficient evidence to conclude similarity between SAR341402 and NovoLog and between SAR341402 and NovoRapid. Kinetics of IGF-1R showed similarity. Apparently thereafter, the results on IRA and IRB were not trusted, and new samples were sent to the CRO. Samples of the same batches were sent except for reference batches NovoLog (FZF0501) and NovoRapid (FP51731), which meanwhile had expired and thus were replaced by new batches NovoLog (HS65D84) and NovoRapid (GS62P40). This time, all results showed acceptable similarity. The statistical results of these new measurements were reported first in Report 2, a draft, and finally in Report 3. However, the Applicant did not submit one of these statistical reports with the initial MAA, and the separate similarity studies (DIVT0110 to DIVT0121), also of other in vitro endpoints, referred in a random way to Report 1, 2 and 3 for the statistical data, which caused confusion on important issues and thus the major objection. To conclude the Applicant provided sufficient information to explain the reasons for re-analyzing samples for studies DIVT0112 and DIVT0113, and provided new updated documents with corrected references satisfactorily addressing the issue.

Pharmacokinetics

Validated assays for the quantitation of SAR341402 and for the assessment of anti-drug antibodies in rat plasma were developed in support of toxicokinetic evaluations performed for the studies on toxicology of SAR341402.

Toxicology

Toxicology studies usually are not required for insulin biosimilar applications. Nevertheless, the Applicant performed two 1-month repeated-dose toxicokinetic studies in rats to determine biosimilarity of SAR341402 with NovoRapid (EU) and NovoLog (US). No difference in toxicity, kinetics and ADA-forming were detected.

2.3.7. Conclusion on the non-clinical aspects

The submitted non-clinical comparability exercise was considered appropriate. Relevant regulatory guidelines were taken into consideration.

Based on the results submitted, Insulin aspart Sanofi can be considered similar to the reference product NovoRapid in terms of *in vitro* functionality and toxicological, toxicokinetic and local tolerance profiles.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The clinical trials were performed in accordance with Good Clinical Practice (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 22 Overview of completed clinical studies supporting SAR341402 solution registration

	PDY12695 Euglycemic clamp study (PK/PD)	EFC15081 Efficacy/safety Phase 3 study	PDY15083 Safety study	PDY15287 Euglycemic clamp study (PK/PD)
Design	Randomized, double-blind, controlled, 3x1 day cross-over study	Randomized, active-controlled, open-label, parallel group study	Randomized, active-controlled, open-label, 2x4 weeks cross-over study	Randomized, double-blind, controlled, 2x1 day cross-over study
Population	Patients with **T1DM**	Patients with **T1DM or T2DM** (T2DM only for US) on multiple daily injection (MDI) regimen with: insulin aspart or insulin lispro for at least 6 months prior to the study and insulin glargine for at least 6 months or insulin detemir for at least 12 months prior to the study	Patients with **T1DM** on Continuous Subcutaneous Insulin Infusion (CSII)	Healthy male Japanese subjects
Comparator and regions	NovoLog (US) NovoRapid (Europe)	NovoLog (US) / NovoRapid (Europe, Japan)	NovoLog (US)	NovoRapid (Japan)
Randomization	1:1:1	1:1	1:1	1:1
Route of administration and injection device for IMP	SC injection Syringes	SC injection before each meal; or immediately after meal intake (if allowed per local label for NovoLog/NovoRapid) SAR341402: SoloStar® NovoLog/NovoRapid: FlexPen®	External pump for CSII (Medtronic with 3 mL reservoir or Animas with 2 mL reservoir)	SC injection Syringes
Objectives	PK and PD (euglycemic clamp technique)	Efficacy, safety and immunogenicity	Safety	PK and PD (euglycemic clamp technique)

Primary endpoint	PK: AUC, AUC_{last}, C_{max} PD: $GIR\text{-}AUC_{0\text{-}12}$	HbA1c (%), change from baseline to Week 26	Number of patients with infusion set occlusions defined as infusion set change due to failure to correct hyperglycemia (plasma glucose ≥250 mg/dL [13.9 mmol/L]) by insulin bolus via the insulin pump	PK: Cmax, AUClast PD: GIRmax, GIR-AUC0-10h
Safety	General safety	Immunogenicity and general safety	Infusion set occlusions and general safety	General safety
Number of patients randomized	N=30	SAR341402: N=301 (T1DM: 250, T2DM: 51) NovoLog/NovoRapid: N=296 (T1DM: 247, T2DM: 49)	N=45	N=40
Duration of treatment	3x1 day	6 months (main study period) 6 months comparative safety extension period	2x4 weeks	2x1 day

2.4.2. Pharmacokinetics

Study PDY12695

The comparative pharmacokinetics of SAR341402 and the insulin aspart EU and US reference products NovoRapid and NovoLog, respectively, were investigated in a single-dose euglycemic clamp study PDY12695 in male patients with type 1 diabetes mellitus. It was a randomized, double-blind cross-over study.

Insulin aspart in plasma was analysed using a validated LC-MS/MS method.

Primary pharmacokinetic parameters were C_{max}, AUC_{last} and AUC_{inf}. Secondary pharmacokinetic parameters were t_{max}, $AUC_{0\text{-}2}$, $AUC_{4\text{-}tlast}$, tx%-AUC, t_{last} and $t_{1/2z}$.

To demonstrate bioequivalence, the 90% confidence intervals were calculated for C_{max}, AUC_{last} and AUC_{inf}, using the (0.80-1.25) acceptance range. Prior to analysis, the parameters were log-transformed (natural log). A linear mixed-effects model was used with fixed terms for sequence, period and treatment and random term for subject-within-sequence, with treatment-specific between-subject and within-subject variances. For $AUC_{0\text{-}2}$, $AUC_{4\text{-}tlast}$ and $t_{1/2z}$, 90% confidence intervals were calculated for the ratios using the linear mixed effect model as described for the primary PK parameters. Tx%-AUC and t_{max} were analyzed non-parametrically based on the Hodges-Lehmann method for paired treatment comparisons. 90% confidence intervals for pair-wise medians of treatment differences were derived.

A total of 30 subjects were included in the study, one of whom discontinued after dosing in the second treatment period.

The 90% confidence interval (CI) was between the acceptance limits of 0.80-1.25 for C_{max}, AUC_{last} and AUC_{inf} for SAR341402 vs EU reference NovoRapid. Unity was included in the CI for C_{max}, but this was not the case for AUC_{last} and AUC_{inf}. Partial AUCs were provided by the Applicant and show that AUC_{0-2} was within the limits, but $AUC_{4-tlast}$ appeared lower for SAR341402 than for NovoRapid with the lower confidence limit for the ratio below 0.8. There was no significant difference in terminal half-life.
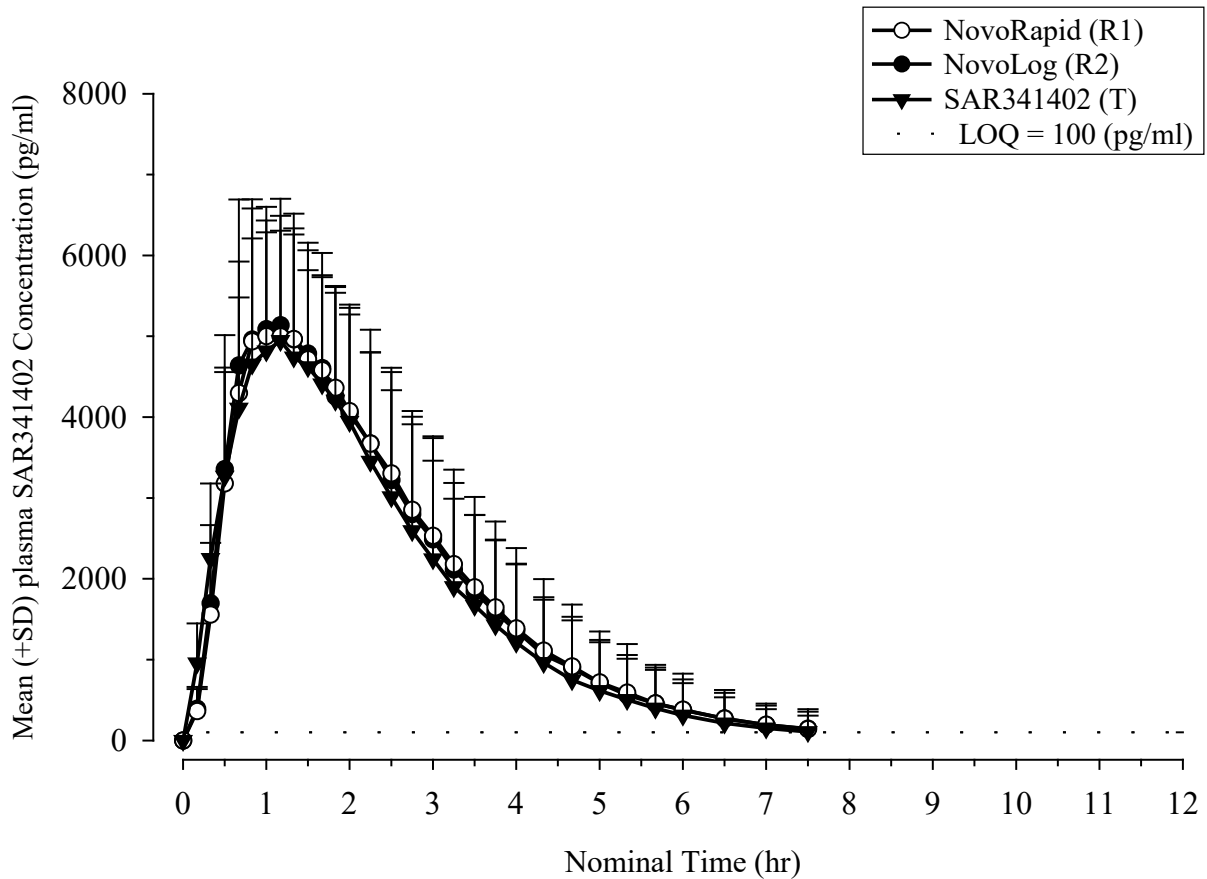
Source = PKS Study : PDY12695; Scenario: P-D-A-EV-OD-E02, Version 8
Date/Time = 6/6/2014 10:17:31 AM

Figure 3 Mean (±SD) plasma concentration versus time profiles for SAR341402, NovoRapid, and NovoLog (linear scale) (Study PDY12695)

Table 23 Statistical analyses of primary pharmacokinetic parameters C_{max}, AUC_{last}, and AUC_{inf} - Point estimates of treatment ratio with 90% confidence intervals (Study PDY12695)

Parameter	Treatment ratio	Estimate	90% CI
C_{max}	SAR341402 vs NovoRapid	0.97	(0.90 to 1.05)
	SAR341402 vs NovoLog	0.93	(0.87 to 1.01)
	NovoLog vs NovoRapid	1.04	(0.96 to 1.12)
AUC_{last}	SAR341402 vs NovoRapid	0.93	(0.88 to 0.97)
	SAR341402 vs NovoLog	0.93	(0.89 to 0.98)
	NovoLog vs NovoRapid	1.00	(0.95 to 1.05)
AUCinf	SAR341402 vs NovoRapid	0.92	(0.88 to 0.96)
	SAR341402 vs NovoLog	0.92	(0.88 to 0.96)
	NovoLog vs NovoRapid	1.00	(0.95 to 1.04)

Table 24 Statistical analyses of secondary pharmacokinetic parameters AUC_{0-2}, AUC_{4-last} and $t_{1/2z}$ – Point estimates of treatment ratios with 90% confidence intervals (Study PDY12695)

Parameter	Treatment ratio	Estimate	90% CI
INS-AUC_{0-2}	SAR341402 vs NovoRapid	1.00	(0.92 to 1.07)
	SAR341402 vs NovoLog	0.98	(0.90 to 1.05)
	NovoLog vs NovoRapid	1.02	(0.95 to 1.10)
INS-AUC_{4-last}	SAR341402 vs NovoRapid	0.73	(0.61 to 0.87)
	SAR341402 vs NovoLog	0.73	(0.60 to 0.87)
	NovoLog vs NovoRapid	1.00	(0.84 to 1.20)
INS-$t_{1/2z}$	SAR341402 vs NovoRapid	0.96	(0.86 to 1.08)
	SAR341402 vs NovoLog	0.99	(0.88 to 1.11)
	NovoLog vs NovoRapid	0.98	(0.87 to 1.10)

T: SAR341402; R1 : NovoRapid; R2 : NovoLog

Study PDY15287

The comparative pharmacokinetics of SAR341402 and the insulin aspart reference product NovoRapid (Japan) were investigated in a single-dose euglycemic clamp study PDY15287 in male healthy Japanese subjects. It was a randomized, double-blind cross-over study. Insulin aspart in plasma was analysed using a validated LC-MS/MS method. Primary pharmacokinetic parameters were Cmax, AUClast and AUCinf. Secondary pharmacokinetic parameters were tmax and $t_{1/2z}$. To demonstrate bioequivalence, the 90% confidence intervals were calculated for C_{max}, AUC_{last} and AUC_{inf}, using the (0.80-1.25) acceptance range. Prior to analysis, the parameters were log-transformed. A linear mixed-effects model was used to analyse C_{max}, AUC_{last}, AUC_{inf} and $T_{1/2z}$. T_{max} was analysed non-parametrically based on the Hodges-Lehmann method.

A total of 40 subjects was included in the study, one of whom withdrew his consent before the second treatment period.

The 90% confidence interval (CI) was between the acceptance limits of 80.00-125.00 for C_{max}, AUC_{last} and AUC_{inf} for SAR341402 vs reference NovoRapid. Unity was included (see table below).
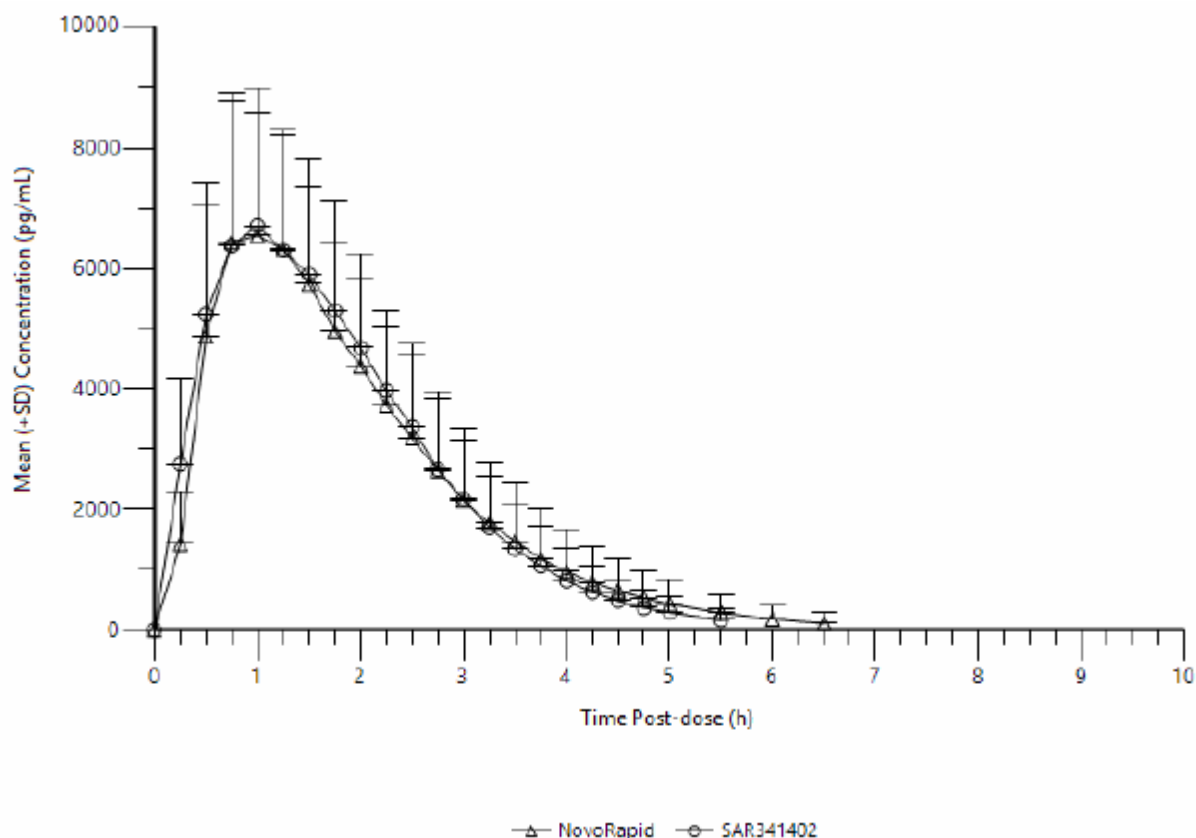
Figure 4 Mean (+SD) SAR341402 / insulin aspart plasma concentrations (pg/mL) following single dose SC administration of SAR341402 and NovoRapid to healthy male Japanese subjects (linear scale) (study PDY15287)

Table 25 Treatment effect on INS-Cmax and INS-AUClast as well as for INS-AUC – Point estimates and 90% confidence intervals (study PDY15287)

Parameter	Treatment ratio	Estimate	90% CI
INS-C_{max} (pg/mL)	SAR341402 vs NovoRapid	1.00	(0.94 to 1.05)
INS-AUC_{last} (pg.h/mL)	SAR341402 vs NovoRapid	1.02	(1.00 to 1.04)
INS-AUC (pg.h/mL)	SAR341402 vs NovoRapid	1.02	(1.00 to 1.03)

2.4.3. Pharmacodynamics

Study PDY12695, was conducted to demonstrate that the proposed commercial formulation of Insulin aspart Sanofi (SAR341402) solution has PK and PD profiles similar to that of NovoLog/NovoRapid. This study was a cross-over, double-blind, euglycemic clamp study, conducted in patients with T1DM, to investigate the relative bioavailability and activity compared to NovoLog and NovoRapid. A Williams design for comparing 3 formulations comprising 6 sequences and 3 periods was chosen for this study. Patients included in the study had fasting serum C-peptide concentrations below 0.3 nmol/L (as assessed by local laboratory) to ensure absence of relevant remaining endogenous insulin secretion. In order to minimize the interference of anti-insulin antibodies on the PK and PD of SAR341402 and NovoLog/NovoRapid, anti-insulin antibody positive patients (based on local laboratory assessment) were excluded from the study.

Insulin aspart Sanofi, NovoLog and NovoRapid were given as single SC injections of 0.3 U/kg; this dose was well characterized to provide strong effects in the euglycemic clamp (i.e. glucose demand reflected in a sizeable glucose infusion rate (GIR) up to 12 hours) in patients with T1DM. Patients were under fasted conditions and remained fasting throughout the test to avoid a confounding effect on study results. Measures were undertaken to minimize carry-over effects from the patients' last insulin injection. In addition, the clamp blood glucose target, without any glucose infusion, was to be achieved for the last hour prior to investigational medicinal product (IMP) dosing.

Due to the short duration of action of insulin aspart after SC administration, a 12-hour clamp was deemed sufficient to adequately monitor the patients and account for individual variations in insulin elimination and PD profile. Accordingly, a minimum washout of 5 days was considered acceptable between each dose administration.

The primary PK endpoints included the area under the concentration versus time curve extrapolated to infinity (AUC), the area under the concentration versus time curve from time 0 to the time corresponding to the last concentration above the limit of quantification (AUClast) and the maximum observed concentration of insulin aspart (Cmax). The primary PD endpoint was the area under the body weight standardized GIR versus time curve from 0 to 12 hours post-insulin aspart administration (GIR AUC0-12h).

Mechanism of action

Insulin aspart, similar to endogenous insulin, binds to the transmembrane insulin receptor that is expressed almost ubiquitously in the cells of the human body. The insulin receptor plays a key role in the regulation of glucose homeostasis, inducing glucose uptake in peripheral tissues and inhibition of hepatic glucose production by decreasing gluconeogenesis and glycogenolysis.

The isoglycaemic clamp technique was originally developed to measure tissue sensitivity to insulin. By keeping the glucose concentration constant, the physiological glucose insulin feedback loop, whereby the glucose concentration directly influences the insulin concentration and vice versa is disrupted. The amount of IV glucose required to maintain (or 'clamp') the glucose concentration at the euglycaemic target level is equal to the glucose uptake of all tissues and is expressed as glucose infusion rate (GIR) over time. When aiming to determine the glucose lowering effect of an insulin preparation the recorded GIR after SC injection provides a quantitative measure of its metabolic activity (i.e. the sum of the decrease in hepatic glucose production and the increase in glucose uptake) over time.

Primary and Secondary pharmacology

Study PDY12695

The PD effect of insulin aspart was evaluated using the euglycemic clamp technique. Insulin aspart formulations were administered as single subcutaneous (SC) injections of 0.3 U/kg under fasted conditions.

During the euglycemic clamp, the blood glucose concentration and the glucose infusion rate (GIR), needed to keep a subject's blood glucose concentration at its target level (5.5 mmol/L (100 mg/dL)), were continuously measured and recorded using a continuous glucose monitoring system (Biostator). The clamp was prematurely terminated in case blood glucose (BG) consistently exceeded 11.1 mmol/L (200 mg/dL) with no glucose infusion for the last 30 minutes.

The primary PD endpoint evaluated in study PDY12695 was the area under the body weight standardized glucose infusion rate (GIR) versus time curve from 0 to 12 hours post-insulin aspart administration (GIR-AUC 0-12h). GIRmax was defined as a secondary PD parameter in the study protocol (finalized 7 August 2012). Other secondary PD parameters were GIR-AUC0-2, GIR-AUC4-12, GIR-tmax, tx%-GIR-AUC0-12, duration of euglycemia at ≤ 5.8 mmol/L/105 mg/dL and durations of blood glucose at ≤ 6.1, 7.2, and 8.3 mmol/L (110, 130, and 150 mg/dL).

The 90% and 95% confidence intervals were calculated for GIR-AUC0-12h, GIRmax, GIR-AUC0-2, and GIR-AUC4-12. An acceptance range of 0.80-1.25 was used to conclude on biosimilarity. Prior to analysis, the parameters were log-transformed (natural log). A linear mixed-effects model was used with fixed terms for sequence, period and treatment and random term for subject-within-sequence, with treatment-specific between-subject and within-subject variances. Tx%-GIR-AUC0-12 and GIR-tmax were analysed non-parametrically based on Hodges-Lehmann method for paired treatment comparisons. 90% CIs for pairwise medians of treatment differences were derived.

A total of 30 subjects were included in the study, one of whom discontinued after dosing in the second treatment period.

Mean smoothed standardized GIR profiles for SAR341402, NovoLog and NovoRapid at 0.3 U/kg were similar (Figure 9).

The primary PD variable GIR-AUC0-12h was similar for all 3 insulin formulations as the 90% CI of ratios were within the predefined acceptance range of 0.80 to 1.25 (Table 32). The corresponding 95% CI also met the acceptance range of 0.80 to 1.25. Furthermore, also the secondary endpoint of GIR$_{max}$ was similar for the 3 insulin aspart products, with 90% and 95% CIs of the treatment ratios entirely within the predefined acceptance range of 0.80 to 1.25 (Table 33).
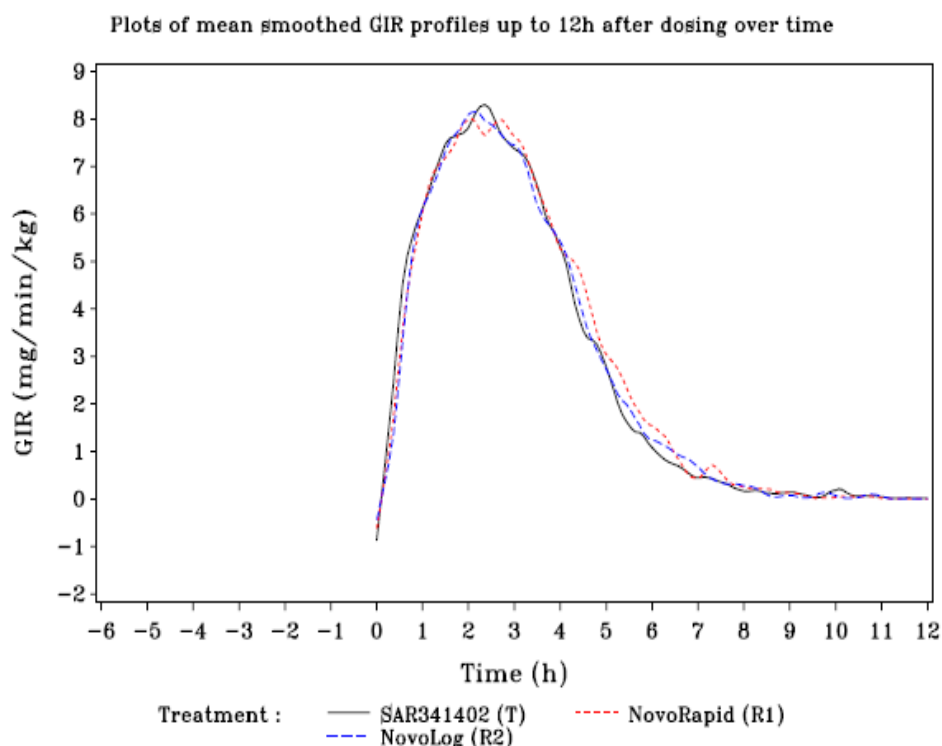
Figure 5 Study PDY12695 - Overlay plots of mean smoothed GIR profiles up to 12 hours after dosing over time

Table 26 . Study PDY12695 - Treatment effect on GIR-AUC0-12h - Point estimates of treatment ratio with 90% and 95% confidence intervals

Parameter	Comparison	Estimate	90% CI	95% CI
GIR-AUC$_{0-12}$	SAR341402 vs NovoRapid	0.96	(0.89 to 1.04)	(0.88 to 1.05)
	SAR341402 vs NovoLog	0.99	(0.91 to 1.07)	(0.90 to 1.08)
	NovoLog vs NovoRapid	0.97	(0.90 to 1.05)	(0.89 to 1.07)

Table 27. Study PDY12695 - Treatment effect on GIR$_{max}$ - Point estimates of treatment ratios with 90% and 95% confidence intervals

Parameter	Comparison	Estimate	90% CI	95% CI
GIR$_{max}$	SAR341402 vs NovoRapid	1.02	(0.95 to 1.09)	(0.94 to 1.10)
	SAR341402 vs NovoLog	1.03	(0.96 to 1.10)	(0.95 to 1.12)
	NovoLog vs NovoRapid	0.99	(0.92 to 1.06)	(0.91 to 1.07)

GIR$_{max}$ denotes the maximum body weight standardized glucose infusion rate (mg/kg/min).

GIR$_{max}$ is based on smoothed GIR profiles. (LOESS smoothing factor is 0.06.)

The partial GIR-AUC0-2 was also similar for the 3 insulin aspart products, with 90% and 95% CIs of the treatment ratios within the predefined acceptance range of 0.80-1.25. Partial GIR-AUC4-12 appears slightly lower for SAR341402 than for NovoRapid (see table below).

Table 28. Statistical analyses of secondary pharmacodynamic variable GIR-AUCs- Point estimates of treatment ratio with 90% and 95% confidence intervals

Parameter	Comparison	Estimate	90% CI	95% CI
GIR-AUC$_{0-2}$	SAR341402 vs NovoRapid	1.06	(0.97 to 1.17)	(0.95 to 1.19)
	SAR341402 vs NovoLog	1.05	(0.96 to 1.15)	(0.94 to 1.18)
	NovoLog vs NovoRapid	1.01	(0.92 to 1.11)	(0.91 to 1.13)
GIR-AUC$_{4-12}$	SAR341402 vs NovoRapid	0.71	(0.56 to 0.91)	(0.53 to 0.95)
	SAR341402 vs NovoLog	0.83	(0.65 to 1.06)	(0.62 to 1.11)
	NovoLog vs NovoRapid	0.86	(0.67 to 1.09)	(0.64 to 1.14)

GIR denotes the body weight standardized glucose infusion rate (mg/kg/min).

Study PDY15287

The PD effect of insulin aspart was evaluated using the euglycemic clamp technique. Insulin aspart formulations were administered as single subcutaneous (SC) injections of 0.3 U/kg under fasted conditions. The target blood glucose level was defined as 5 mg/dL (0.28 mmol/L) below the subject's fasting baseline blood glucose concentration. The primary pharmacodynamic endpoints were GIR$_{max}$ and GIR-AUC$_{0-10h}$. Secondary pharmacodynamics endpoint was GIR-tmax. To demonstrate bioequivalence, the 90% confidence intervals were calculated for GIR$_{max}$ and GIR-AUC$_{0-10h}$, using the (0.80-1.25) acceptance range. Prior to analysis, the parameters were log-transformed. A linear mixed-effects model was used to analyse GIR$_{max}$ and GIR-AUC$_{0-10h}$. GIR-t$_{max}$ was analysed non-parametrically based on the Hodges-Lehmann method.

A total of 40 subjects was included in the study, one of whom withdrew his consent before the second treatment period. Five other subjects were not included in the statistical analyses due to operational errors during the clamp procedure.

The 90% confidence interval (CI) was between the acceptance limits of 0.80-1.25 for GIR-AUC$_{0-10h}$ and for GIR$_{max}$ for SAR341402 versus reference NovoRapid. Unity was included (see table below).
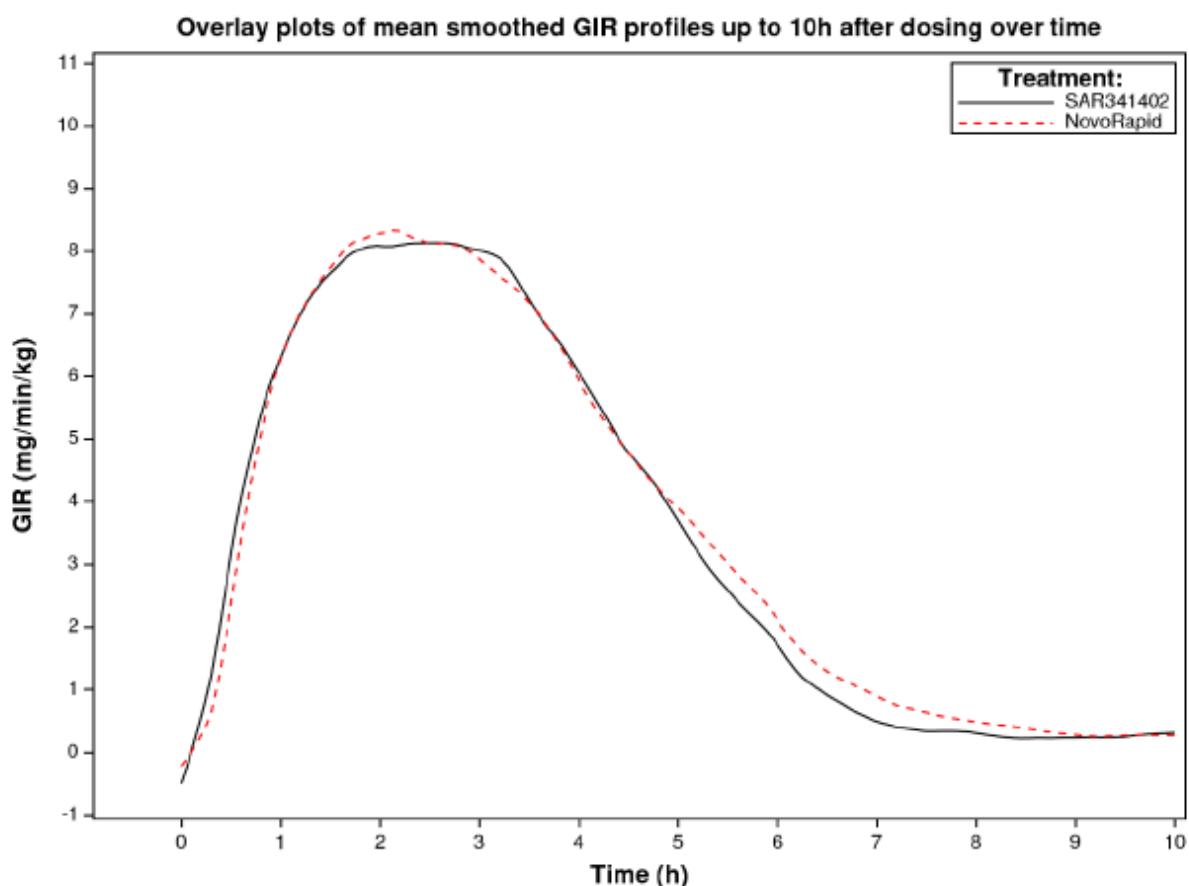
Figure 6 Overlay plots of mean smoothed GIR profiles (study PDY15287)

Table 29 Treatment effect on GIR-AUC0-10h and GIRmax point estimates of treatment ratio with 95% confidence intervals (study PDY15287)

Parameter	Treatment ratio	Estimate	90% CI	95% CI
GIR-AUC$_{0-10h}$(mg/kg)	SAR341402 vs NovoRapid	1.00	(0.94 to 1.05)	(0.93 to 1.06)
GIRmax (mg/kg/min)	SAR341402 vs NovoRapid	1.01	(0.96 to 1.07)	(0.95 to 1.08)

GIR = body weight standardized glucose infusion rate. GIRmax is based on smoothed GIR profiles

2.4.4. Discussion on clinical pharmacology

The study design of the euglycemic clamp study PDY12695 was in accordance with the guideline on the non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005_Rev 1).

The methods for the analyses of insulin aspart and anti-SAR341402 antibodies in plasma were adequately validated. The content of test and reference product was similar.

Regarding the comparison of SAR341402 and the EU reference product NovoRapid, the 90% confidence intervals for the primary PK parameters Cmax, AUClast and AUCinf were within the limits of 0.80-1.25. No apparent difference was observed for t1/2. Unity was included in the confidence interval

for Cmax, but not for AUClast and AUCinf. Further, partial AUC in the first two hours after administration was within the 0.80-1.25 limits but partial AUC4-12 hours appears lower for SAR341402 than for NovoRapid with the lower confidence limit for the ratio below 0.8. A discussion on these topics was provided by the Applicant. Considering that AUC4h-last actually only covers a minor part of total AUC (less than 15%), and considering the high variability in AUC after 4 h, the relevance of this difference is considered limited. With respect to unity not being included in the 90% CI for AUC, no further indications for differences in elimination of the products were apparent. Furthermore, in the additional euglycemic clamp study PDY15287 conducted in Japanese healthy subjects which was provided by the Applicant during the evaluation, the 90% confidence interval was between the acceptance limits of 0.80-1.25 for Cmax, AUClast and AUCinf for SAR341402 versus reference NovoRapid, with unity included. This study provides therefore additional support for the biosimilarity of SAR341402 and NovoRapid.

The large variation in half-life appeared to be caused by an unusual long half-life in one subject. The exclusion of this value from the statistical analysis reduced the standard deviation for SAR341402 from 1.46 h to 0.378 h and the coefficient of variation from 126.3% to 42.5%. Furthermore, the arithmetic and geometric means decreased from 1.15 h to 0.890 h and from 0.897 h to 0.827 h, respectively. These values obtained after exclusion of the unusual long half-life value are similar to the respective values measured for the reference products.

The unbalanced time profile suggests that the absorption is initially faster in SAR341402 compared with the reference NovoRapid. To better understand the absorption rate difference between the two products, the Applicant was asked to consider population PK/PD modelling of study PDY12695 data. The POP-PK analysis showed slight differences in typical values of AUC4h-12 of insulin aspart concentrations and corresponding PD parameter GIR AUC4h-12. However, given the overlap between the confidence intervals formed by the uncertainty of the typical values, it is apparent that neither the profiles nor the derived AUCs allows to conclude that they are different. Considering the limited contribution of AUC4h-last to the total AUC and the result of the additional study in Japanese subjects, as mentioned above, the difference in concentrations of insulin aspart in the 4-12 h period is not considered clinically relevant.

The Insulin aspart Sanofi formulation is different from the originator in several aspects. The Applicant was asked to justify the composition of Insulin aspart Sanofi from a biopharmaceutical viewpoint by showing that composition difference is not expected to affect the *in vivo* oligomer association rates. The Applicant performed additional *in vitro* studies to investigate the formulation effect which were submitted during the evaluation. A difference was observed regarding the maximum dimension, which was however difficult to interpret. It is agreed that further *in vitro* modelling studies would not help to understand the formulation effect on the absorption process.

According to the guideline on non-clinical and clinical development of similar biological medicinal producs containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005_Rev 1), GIR-AUC(0-t) and GIRmax should be the primary endpoints for rapid insulins and for primary PD parameters and the 95% confidence intervals of the ratio test/reference should be contained within the pre-defined equivalence margins. In contrast to the relevant CHMP guideline, GIR_{max} was defined as secondary endpoint in the study protocol. However, as the study protocol was finalised before the first draft revision of the guideline on the clinical development of similar biological medicinal products containing recombinant insulin analogues was published, this is considered acceptable by the CHMP. Nevertheless, $GIR-AUC_{(0-t)}$ and GIR_{max} were assessed as primary endpoints according to the guideline.

The 95% CI for the ratio of treatments of both GIR-AUC0-12h (primary endpoint) and GIRmax (secondary endpoint) were narrow and well within the equivalence margin of 80%-125%, indicating

similar PD profiles of SAR341402, NovoRapid and Novolog. Partial GIR-AUC after 4 hours appears lower for SAR341402 than for NovoRapid with the lower confidence limit for the ratio below 0.8, apparently in line with the lower insulin aspart partial AUC after 4 hours. However, considering the low contribution of GIR-AUC after 4 h to total GIR-AUC (less than 20%), the relevance of this difference can be considered limited. Moreover, in the additional euglycemic clamp study PDY15287 in Japanese healthy subjects which was provided in the second round, the 90% confidence interval was between the acceptance limits of 0.80-1.25 for GIR-AUC0-10h and for GIRmax for SAR341402 versus reference NovoRapid, with unity included. This study provides therefore additional support for the biosimilarity of SAR341402 and NovoRapid. The derivation of GIRmax and GIR-tmax was based upon the smoothed individual profiles using a locally weighted regression in smoothing scatter plots (LOESS smoothing technique). In this technique, a smoothing factor of 6% was used. The smoothing factor was selected to balance the noise in the GIR to a reasonable extent, as stronger smoothing could reduce the sensitivity of the study whereas weaker smoothing could leave much of the noise with potentially higher variability. The factor of 6% was chosen based on previous experience with GIR profiles for other fast acting insulins. The quality of the glucose clamp is considered acceptable.

2.4.5. Conclusions on clinical pharmacology

Overall, the PK and PD results from study PDY12695 demonstrated similarity between SAR341402 and NovoLog/NovoRapid. This is supported by the results from the comparative PK/PD study in healthy Japanese subjects (study PDY15287).

2.5. Clinical efficacy

2.5.1. Dose response studies

As this application relates to a biosimilar product, there is no requirement for dose-response studies. The proposed dosing regimens for Insulin aspart Sanofi are identical to those approved for NovoRapid.

2.5.2. Main studies

In support of similar efficacy of SAR341402, one phase 3 study, EFC15081, was conducted in patients with diabetes mellitus (T1DM or T2DM) to compare the efficacy, safety and immunogenicity of SAR341402 to NovoLog/NovoRapid in the target populations. No additional clinical study was planned to support the registration of SAR341402 solution in the EU.

Study EFC15081: Six-month, Randomized, Open-label, Parallel-group Comparison of SAR341402 to NovoLog/NovoRapid in Adult Patients With Diabetes Mellitus Also Using Insulin Glargine, with a 6-month Safety Extension Period

Methods

Study Participants

Important inclusion criteria included adult patients who had been diagnosed with T1DM or T2DM for at least 1 year at the time of the screening visit, who had been on a multiple daily injection regimen of

NovoLog/NovoRapid or insulin lispro (100 U/mL) for at least 6 months before screening in combination with insulin glargine for at least 6 months or in combination with insulin detemir for at least 12 months before the screening visit and who had a screening HbA1c between 7.0% and 10.0%.

Exclusion criteria were mainly related to the patients' underlying health status and especially unstable conditions that might interfere with the evaluation of efficacy and safety of SAR341402.

With respect to background therapy, any glucose-lowering agents other than the IMP (i.e. SAR341402 or NovoLog/NovoRapid) and the mandatory basal insulin (Lantus) were prohibited during the study. However, patients with T2DM using oral antidiabetic drugs (OADs) at a stable dose in the last 3 months before screening could continue using them on stable dose except sulfonylureas, which were to be discontinued at baseline and were prohibited during the study. Furthermore, systemic glucocorticoids at doses greater than a replacement for more than 10 days and initiation of body weight loss drugs were also not permitted during the screening period and the randomized open-label treatment periods.

Treatment

The study included 4 periods (see figure below):

- An up to 2-week screening period, during which the patients' eligibility criteria were checked and patients were trained on study procedures such as regular SMPG measurements, diary entries (e-diary) and how to correctly inject the IMP (SAR341402 or NovoLog/NovoRapid) and non-investigational medicinal product (NIMP) (Lantus);

- A main 26 weeks open-label comparative efficacy and safety period;

- A 26 weeks open-label comparative safety extension period;

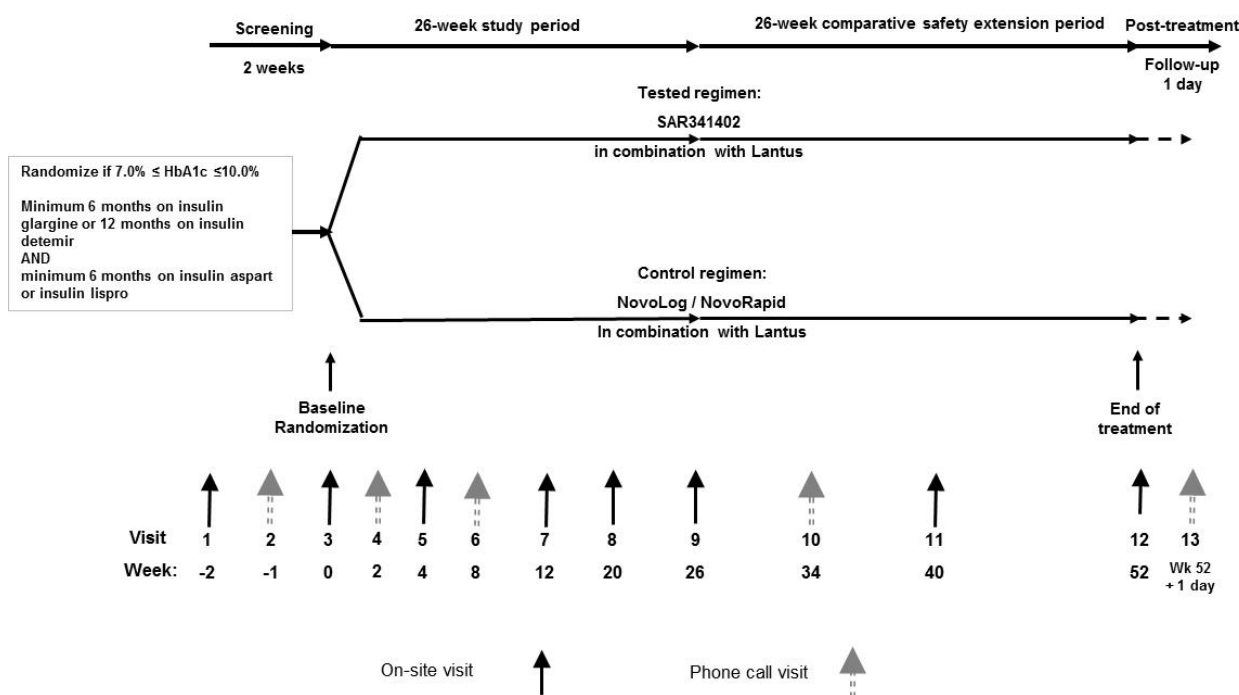- A 1-day post-treatment safety follow-up period.

Figure 7 Study design

Investigational medicinal products (IMP)

All subjects received diet and lifestyle counselling consistent with the recommendations of international or local guidelines and practices by a Healthcare professional at randomization.

In the 26-week study period and 26-week comparative safety extension period, SAR341402 was compared with Novolog (investigational sites in the US) and NovoRapid (investigational sites in Europe and Japan).

SAR341402 was self-administered by SC injection using disposable SoloStar prefilled pens containing a 3 ml cartridge, allowing a maximum dose of SAR341402 per injection of 80 units and a minimum dose of 1 unit.

NovoLog/NovoRapid was self-administered by SC injection using the disposable FlexPen prefilled pen, allowing a maximum dose of the insulin aspart, per injection, of 60 units and a minimum dose of 1 unit.

SAR341402 or NovoLog/NovoRapid were to be injected before the start of a meal, as part of a multiple daily injection (MDI) regimen, according to NovoLog and NovoRapid labelling. Occasional postprandial injections soon after a meal were to be done if deemed necessary and if allowed by the national product label for NovoLog/NovoRapid.

Patients randomized to SAR341402 or NovoLog/NovoRapid, started treatment with a unit to unit conversion from the insulin lispro or NovoLog/NovoRapid dose used prior to the trial or with a dose at the discretion of the investigator, taking into account the glucose control at the time of randomization. During the study, doses of either SAR341402 or NovoLog/NovoRapid were to be adjusted to achieve a 2-hour postprandial plasma glucose <10.0 mmol/L (180 mg/dL), while avoiding hypoglycemia. For the purpose of the protocol, 2 hours postprandial is defined as 2 hours after the start of the meal. If pre-prandial glucose tests were used, the recommended target range for fasting, pre-prandial plasma glucose was 4.4 to 7.2 mmol/L (80 to 130 mg/dL), while avoiding hypoglycaemia.

Non-investigational medicinal products (NIMP)

All the patients used Lantus (SC injection once daily) as the mandatory basal insulin therapy during the study. The time of injection (hh:mm) was to be determined at randomization according to patient and site preference and was not to be changed throughout the study.

Objectives/endpoints

The primary objective was to demonstrate non-inferiority of SAR341402 solution compared to NovoLog/NovoRapid in terms of HbA1c change from baseline to Week 26. A non-inferiority margin of 0.3% HbA1c was defined, in line with recommendations by regulatory agencies and based on historical precedent for comparative insulin studies in which a 0.3% non-inferiority margin is often used.

Secondary efficacy objectives included:

- Relationship of anti-insulin aspart antibodies (AIAs) with efficacy parameters (HbA1c) and insulin dose

- Efficacy of SAR341402 and NovoLog/NovoRapid in terms of:

  - Percentage of patients reaching HbA1c <7% at Week 26

  - Change from baseline to Week 26 in fasting plasma glucose (FPG)

- Change from baseline to Week 26 in mean 24-hour plasma glucose concentration based on 7-point self-measured plasma glucose (SMPG) profiles taken before and 2 hours after each main meal, and at bedtime

- Change from baseline to Week 26 in postprandial plasma glucose excursions (the difference between 2-hour postprandial and pre-prandial plasma glucose values at breakfast, lunch and dinner) based on 7-point SMPG profiles.

In addition, the potential effect of anti-insulin aspart antibody on glycemic control and insulin dose was assessed.

Randomisation

Randomization was stratified by geographical region (Europe, US, Japan), type of diabetes mellitus (T1DM, T2DM [T2DM only for US]), glycated hemoglobin (HbA1c) value at screening (<8.0%, ≥8.0%), and prior use of NovoLog/NovoRapid (Yes, No). The patients were randomized to either SAR341402 or NovoLog/NovoRapid in a 1:1 ratio. Depending on the geographical location of the investigational sites, patients randomized to the comparator received the regionally approved product: patients with T1DM or T2DM in the US received NovoLog; patients with T1DM in Europe and Japan received NovoRapid.

Blinding (masking)

Study EFC15081 used an open-label design as the pre-filled, disposable pen injection devices for SAR341402 and NovoLog/NovoRapid were distinguishable and could not be made identical. Use of a double-dummy design was not deemed adequate for practical and ethical reasons as such design would require doubling of the number of prandial injections, which may increase the risk of medication errors (including lack of compliance to double dosing of prandial injections) and a comparator placebo product is not available.

HbA1c (for the primary efficacy endpoint analysis), FPG and AIA were measured at central certified laboratories blinded to the treatment received.

Statistical methods

The primary analysis of non-inferiority for change in HbA1c from baseline was performed on the ITT population using an ANCOVA model including treatment group, randomisation strata and baseline HbA1c, with a non-inferiority margin of 0.3%. If the primary endpoint was statistically significant, the secondary endpoint inverse non-inferiority was tested in a sequential inferential approach.

Missing data were handled with a multiple imputation approach, which took into account the treatment status of the patients (adhering or not), using observed data from patients with the same status to impute missing data. As sensitivity analyses, a return to baseline imputation and a tipping-point analysis were planned, and the primary analysis was repeated in the PP population.

Secondary endpoints were analysed with the same ANCOVA model as for the primary endpoint. Responder endpoints were analysed using a logistic regression model with the same terms as in the ANCOVA model.

Results

Participant flow

A total of 597 adult patients (SAR341402: 301; NovoLog/NovoRapid: 296 [165/131, respectively]) were randomized in the Phase 3 study EFC15081 (see figure below). A similar percentage of patients in each treatment group completed the main 6-month treatment period (SAR341402: 92.7%, NovoLog/NovoRapid: 92.6%). The most common reason for treatment discontinuation occurred in the category "Other" (SAR341402: 4.3% [13 patients]; NovoLog/NovoRapid: 5.4% [16 patients]) and was primarily related to a patient decision or consent withdrawal.
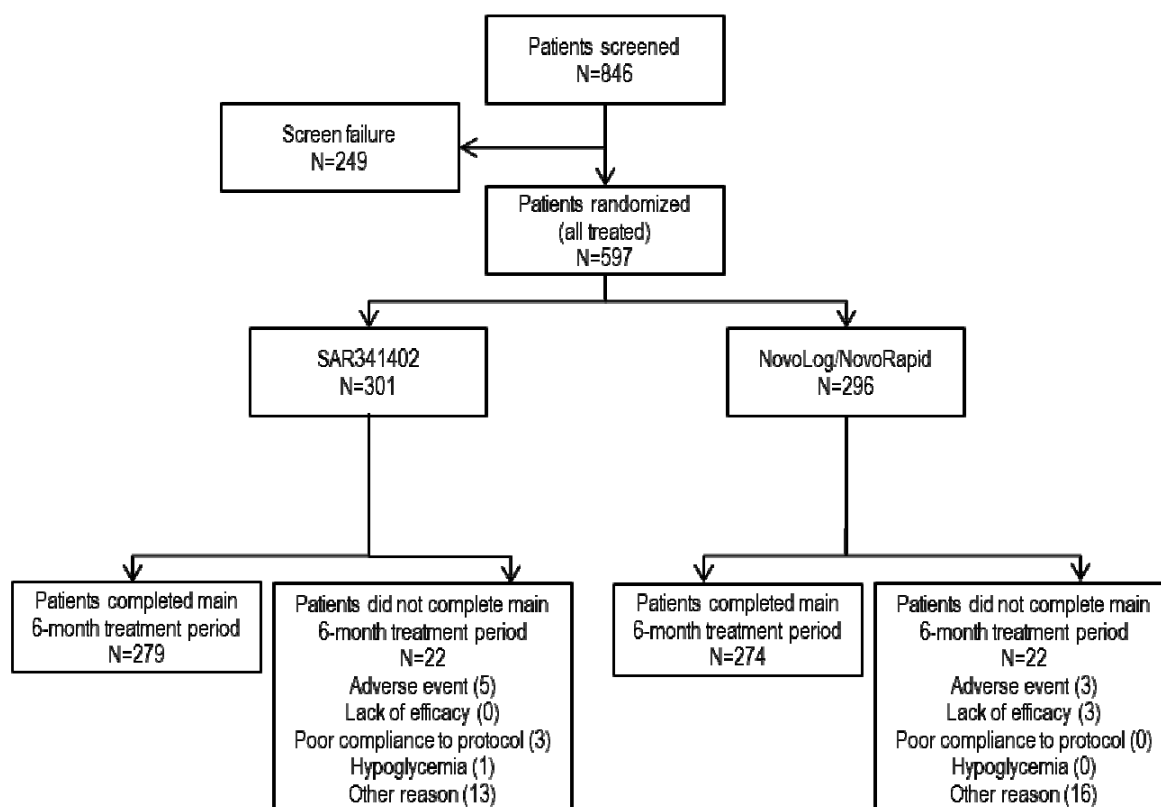
Figure 8 Study EFC15081- Patient disposition

Protocol deviations

The percentage of critical or major deviations were generally comparable between both groups (43.2% and 38.5% in the SAR341402 and NovoLog/NovoRapid groups, respectively), and also well balanced across the treatment groups within the different categories of protocol deviations.

During the conduct of the phase 3 study, the majority of the patients (70.9%; 197/197 (100%) of the patients in Europe, 226/335 (67%) in the US and 0% in Japan) have been exposed to defective glucose test strips to be used for collecting SMPG measurements. The average blood glucose reading with the defective strips was between 0.1% and 14.8% higher than the average values obtained with non-defective test strips.

Baseline data

Baseline characteristics of study EFC15081 are presented in Table 36 and Table 37. The demographic and disease characteristics are well distributed across the two treatment groups. The majority of the patients had T1DM (83.2%), 82.6% of the patients were white and the median age was 49.0 years with approximately 17% of the patients who were 65 years or older. This study was a multicentre study and patients were recruited across the globe. 33% of the patients were from Europe, 56% from US and 11% from Japan.

Table 30. Study EFC15081 - Summary of patient demographics and patient characteristics at baseline - Randomized population

Number of patients randomized	SAR34140 (N=301)	NovoLog/Novo (N=296)	All (N=597)
Age (years) (median)	49.0	49.5	49.0
≥65 years [n (%)]	47 (15.6)	52 (17.6)	99 (16.6)
Male [n (%)]	179 (59.5)	177 (59.8)	356 (59.6)
Weight (kg) [mean (SD)]	81.7 (17.6)	81.6 (17.8)	81.6 (17.7)
BMI (kg/m²) [mean (SD)]	27.45 (4.58)	27.46 (4.99)	27.45
≥30 kg/m² [n (%)]	94 (31.2)	87 (29.4)	181 (30.3)
GFR (MDRD) <60 mL/min/1.73m² [n (%)]	28 (9.3)	28 (9.5)	56 (9.4)
Race [n (%)]			
White	248 (82.7)	242 (82.6)	490 (82.6)
Black or African American	11 (3.7)	8 (2.7)	19 (3.2)
Asian	37 (12.3)	37 (12.6)	74 (12.5)
Ethnicity [n (%)]			
Hispanic or Latino	27 (9.0)	19 (6.4)	46 (7.7)
Randomization strata of type of diabetes [n (%)]			
T1DM	250 (83.1)	247 (83.4)	497 (83.2)
T2DM	51 (16.9)	49 (16.6)	100 (16.8)
Type of comparator [n (%)]			
NovoLog	170 (56.5)	165 (55.7)	335 (56.1)
NovoRapid	131 (43.5)	131 (44.3)	262 (43.9)
Randomization strata of prior use of			
No	109 (36.2)	108 (36.5)	217 (36.3)
Yes	192 (63.8)	188 (63.5)	380 (63.7)
Randomization strata of geographical region [n			
Europe	98 (32.6)	99 (33.4)	197 (33.0)
Japan	33 (11.0)	32 (10.8)	65 (10.9)
US	170 (56.5)	165 (55.7)	335 (56.1)
Randomization strata of screening HbA1c			
HbA1c < 8.0%	143 (47.5)	138 (46.6)	281 (47.1)
HbA1c ≥ 8.0%	158 (52.5)	158 (53.4)	316 (52.9)
Duration of diabetes (years) (median)	16.9	17.3	17.2
≥10 years [n (%)]	235 (78.1)	229 (77.4)	464 (77.7)
Diabetic late complications [n (%)]	142 (47.2)	137 (46.3)	279 (46.7)
Diabetic retinopathy	90 (29.9)	85 (28.7)	175 (29.3)
Diabetic neuropathy	86 (28.6)	82 (27.7)	168 (28.1)
Use of insulin glargine in the 6 months prior to the study [n (%)]	238 (79.1)	237 (80.1)	475 (79.6)
Use of insulin aspart in the 6 months prior to the study [n (%)]	169 (56.5)	161 (54.4)	330 (55.5)
Insulin dose at baseline (U/kg) [mean (SD)]			
Basal insulin	0.390	0.386 (0.231)	0.388
Mealtime insulin	0.398	0.394 (0.247)	0.396
Total insulin	0.789	0.777 (0.404)	0.783
HbA1c (%) [mean (SD)]	8.00 (0.77)	7.94 (0.70)	7.97 (0.74)

Table 31. Disease characteristics at baseline - Randomized population

	SAR341402 (N=301)	NovoLog/NovoRapid (N=296)	All (N=597)
Type of Diabetes [n(%)]			
Number	301	296	597
Type 1	250 (83.1)	247 (83.4)	497 (83.2)
Type 2	51 (16.9)	49 (16.6)	100 (16.8)
Duration of Diabetes (years)			
Number	301	296	597
Mean (SD)	19.5 (11.9)	19.4 (11.8)	19.5 (11.8)
Median	16.9	17.3	17.2
Min ; Max	1 ; 53	1 ; 61	1 ; 61
Category of duration of Diabetes (years) [n(%)]			
Number	301	296	597
< 10	66 (21.9)	67 (22.6)	133 (22.3)
≥ 10	235 (78.1)	229 (77.4)	464 (77.7)
Age at onset of Diabetes (years)			
Number	301	296	597
Mean (SD)	29.3 (15.9)	28.9 (15.2)	29.1 (15.5)
Median	28.0	27.8	27.8
Min ; Max	0 ; 66	1 ; 67	0 ; 67

	SAR341402 (N=301)	NovoLog/NovoRapid (N=296)	All (N=597)
Duration of basal insulin treatment (years)			
Number	301	296	597
Mean (SD)	16.4 (12.1)	16.6 (12.2)	16.5 (12.1)
Median	13.3	14.3	13.5
Min ; Max	1 ; 53	1 ; 61	1 ; 61
Duration of mealtime insulin treatment (years)			
Number	301	296	597
Mean (SD)	16.4 (12.3)	16.4 (11.5)	16.4 (11.9)
Median	13.4	15.2	14.3
Min ; Max	1 ; 53	1 ; 54	1 ; 54
Previous basal insulin type [n(%)]			
Number	301	296	597
Insulin Glargine	238 (79.1)	237 (80.1)	475 (79.6)
Insulin Detemir	62 (20.6)	59 (19.9)	121 (20.3)
Both Insulin Glargine and Insulin Detemir	1 (0.3)	0	1 (0.2)
Duration of insulin Glargine treatment (years)			
Number	239	237	476
Mean (SD)	7.0 (5.6)	6.0 (5.5)	6.5 (5.6)
Median	5.2	3.7	4.4
Min ; Max	1 ; 18	0 ; 17	0 ; 18
Duration of insulin Detemir treatment (years)			
Number	63	59	122
Mean (SD)	5.4 (3.8)	5.5 (3.7)	5.5 (3.7)
Median	3.6	5.1	4.2
Min ; Max	1 ; 13	1 ; 13	1 ; 13
Previous mealtime insulin type [n(%)]			
Number	299	296	595
Humalog/Liprolog	125 (41.8)	123 (41.6)	248 (41.7)
NovoLog/NovoRapid	169 (56.5)	161 (54.4)	330 (55.5)
Both Humalog/Liprolog and NovoLog/NovoRapid	5 (1.7)	12 (4.1)	17 (2.9)
Duration of previous treatment with Humalog/Liprolog (years)			
Number	130	135	265
Mean (SD)	7.3 (6.1)	6.9 (6.4)	7.1 (6.3)
Median	5.0	4.3	4.5
Min ; Max	1 ; 22	0 ; 21	0 ; 22
Duration of previous treatment with NovoLog/NovoRapid (years)			
Number	174	173	347
Mean (SD)	6.2 (5.6)	5.7 (5.2)	6.0 (5.4)

Numbers analysed

All randomized patients (597) were included in the ITT population for the efficacy analyses (Table 38). All randomized patients received the IMP and were included in the safety population

Table 32. Analysis populations

n (%)	SAR341402	NovoLog/NovoRapid	All
Randomized population	301 (100)	296 (100)	597 (100)
Efficacy populations			
Intent-to-Treat (ITT)	301 (100)	296 (100)	597 (100)
Per protocol (PP)	268 (89.0)	265 (89.5)	533 (89.3)
Safety population	301	296	597
Anti-insulin antibody population	296	292	588

Note: The safety and anti-insulin antibody population patients are tabulated according to treatment actually received (as treated)
For the other populations, patients are tabulated according to their randomized treatment

Outcomes and estimation

Primary efficacy endpoint

The primary objective of study EFC15081 in T1DM and T2DM was to show non-inferiority of SAR341402 versus NovoLog/NovoRapid based on the change in HbA1c from baseline to Week 26 with a non-inferiority margin of 0.3%.

Non-inferiority of SAR341402 over NovoLog/NovoRapid was demonstrated as the upper bound of the 2-sided 95% CI of the difference between SAR341402 and NovoLog/NovoRapid was below the predefined non-inferiority margin of 0.3%, indicating that the primary objective was met (see table and figure below).

There were few missing data for HbA1c. At Week 26, 36 patients (SAR341402: 18 patients [6.0%]; NovoLog/NovoRapid: 18 patients [6.1%]) had missing HbA1c, half of them due to premature treatment discontinuation and subsequent study discontinuation. Sensitivity analyses assessing the effect of missing data (return-to-baseline multiple imputation and tipping point analyses) were consistent with those of the primary efficacy analysis. The sensitivity analysis using return-to-baseline supported the primary analysis results with a LS mean difference in HbA1c change from baseline to Week 26 between SAR341402 and NovoLog/NovoRapid of -0.07% (95% CI: -0.178 to 0.036). In the tipping point analysis, non-inferiority of SAR341402 versus NovoLog/NovoRapid was not demonstrated only in extreme scenarios.

Per-protocol analyses further support the results of the primary efficacy analysis on the ITT population.

Table 33. Study EFC15081- Summary of change in HbA1c (%) from baseline to Week 26 using ANCOVA analysis (with retrieved dropout multiple imputation)- ITT population

HbA1c (%)	SAR341402 (N=301)	NovoLog/NovoRapid (N=296)
Baseline		
Number	301	296
Mean (SD)	8.00 (0.77)	7.94 (0.70)
Median	7.90	7.90
Min ; Max	6.3 ; 10.7	6.5 ; 10.1
Change from baseline to Week 26		
Combined LS Mean (SE)a	-0.38 (0.042)	-0.30 (0.041)
95% CI	(-0.459 to -0.294)	(-0.381 to -0.219)
Combined LS Mean difference (SE) vs NovoLog/NovoRapida	-0.08 (0.059)	
95% CI	(-0.192 to 0.039)	

ANCOVA=Analysis of covariance

a   Retrieved dropout multiple imputations of missing changes at Week 26 (10 000 imputations using separate models for patients who prematurely discontinued or completed the main 6-month treatment period) followed by ANCOVA with treatment group (SAR341402, NovoLog/NovoRapid), the randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM) and prior use of NovoLog/NovoRapid (Yes, No) as fixed categorical effects, as well as the continuous fixed covariate of baseline HbA1c value. Results were combined using Rubin's formulae
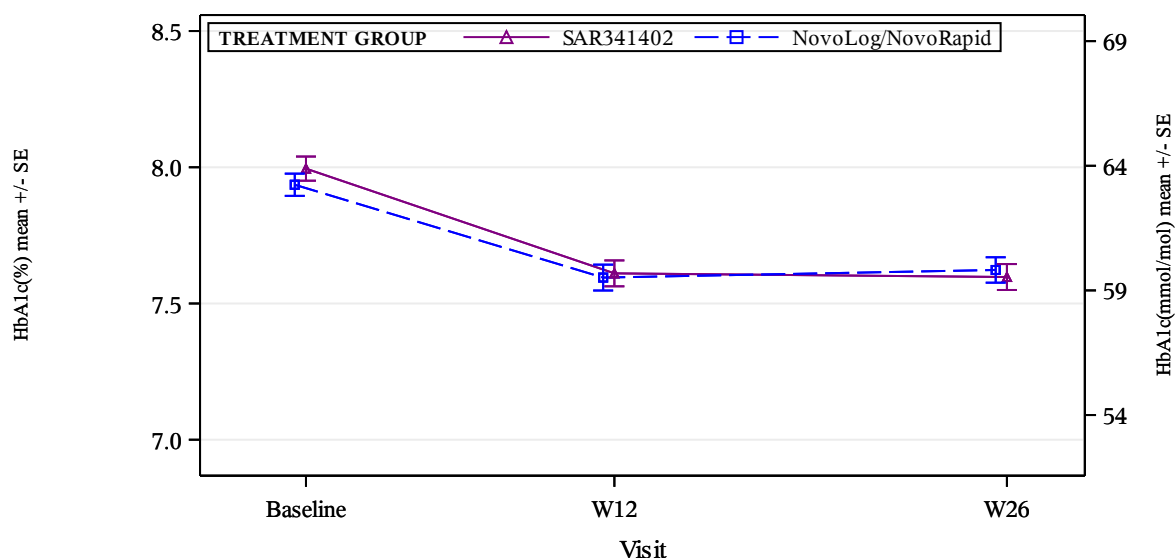
Subjects

|	Baseline	W12	W26
SAR341402	301	293	283
NovoLog/NovoRapid	296	287	278

Figure 9. Study EFC15081 - HbA1c (% and mmol/mol) - Mean (+/- SE) by visit - ITT population

Secondary efficacy endpoints

Secondary endpoints included the percentage of HbA1c responders (HbA1c <7.0%) as well as change from baseline to Week 26 in FPG, mean 24-hour plasma glucose concentration, glucose excursions and 7-point SMPG profiles (Table 40 and Figure 14). The results of these secondary endpoint analyses do not suggest any clinically relevant differences between SAR341402 and NovoLog/NovoRapid.

Table 34. Study EFC15081 - Summary of secondary efficacy endpoints – ITT population

	SAR341402 (N=301)	NovoLog/NovoRapid (N=296)
Responders HbA1c <7.0% at Week 26		
n (%)	50 (16.6)	43 (14.5)
OR (95% CI) versus NovoLog/NovoRapid	1.170 (0.735 to 1.861)	
FPG (mmol/L)		
Baseline: mean (SD), number	9.87 (3.87), n=290	9.97 (4.39), n=285
Combined LS Mean change from baseline to Week 26 (SE)	-0.49 (0.249)	-0.17 (0.245)
Combined LS Mean diff (SE) vs. NovoLog/NovoRapid [95% CI]	-0.31 (0.348) [-0.997 to 0.368]	
Postprandial plasma glucose excursions (mmol/L)		
At breakfast		
Baseline: mean (SD), number	0.64 (4.24), n=288	0.91 (3.93), n=288
Week 26: mean (SD), number	0.82 (4.18), n=240	1.06 (3.77), n=235
Combined LS Mean change (SE)	0.50 (0.232)	0.65 (0.233)
Combined LS Mean diff (SE) vs. NovoLog/NovoRapid [95% CI]	-0.15 (0.329) [-0.795 to 0.493]	
At lunch		
Baseline: mean (SD), number	0.91 (4.31), n=290	0.77 (3.71), n=291
Week 26: mean (SD), number	0.68 (3.72), n=245	0.70 (4.04), n=252
Combined LS Mean change (SE)	0.18 (0.230)	0.12 (0.228)
Combined LS Mean diff (SE) vs. NovoLog/NovoRapid [95% CI]	0.06 (0.324) [-0.569 to 0.699]	
At dinner		
Baseline: mean (SD), number	0.49 (3.99), n=290	0.24 (4.15), n=292
Week 26: mean (SD), number	0.37 (4.45), n=241	0.62 (3.83), n=242
Combined LS Mean change (SE)	0.36 (0.243)	0.66 (0.243)
Combined LS Mean diff (SE) vs. NovoLog/NovoRapid [95% CI]	-0.30 (0.344) [-0.974 to 0.374]	
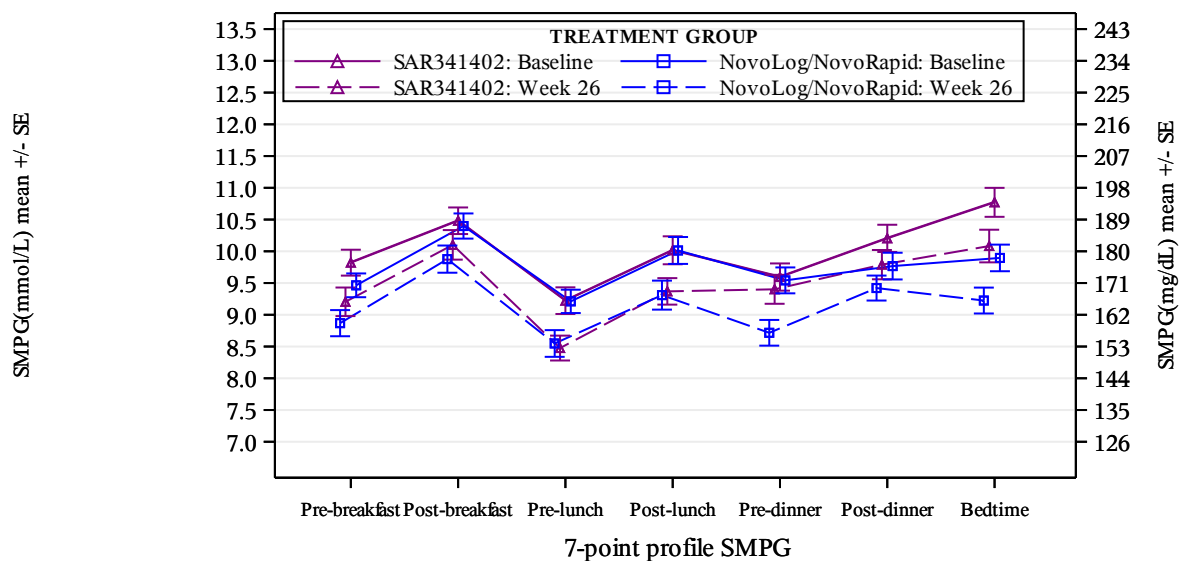
# Subjects							
SAR341402 baseline	298	291	297	295	299	294	294
SAR341402 week 26	255	245	253	252	257	244	244
NovoLog/NovoRapid baseline	295	288	294	294	295	293	287
NovoLog/NovoRapid week 26	254	236	255	252	252	247	245

Figure 10. Study EFC15081 - 7-point SMPG profile (mmol/L and mg/dL) - Mean (+/- SE) at baseline and Week 26 per time point - ITT population

Insulin doses

Daily basal and mealtime insulin doses (U/kg) at baseline and week 26 in the SAR341402 and NovoLog/NovoRapid groups are presented in Table 41. Basal insulin doses remained almost unchanged during the main 6-month treatment period in the 2 treatment groups. Changes in mealtime insulin doses from baseline to Week 26 was -0.011 U/kg in the SAR341402 group and 0.011 U/kg in the NovoLog/NovoRapid group.
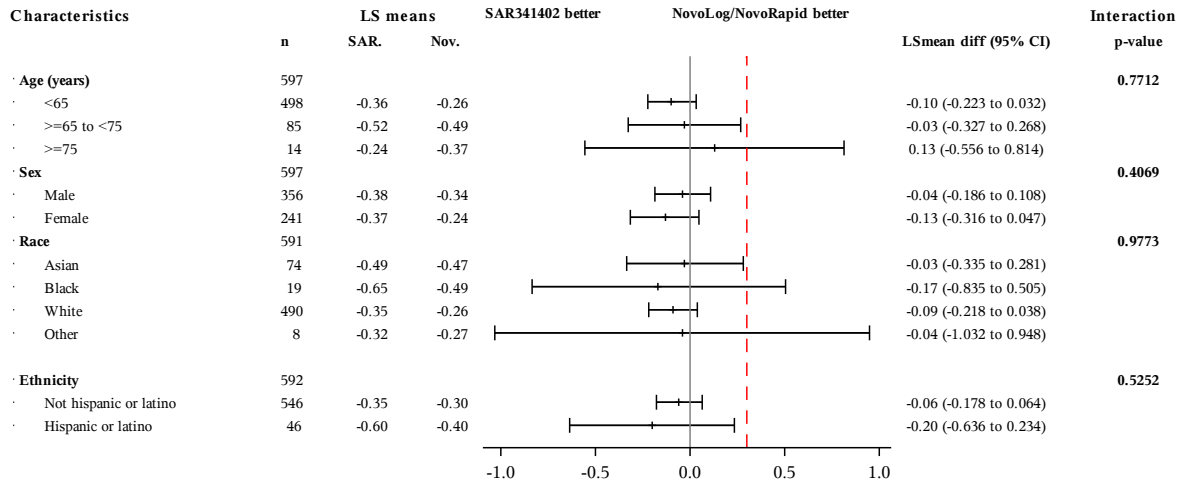
Table 35. Summary of daily insulin dose (U/kg) observed and change from baseline values during the main 6-month on-treatment period - Safety population

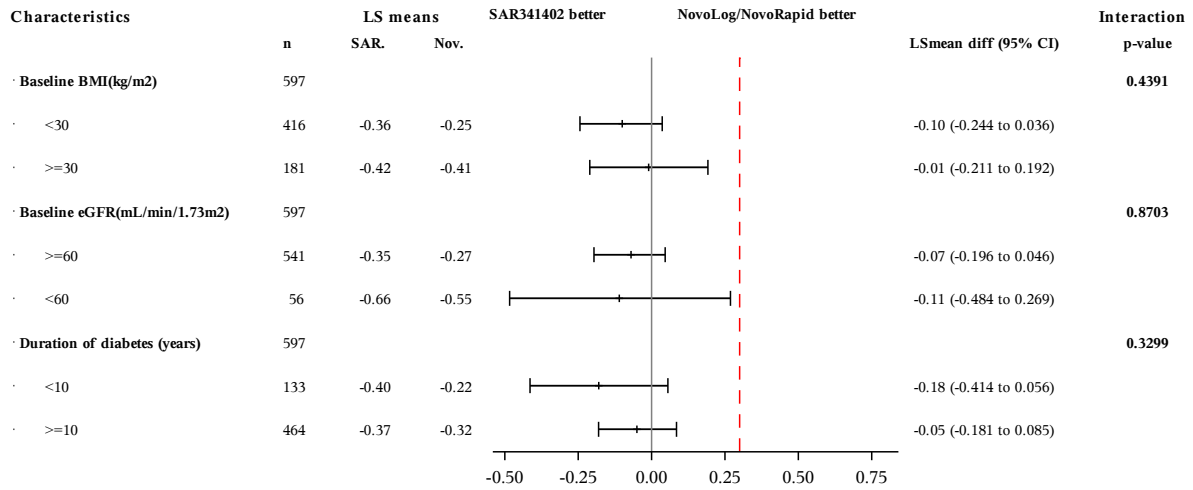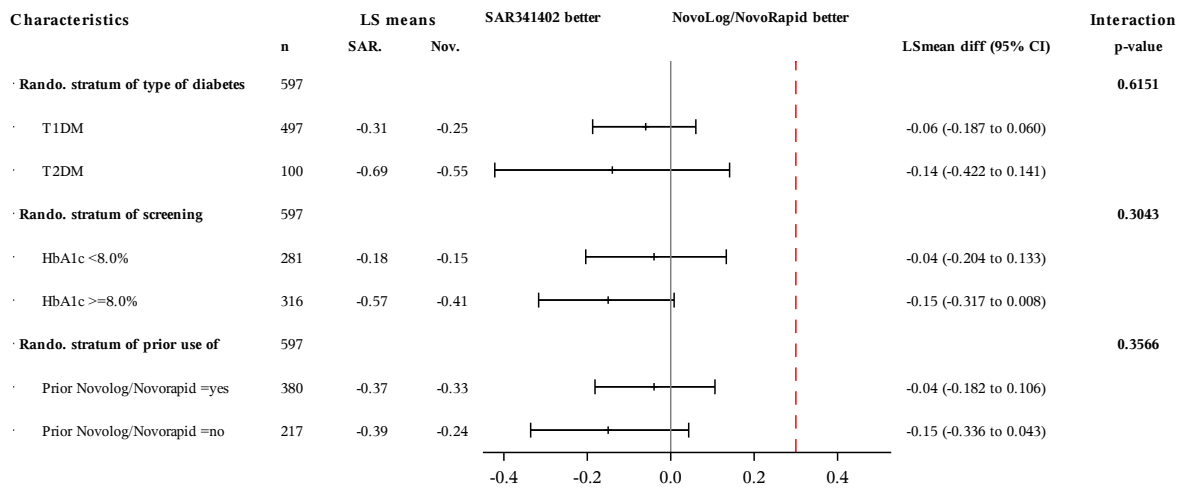| Daily insulin dose (U/kg)	SAR341402 (N=301)	NovoLog/NovoRapid (N=296)
Basal insulin		
Baseline		
Number	297	294
Mean (SD)	0.390 (0.191)	0.386 (0.231)
Week 26		
Number	273	272
Mean (SD)	0.396 (0.178)	0.388 (0.210)
Change from baseline to Week 26		
Number	271	270
Mean (SD)	0.005 (0.081)	0.003 (0.088)
Mealtime insulin		
Baseline		
Number	299	293
Mean (SD)	0.398 (0.229)	0.394 (0.247)
Week 26		
Number	270	266
Mean (SD)	0.391 (0.228)	0.413 (0.233)
Change from baseline to Week 26		
Number	268	265
Mean (SD)	-0.011 (0.133)	0.011 (0.116)
Total insulin		
Baseline		
Number	295	291
Mean (SD)	0.789 (0.340)	0.777 (0.404)
Week 26		
Number	267	265
Mean (SD)	0.790 (0.341)	0.803 (0.372)
Change from baseline to Week 26		
Number	263	262
Mean (SD)	-0.007 (0.167)	0.015 (0.170)

Ancillary analyses

Subgroup analyses

Subgroup analyses regarding type of diabetes, type of comparator, prior use of NovoLog/NovoRapid, race, ethnicity, age group, sex, baseline body max index (BMI), baseline eGFR, randomization stratum of screening HbA1c, duration of diabetes, and region showed a consistent comparable effect between the two treatment groups (Figure 15).

Panel 1

Characteristics	n	LS means SAR.	LS means Nov.		LSmean diff (95% CI)	Interaction p-value
				SAR341402 better / NovoLog/NovoRapid better		
Age (years)	597					0.7712
<65	498	-0.36	-0.26		-0.10 (-0.223 to 0.032)	
>=65 to <75	85	-0.52	-0.49		-0.03 (-0.327 to 0.268)	
>=75	14	-0.24	-0.37		0.13 (-0.556 to 0.814)	
Sex	597					0.4069
Male	356	-0.38	-0.34		-0.04 (-0.186 to 0.108)	
Female	241	-0.37	-0.24		-0.13 (-0.316 to 0.047)	
Race	591					0.9773
Asian	74	-0.49	-0.47		-0.03 (-0.335 to 0.281)	
Black	19	-0.65	-0.49		-0.17 (-0.835 to 0.505)	
White	490	-0.35	-0.26		-0.09 (-0.218 to 0.038)	
Other	8	-0.32	-0.27		-0.04 (-1.032 to 0.948)	
Ethnicity	592					0.5252
Not hispanic or latino	546	-0.35	-0.30		-0.06 (-0.178 to 0.064)	
Hispanic or latino	46	-0.60	-0.40		-0.20 (-0.636 to 0.234)	

Combined LSmean diff vs. NovoLog/NovoRapid at Week 26

Panel 2

Characteristics	n	LS means SAR.	LS means Nov.		LSmean diff (95% CI)	Interaction p-value
				SAR341402 better / NovoLog/NovoRapid better		
Baseline BMI(kg/m2)	597					0.4391
<30	416	-0.36	-0.25		-0.10 (-0.244 to 0.036)	
>=30	181	-0.42	-0.41		-0.01 (-0.211 to 0.192)	
Baseline eGFR(mL/min/1.73m2)	597					0.8703
>=60	541	-0.35	-0.27		-0.07 (-0.196 to 0.046)	
<60	56	-0.66	-0.55		-0.11 (-0.484 to 0.269)	
Duration of diabetes (years)	597					0.3299
<10	133	-0.40	-0.22		-0.18 (-0.414 to 0.056)	
>=10	464	-0.37	-0.32		-0.05 (-0.181 to 0.085)	

Combined LSmean diff vs. NovoLog/NovoRapid at Week 26

Panel 3

Characteristics	n	LS means SAR.	LS means Nov.		LSmean diff (95% CI)	Interaction p-value
				SAR341402 better / NovoLog/NovoRapid better		
Rando. stratum of type of diabetes	597					0.6151
T1DM	497	-0.31	-0.25		-0.06 (-0.187 to 0.060)	
T2DM	100	-0.69	-0.55		-0.14 (-0.422 to 0.141)	
Rando. stratum of screening	597					0.3043
HbA1c <8.0%	281	-0.18	-0.15		-0.04 (-0.204 to 0.133)	
HbA1c >=8.0%	316	-0.57	-0.41		-0.15 (-0.317 to 0.008)	
Rando. stratum of prior use of	597					0.3566
Prior Novolog/Novorapid =yes	380	-0.37	-0.33		-0.04 (-0.182 to 0.106)	
Prior Novolog/Novorapid =no	217	-0.39	-0.24		-0.15 (-0.336 to 0.043)	

Combined LSmean diff vs. NovoLog/NovoRapid at Week 26

Characteristics	n	LS means SAR.	Nov.		LSmean diff (95% CI)	Interaction p-value
Type of comparator	597					0.7544
NovoLog	335	-0.36	-0.30		-0.06 (-0.224 to 0.101)	
NovoRapid	262	-0.40	-0.30		-0.10 (-0.261 to 0.065)	
Region	597					0.8501
United States	335	-0.36	-0.30		-0.06 (-0.224 to 0.101)	
Western Europe	49	-0.29	-0.06		-0.23 (-0.600 to 0.136)	
Eastern Europe	148	-0.39	-0.34		-0.05 (-0.269 to 0.168)	
Japan	65	-0.47	-0.35		-0.12 (-0.443 to 0.207)	

Combined LSmean diff vs. NovoLog/NovoRapid at Week 26

Figure 11. Forest plot of change in HbA1c (%) from baseline to Week 26 by subgroup using ANCOVA analysis (with retrieved dropout multiple imputation) - ITT population

Treatment effect by anti-insulin aspart antibody

The analyses of immunogenicity data were descriptive (no formal statistical testing) and based on the AIA population. Separate analyses were performed for patients with T1DM and T2DM.

The change in HbA1c from baseline to Week 26 was similar between treatment groups in both subgroups of patients, those with treatment-emergent AIA and those without treatment-emergent AIAs (Table 42). Additionally, changes in mean mealtime and total insulin doses were independent of AIA incidence, in patients with T1DM or T2DM.

Table 36. Summary of effects of treatment-emergent AIAs on the efficacy

	Treatment-emergent AIA: Yes		Treatment-emergent AIA: No	
	SAR341402 (N=50)	NovoLog/Novo Rapid (N=60)	SAR341402 (N=242)	NovoLog/Novo Rapid (N=232)
HbA1c (%)				
Baseline: mean (SD)	8.02 (0.85)	7.93 (0.72)	7.99 (0.75)	7.93 (0.70)
Change from BL to W26				
Combined LS mean (SE) **Error! Reference source**	-0.33 (0.098)	-0.20 (0.087)	-0.39 (0.046)	-0.33 (0.046)
Combined LS mean difference (SE) vs NovoLog/NovoRapid 95% CI	-0.14 (0.131) (-0.395 to 0.119)		-0.06 (0.066) (-0.185 to 0.072)	
Mealtime insulin dose				
Baseline: mean (SD)	0.424 (0.218)	0.413 (0.280)	0.396 (0.234)	0.393 (0.238)
Change from BL to W26: mean (SD)	-0.029 (0.180)	0.003 (0.131)	-0.008 (0.122)	0.013 (0.112)
Total insulin dose (U/kg)				

	Treatment-emergent AIA: Yes		Treatment-emergent AIA: No	
	SAR341402 (N=50)	NovoLog/Novo Rapid (N=60)	SAR341402 (N=242)	NovoLog/Novo Rapid (N=232)
Baseline: mean (SD)	0.841 (0.372)	0.827 (0.562)	0.779 (0.334)	0.771 (0.352)
Change from BL to W26: mean (SD)	-0.031 (0.215)	-0.007 (0.244)	-0.002 (0.156)	0.021 (0.145)

<u>Potential impact of the usage of defective test strips on the insulin doses</u>

During the conduct of the phase 3 study, the majority of the patients (70.9%; 197/197 (100%) of the patients in Europe, 226/335 (67%) in the US and 0% in Japan) have been exposed to defective glucose test strips. The average blood glucose reading with the defective strips was between 0.1% and 14.8% higher than the average values obtained with non-defective test strips. Considering that none of the patients in Japan has been exposed to defective test strips (although the number of patients recruited in Japan is relatively low), while this was 100% in Europe and 67% in the US, the impact of defective test strips on the parameters of interest could be evaluated by region.

Exploratory analyses by geographical regions (US, Europe, Japan) with respect to change in HbA1c (primary endpoint) (Table 43) and other secondary endpoints showed no clinically relevant differences in treatment effect across regions.

Table 37. Descriptive statistics: HbA1c (%) observed and change from baseline values by visit and by randomization stratum of geographical region during the main 6-month randomized period – ITT population

HbA1c (%)	Europe		Japan		US	
	SAR341402 (N=98)	NovoLog/NovoRapid (N=99)	SAR341402 (N=33)	NovoLog/NovoRapid (N=32)	SAR341402 (N=170)	NovoLog/NovoRapid (N=165)
Change from baseline						
Number	96	95	32	32	155	151
Mean (SD)	-0.40 (0.67)	-0.29 (0.55)	-0.47 (0.54)	-0.29 (0.55)	-0.36 (0.74)	-0.30 (0.72)
Median	-0.40	-0.30	-0.55	-0.20	-0.30	-0.30
Min ; Max	-2.8 ; 1.0	-1.4 ; 1.5	-1.4 ; 1.0	-1.9 ; 0.8	-2.4 ; 1.4	-3.5 ; 2.3

Summary of main efficacy results

The following table summarises 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 biosimilarity assessment (see later sections).

Table 38. Summary of efficacy endpoints in study EFC15081

Title: Six-month, Randomized, Open-label, Parallel-group Comparison of SAR341402 to NovoLog/NovoRapid in Adult Patients With Diabetes Mellitus Also Using Insulin Glargine, with a 6-month Safety Extension Period	
Study identifier	EFC15081 (EudraCT: 2017-000091-28)

Design	a Phase 3, 6 month, multicenter, multinational, randomized, open-label, active-controlled, 2 arm parallel group study followed by a 6 month safety extension period to compare SAR341402 to NovoLog/NovoRapid in adult patients T1DM or T2DM (T2DM in the US only) diagnosed for at least 12 months at the time of the screening, with HbA1c >7% and <10%, and who had been treated with NovoLog/NovoRapid or insulin lispro (100 U/mL) in the last 6 months prior to screening visit and with insulin glargine (100 U/mL) in the last 6 months prior to screening visit or Levemir® (insulin detemir) in the last 12 months prior to screening visit. Patients were randomized to receive SAR341402 or NovoLog/NovoRapid (randomization ratio 1:1). Randomization was stratified by geographical region (Europe, US, Japan), by type of diabetes (T1DM, T2DM [T2DM only for US]), by HbA1c obtained at the screening visit (<8.0%, ≥8.0%), and by prior use of NovoLog/NovoRapid (Yes, No).		
	Screening phase:		Up to 2 weeks
	Main treatment phase:		26 weeks
	Safety extension phase:		26 weeks
	Post-treatment follow-up:		1 days
Hypothesis	Non-inferiority (margin of 0.3% HbA1c on primary end point)		
Treatments groups	SAR341402 in combination with Lantus		SAR341402 (100 U/mL), self-administered s.c. and self-titrated to achieve 2 hour postprandial plasma glucose of < 10.0, while avoiding hypoglycemia, 26 weeks, N= 301
	NovoLog/NovoRapid in combination with Lantus		NovoLog/NovoRapid (100 U/mL insulin aspart solution) self-administered s.c. and self-titrated to achieve 2 hour postprandial plasma glucose of < 10.0, while avoiding hypoglycemia, 26 weeks, N= 296
Endpoints and definitions	Primary endpoint	**Change in HbA1c (%)**	Change in HbA1c (%) from baseline to Week 26
	Secondary endpoint	**HbA1c <7%**	Percentage of HbA1c responders (patients with HbA1c <7%) at Week 26
		Change in FPG (mmol/L)	Change in FPG (fasting plasma glucose mmol/L) from baseline to Week 26
		Change in 24-hour plasma glucose (mmol/L)	Change in the mean 24-hour plasma glucose concentration (mmol/L) from baseline to Week 26 based on the 7-point SMPG profile
		Change in PPG (mmol/L)	Change in postprandial plasma glucose (PPG) excursions (mmol/L) from baseline to Week 26 based on the 7-point SMPG profiles
		Change in 7-point SMPG profiles	Change in 7-point SMPG profiles per time-point from baseline to week 26
		Change in daily basal, mealtime, and total insulin does (U/kg)	Change in daily basal, mealtime, and total insulin does (U/kg) from baseline to Week 26
Database lock	21 September 2018		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time	Intent -to treat (ITT) population – change from baseline to Week 26 (primary analysis: ANCOVA with retrieved dropout multiple imputation), 26 weeks		
Descriptive statistics and estimate variability	Treatment group	SAR341402	NovoLog/NovoRapid
	Number of subject	n= 301	n= 296
	Percent change in HbA1c (Combined LS Mean (SE)[95% CI])	-0.38 (0.042) [-0.459 to -0.294]	-0.30 (0.041) [-0.381 to -0.219]
	Combined LS Mean difference (SE) vs Novolog/NovoRapid [95%CI]	-0.08 (0.059) [-0.192 to 0.039]	
Analysis description	**Secondary Analysis**		
	HbA1c <7% n(%)	50 (16.6)	43 (14.5)
	OR (95% CI) versus NovoLog/ NovoRapid	1.170 (0.735 to 1.861)	
	Change in FPG (mmol/L) (Combined LS Mean (SE))	-0.49 (0.249)	-0.17 (0.245)
	Combined LS Mean diff (SE) vs. NovoLog/NovoRapid [95% CI]	-0.31 (0.348) [-0.997 to 0.368]	
	Change in 24-hour plasma glucose (mmol/L) (Combined LS Mean (SE))	-0.34 (0.120)	-0.53 (0.121)
	Combined LS Mean diff (SE) vs. NovoLog/NovoRapid [95% CI]	0.18 (0.171) [-0.151 to 0.518]	

	Change in PPG (mmol/L)		
	Breakfast (Combined LS Mean (SE))	0.50 (0.232)	0.65 (0.233)
	Combined LS Mean diff (SE) vs. NovoLog/NovoRapid [95% CI]	-0.15 (0.329) [-0.795 to 0.493]	
	Lunch (Combined LS Mean (SE))	0.18 (0.230)	0.12 (0.228)
	Combined LS Mean diff (SE) vs. NovoLog/NovoRapid [95% CI]	0.06 (0.324) [-0.569 to 0.699]	
	Dinner (Combined LS Mean (SE))	0.36 (0.243)	0.66 (0.243)
	Combined LS Mean diff (SE) vs. NovoLog/NovoRapid [95% CI]	-0.30 (0.344) [-0.974 to 0.374]	
	Change in daily basal, mealtime, and total insulin does (U/kg)		
	Basal (Mean (SD))	0.005 (0.081)	0.003 (0.088)
	Mealtime (Mean (SD))	-0.011 (0.133)	0.011 (0.116)
	Total (Mean (SD))	-0.007 (0.167)	0.015 (0.170)

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The main focus of this application is the demonstration of biosimilarity of SAR341402 to the reference products. In this respect the euglycemic PK/PD clamp study PDY12695 is considered pivotal to demonstrate comparable efficacy. According to the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005_Rev.1), there is no anticipated need for specific efficacy studies since endpoints used in such studies, usually HbA1c, are not considered sensitive enough to detect potentially clinically relevant differences between insulins. Therefore, the phase 3 study EFC15081 can be considered as supportive for efficacy. Nevertheless, this clinical efficacy and safety study provides the pivotal immunogenicity and safety data, which is required to complete the biosimilar clinical comparability of SAR341402 and NovoLog/NovoRapid.

Study EFC15081 was a 26-week, multinational, multicenter, randomized, controlled, parallel-group open-label study with a 26-week comparative safety extension period.

General inclusion and exclusion criteria are appropriate to identify an eligible target population for evaluation of comparability of SAR341402 and NovoLog/NovoRapid. The study included adult patients who had been diagnosed with T1DM or T2DM for at least 1 year at the time of the screening visit, who had been on a multiple daily injection regimen of NovoLog/NovoRapid or insulin lispro (100 U/mL) for at least 6 months before screening in combination with insulin glargine for at least 6 months or in combination with insulin detemir for at least 12 months before the screening visit and who had a screening HbA1c between 7.0% and 10.0%. Inclusion of both type 1 and type 2 diabetes patients is acceptable since the type of diabetes was a randomization stratum.

The design of the study appears appropriate to answer the objective of the study. A 26-weeks treatment duration is considered sufficient for achieving steady-state conditions with SAR341402 or NovoLog/NovoRapid in combination with basal insulin (Lantus). The 26-weeks open-label comparative efficacy and safety treatment duration period followed by a 26 weeks comparative safety extension period is appropriate for evaluation of differences in immunogenicity. The results of this safety extension period have been submitted by the Applicant with their responses to the D120 List of Questions. Randomization was stratified by geographical region (Europe, US, Japan), type of diabetes mellitus (T1DM, T2DM [T2DM only for US]), glycated hemoglobin (HbA1c) value at screening (<8.0%, ≥8.0%), and prior use of NovoLog/NovoRapid (Yes, No). The open-label study design is acceptable since the pre-filled, disposable pen injection devices for SAR341402 and NovoLog/NovoRapid cannot be made indistinguishable. Moreover, HbA1c (primary endpoint), FDG and anti-insulin aspart antibody (AIA) data were measured at central certified laboratories blinded to the treatment received.

The primary objective was to demonstrate non-inferiority of SAR341402 solution compared to NovoLog/NovoRapid in terms of HbA1c change from baseline to Week 26, which is accepted since it is in line with the draft guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (29 January 2018 CPMP/EWP/1080/00 Rev.1). A non-inferiority margin of 0.3% HbA1c was defined, which is appropriate since it is in accordance with the recommendations by regulatory agencies and based on historical precedent for comparative insulin studies.

Secondary endpoints included the percentage of HbA1c responders (HbA1c <7.0%) as well as change from baseline to Week 26 in FPG, mean 24-hour plasma glucose concentration, glucose excursions and 7-point SMPG profiles are appropriate and provide further insight on similarity of SAR341402 to NovoLog/NovoRapid.

The statistical analysis of primary and secondary endpoints use ANCOVA or logistic regression with treatment groups, randomisation strata and baseline values included in the model. Missing data were handled taking into account the treatment status of patients (adhering or not). Sensitivity analyses were defined to support the primary analysis. The methods are considered standard and acceptable.

Efficacy data and additional analyses

Discontinuation rates of the 26-week efficacy and safety treatment period were low and similar in both treatment arms (7.3% (22 patients) and 7.4% (22 patients) in the SAR341402 and NovoLog/NovoRapid groups, respectively). The most common reason for treatment discontinuation was "other reason" (4.3% (13 patients) and 5.4% (16 patients) in the SAR341402 and NovoLog/NovoRapid groups, respectively), which was primarily related to a patient decision or consent withdrawal, followed by site closure and patients lost to follow-up. The discontinuation rate due to adverse event (AE) was low and approximately similar in both treatment arms (1.7% (5 patients) and 1.0% (3 patients) in the SAR341402 and NovoLog/NovoRapid groups, respectively).

The percentage of critical or major deviations were generally comparable between both groups (43.2% and 38.5% in the SAR341402 and NovoLog/NovoRapid groups, respectively), and also well balanced across the treatment groups within the different categories of protocol deviations. Moreover, the deviations are expected not to have had an effect on the primary outcome of the study.

The demographic and diseases characteristics are sufficiently well distributed across the two treatment groups. The majority of the patients had T1DM (83.2%), 82.6% of the patients were white and the median age was 49.0 years with approximately 17% of the patients who were 65 years or older. Patients were enrolled primarily from the US (56%) followed by Europe (33%) and Japan (11%).

In the primary analysis, non-inferiority in change in HbA1c of SAR341402 over NovoLog/NovoRapid was demonstrated as the upper bound of the 2-sided 95% CI of the difference between SAR341402 and NovoLog/NovoRapid was below the predefined non-inferiority margin of 0.3% (LS mean difference of -0.08% [95%CI: -0.192 to 0.039]). This was additionally substantiated by the demonstration of the inverse non-inferiority of NovoLog/NovoRapid over SAR341402. The sensitivity analyses and the per-protocol analyses further support the results of the primary efficacy analysis on the ITT population.

Regarding daily insulin dose, basal insulin doses were similar between SAR341402 and NovoLog/NovoRapid at baseline and remained approximately unchanged during the 6-month treatment period (change from baseline to week 26 [mean]: 0.005 and 0.003 U/kg in the SAR341402 and NovoLog/NovoRapid group, respectively). However, there was a small difference in change from baseline to week 26 in mealtime insulin doses with a mean decrease of -0.011 U/kg in the SAR341402 and a mean increase of 0.011 U/kg in the NovoLog/NovoRapid. When T1DM and T2DM were analysed separately, at week 12 a slight difference can be seen favouring the test product to the reference products regarding the mealtime insulin doses in both for T1DM and T2DM. However it was mostly levelling off at week 26. For the basal insulin doses this difference is even less observable with the same trend at week 26 as for mealtime insulin doses. The observed changes are likely related to the regular insulin dose adjustment process.

Subgroup analyses regarding the type of diabetes, type of comparator and prior use of NovoLog/NovoRapid showed consistent comparable effects in the change in HbA1c between the two treatment groups. Furthermore, also no heterogeneity of treatment effect between the two treatment groups was observed with respect to other screening and baseline factors (race, ethnicity, age group, sex, baseline BMI, baseline eGFR, randomization stratum of screening HbA1c, duration of diabetes, region) and baseline and post-baseline AIA status.

Furthermore, there were no clinically relevant differences observed between SAR341402 and NovoLog/NovoRapid for any of the secondary endpoints, including the percentage of HbA1c responders (HbA1c <7.0%) as well as change from baseline to Week 26 in FPG, mean 24-hour plasma glucose concentration, glucose excursions and 7-point SMPG profiles.

During the conduct of the phase 3 study, the majority of the patients (70.9%; 197/197 (100%) of the patients in Europe, 226/335 (67%) in the US and 0% in Japan) have been exposed for various durations between September 2017 and April 2018 to defective glucose test strips to be used for collecting SMPG measurements. The average blood glucose reading with the defective strips were between 0.1% and 14.8% higher than the average values obtained with non-defective test strips.

Although the lot reference numbers of the test strips could not be tracked at the patient level, it is agreed with the Applicant that it could be expected that the extent of usage of defective test strips was not substantially different between the treatment groups and that the potential impact would be similar between groups and would not affect the between-group comparison. Moreover, considering that none of the patients in Japan has been exposed to defective test strips (although the number of patients recruited in Japan is relatively low), while this was 100% in Europe and 67% in the US, the

impact of defective test strips on the parameters of interest could be evaluated by region. Exploratory analyses by geographical regions (US, Europe, Japan) with respect to change in HbA1c (primary endpoint) and other secondary endpoints showed no clinically relevant differences in treatment effect across regions.

Results of the 26-week safety extension period of study EFC15081

As requested, the Applicant submitted the results of the 26-week safety extension period of study EFC15081 during the evaluation procedure. The efficacy of SAR341402 and NovoLog/NovoRapid was similar after 12 months of treatment in study EFC15081 in adult patients with T1DM or T2DM. The decrease in HbA1c from baseline to Week 52 was similar in the SAR341402 group (LS mean change from baseline -0.25%; standard error [SE] 0.057) and NovoLog/NovoRapid group (LS mean change from baseline -0.26%; SE 0.059; LS mean difference SAR341402 versus NovoLog/NovoRapid 0.01% [SE 0.082], 95% confidence interval [CI] [-0.146 to 0.173]). Basal, mealtime and total insulin doses remained almost unchanged during this treatment period in both treatment groups.

2.5.4. Conclusions on the clinical efficacy

For the purpose of the clinical biosimilarity exercise for biosimilar insulin products, the evaluation of HbA1c is not a sensitive endpoint and therefore efficacy studies evaluating HbA1c are not requested (EMEA/CHMP/BMWP/32775/2005_Rev. 1). Nevertheless, the applicant has conducted one efficacy and safety (phase III) non-inferiority studies comparing the test and reference products in order to investigate how PK/PD features of the biosimilar candidate product translate into clinical parameters relevant for the management of patients with T1DM and T2DM. This data is considered supportive in establishing biosimilarity. This study demonstrated that SAR341402 is non-inferior to NovoLog/NovoRapid in improvement of glycaemic control by Week 26 and therefore provided strong supportive evidence about the comparability/ biosimilarity of the two products.

2.6. Clinical safety

The main focus of this application is to show biosimilarity between SAR341402 and NovoLog/NovoRapid in terms of quality, pharmacology, clinical efficacy and clinical safety. In support of demonstration of similarity in safety between SAR341402 and NovoLog/NovoRapid, the Applicant provided safety information from three different sources:

- The phase 1 PK/PD single-dose euglycemic clamp study PDY12695 in 30 patients with T1DM

- The 6-month open-label comparative efficacy and safety phase 3 study EFC15081 in 597 patients with T1DM or T2DM, with a 6-month safety extension period

- The phase 3 study PDY15083 for the safety assessment of SAR341402 and NovoLog used in continuous subcutaneous insulin infusion in 45 patients with T1DM.

The primary safety data are derived from study EFC15081. Therefore, this study will be extensively discussed below.

Patient exposure

In study EFC15081, the median duration of exposure was the same in the 2 treatment groups (183.0 days for both SAR341402 and NovoLog/NovoRapid). The vast majority of patients in the 2 treatment groups were exposed to IMP for more than 25 weeks (SAR341402: 277 patients [92.0%]; NovoLog/NovoRapid: 272 patients [91.9%]). The cumulative duration of treatment exposure during the main 6-month treatment period was similar between the two treatment groups (145.86 patient-

years and 143.03 patient-years in the SAR341402 and in the NovoLog/NovoRapid groups, respectively).

Adverse events

Overall summary of adverse events

The percentage of patients with any TEAEs was approximately similar between the two treatment groups (51.8% and 49.3% for SAR341402 and NovoLog/NovoRapid, respectively) (Table 45). The percentage of serious TEAES and patients with TEAEs leading to permanent treatment discontinuation was slightly higher in the SAR341402 group compared with NovoLog/NovoRapid (8.3% versus 6.1% and 1.7% versus 1.0, respectively).

Table 39. Overview of adverse event profile: Treatment-emergent adverse events during the main 6-month on-treatment period of study EFC15081- Safety population

n (%)	SAR341402 (N=301)	NovoLog/NovoRapid (N=296)
Patients with any TEAE	156 (51.8)	146 (49.3)
Patients with any treatment-emergent SAE	25 (8.3)	18 (6.1)
Patients with any TEAE leading to death	0	2 (0.7)
Patients with any TEAE leading to permanent treatment discontinuation	5 (1.7)	3 (1.0)

TEAE: Treatment-emergent adverse event, SAE: Serious adverse event
n (%) = number and percentage of patients with at least one TEAE

Common adverse events

Adverse events were mainly mild to moderate in intensity in the 2 treatment groups. The most frequently reported adverse events (preferred term (PT)) were nasopharyngitis (8.3 versus 8.4% for SAR341402 and NovoLog/NovoRapid, respectively), upper respiratory tract infection (5.3% versus 8.8%) and influenza (5.0% versus 3.0%) and reported by a general similar percentage of patients between the two treatment groups (Table 46). All other TEAEs were reported in less than 3% of patients regardless of the treatment group.

The percentage of patients with TEAEs considered related to study drug was slightly higher for SAR341402 compared with NovoLog/NovoRapid (4.0% [12 patients] versus 2.4% [7 patients]) and included , hypoglycemic unconsciousness (5 patients in the SAR341402 group and 1 patient in the NovoLog/NovoRapid group), accidental overdose (4 patients in the SAR341402 group and 2 patients in the NovoLog/NovoRapid group), device use error (3 patients in the SAR341402 group and 1 patient in the NovoLog/NovoRapid group), hypoglycemia (2 patients in the SAR341402 group), and injection site bruising (3 patients in the NovoLog/NovoRapid group).

Table 40. Number (%) of patients with TEAE(s) that occurred with HLT ≥ 2% in any treatment group by Primary SOC, HLT and PT during the main 6-month on-treatment period of study EFC15081- Safety population

Primary System Organ Class HLT: High Level Term Preferred Term n(%)	SAR341402 (N=301)	NovoLog/NovoRapid (N=296)
Any class	156 (51.8)	146 (49.3)
INFECTIONS AND INFESTATIONS	87 (28.9)	84 (28.4)
HLT: Abdominal and gastrointestinal infections	8 (2.7)	4 (1.4)
Gastroenteritis	8 (2.7)	4 (1.4)
HLT: Influenza viral infections	15 (5.0)	9 (3.0)
Influenza	15 (5.0)	9 (3.0)

Primary System Organ Class HLT: High Level Term Preferred Term n(%)	SAR341402 (N=301)	NovoLog/NovoRapid (N=296)
HLT: Upper respiratory tract infections	53 (17.6)	56 (18.9)
Acute sinusitis	0	1 (0.3)
Laryngitis	1 (0.3)	0
Nasopharyngitis	25 (8.3)	25 (8.4)
Pharyngitis	4 (1.3)	2 (0.7)
Rhinitis	2 (0.7)	0
Sinusitis	5 (1.7)	6 (2.0)
Tonsillitis	2 (0.7)	0
Tracheitis	1 (0.3)	0
Tracheobronchitis	0	1 (0.3)
Upper respiratory tract infection	16 (5.3)	26 (8.8)
HLT: Viral infections NEC	3 (1.0)	9 (3.0)
Bronchitis viral	0	2 (0.7)
Gastroenteritis viral	2 (0.7)	2 (0.7)
Respiratory tract infection viral	1 (0.3)	1 (0.3)
Viral pharyngitis	0	2 (0.7)
Viral upper respiratory tract infection	0	3 (1.0)
NERVOUS SYSTEM DISORDERS	28 (9.3)	16 (5.4)
HLT: Disturbances in consciousness NEC	7 (2.3)	4 (1.4)
Hypoglycemic unconsciousness	6 (2.0)	3 (1.0)
Loss of consciousness	0	1 (0.3)
Syncope	1 (0.3)	0
VASCULAR DISORDERS	6 (2.0)	11 (3.7)
HLT: Vascular hypertensive disorders NEC	5 (1.7)	8 (2.7)
Hypertension	5 (1.7)	8 (2.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	16 (5.3)	12 (4.1)
HLT: Coughing and associated symptoms	7 (2.3)	2 (0.7)
Cough	7 (2.3)	2 (0.7)
GASTROINTESTINAL DISORDERS	26 (8.6)	20 (6.8)
HLT: Diarrhoea (excl infective)	4 (1.3)	6 (2.0)
Diarrhoea	4 (1.3)	6 (2.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	32 (10.6)	24 (8.1)
HLT: Joint related signs and symptoms	2 (0.7)	6 (2.0)
Arthralgia	2 (0.7)	6 (2.0)
HLT: Musculoskeletal and connective tissue pain and discomfort	12 (4.0)	11 (3.7)
Back pain	4 (1.3)	3 (1.0)
Musculoskeletal pain	3 (1.0)	4 (1.4)
Neck pain	1 (0.3)	1 (0.3)
Pain in extremity	4 (1.3)	3 (1.0)

TEAE: Treatment-emergent adverse event, SOC: System organ class, HLT: High level term, PT: Preferred term

MedDRA dictionary: MedDRA 21.0

n (%) = number and percentage of patients with at least one TEAE

Note: Table sorted by SOC internationally agreed order and HLT, PT by alphabetic order

Only HLT with at least one HLT >=2% in at least one group are presented

<u>Adverse events of specific interest</u>

Hypoglycemia

The percentage of patients with any hypoglycemia reported at any time of the day was similar between SAR341402 and NovoLog/NovoRapid (96.7% versus 96.3%, respectively). However, the hypoglycemia event rate per patient-years was slightly higher in the SAR341402 group compared with the NovoLog/Rapid group (72.96 versus 69.31). Both the percentage and event rate per patient-years of severe hypoglycemia also seems to be higher in the SAR 341402 group compared with the NovoLog/Rapid group (4.0% versus 3.4% and 0.14 and 0.10 rate per patient-year, respectively) (Table 47 andTable 48).

Subgroup analysis by randomization stratum of type of diabetes indicated potential heterogeneity of treatment effect in patients with T1DM versus patients with T2DM for the categories 'any' hypoglycemia (p-value=0.0514) and documented symptomatic hypoglycemia (<3.0 mmol/L [54 mg/dL]) (p-value=0.0924). No differences in hypoglycemia risk between SAR341402 and NovoLog/NovoRapid was identified in the other subgroup with regard to type of comparator, race, ethnicity, age group, sex, baseline BMI, baseline eGFR, randomization stratum of screening HbA1c, randomization stratum of prior use of NovoLog/NovoRapid, regions, and duration of diabetes.

Table 41. Number (%) of patients with at least one hypoglycemia during the main 6-month on-treatment period of study EFC15081- Safety population

Type of hypoglycemia n(%)	SAR341402 (N=301)	NovoLog/NovoRapid (N=296)
Any hypoglycemia	291 (96.7)	285 (96.3)
Severe hypoglycemia	12 (4.0)	10 (3.4)
Documented symptomatic hypoglycemia		
≤ 3.9 mmol/L (70 mg/dL)	264 (87.7)	251 (84.8)
< 3.0 mmol/L (54 mg/dL)	206 (68.4)	193 (65.2)
Asymptomatic hypoglycemia		
≤ 3.9 mmol/L (70 mg/dL)	251 (83.4)	227 (76.7)
< 3.0 mmol/L (54 mg/dL)	125 (41.5)	117 (39.5)
Probable symptomatic hypoglycemia	53 (17.6)	46 (15.5)
Relative hypoglycemia	138 (45.8)	140 (47.3)
Non classified hypoglycemia (No severe)	6 (2.0)	3 (1.0)

n (%)=number and percentage of patients with at least one treatment-emergent hypoglycemia

Table 42. Number of hypoglycemia per patient-year of exposure during the main 6-month on-treatment period of study EFC15081 - Safety population

Type of hypoglycemia Number of events (rate per patient-years)	SAR341402 (N = 301)	NovoLog/NovoRapid (N = 296)
Total patient years	145.92	143.09
Any hypoglycemia	10646 (72.96)	9917 (69.31)
Severe hypoglycemia	20 (0.14)	14 (0.10)
Documented symptomatic hypoglycemia		
≤ 3.9 mmol/L (70 mg/dL)	5872 (40.24)	5190 (36.27)

Type of hypoglycemia Number of events (rate per patient-years)	SAR341402 (N = 301)	NovoLog/NovoRapid (N = 296)
< 3.0 mmol/L (54 mg/dL)	1619 (11.10)	1400 (9.78)
Asymptomatic hypoglycemia		
≤ 3.9 mmol/L (70 mg/dL)	3671 (25.16)	3834 (26.80)
< 3.0 mmol/L (54 mg/dL)	592 (4.06)	655 (4.58)
Probable symptomatic hypoglycemia	170 (1.17)	105 (0.73)
Relative hypoglycemia	878 (6.02)	770 (5.38)
Non classified hypoglycemia (No severe)	35 (0.24)	4 (0.03)

Potential impact of the usage of defective strips on the hypoglycaemia evaluations

The cumulative duration of the period when defective test strips were used was approximately 55 patient-years (SAR341402: 55.18; NovoLog/NovoRapid: 55.71) as compared to close to 90 patient-years for the period when non-defective test strips were used (SAR341402: 90.74; NovoLog/NovoRapid: 87.37) (Table 49).

Regardless of the treatment group, the event rate per patient-year of exposure of any hypoglycemia was numerically higher with the use of defective test strips (79.12 and 74.58 for the SAR341402 and NovoLog/NovoRapid group, respectively) compared with the non-defective test strips (68.30 and 65.33 for the SAR341402 and NovoLog/NovoRapid group, respectively). The event rate of severe hypoglycemia per patient-year of exposure remained low with the use of defective test strips compared with non-defective strips in the SAR341042 group (0.13 versus 0.14).

Table 43. Study EFC15081 - Number of hypoglycemia per patient-year of exposure by period of use of defective test strips during the main 6-month on-treatment period – Safety population

Type of hypoglycemia Number of events (rate per patient-years)	Period when defective test strips were used		Period when non-defective test strips were used	
	SAR341402 (N=207)	NovoLog/NovoRapid (N=214)	SAR341402 (N=300)	NovoLog/NovoRapid (N=292)
Total patient years	55.18	55.71	90.74	87.37
Any hypoglycemia	4366 (79.12)	4155 (74.58)	6197 (68.30)	5708 (65.33)
Severe hypoglycemia	7 (0.13)	10 (0.18)	13 (0.14)	4 (0.05)
Documented symptomatic hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	2604 (47.19)	2113 (37.93)	3243 (35.74)	3060 (35.02)
< 3.0 mmol/L (54 mg/dL)	812 (14.72)	660 (11.85)	800 (8.82)	734 (8.40)
Asymptomatic hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	1278 (23.16)	1651 (29.63)	2386 (26.30)	2175 (24.89)
< 3.0 mmol/L (54 mg/dL)	204 (3.70)	329 (5.91)	387 (4.27)	325 (3.72)

Injections site and hypersensitivity reactions

The percentage of injection site reactions (0.7% and 1.4 % for SAR341042 and NovoLog/NovoRapid, respectively) and hypersensitivity reactions (3.7% each) was relatively low. Furthermore, no relevant difference between the two treatment groups could be observed.

Serious adverse events and deaths

Serious adverse events (SAEs)

The incidence of SAE was slightly higher in the SAR341402 group compared with the NovoLog/NovoRapid group (8.3% versus 6.1%) (Table 50). The most frequently reported serious TEAE at the PT level was hypoglycemia unconsciousness in the 2 treatment groups (SAR341402: 2.0% [6 patients with a total of 9 events]; NovoLog/NovoRapid: 1.0% [3 patients with a total of 4 events]).

The incidence in serious TEAEs considered as related to study drug was low, however, also slightly higher in the SAR341402 group compared with the NovoLog/NovoRapid group (7 patients [2.3%] versus 1 patient [0.3%], respectively). These treatment related SAE included hypoglycemic unconsciousness (5 patients [1.7%] versus 1 patient [0.3%] for SAR341402 and NovoLog/NovoRapid, respectively), hypoglycemia (2 patients [0.7%] versus 0 patients), accidental overdose (3 patients [1.0%] versus 1 patient [0.3%]), and device error (2 patients [0.7%] versus 0 patients).

Table 44. Number (%) of patients with treatment-emergent SAEs regardless of relationship and related to IMP by primary SOC and PT during the main 6-month on-treatment period – Safety population

Primary System Organ Class Preferred Term n(%)	SAR341402 (N=301)		NovoLog/NovoRapid (N=296)	
	ALL	RELATED	ALL	RELATED
Any class	25 (8.3)	7 (2.3)	18 (6.1)	1 (0.3)
INFECTIONS AND INFESTATIONS	3 (1.0)	0	3 (1.0)	0
Bronchitis bacterial	1 (0.3)	0	0	0
Clostridium difficile colitis	1 (0.3)	0	0	0
Herpes zoster	1 (0.3)	0	0	0
Pyelonephritis acute	1 (0.3)	0	0	0
Cellulitis	0	0	2 (0.7)	0
Diabetic foot infection	0	0	1 (0.3)	0
Osteomyelitis chronic	0	0	1 (0.3)	0
Pneumonia	0	0	1 (0.3)	0
Wound infection	0	0	1 (0.3)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	3 (1.0)	0
Colon adenoma	0	0	1 (0.3)	0
Hepatic cancer	0	0	1 (0.3)	0
Pancreatic carcinoma	0	0	1 (0.3)	0
Prolymphocytic leukaemia	0	0	1 (0.3)	0
METABOLISM AND NUTRITION DISORDERS	5 (1.7)	2 (0.7)	1 (0.3)	0
Hypoglycaemia	3 (1.0)	2 (0.7)	1 (0.3)	0
Diabetic ketoacidosis	2 (0.7)	0	0	0
NERVOUS SYSTEM DISORDERS	9 (3.0)	5 (1.7)	7 (2.4)	1 (0.3)
Hypoglycaemic unconsciousness	6 (2.0)	5 (1.7)	3 (1.0)	1 (0.3)
Carpal tunnel syndrome	1 (0.3)	0	0	0
Syncope	1 (0.3)	0	0	0

Deaths

Four deaths are reported in this study (1 in the SAR341402 group and 3 patients in the NovoLog/NovoRapid group), of which none were considered related to the IMP or the NIMP.

Laboratory findings

No clinically relevant differences between SAR341402 and NovoLog/NovoRapid were identified for any of the laboratory parameters (chemistry, haematology) and vital sign parameters during the main 6-month on-treatment period of study EFC15081.

Safety in special populations

Not applicable.

Immunological events

Among patients with available anti-insulin aspart antibody (AIA) sample at baseline, similar percentages of patients in the 2 treatment groups had detectable AIAs at baseline (SAR341402: 35.3% [96/272 patients]; NovoLog/NovoRapid: 36.7% [98/267 patients]) (Table 51). The percentage of patients with a treatment-emergent AIA response (i.e. treatment-boosted or treatment-induced AIAs) during the main 6-month on-treatment period was slightly lower in the SAR341402 group compared with the NovoLog/NovoRapid groups (16.9% versus 20.5%; risk difference -3.5% [95%CI: -8.75%-1.73]). Similarly, the AIA incidence in patients with treatment-boosted AIA and patients with treatment-induced AIA was slightly lower in the SAR341402 group compared with the NovoLog/NovoRapid group (4.2% versus 5.1% and 23.0% versus 28.4%, respectively).

Furthermore, there were no relevant differences in maximal AIA titer between the two treatment groups, regardless of the AIA status.

Among patients positive for AIA, cross-reactivity to human insulin was found in more than 90% of the patients at baseline. The percentage of patients with antibodies cross-reacting with human insulin was generally similar between both groups and ranged between 87.5% and 96.8% during the main 6-month on-treatment period.

Table 45. Summary of AIA response during the main 6-month on-treatment period of study EFC15081 - AIA population

	SAR341402 (N=296)	NovoLog/NovoRapid (N=292)
Patients with AIA positive at baseline, n(%)	96/272 (35.3)	98/267 (36.7)
Median titer (1/dil)	8.0	8.0
Q1 ; Q3	4.0 ; 16.0	4.0 ; 16.0
Patients with treatment-boosted AIA, n(%)	4/96 (4.2)	5/98 (5.1)
Median peak titer [a] (1/dil)	24.0	64.0
Q1 ; Q3	16.0 ; 144.0	16.0 ; 256.0
Transient AIA response, n(%)	1/4 (25.0)	3/5 (60.0)
Persistent AIA response, n(%)	0/4	0/5
Indeterminate AIA response, n(%)	3/4 (75.0)	2/5 (40.0)
Patients with AIA negative or missing at baseline, n(%)	200/296 (67.6)	194/292 (66.4)
Patients with treatment-induced AIA, n(%)	46/200 (23.0)	55/194 (28.4)
Median peak titer [a] (1/dil)	8.0	8.0
Q1 ; Q3	4.0 ; 16.0	4.0 ; 16.0
Transient AIA response, n(%)	9/46 (19.6)	14/55 (25.5)
Persistent AIA response, n(%)	13/46 (28.3)	10/55 (18.2)
Indeterminate AIA response, n(%)	24/46 (52.2)	31/55 (56.4)

	SAR341402 (N=296)	NovoLog/NovoRapid (N=292)
Patients with at least one positive AIA sample (prevalence) [b], n(%)	142/296 (48.0)	153/292 (52.4)
Patients with treatment-emergent AIA (incidence) [c], n(%)	50/296 (16.9)	60/292 (20.5)
Patients without treatment emergent AIA, n(%)	242/296 (81.8)	232/292 (79.5)
Inconclusive patients, n(%)	4/296 (1.4)	0/292

AIA: Anti-insulin aspart antibody

a   Maximal titer measured during the main 6-month on-treatment period

b   Prevalence: patients AIA positive at baseline or with treatment-induced AIAs

c   Incidence: patients with treatment-boosted or treatment-induced AIAs (ie, patients with treatment-emergent AIAs)

Note: Percentages are calculated using as denominator the number of patients: with positive or negative AIA sample at baseline (for patients with AIA positive at baseline), with AIA positive (resp. negative or missing) at baseline (for treatment-boosted [resp. treatment-induced] AIA), with treatment-boosted (or treatment-induced) AIA for transient / persistent / indeterminate AIA response, in the AIA population for all other categories

Effects of AIA on safety parameters

Hypoglycemia

The incidence of severe hypoglycemia during the on-treatment period was approximately similar between the treatment groups in patients with treatment-emergent AIA (SAR341402: 2/50 [4.0%] patients; and NovoLog/NovoRapid: 4/60 [6.7%] patients) and in patients without treatment-emergent AIA (SAR341402: 10/242 [4.1%] patients; and NovoLog/NovoRapid: 6/232 [2.6%] patients).

Injection site and hypersensitivity reactions

The incidences in injection site reactions (1 patient in the SAR341402 group) and hypersensitivity reactions (3 versus 2 patients in the SAR341402 group and NovoLog/NovoRapid group, respectively) in patients with AIA were rare, as such, conclusions can not be made.

Common TEAEs and SAEs

The incidence of TEAEs in patients with treatment-emergent AIAs was higher in the SAR341402 group than in the NovoLog/NovoRapid group (SAR341402: 56.0% [28/50] patients; NovoLog/NovoRapid: 45.0% [27/60] patients). However, no single event contributed to this difference and the pattern of common TEAEs was comparable between treatment groups.

Subgroup analyses

Patients with T1DM showed a higher treatment-emergent AIA response compared with T2DM (17.4% versus 23.0% in patients with T1DM and 14.3% vs 8.2% in patients with T2DM for SAR341402 and NovoLog/NovoRapid, respectively). Prior use of NovoLog/NovoRapid did not affect the incidence of AIA.

Safety related to drug-drug interactions and other interactions

Not applicable.

Discontinuation due to AES

The incidence of TEAEs leading to permanent treatment discontinuation was low and slightly higher in the SAR341402 group compared with the NovoLog/NovoRapid group (1.7% [5 patients] versus 1.0% [3 patients]) (see table below).

Table 46. Number (%) of patients with TEAE(s) leading to permanent IMP discontinuation by Primary SOC and PT during the on-treatment period of study EFC15081- Safety population

Primary System Organ Class Preferred Term n(%)	SAR341402 (N=301)	NovoLog/NovoRapid (N=296)
Any class	5 (1.7)	3 (1.0)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	1 (0.3)
Prolymphocytic leukaemia	0	1 (0.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.3)	0
Neutropenia	1 (0.3)	0
NERVOUS SYSTEM DISORDERS	1 (0.3)	0
Headache	1 (0.3)	0
CARDIAC DISORDERS	0	1 (0.3)
Myocardial infarction	0	1 (0.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (0.7)	1 (0.3)
Dermatitis allergic	1 (0.3)	0
Urticaria	1 (0.3)	1 (0.3)
RENAL AND URINARY DISORDERS	1 (0.3)	0
Renal pain	1 (0.3)	0

IMP: Investigational medicinal product , TEAE: Treatment-emergent adverse event, SOC: System organ class, PT: Preferred term

MedDRA dictionary: MedDRA 21.0

n (%) = number and percentage of patients with at least one TEAE leading to permanent treatment discontinuation

Note: Table sorted by SOC internationally agreed order and PT sorted by decreasing frequency according to all TEAE summary.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

In support of demonstration of similarity in safety between SAR341402 and NovoLog/NovoRapid, the Applicant provided safety information from three different sources, i.e. the phase 1 PK/PD singe-dose euglycemic clamp study PDY12695, the 6-month open-label comparative efficacy and safety phase 3 study EFC15081, and the phase 3 safety study PDY15083. The primary safety data are derived from study EFC15081, consequently, only this study will be extensively discussed below.

Patient exposure

Based on study EFC15081, safety data is available for 277 patients with SAR341402 and 272 patients with NovoLog/NovoRapid for > 25 weeks. The duration of exposure and the number of patients is considered sufficient for safety evaluation according to the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/2005_Rev.1). During the evaluation, the Applicant provided additional safety data, particularly immunogenicity data from the 6-month safety extension period of study EFC15081.

Adverse events

The percentage of patients with any treatment-emergent adverse events (TEAEs) was approximately similar between the SAR341402 and the NovoLog/NovoRapid groups (51.8% and 49.33%, respectively). The most frequently reported adverse events (PT) were nasopharyngitis (8.3 versus 8.4% for SAR341402 and NovoLog/NovoRapid, respectively), upper respiratory tract infection (5.3% versus 8.8%) and influenza (5.0% versus 3.0%) and reported by a general similar percentage of patients between the two treatment groups. All other TEAEs were reported in less than 3% of patients regardless of the treatment group. The percentage of patients with TEAEs considered related to study drug was relatively low, however, slightly higher in the SAR341402 compared with the NovoLog/NovoRapid group (4.0% [12 patients] versus 2.4% [7 patients]).

Serious AEs

The incidence of SAE was slightly higher in the SAR341402 group compared with the NovoLog/NovoRapid group (8.3% versus 6.1%). The incidence in serious TEAEs considered as related to study drug was low, however, also slightly higher in the SAR341402 group compared with the NovoLog/NovoRapid group (7 patients [2.3%] versus 1 patient [0.3%], respectively). This slightly higher incidence was due to an imbalance in treatment-related SAEs of hypoglycemic unconsciousness (5 patients [1.7%] versus 1 patient [0.3%] for SAR341402 and NovoLog/NovoRapid, respectively), hypoglycemia (2 patients [0.7%] versus 0 patients), accidental overdose (3 patients [1.0%] versus 1 patient [0.3%]), and device error (2 patients [0.7%] versus 0 patients). SAEs of accidental overdose led to serious hypoglycemic events in 3 patients in the SAR341402 group and 1 patient in the NovoLog/NovoRapid group. It was caused by device use error in 2 patients in the SAR341402 group. The differences are small and do not suggest any particular risk associated with the IMP or the devices.

Deaths

Four deaths have been reported in study EFC15081 (1 and 3 patients in the SAR341402 and the NovoLog/NovoRapid group, respectively), of which none were considered as related to study drug.

AE of special interest

The percentage of patients with any hypoglycemia reported at any time of the day was similar between SAR341402 and NovoLog/NovoRapid (96.7% versus 96.3%, respectively). However, the hypoglycemia event rate per patient-years was slightly higher in the SAR341402 group compared with the NovoLog/Rapid group (72.96 versus 69.31). Additionally, both the percentage and event rate per patient-years of severe hypoglycemia seems to be higher in the SAR341402 group compared with the NovoLog/Rapid group (4.0% versus 3.4% and 0.14 and 0.10 rate per patient-year, respectively). This imbalance could also be observed in other categories of hypoglycemia. However, given the large confidence intervals of the relative difference between groups, the CHMP agrees with the applicant that the differences are too small to be considered clinically meaningful. No relevant differences were observed between treatment groups with regards to treatment-emergent SAEs involving hypoglycemia.

Subgroup analysis by randomization stratum of type of diabetes indicated potential heterogeneity of treatment effect in patients with T1DM versus patients with T2DM for the categories 'any' hypoglycemia (p-value=0.0514) and documented symptomatic hypoglycemia (<3.0 mmol/L [54 mg/dL]) (p-value=0.0924), which can be explained by the fact that T1DM patients are more sensitive in respect to hypoglycaemia. No differences in hypoglycemia risk between SAR341402 and NovoLog/NovoRapid was identified in the other subgroup analyses.

During the conduct of the phase 3 study, the majority of the patients (70.9%) have been exposed to defective glucose test strips to be used for collecting SMPG measurements. The average blood glucose

readings with the defective test strips were between 0.1% and 14.8% higher than the average values obtained with non-defective test strips. The Applicant has performed exploratory analyses in order to evaluate the potential impact of the use of defective strips on hypoglycaemia events. The cumulative duration of the period when defective test strips were used was approximately 55 patient-years and similar between the two treatment groups (SAR341402: 55.18; NovoLog/NovoRapid: 55.71). Of note, the cumulative duration of the use of non-defective test strips was 90.74 and 87.37 for SAR341402 and NovoLog/NovoRapid, respectively. Regardless of the treatment group, the event rate per patient-year of exposure of any hypoglycemia was numerically higher with the use of defective test strips (79.12 and 74.58 for the SAR341402 and NovoLog/NovoRapid group, respectively) compared with the non-defective test strips (68.30 and 65.33 for the SAR341402 and NovoLog/NovoRapid group, respectively), which can be explained by the high average blood glucose readings and consequently administration of higher doses of insulin. However, similar as observed in the overall population, the event rated was numerically higher in the SAR341402 group compared with the NovoLog/NovoRapid group regardless of the use of defective or non-defective strips.

The event rate of severe hypoglycemia per patient-year of exposure remained low with the use of defective test strips (0.13 and 0.18 for SAR341402 and NovoLog/NovoRapid) and approximately similar compared with the use of non-defective test strips (0.14 and 0.05 for SAR341402 and NovoLog/NovoRapid), which is reassuring.

One could say that the use of defective test strips has made this study more sensitive for hypoglycemia events. Therefore, it is reassuring that the event rate of severe hypoglycemia in patients who has used defective strips remained relatively low. Based on this it can be concluded that the use of defective strips does not seems to have had a large impact on the severe hypoglycemia events.

Injection site reactions were rare and no relevant differences between SAR341402 and NovoLog/NovoRapid were observed. The percentage of hypersensitivity reactions was relatively low and similar between the two treatment groups (3.7%).

Immunogenicity

In study EFC15081, the percentage of patients with detectable anti-insulin aspart antibodies (AIAs) at baseline was similar between the two treatment groups (35.3% and 36.7% in the SAR341402 and the NovoLog/NovoRapid groups, respectively). The percentage of patients with a treatment-emergent AIA response (i.e. treatment-boosted or treatment-induced AIAs) during the main 6-month on-treatment period was slightly lower in the SAR341402 group compared with the NovoLog/NovoRapid groups (16.9% versus 20.5%; risk difference -3.5% [95%CI: -8.75%-1.73]). The same pattern of a slightly lower AIA incidence in the SAR341402 group compared with the reference product could be observed with respect to AIA status at baseline (patients with treatment-boosted AIA: 4.2 % and 5.1% and patients with treatment-induced AIA: 23.0% and 28.4% for the SAR341402 and NovoLog/NovoRapid groups, respectively). Furthermore, no relevant differences in terms of duration of the AIA response (transient or persistent) could be observed between the two treatment groups.

Prior use of NovoLog/NovoRapid did not affect the incidence of AIA since a slightly lower AIA incidence in the SAR341402 group could be observed compared with NovoLog/NovoRapid regardless of the AIA status at baseline. With respect to immunogenicity by type of diabetes, patients with T1DM showed a higher treatment-emergent AIA response compared with T2DM (17.4% versus 23.0% in patients with T1DM and 14.3% versus 8.2% in patients with T2DM) which is expected as patients with T1DM are more sensitive in respect to immune responses as compared with the T2DM population.

Overall, the immunogenicity data are reassuring and do not indicate an increased risk for development of AIAs.

Treatment-emergent AIA did not have an effect on the incidence of TEAEs of SAR341402. More specifically, treatment-emergent AIA did not seem to affect the incidence of severe hypoglycemia, although the number of hypoglycemic events is too low to draw firm conclusions. Similarly, the incidence in injection site reactions and hypersensitivity reactions in patients with AIA were rare, as such, conclusions cannot be made.

Laboratory findings and vital signs

No clinically relevant differences between SAR341402 and NovoLog/NovoRapid were identified for any of the laboratory parameters (chemistry, haematology) and vital sign parameters during the main 6-month on-treatment period of study EFC15081.

Discontinuations due to AEs

The incidence of TEAEs leading to permanent treatment discontinuation in study EFC15081 was low but slightly higher in the SAR341402 group compared with the NovoLog/ NovoRapid group. Nevertheless, no pattern indicative for a safety signal could be identified, which is reassuring.

The Applicant stated that one permanent treatment discontinuation in the SAR341402 group was caused by hypoglycemia, however, this event has not been included in the overall incidence of TEAEs leading to permanent treatment discontinuation (Table "Number (%) of patients with TEAE(s) leading to permanent IMP discontinuation by Primary SOC and PT during the on-treatment period of study EFC15081- Safety population"). The applicant clarified why one permanent treatment discontinuation in the SAR341402 group related to hypoglycemia, was not included in the overall incidence of TEAEs leading to permanent treatment discontinuation. This issue is now resolved because it does not result in change to the overall safety assessment.

Results of the 26-week safety extension period of study EFC15081

As requested, the applicant submitted the results of the 26-week safety extension period of study EFC15081 during the evaluation.

The safety profile of SAR341402 was similar to that of NovoLog/NovoRapid, in terms of incidence and rate of hypoglycemia, including severe hypoglycemia, and TEAEs including hypersensitivity and injection site reactions. No major safety findings or signals were identified during the 12-month study period.

Immunogenicity evaluation as assessed by AIAs and neutralizing antibodies (NAbs) in patients with T1DM and T2DM showed no clinically meaningful difference between SAR341402 and NovoLog/NovoRapid. Treatment-emergent AIA had no impact on the efficacy (i.e. HbA1c levels), insulin doses, or safety (as assessed by the incidence and rate of hypoglycemia, hypersensitivity and injection site reactions and common TEAEs) in either treatment group in patients with T1DM or patients with T2DM. Treatment-emergent NAbs had no impact on the efficacy (i.e. HbA1c levels) and insulin doses in patients with T1DM or patients with T2DM.

From the safety database. all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile of SAR341402 was similar to that of NovoLog/NovoRapid, in terms of incidence and rate of hypoglycemia, including severe hypoglycemia, and TEAEs including hypersensitivity and injection site reactions. No major safety findings or signals were identified.

In a biosimilar application, specifically similarity with respect to immunogenicity is of importance. In study EFC15081, no increased immunogenicity of SAR341402 compared with NovoLog/NovoRapid or has been identified, supporting biosimilarity.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance plan

There are no planned additional pharmacovigilance activities. The safety profile of this medicinal product will be further characterised by routine pharmacovigilance in the post-marketing setting, which is considered appropriate.

Risk minimisation measures

No routine or additional risk minimisation measures are applicable for this medicinal product, as there are no important identified/potential risks or missing information included in the RMP for insulin aspart.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 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.

Periodic Safety Update Reports submission requirements

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.

In the first PSUR for insulin aspart, the applicant should discuss the risk of medication errors on prescribing and dispensing due to the similarity of the biosimilar insulin names (e.g. Insulin lispro Sanofi versus Insulin aspart Sanofi), in section 9.2 of the PSUR (i.e. information from other sources: medication errors) and include an overview and analysis of cases of such medication errors linked to

an adverse event. Based on the review of this data, the applicant should also discuss whether this risk should warrant inclusion in the summary of safety concerns in the PSUR (i.e. in section 16.1 of the PSUR) and whether further risk minimisation measures should be proposed.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of bridging reports making reference to NovoRapid 100 units/ml solution for injection and to Toujeo 300 units/ml solution for injection. The bridging reports submitted by the applicant has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Insulin aspart Sanofi (insulin aspart) is included in the additional monitoring list as it is a biological substance 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.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

This application is a centralised procedure made according to Article 10(4), Directive 2001/83/EC, biosimilar application. SAR341402, insulin aspart, solution for injection was developed as a biosimilar of NovoRapid/Novolog (insulin aspart 100 U/ml), which is marketed by Novo Nordisk A/S and authorized in the EU since 1999. The Applicant is seeking approval for the same indication as NovoRapid:

Insulin aspart Sanofi is indicated for the treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.

Demonstration of similarity of SAR341402 to the reference product NovoLog/NovoRapid was based on comprehensive physicochemical and functional characterizations, PK/PD profiles, efficacy and safety (including immunogenicity) data, as described below.

Quality

Insulin aspart is a relatively small and less complex protein molecule enabling thorough and reliable comparison of quality attributes covering structure and impurity pattern. The drug product formulations of SAR341402 and the reference product NovoRapid are similar but also different in some respects.

The solution for SC injection SAR341402 is presented in cartridges and prefilled pens, which are also the common presentations of the reference product.

A comprehensive analytical comparability study was performed to evaluate the similarity between SAR341402 and the reference product NovoRapid.

The applicant's strategy to establish similarity of SAR341402 with the reference product is generally endorsed. The attributes tested in the biosimilarity study focus in particular on structure and impurity pattern and they cover all attributes relevant for the analytical comparison. Justification is provided for attributes not included such as process-related impurities and general pharmaceutical aspects which are covered by the control of drug product section.

For several attributes (pH, insulin aspart, m-cresol, phenol and zinc content) compliance to the reference product label claim is shown as well as similarity in analytical studies. In analytical studies, SAR341402 batches have been tested side by side to EU sourced NovoRapid batches as well as to USA sourced Novolog batches. The number of drug product batches chosen for each test is appropriate to accommodate the expected variability of the analytical method and where relevant isolation of the API was performed and suitability of the isolation process had been investigated. The SAR341402 drug product batches are obtained from two variants of the drug substance manufacturing process. These processes are on the commercial scale and differ only in minor process changes. Comparability between the drug substances batches is sufficiently supported by a comparability exercise comprising release and extended characterization.

The primary/secondary/tertiary structure studies have been applied to two SAR341402 drug product batches derived from the two drug substances process, three batches NovoRapid and three batches of Novolog.

The SAR341402 drug product batches included in the analytical studies are considered sufficiently representative for the commercial product. Their age at the time of testing is generally lower compared to the age of the reference batches of EU sampled and the USA sampled products. The comparative stability and degradation studies indicate that only minor effects on quality attributes could have occurred upon storage of SAR341402 and reference products.

Quantitative results for contents of insulin aspart, excipients and related substances/related impurities have been presented in clear graphs plotted in age of the sample tested. This graphical presentation enables a satisfactory comparison of results. The latter is feasible due to the fact that values of different batches are in relatively good agreement with each other and biosimilar and reference product appear to be rather stable in time. In addition to presentation of the actual results, the applicant applies a statistical evaluation of the data in order to predict sample values at the same age (12 months) and subsequently assess similarity of the 'prediction at 12 months' in an interval approach. This statistical procedure has been applied to each quantitative result. It presents a model which may involve some inevitable flaws but, for the present evaluation, these will not challenge the conclusions on similarity of individual attributes which can reliably be drawn from the actual results and the stability information.

Non-clinical

According to the Guideline on the non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues, sufficient different biological assays have been performed to demonstrate the biosimilarity of Insulin aspart Sanofi for in vitro receptor binding, receptor autophosphorylation and metabolic activity assays with the reference product NovoRapid.

Clinical

Study PDY12695, a cross-over, double-blind, single-dose euglycemic study in patients with type 1 diabetes mellitus, was conducted to demonstrate that the proposed commercial formulation of

SAR341402 solution has PK and PD profiles similar to that of NovoLog/NovoRapid. The performance of an euglycemic clamp study in T1DM patients to demonstrate similarity is in accordance with the Guideline on the non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005_Rev 1).

Study EFC15081, a 6-month, multinational, multicenter, randomized, controlled, parallel-group, open-label non-inferiority study with a 6-month comparative safety extension period has been conducted to compare the efficacy and safety of SAR341402 with NovoLog/NovoRapid. According to the guideline on human insulin and insulin analogues similar biological medicinal products (EMEA/CHMP/BMWP/32775/2005_Rev 1), there is no anticipated need for specific efficacy studies since endpoints used in such studies; usually HbA1c, are not considered sensitive enough to detect potentially clinically relevant differences between insulins. Therefore, efficacy studies are only considered as supportive for efficacy. The euglycemic PK/PD clamp study PDY12695 is considered pivotal to demonstrate comparable efficacy. With respect to safety, in a biosimilar application the main focus lies on the immunogenicity of the new product compared to the reference product. The PK/PD euglycemic study does not contribute much to the safety assessment due to the short duration and limited number of participants, as such study EFC15081 is considered sufficient to demonstrate comparability in terms of safety, particularly immunogenicity.

An additional study was submitted in the second round, study PDY15287. This cross-over, double-blind, single-dose euglycemic clamp study was performed in healthy Japanese subjects to compare the PK and PD profiles of SAR341402 with NovoRapid.

3.2. Results supporting biosimilarity

Quality

Insulin aspart is a relatively small and less complex protein molecule enabling thorough and reliable comparison of structure and impurity pattern. The similarity in primary, secondary, tertiary structure as well as higher-order structure between SAR341402, NovoRapid and NovoLog as well as between NovoRapid and NovoLog has been clearly established in a panel of orthogonal analytical techniques. The study design is considered sufficient to detect any possible difference in the structure of insulin aspart. Results of comparative *in vitro* and *in vivo* biological activity assays further confirm the similarity in structure.

The comparative RP-HPLC side by side analysis results are very close. The comparative in-use stability study demonstrates similarity of biosimilar with the reference product under the in-use conditions. No major qualitative or quantitative differences in impurity profiles are observed. As confirmed in sensitive LC-MS studies similar impurities are present in SAR341402 and LC-MS. Similar degradation profiles are also reported in comparative side-by-side stability studies and thermal, hydrolytic and light stress studies.

Non-clinical

The Applicant performed comparative receptor binding assays on both human insulin receptors (IR-A and IR-B), including on-off kinetics, with the product SAR341402 (four batches) and reference compounds (three batches each of NovoLog and NovoRapid). All 90% confidence intervals of the ratios of mean normalized binding affinities (IC50) and binding constants (Ka1, Ka2, Kd1 and Kd2) were well within the 0.80 – 1.25 acceptance interval. Also for the IGF-1 receptor, these binding constants were well within the 0.80 – 0.125 acceptance interval. Therefore, SAR341402, NovoLog and NovoRapid could be considered as similar in these in vitro assays.

Four batches of SAR341402 and three batches each of NovoLog and NovoRapid were studied in a side-by-side biological similarity assessment in a number of in vitro assays. Biological activity was measured by autophosphorylation of IR-A, IR-B and IGF-1R, by inhibition of lipolysis in human adipocytes, stimulation of glucose uptake in L6 myocytes, gene regulation of G6PC in primary human hepatocytes and mitogenic potency by stimulation of radiolabelled thymidine incorporation into DNA of MCF-7 cells. All ratios of the mean normalized EC50 and IC50 values with 90% confidence intervals of SAR341402 and the reference NovoRapid were well within the 0.80 – 1.25 acceptance interval. Therefore it can be concluded that SAR341402 shows a similar metabolic and mitogenic activity as the reference product.

Clinical

Efficacy

In the pivotal phase 1 PK/PD study PDY12695 in patients with T1DM, the primary PK parameters Cmax, AUC_{last} and AUC_{inf} support biosimilarity between SAR341402 and NovoRapid because the 90% CI for the ratio of treatments of these parameters were within the acceptance range of 80-125%. This is supported by the results of study PDY15287 in Japanese healthy subjects.

In study PDY12695, the primary PD parameter $GIR\text{-}AUC_{0\text{-}12h}$ and key secondary PD parameter GIR_{max} support biosimilarity between SAR341402 and NovoRapid, since the 95% CI for the ratio of treatments of these PD parameters were narrow and well within the equivalence margin of 80%-125%. This is supported by the results of study PDY15287 in Japanese healthy subjects.

In the phase 3 study EFC15081, non-inferiority in change in HbA1c of SAR341402 over NovoLog/NovoRapid was demonstrated as the upper bound of the 2-sided 95% CI of the difference between SAR341402 and NovoLog/NovoRapid was below the predefined non-inferiority margin of 0.3% (LS mean difference of -0.08% [95%CI: -0.192 to 0.039]), thereby providing supportive evidence with respect to the biosimilarity of SAR341402 to NovoLog/NovoRapid.

Additionally, the secondary endpoints of the percentage of HbA1c responders (HbA1c <7.0%), as well as change from baseline to Week 26 in FPG, mean 24-hour plasma glucose concentration, glucose excursions, and 7-point SMPG profiles support the primary outcome, since there were no clinically relevant differences observed between SAR341402 and NovoLog/NovoRapid for these endpoints.

After 12 months of treatment in study EFC15081, the efficacy of SAR341402 and NovoLog/NovoRapid was similar in adult patients with T1DM or T2DM. Basal, mealtime and total insulin doses remained almost unchanged during this treatment period in both treatment groups.

Safety

No increased immunogenicity of SAR341402 compared with NovoLog/NovoRapid have been identified. The percentage of patients with a treatment-emergent AIA response (i.e. treatment-boosted or treatment-induced AIAs) during the main 6-month on-treatment period was slightly lower in the SAR341402 group compared with the NovoLog/NovoRapid groups (16.9% versus 20.5%; risk difference -3.5% [95%CI: -8.75%-1.73]). The same pattern of a slightly lower AIA incidence in the SAR341402 group compared with the reference product could be observed with respect to AIA status at baseline (patients with treatment-boosted AIA: 4.2 % and 5.1% and patients with treatment-induced AIA: 23.0% and 28.4% for the SAR341402 and NovoLog/NovoRapid groups, respectively). Furthermore, no differences in tolerability have been identified.

Immunogenicity evaluation as assessed by AIAs and neutralizing antibodies (NAbs) in patients with T1DM and T2DM showed no clinically meaningful difference between SAR341402 and NovoLog/NovoRapid during the 26-week safety extension period of study EFC15081. Immunogenicity evaluation as assessed by AIAs and neutralizing antibodies (NAbs) in patients with T1DM and T2DM

showed no clinically meaningful difference between SAR341402 and NovoLog/NovoRapid. Treatment-emergent AIA had no impact on the efficacy (i.e. HbA1c levels), insulin doses, or safety (as assessed by the incidence and rate of hypoglycemia, hypersensitivity and injection site reactions and common TEAEs) in either treatment group in patients with T1DM or patients with T2DM. Treatment-emergent NAbs had no impact on the efficacy (i.e. HbA1c levels) and insulin doses in patients with T1DM or patients with T2DM.

3.3. Uncertainties and limitations about biosimilarity

Quality

The analytical studies in 3.2R present strong support on the similarity of SAR341402 and Novorapid. Concerns were raised whether the differences in formulation between SAR34140 and the reference product impact the oligomeric structure of the active substance. These issues were resolved by additional data submitted during the evaluation.

Non-clinical

There are no uncertainties or limitations about the similarity of SAR341402 with NovoLog and Novorapid from a non-clinical point of view.

Clinical

Efficacy

In the pivotal phase 1 PK/PD study PDY12695, unity was not included in the CI for AUClast and AUCinf. Further, the secondary parameter $GIR-AUC_{4-12h}$ appears lower for SAR341402 than for NovoRapid with the lower confidence limit for the ratio below 0.8, as was also insulin aspart AUC after 4 hours. However, considering the minor contribution of AUC4h-last and GIR-AUC4-12h to total AUC and GIR-AUC respectively, and considering the large variability in AUC after 4 h, the relevance of these differences concerning the last part of the study is considered limited. In study PDY15287 in healthy Japanese subjects, which was submitted during the evaluation, no significant differences were found between SAR341402 and NovoRapid.

Safety

According to the safety data obtained from study EFC15081 there seem to be a slightly increased risk of hypoglycemia with SAR341402 compared with NovoLog/NovoRapid. In this study, both the percentage and event rate per patient-years of hypoglycemia seemed to be higher in the SAR341402 group compared with the NovoLog/Rapid group. The differences are however too small to be clinically meaningful.

Immunogenicity evaluation as assessed by AIAs and neutralizing antibodies (NAbs) in patients with T1DM and T2DM also showed no clinically meaningful difference between SAR341402 and NovoLog/NovoRapid during the 26-week safety extension period of study EFC15081.

3.4. Discussion on biosimilarity

Based on the PK/PD euglycemic clamp study, the Applicant has demonstrated PK/PD comparability in the relevant PK and PD parameters (Cmax, AUClast AUCinf, $GIR-AUC_{0-12h}$, Gmax). Demonstration of PK/PD similarity by this euglycemic clamp study is considered key for the assessment for similar efficacy. For secondary endpoints, a lower partial $GIR-AUC_{4-12}$ and AUC_{4-last} were observed for SAR341402 with the lower confidence limit for the ratio below 0.8. However, considering the minor contribution of AUC4h-last and GIR-AUC4-12h to total AUC and GIR-AUC respectively, and considering

the large variability in AUC after 4 h, the relevance of these differences concerning the last part of the study is considered limited. In study PDY15287 in healthy Japanese subjects, which was submitted in the second round, no significant differences were found between SAR341402 and NovoRapid. Demonstration of non-inferiority in a change in HbA1c of SAR341402 over NovoLog/NovoRapid in the phase 3 study EFC15081 further supports the outcome of the clamp study. With respect to safety, in a biosimilar application the main focus lies on the immunogenicity of the new product compared to the reference product. No increased risk for development of anti-insulin aspart antibodies of SAR341402 compared with NovoLog/NovoRapid have been identified, indicating similarity in term of risk immunogenicity. No relevant differences were observed between treatment groups with regards to treatment-emergent AEs involving hypoglycemia.

3.5. Extrapolation of safety and efficacy

Not applicable.

3.6. Additional considerations

Not applicable.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Insulin aspart Sanofi is considered biosimilar to NovoRapid. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Insulin aspart Sanofi is not similar to Amglidia within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

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

Insulin aspart Sanofi is indicated for the treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other 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.

In the first PSUR for insulin aspart, the applicant should discuss the risk of medication errors on prescribing and dispensing due to the similarity of the biosimilar insulin names (e.g. insulin lispro Sanofi versus insulin aspart Sanofi), in section 9.2 of the PSUR (i.e. information from other sources: medication errors) and include an overview and analysis of cases of such medication errors linked to an adverse event. Based on the review of this data, the applicant should also discuss whether this risk should warrant inclusion in the summary of safety concerns in the PSUR (i.e. in section 16.1 of the PSUR) and whether further risk minimisation measures should be proposed.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.