18 May 2017
EMA/351195/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Insulin lispro Sanofi

International non-proprietary name: insulin lispro

Procedure No: EMEA/H/C/004303/0000

Note

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

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List of abbreviations

AAS	Atomic absorption spectrometry
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
AESI	Adverse event of specific interest
AIA	Anti-insulin antibodies
ANCOVA	Analysis of covariance
ARAC	Allergic reaction assessment committee
AST	Aspartate transaminase
AUC	Area under the concentration-time curve
%B/T	Per cent bound radioactivity relative to the total amount of radioactivity present
BMI	Body mass index
BP	Blood pressure
CFR	Code of Federal Regulations
CI	Confidence interval
Cmax	Maximal concentration
CRU	Clinical research unit
CSII	Continuous subcutaneous insulin infusion
CSR	Clinical study report
dL	Decilitre
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
E. coli	Escherichia coli
EC	European Commission
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPC	End of Production Cells
ERC	Ethical Review Committee
EU	European Union

FAS	Full Analysis Set
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GIR	Body weight standardized glucose infusion rate
GIR-AUC_{0-12h}	Area under the body weight standardized GIR versus time curve from 0 to 12 hours
GIRmax	Maximum smoothed body weight standardized GIR
GIR-tmax	time to GIRmax
GM	Geometric mean
GMR	Geometric mean ratio
HA	Hypoglycaemia assessment
HbA1c	Glycated haemoglobin
HPLC	High pressure liquid chromatography
HLT	High level term
Hr	Hour
ICH	International Conference on Harmonisation
ID	Identification
IGF-1R	Insulin-like growth factor 1 receptor
IMP	Investigational medicinal product
INS-AUC infinity	Area under the concentration of insulin (lispro) versus time curve extrapolated to
INS-AUClast	Area under the concentration of insulin (lispro) versus time curve from time 0 until the time corresponding to the last concentration above the limit of quantification
INS-Cmax	Maximum observed concentration of insulin (lispro)
IR-A	Insulin receptor, subtype A
IR-B	Insulin receptor, subtype B
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive voice response system
IWRS	Interactive web response system
L	Litre
LADA	Late autoimmune diabetes in adults
LOCF	Last observation carried forward

LOESS	Locally weighted regression in smoothing scatter plots
LOQ	Limit of quantitation
LS means	Least squares means
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MBC	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mL	Millilitre
MODY	Maturity-onset diabetes in the young
ND	Not done
NEC	Not Elsewhere Classified
NIMP	Non-investigational medicinal product
OHA	Oral anti-hyperglycaemic medication
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred term
rDNA	Recombinant deoxyribonucleic acid
ROW	Rest of the world
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SMPG	Self-monitored plasma glucose
SMQ	Standardized MedDRA Query
SOC	System organ class
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
Tmax	Time to maximal concentration
TAMC	Total aerobic microbe count

TYMC	Total yeast microbe count
U/kg	Units/kilogram
U100	100 Units/millilitre
ULN	Upper limit of normal
US	United States
WBC	White blood (cell) count
WCB	Working cell bank
WFI	Water for injections

1. Background information on the procedure

1.1. Submission of the dossier

The applicant sanofi-aventis groupe submitted on 7 September 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Insulin lispro 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:

"For the treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Insulin lispro Sanofi is also indicated for the initial stabilisation of diabetes mellitus."

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a 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 Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Humalog 100 U/ml solution for injection
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 30-04-1996
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EMEA/H/C/000088

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

- Product name, strength, pharmaceutical form: Humalog 100 U/ml solution for injection
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 30-04-1996
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EMEA/H/C/000088

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

- Product name, strength, pharmaceutical form: Humalog 100 U/ml solution for injection
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 30-04-1996
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EMEA/H/C/000088

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

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

Scientific Advice

The applicant received Scientific Advice from the CHMP on 25/09/2014. The Scientific Advice pertained to insert quality and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Martina Weise

- The application was received by the EMA on 7 September 2016.
- The procedure started on 29 September 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 December 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 December 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 16 December 2016.
- During the meeting on 26 January 2017, the CHMP agreed on the consolidated List of Questions

to be sent to the applicant.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 February 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 March 2017.
- During the PRAC meeting on 06 April 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 21 April 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 25 April 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 03 May 2017.
- During the meeting on 18 May 2017, 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 lispro Sanofi on 18 May 2017.

2. Scientific discussion

2.1. Introduction

Problem statement

Insulin lispro Sanofi (also referred to in this report as SAR342434), has been developed as an insulin lispro biosimilar. The EU reference medicinal product is Humalog solution for injection 100 U/mL, which was authorised through the centralised procedure in 30 April 1996.

Insulin lispro is approved and marketed in several countries worldwide, including the EU and USA, for the treatment of patients with type 1 diabetes (T1DM) and type 2 diabetes (T2DM).

About the product

Insulin lispro Sanofi is an insulin lispro, an analogue protein of human insulin. It is a genetically engineered recombinant protein produced in *Escherichia coli* cells. Insulin lispro belongs to the pharmacotherapeutic group: drugs used in diabetes, insulins and analogues for injection, fast-acting, ATC code: A10AB04.

Insulin lispro Sanofi is available in three presentations, as a cartridge or a pre-filled pen (3 ml, 300 U) and as a vial (10 ml, 1000 U). The cartridge can either irreversibly be assembled into a multiple-use, disposable pen injector by the applicant or it can be used with the marketed reusable CE-marked pens JuniorStar and AllStar.

In accordance with its reference product, the applied indications for Insulin lispro Sanofi were for the treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis and for the initial stabilisation of diabetes mellitus.

Mechanism of Action

Insulin lispro is homologous to human insulin with the exception of the penultimate lysine and proline residues on the C-terminal end of the B-chain at B28 and B29, which are reversed. This structural change renders lispro insulin less prone to self-association than human insulin. The relatively unstable lispro hexamers readily dissociate to monomer subunits (without the intermediate dimerization as human insulin); as a result lispro insulin is absorbed more rapidly after subcutaneous injection than human regular insulin. Consequently, insulin lispro has a faster onset and shorter duration of hypoglycaemic action than human regular insulin when administered subcutaneously.

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 lispro 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)
- "International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines (ICH E6)

2.2. Quality aspects

2.2.1. Introduction

Insulin lispro, the active substance is a rapid-acting insulin with faster onset and shorter duration of action when compared with human regular insulin. Insulin lispro differs from human insulin in that the amino acid proline at position B28 is replaced by lysine and the lysine in position B29 is replaced by proline.

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

The finished product is presented as a solution for injection containing 100 units/ml of insulin lispro as the active substance. Other ingredients are: metacresol, glycerol, disodium hydrogen phosphate heptahydrate, zinc oxide, water for injections, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

The product will be available in a 10 ml vial, a 3 ml cartridge for use in compatible CE-marked re-usable pens (AllStar and JuniorStar) and a 3 ml disposable pre-filled pen injector (3 ml cartridge irreversibly integrated in a disposable pen injector). Insulin lispro Sanofi pen injector is a fully mechanical device, containing no electronic components. The pen injector is designed to deliver multiple doses of variable volume.

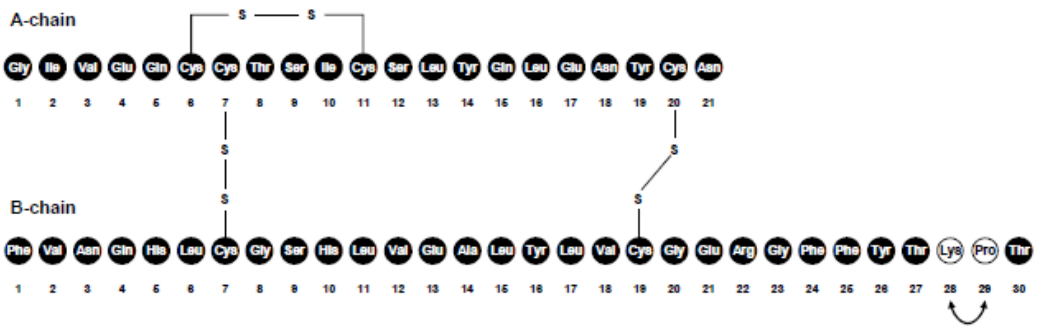
2.2.2. Active Substance

General information

The active substance is a two-chain peptide consisting of 51 amino acids. The international non-proprietary name (INN) is insulin lispro. The A-chain is composed of 21 amino acids and the B-chain is composed of 30 amino acids. It is identical in primary structure to human insulin, only differing in amino acid sequence at positions 28 and 29 of the B-chain. Human insulin is 28^{B}-L-Proline-29^{B}-L-lysine, whereas insulin lispro is 28^{B}-L-Lysine-29^{B}-L-Proline.

As human insulin, insulin lispro contains 2 interchain disulfide bonds and 1 intrachain disulfide bond, in total 3 disulfide bonds. All amino acids are natural L-amino acids. The structure, including the change in comparison to human insulin, is outlined in Figure 1 below.

Figure 1: Schematic amino acid sequence indicating the change in comparison to human insulin



Primary, secondary and tertiary structures are well-defined without considerable inherent heterogeneity and without glycosylation or other post-translational modifications.

Manufacture, characterisation and process controls

Description of manufacturing process and process controls

Insulin lispro is produced by recombinant DNA technology using an *Escherichia coli* strain as host cell for the expression plasmid. The upstream process starts with one vial from the Working Cell Bank (WCB) that is expanded via shake flask followed by seed fermentation and main fermentation. The manufacturing process can be divided into three parts; cultivation steps, basic downstream processing and final purification phase. Following transfer of cell suspensions from shake flask via seed fermenter to the production fermenter, cells are further expanded in the production fermenter to reach the required cell density level for induction of expression of insulin lispro.

The fusion protein can be synthesized in such amounts that it precipitates within the cell, forming inclusion bodies. The cells with the inclusion bodies are harvested by centrifugation and disrupted to liberate the inclusion bodies. Thereafter the fusion protein is dissolved and the insulin lispro precursor is formed by refolding reaction, followed by enzymatic cleavage and chromatographic purification steps to obtain a solution of insulin lispro. Centrifuged precipitate is washed and dried. Dried active substance is filled, homogenised, divided in suitable portions, if desired, and stored. Adequate information has been provided for the container closure system of the active substance.

The process for insulin lispro 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.

Control of materials

In the manufacturing of insulin lispro no materials of human or animal origin are used. The raw materials used in the manufacturing have been adequately described in the dossier.

The cell bank system has been established according to ICH guidelines comprising Master Cell Bank (MCB) and Working Cell Bank (WCB). The history and development of the expression system is presented as well as a protocol to establish a new WCB. The cell bank stability show good stability.

Manufacturing process development

The insulin lispro manufacturing process is based on Sanofi's platform process for recombinant proteins expressed in *E. coli.* For the development of the manufacturing process of insulin lispro elements of

QbD were added in an otherwise conventional manufacturing development in order to implement a risk based strategy.

The criticality of parameters was determined by a risk-based approach based on the severity, occurrence and detectability of the process failure which has been adequately described including a list of the critical quality attributes and non-critical attributes. The determination of proven acceptable ranges has also been sufficiently described. Critical process parameters are controlled during manufacturing.

All predefined ranges for operational parameters and specifications for performance parameters were consistently met.

Process development addressed the intended quality target product profile (QTPP) of insulin lispro solution for injection which was found to be similar to Humalog. Critical quality attributes were defined based on the QTPP, available knowledge about the originator active substance (AS) and on the experience of Sanofi from other insulin analogues produced from recombinant *E. coli.*

Process characterisation and development from pilot scale to commercial scale has been adequately presented. The comparability from pilot scale to final process confirmed the comparability of the active substance throughout development.

Process Validation

The manufacturing process has been adequately validated. The results from the validation runs for each manufacturing step are very consistent and therefore the robustness of manufacturing is acceptable and the process well controlled. In addition it has been validated that the process and product related impurities are efficiently removed during downstream steps.

Holding times have been validated to demonstrate the stability of the concerned intermediate.

Characterisation

The structural elucidation and confirmation of insulin lispro has been carried out on batches of insulin lispro with the following orthogonal analytical techniques: amino acid sequencing, MS, peptide mapping, isoelectric point determination by capillary isoelectric focusing, ultraviolet (UV) / visible absorption spectrophotometry, CD, FT-IR and NMR. In addition, comparisons have been performed with insulin lispro batch and the current USP and Ph. Eur. reference standards, to demonstrate similarity of structure, using the following techniques: UV/visible absorption spectrophotometry, CD, FT-IR and NMR.

The biological activity has been adequately presented and discussed. All tests gave acceptable and predicted results verifying the correct structural construction of insulin lispro molecule.

Potential impurities arising from the expression system, the process and product related impurities arising during production and purification steps have been described and presented. Removal of impurities is demonstrated to be well below the limits given in the Ph. Eur. For insulin lispro no viral contamination is foreseen, since no animal or human material is used and the peptide is expressed in *E.coli* not supporting viral expression.

Metal catalysts, reagents and elemental impurities are addressed as required by ICH Q3D, and the very low amounts found do not raise any concern.

Specification

The proposed specifications for insulin lispro active substance are considered appropriate for control of the active substance.

The analytical methods used for active substance release are mainly based on the pharmacopoeial monograph for insulin lispro, so that no respective validation data is required in the dossier. For the in-house methods, validation data have been provided demonstrating the suitability of the methods.

Production batches of insulin lispro active substance as well as batches that have been used during development for toxicological, clinical and primary stability studies have been presented. All batch results were in accordance with the active substance specifications.

As official standards for insulin lispro are available (Ph. Eur. and USP.) no in-house primary standard for insulin lispro was established. A secondary/working standard has been prepared and the criteria for establishment of new batches of reference standard have been stated and are considered acceptable.

Stability

Insulin lispro stability studies have been performed according to ICH guidelines for three primary batches manufactured at production scale and filled in containers representative of the container closure system proposed for commercial manufacture. Stability data have been presented.

Photostability in accordance with ICH Q1B has been tested. The results under conditions of -20 ± 5 °C, and under +5 °C ± 3 °C show good stability for the tested period. Under stress conditions and under light, out of specifications are obtained as expected, which is acceptable.

A suitable post-approval stability protocol and commitments have been provided.

The results generated during the stability studies support the proposed shelf life and storage conditions for the active substance stored in an airtight container, protected from light.

Comparability exercise for Active Substance

Comparability of the active substance was demonstrated from laboratory scale to production scale.

Supportive data related to process related impurities have been presented for the clinical program and the intended commercial process side by side. There are no significant differences between the results.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Insulin lispro Sanofi, solution for injection finished product (FP) is intended for subcutaneous administration and it may also be administered intravenously. The FP has the same excipients as the reference product, Humalog. The excipients (metacresol, glycerol, disodium hydrogen phosphate heptahydrate, zinc oxide, water for injections, hydrochloric acid, sodium hydroxide) have been justified based on formulation development studies and are in compliance with Ph. Eur. and USP.

The product is presented as:

- Insulin lispro Sanofi 100 units/ml solution for injection in vial

  10 ml vial containing 10 ml nominal volume of FP solution to be administered by use of a syringe, a pump device or to be diluted in an infusion bag. The type I colourless glass vial is closed with a flanged cap (aluminium) with a sealing disk (chlorobutyl rubber) and a tear-off cap (polypropylene).

- Insulin lispro Sanofi 100 units/ml solution for injection in cartridge

  Type I colourless glass cartridge with a black plunger (bromobutyl rubber) and a flanged cap (aluminium) with a sealing disk (laminate of isoprene and bromobutyl rubber). Each cartridge contains 3 ml of solution.

- Insulin lispro Sanofi 100 units/ml solution for injection in a pre-filled pen

  Type I colourless glass cartridge with a black plunger (bromobutyl rubber) and a flanged cap (aluminum) with a sealing disk (laminate of isoprene and bromobutyl rubber) sealed in a disposable pen injector. Each pre-filled pen contains 3 ml of solution.

EC certificates for quality assurance system issued by Notified Body TUV SUD Product Service GmbH (Stuttgart, Germany) have been provided for the manufacturers of the reusable pens. Information on the human factors validation study for the pen injector has been provided.

Pharmaceutical development

The applicant has performed an appropriate formulation study with varying quantities of the formulation excipients. For this study, a suitable design of experiment (DoE) approach was applied based on FP physicochemical test parameters which had been evaluated by a risk assessment. The outcome of the study confirmed the composition to be comparable to Humalog and to be adequate and justified in view of FP quality and stability.

The degradation of Insulin lispro Sanofi FP solution was adequately studied by applying appropriate stress conditions such as elevated temperature, different pH and light exposure. The optimum concentration of the preservative metacresol in Insulin lispro Sanofi FP solution was adequately evaluated to ensure sufficient antimicrobial efficacy up to the end of shelf life.

In order to demonstrate the suitability of the selected container closure systems different tests and studies were conducted. Extractables and leachables (E&L) studies were adequately designed and ensured a comprehensive E&L evaluation by covering all different components of the container closure systems. A toxicological assessment on the quantities of the leachables found in Insulin lispro Sanofi FP concluded that these leachables do not present a toxicological concern.

Functional performance of the Insulin lispro Sanofi disposable pen and of the re-usable pen injectors after assembly with Insulin lispro Sanofi cartridges was appropriately investigated according to the relevant ISO standards.

Integrity of the container closure systems was confirmed by using an adequate container closure integrity evaluation study by using a microbial challenges test.

Manufacture of the product and process controls

The finished product manufacturing process has been sufficiently described and validated. Flow charts and descriptions of each unit operation of the manufacturing processes have been provided for cartridges, vials and disposable pen injectors.

The critical steps of the insulin lispro solution manufacturing process have been determined. The validated process is controlled by “critical process controls”.

Process Validation

The process validation has been adequately performed. The process controls and release testing results of all cartridge and vial batches are coherent and within the pre-defined acceptance criteria and specification limits. The impact of different manufacturing activities on the degradation of insulin lispro had been adequately evaluated during pharmaceutical development.

Sterilization of equipment, filling of sterile product into cartridges and vials has been validated. The provided validation results met their pre-defined acceptance criteria.

Product specification

The finished product release specifications for the cartridge and vial are identical with the exception of the acceptance criteria for extractable volume that has been set according to the container.

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., BP and USP monographs for insulin preparations. In addition, an appropriate specification for the pre-filled Insulin lispro Sanofi pen injector has been established.

Bach release data of commercial scale and pilot scale batches has been presented. The provided results fulfil the specification criteria for all attributes.

Stability of the product

Insulin lispro Sanofi finished product has been placed in stability studies in line with ICH Q5C. The stability protocols for the storage conditions and testing frequency have been provided. The protocols provided for cartridge and vial presentations cover long term, accelerated and stressed conditions for a maximum of 36, 6 and 1 month’s storage, respectively.

The results of the cartridges and vials remain within the specification limits for all parameters tested at long term and accelerated storage. In-use testing of 28 days has been performed.

Pen functionality and dose accuracy was tested. The dose accuracy study results remained within the specifications.

Photostability studies performed according to ICH Q1B demonstrate that the finished product in vials and cartridges is photosensitive. The carton box and pen injector are sufficient to protect the finished product from light.

Temperature cycling studies have been performed. The stability parameters tested are found adequate. Based on the results it can be concluded that the finished product presented in cartridges and vials is stable when stored at 2°C - 8°C but becomes unstable at high temperatures (+37/40°C)

and during exposure to light. Excursions of one month at room temperature do not have a major impact on the quality parameters tested.

Based on the primary and supportive stability data the claimed 36 months shelf life stored at 2°C - 8°C can be accepted. The in-use stability data support a storage temperature of below 30°C after first use and the product should be disposed of 4 weeks after first use.

Comparability exercise for finished product

The finished product process development has started at lab scale and has been increased via pilot scale to final commercial scale processes for 3 ml cartridges and 10 ml vials. By conducting appropriate process characterisation studies, the impact of process parameters on FP quality and stability were evaluated. Based on the outcome of the process characterisation studies, an adequate process control strategy was established including raw material control, process controls and process parameters to be monitored.

The analytical comparability of pilot scale and production scale batches has been assessed using lot release testing. The release results of both batches fit well within the specification limits and are highly similar. Stability testing at long term, accelerated and stress testing conditions showed comparable profiles for both batches. The analytical comparability testing has been appropriately performed for the finished product batches manufactured at pilot scale and commercial scale processes.

Adventitious agents

For the manufacturing of the finished product Insulin lispro Sanofi solution for injection 100 U/mL no animal and/or human derived material is used. This applies to the active substance and all excipients used. Moreover, the finished product complies with the requirements of the note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01, current revision).

Biosimilarity

Insulin lispro Sanofi has been developed as a biosimilar to Humalog (Insulin lispro). The reference product is marketed worldwide, and the studies were designed to demonstrate similarity between Insulin lispro Sanofi derived from different active substance batches, Humalog purchased from the EU market (Humalog EU) and Humalog purchased from the US market (Humalog US). In the clinical studies Humalog sourced both from the EU and the US has been used and therefore a bridging study between EU and US Humalog is necessary to demonstrate that US Humalog is representative of EU Humalog.

The composition of the biosimilar is comparable to the reference product. The composition of Humalog with respect to content of insulin lispro, m-cresol and zinc as well pH is available from the product information. For these parameters, the applicant´s approach to demonstrate similarity has been to compare Insulin lispro Sanofi with the available Humalog information. Analytical data of Humalog batches regarding these parameters have been submitted. The results support that Insulin lispro Sanofi is similar to Humalog with regard to the composition.

Similarity is established based on physicochemical properties, biological properties and on comparison of purity and product related proteins. The similarity is demonstrated also by performing comparative stability studies under long term, accelerated and stress conditions and by performing photostability tests.

A set of state-of-the-art analytical methods was used to characterize side-by-side Insulin lispro Sanofi and Humalog and to address physicochemical characteristics of insulin lispro. A statistical evaluation has been applied to demonstrate similarity of product related impurities. Process-related impurities have not been tested in side by side analysis but their levels are controlled as part of the control strategy.

Similarity assessment results

Physicochemical studies

The primary structure was investigated by mass spectrometry and Edman degradation. Experimental results derived from the biosimilar and reference product were compared to the theoretical primary structure of insulin lispro that is available in literature. No differences in the amino acid sequences were detected between Humalog US, Humalog EU, and Insulin lispro Sanofi. The intact masses were determined by MALDI MS and comparable molecular masses were observed for Humalog US, Humalog EU, and Insulin lispro Sanofi. Similarly the reduced masses of insulin lispro A- and B-chain were determined by MALDI MS. The masses comply with the theoretical masses and no differences between the samples were observed. Secondary structure was investigated by FT-IR and Far-UV spectroscopy.

The results for secondary structure determination demonstrate correctly folded secondary structures of the insulin lispro that are identical in the products.

Near-UV CD spectroscopy was used for side-by-side comparison of the tertiary structure of Insulin lispro Sanofi and Humalog. Overlapping near-UV CD spectra were observed indicating identical tertiary structures.

The structure was verified also by NMR spectroscopy. Coinciding NMR spectra for all samples investigated were obtained. Investigation of higher order structure revealed that Insulin lispro Sanofi, Humalog US and Humalog EU mainly contain the insulin hexamer.

The molecular mass was measured with an analytical ultracentrifuge. All samples contained mainly hexamer and small amounts of the putative monomer and higher oligomers. No differences between the Insulin lispro Sanofi batches, Humalog US batches and Humalog EU batches were observed. pH, zinc content and preservative were all within the same range of Humalog and within the specifications.

Biological properties

The biological activity of Insulin lispro Sanofi, Humalog US and Humalog EU was assessed by the rabbit blood sugar method according to USP 37 <121>. According to the applicant an effect of lot-to-lot variability could be excluded based on the physicochemical data on potency and purity. Therefore, the test was performed on one batch per product. Results revealed comparable biological activity that complies with the label of Humalog, 100 U/ml.

The applicant has used two different HPLC methods to assess the purity of the products. Several batches of Insulin lispro Sanofi and several batches of Humalog EU and Humalog US were used. Similarity ranges were defined on the basis of batch to batch variability of Humalog EU, and the

applicant defined similarity ranges such that equivalence can be shown for the comparison of Humalog EU in cartridges and Humalog EU in vials.

A side-by-side analysis of Insulin lispro Sanofi with Humalog EU and Humalog US was performed to investigate the samples with respect to desamido variants and other impurities, applying a method that is orthogonal to RP-HPLC. No major differences were detected. For the results of high molecular weight proteins (HMWP) analysis no major differences were observed as well.

Overall, several batches (Humalog vials and cartridges from EU and US market) were analysed. The impurity profiles of Humalog and Insulin lispro Sanofi were found to be similar for all batches investigated.

Comparative stability studies

A comparison of the stability profiles of Insulin lispro Sanofi, Humalog US, and Humalog EU was performed under in-use conditions, (+25 °C; 28 days), accelerated (+25 °C, 6 months) and stress (+37 °C, 3 months) conditions as well as for long term conditions (+5 °C). A photostability study, where samples were exposed to indoor light for a period of 14 days, was also carried out.

The data indicate that the degradation pathways of Insulin lispro Sanofi, Humalog EU and Humalog US under the stability conditions investigated are comparable. No additional degradation products were detected in Insulin lispro Sanofi.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Active substance

Manufacturing

Fermentation of *E.coli* bacteria and expression of the insulin lispro is a common process for production of insulin and its analogues. The relevant parameters have been discussed. There are no intermediates in the process. The holding times during the process are intended only for short term storages. Hold time studies have been conducted. The results for different process steps are stable along the holding time applied for the step. All containers used for the collection/storage of the intermediates are considered inherent material.

Cell banks

Generation and characterisation of the MCB and WCB have been adequately described. The end of production cells are shown to be stable. The specification for establishing a new WCB is provided and the protocol is agreed.

Process Validation

The validation of the process is considered to be adequate. A traditional approach was chosen for process validation at commercial scale. Overall, the results presented during process verification were homogenous and therefore allow the conclusion of successful process verification. The batch definition has been adequately described.

Characterisation

The primary and higher order structure of insulin lispro has been investigated. Amino acid sequence and molecular mass verify the primary structure. The spectroscopic analysis reveals the secondary and

tertiary structure. The chromatograms for peptide mapping, RP-HPLC and SEC for insulin lispro have been provided.

Finished Product

Manufacturing

The manufacturing process of the finished product has been appropriately described. The vial is intended to be used with a syringe, a pump designed for subcutaneous infusion or infusion bags for intravenous infusion. The compatibility of the finished product with infusion bags has been presented. The results of simulated infusion studies demonstrated that the diluted Insulin lispro remains stable for use at room temperature for 48 hours. Additionally examples of commercially available pumps have been provided. The manufacturer's instructions of the pump devices facilitate the proper use of the vial with the pumps.

Validation

The validation results demonstrate that finished product manufacturing process operates appropriately within the established parameters and performs reproducibly under controlled conditions. The filter validations were performed by the manufacturer and appropriate filter validation reports of the manufacturer have been provided. Data has been provided verifying that the disposable pen injector assembly process is validated. Simulated transfer validation studies have been appropriately performed and study reports provided for vials, cartridges and pen.

Specification

The test parameters in the proposed specifications are considered appropriate for the finished product control. Upon request, the specification limits were tightened taking into consideration actual batch data of Insulin lispro Sanofi (including the clinical batch) and of the reference product. The requested information has been provided and the respective sections of the dossier updated for the storage conditions (i.e. temperature, container closure etc.) of the reference materials.

Stability

Stability studies have been appropriately performed and included long term, accelerated, stressed, in-use testing and temperature cycling studies. The stability parameters tested are adequate.

Biosimilarity

The applicant has performed extensive biosimilarity study. A considerable number of batches have been analysed in the study, and Insulin lispro Sanofi was compared to both EU and US Humalog products. The comparability exercise covered similarity between Insulin lispro Sanofi and the reference product and demonstrated that Humalog US can be considered representative of Humalog EU. The number of batches analysed in each individual study has been justified by the expected variability of the parameter selected for comparison. An appropriate number of reference product lots was tested to assess lot-to-lot variability and differences due to sample age. Humalog batches were selected from the sample pool on a random basis to perform structure, purity and potency assays.

Insulin lispro Sanofi and Humalog have been analysed side-by-side in structural and functional characterization studies. The applicant has chosen the relevant parameters for the biosimilarity studies. Biological activity with blood sugar test (USP) was investigated. The biological activity was

further addressed in the non-clinical section using several other assays and batches. Results were been presented and discussed.

Potency of Insulin lispro Sanofi was determined by HPLC compared to the label of Humalog. The results obtained for Insulin lispro Sanofi content were in accordance with the specification limits. For the purpose of labelling 3.47 mg insulin lispro is equivalent to 100 U.

The approach chosen by the applicant for defining the equivalence/similarity range was questioned, since it did not take account the variability of Humalog batches for each attribute. In addition, some concerns were raised with respect to the underlying assumptions of the applied statistical approach and with respect to general validity of the statistical approach. In order to address these issues, the applicant provided clarifications and presented a new statistical analysis of similarity where several aspects were changed compared to the original analysis, including re-defined similarity ranges. The overall data package provided supports biosimilarity.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality documentation provided in the Insulin lispro Sanofi marketing authorisation application is of adequate quality and support biosimilarity to the reference product Humalog. In addition, it has been demonstrated that Humalog sourced from the US can be considered representative of the reference product Humalog EU. In conclusion, based on the review of the quality data provided, the marketing authorisation application for Insulin lispro Sanofi is approvable from the quality point of view.

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical development of SAR342434 was done in accordance with the guidelines 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 “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, binding kinetics and their activation, metabolic responses, insulin-like growth factor-1 receptor (IGF-1R) binding and activation, and mitogenic activities.

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

The 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 panel of comparative *in vitro* receptor binding and biological activity studies with SAR342434 and reference product Humalog were conducted for demonstration of similarity. The comparability exercise was done in three-way comparability approach with SAR342434, Humalog sourced from EU and US.

The studies were arranged in three sets; sets 1 and 2 compared 2 batches of SAR342434 to 1 batch of Humalog, and set 3 included an extended *in vitro* characterisation studies (4 batches of SAR342434 compared to 4 batches of Humalog). An overview of the most extensive third set of studies is summarised in **Table 1.** Results in the table shown are only for Humalog sourced from the EU.

The acceptance criteria on the ratio for each study were defined (based on the Coefficient of Variation of the individual assay parameters and the number of determinations/batch). SAR342434 was considered similar to Humalog, if the 90% confidence interval of the ratio was within the acceptance region.

Concentration-response curves, both for raw data and normalised to maximal response=100% were also submitted for each PD study to derive and compare EC_{50} or IC_{50} values including statistical evaluation.

Concentration–response curves of the raw and normalized data from a representative run (out of four experiments) from study DIVT0076 experiment 4 are shown in **Figure 2.**

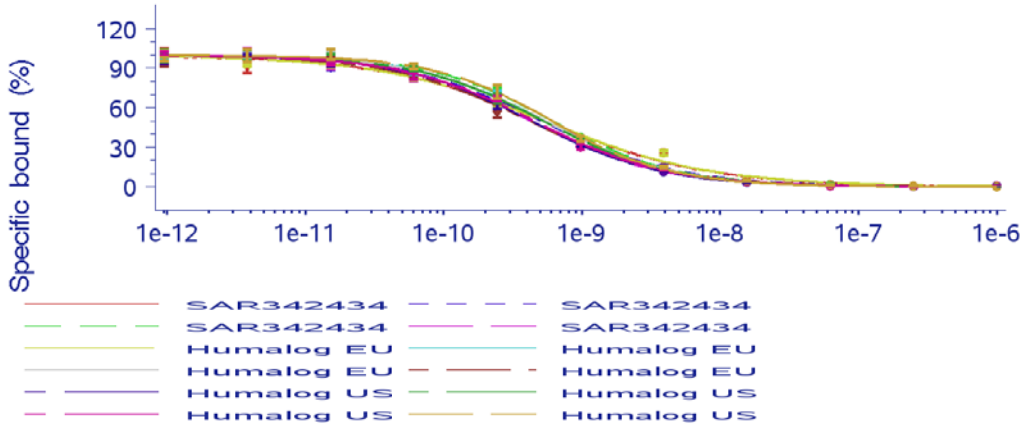
In this study, the binding of SAR342434 and Humalog (both EU and US sourced) to IR-B was assessed using a competition-inhibition binding assay.

To quantify the difference of the *in vitro* affinity to human IR-B the difference in means of the log-transformed IC_{50} values with 90% confidence interval were determined and converted to ratio of means with 90% confidence interval via the anti-log transformation or an equivalence approach was used.

Table 1. Overview of primary pharamcodynamic *in vitro* bioassays for demonstration of the similarity of SAR342434 and Humalog

Type of Study		Ratio [90 % CI] SAR342434/Humalog	Acceptance region	Results	Study number
Binding to insulin receptors	**IR-B binding (IC_{50} nM)**	1.032 [0.9745;1.0925]	[0.80;1.25]	Similar	DIVT0076
	IR-A binding (IC_{50}, nM)	0.993 [0.9052;1.0894]	[0.75;1.33]	Similar	DIVT0077
	IR-B binding kinetics	ka1 0.982 [0.948;1.017] kd1 0.977 [0.946;1.009] ka2 1.000 [0.962;1.040] kd2 0.977 [0.958;0.997] K_D1 1.007 [0.98; 1.04] K_D2 0.936 [0.89; 0.98]	[0.80;1.25]	Similar	DIVT0091
	IR-A binding kinetics	ka1 0.971 [0.935;1.009] kd1 0.978 [0.937;1.021] ka2 0.981 [0.942;1.021] kd2 0.969 [0.934;1.005] K_D1 1.030 [0.99; 1.07] K_D2 0.980 [0.93; 1.03]	[0.80;1.25]	Similar	DIVT0090
Biological activity studies	**Activation of IR-B** Auto-phosphorylation	1.038 [0.939; 1.113]	[0.75;1.33]	Similar	DIVT0080
	Activation of IR-A Auto-phosphorylation	0.943 [0.874 ; 1.017]	[0.75;1.33]	Similar	DIVT0079
	Metabolic activity Inhibition of lipolysis	1.043 [0.971;1.121]	[0.75;1.33]	Similar	DIVT0081
	Metabolic activity Stimulation of glucose uptake	0.991 [0.904;1.087]	[0.70;1.43]	Similar	DIVT0082
	Metabolic activity: Regulation of glucose 6-phosphatase gene expression	1.089 [0.892;1.330]	[0.70;1.43]	Similar	DIVT0087

Figure 2. Representative of four experiments of concentration-response curve for binding of SAR342434 and different batches of Humalog (EU, US) to human IR-B (normalised data, Study DIVT0076)



Secondary pharmacodynamic studies

In addition to the studies required by the CHMP guideline on similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005 Rev. 1), the *in vitro* comparability program included also the analyses of binding to and activation of the insulin-like growth factor-1 receptor (IGF-1R) and mitogenic activity.

As with the primary PD studies, three sets of studies were conducted, the third being the most extensive for which the acceptance criterion for each assay ratio (weighted geometric means) was defined. The results from this set of studies, comparing SAR342434 and EU Humalog are summarised in **Table 2.**

Table 2. Overview of secondary pharmacodynamic *in vitro* bioassays for demonstration of the similarity of SAR342434 and Humalog (insulin lispro)

Type of Study	**Ratio [90% CI] SAR342434/Humalog**	**Results**	**Study number**
Binding to IGF-1R	1.111 [0.988;1.251]	Similar	DIVT0078
Activation of IGF-1R Autophosphorylation	1.057 [0.969; 1.154]	Similar	DIVT0083
Mitogenic activity Stimulation of labelled thymidine incorporation into DNA (MCF- cells)	1.069 [0.917;1.247]	Similar	DIVT0088

Safety pharmacology programme

No safety pharmacology studies were submitted in line with the CHMP guidance on similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005 Rev. 1).

Pharmacodynamic drug interactions

No comparative studies assessing PD 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

Pharmacokinetic (toxicokinetic, TK) data for SAR342434 and Humalog (EU, US) were assessed as part of the 1-month repeat toxicity studies in rats. The TK data are presented in the toxicology section below.

2.3.4. Toxicology

The toxicology program of SAR342434 consisted of two GLP-compliant 1-month repeat-dose toxicity studies with toxicokinetics in rats and a local tolerability study in rabbits (**Table 3**).

One repeat-dose toxicity study was conducted with Humalog EU and one with Humalog US as a comparator.

The maximum dose tested was 200 U/kg/day (100 U/kg/twice daily). The SAR342434 formulation used in the toxicology studies was the final to-be-marketed formulation.

Table 3. Toxicology studies with SAR342434 and Humalog

Species (Strain) (sex/group)	**Test products**	**Duration of Dosing** (method of admin.)	**Doses**	**GLP**	**Testing Facility**	**Study Number**
Repeated dose toxicity						
Rat Sprague-Dawley Crl:CD(SD) (10M / 10F)	SAR342434 Humalog EU	1 month SC	10, 50, 200 U/kg	yes	Covance Laboratories Ltd, Willowburn Avenue, Alnwick, Northumberland, NE66 2JH, ENGLAND	TSA1505
Rat Sprague-Dawley Crl:CD(SD) (10M / 10F)	SAR342434 Humalog US	1 month SC	10, 50, 200 U/kg	yes	Covance Laboratories Inc., Kinsman Boulevard, Madison, Wisconsin, USA	TSA1519
Local tolerance						
Rabbit New Zealand White (3M)	SAR342434 Humalog EU	0.1 ml subcutaneous, paravenous 0.5 ml intramuscular	100 U/ml	yes	Sanofi-Aventis recherche & développement Montpellier, FRANCE	TOL1162

Repeat dose toxicity

To compare toxicity profile and exposure of SAR342434 and the reference products Humalog EU (Study TSA1505) or US (Study TSA1519) Sprague-Dawley rats received either solutions of Humalog or SAR342434 at 0, 5, 25 or 100 U/kg/administration by subcutaneous injection twice daily for 1 month, i.e. 0, 10, 50 or 200 IU/kg/day.

Mortality, clinical observations, body weight, food consumption, ophthalmology, blood glucose monitoring (n=4/sex/dose), haematology, coagulation, clinical chemistry, and urinalysis assessments were done. Plasma samples were obtained for toxicokinetic determinations and anti-insulin antibody (AIA) assessment. Surviving rats were euthanized and necropsied at the end of the treatment. Organ weights were recorded and representative tissue samples were examined microscopically from rats in the control and in the 200 U/kg/day groups. Ki-67 staining of the mammary glands was done as a parameter for a mitogenic potential.

Hypoglycaemia related unscheduled deaths at 50 U/kg/day (one male treated with SAR342434) and 200 U/kg/day (two animals treated with Humalog EU) were reported in the study TSA1505. One of the Humalog EU treated animals was euthanized due to marked lethargy. The related microscopic changes (astrocytic swelling in brains, decrease in glycogenic vacuolation in liver) were revealed in the examinations of two other animals which were culled prescheduled.

In study TSA1519, two rats (F) given 50 U/kg/day of SAR342434 died or were euthanized in moribund condition during the dosing phase. No clinical signs were noted at 50 or 200 U/kg/day from the SAR342434 treated animals and the deaths were considered unlikely related to SAR342434 but to stress or blood collection.

Effects on the urinalysis parameters (increases in phosphorus, urine volume increase, osmolality decrease, and urinary protein concentration decrease) were also noted and were similar in SAR342434 and Humalog treated animals.

Toxicokinetic data

Toxicokinetic specimen (3 rats/timepoint) were collected at days 1 and 29 pre-dose and 0.33h, 1h, 2h, 3h, 4h - following first and second daily dose administration. The toxicokinetic parameters are shown in **Table 4.**

Table 4. Toxicokinetic parameters for SAR342434 and Humalog EU in rats, Study TSA1505 (SC administration, dose U/kg/day)

Sex	Dose (mg/kg)	SAR342434				Humalog 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	235	288	311	579	386	519	495	767
	50	365	1140	1300	3650	1390	1810	2710	4750
	200	3390	3170	11800	12900	3090	5590	6300	17700
Female	10	277	480	358	660	276	821	327	1260
	50	719	3070	1150	6430	1320	1770	2330	6050
	200	2210	4460	6810	18700	2810	7640	6750	22300

[a] Values are rounded to 3 significant figures.

Local Tolerance

The local tolerance for SAR342434 was compared to Humalog EU in male rabbits (n=3/group).

Rabbits received SAR342434 or Humalog EU with subcutaneous (0.1 ml, 100 U/mL (3.5 mg/ml), SC), intravenous (0.5 ml, IV), paravenous (0.1 ml, PV) or intramuscular (0.5 ml, IM) routes. Each rabbit was dosed either by the combination of the IM and the PV routes or the IV and the SC routes.

Local tolerance at the injection site, mortality, clinical signs and body weights were assessed. Histological assessment of the injection sites were conducted at necropsy 24 h or 120 h after drug administration.

No significant differences were observed between the SAR342434 and Humalog treated animals in their injection site reactions.

Local tolerance findings erythema, oedema, hematoma and eschar/ulcer were classified as slight to severe or marked. Erythema, oedema and hematoma were observed in three SAR342434 (SC) treated rabbits and in two Humalog (SC) treated rabbits.

Injection site findings included subcutaneous inflammation, haemorrhage, necrosis and fibrosis in rats and erythema, oedema, hematoma and eschar/ulcer in rabbits after subcutaneous administration.

In rabbits, Humalog EU was slightly better tolerated. After IM delivery of SAR342434 moderate multifocal necrosis/degeneration with mild-haemorrhagic infiltration and acute inflammation was noted in one rabbit. After SC delivery, the findings were slightly more frequent in rabbits treated with SAR342434 than with Humalog EU, but more frequent in rats treated with Humalog in comparison to SAR342434.

Antigenicity

Samples for anti-drug antibody analysis were collected from all toxicokinetic phase animals on Day 29 (following the last TK sampling time point). Dose–dependent increase in incidence on formation of the anti-insulin antibodies was detected in 67 - 100% of treated animals in study TSA1505 (data not shown).

2.3.5. Ecotoxicity / environmental risk assessment

In accordance with the guideline on environmental risk assessment (EMEA/CHMP/SWP/4447/00 corr 2), the applicant did not submit any ERA studies as the active substance of SAR342434 (insulin lispro) is a natural substance (insulin analogue), the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, SAR342434 is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The applicant has performed all pharmacodynamic tests which are required to demonstrate biosimilarity at the non-clinical level, evaluating the receptor binding and activation, and metabolic activity characteristics of SAR342434 and Humalog. In addition, activation of the IGF-1 receptor and effect on tumour cell proliferation was also investigated. All experiments were conducted *in vitro*, in line with the requirements of 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*). In vitro* tests are preferred over *in vivo* studies because the former are usually more accurate in this setting.

The studies were conducted in three sets, of which the third was the most extensive and relevant for determination of similarity as in this set of experiments, acceptance criterion for each assay ratio (weighted geometric means) was defined. SAR342434 was considered similar to Humalog, if the 90% CV of the ratio was within the acceptance region.

The applicant also submitted concentration-response relationships in all studies, thereby covering the relevant concentration range. Raw data could be well fitted to a sigmoid curve which allowed reliable determination of EC_{50} or IC_{50} values. The EC_{50}/IC_{50} values as well as the concentration-response relationship were highly similar between SAR and the reference product.

The comparative competition-inhibition binding analysis to IR-B indicates similar binding activity of SAR342434 and Humalog (EU). There were no significant differences in SAR342434 or Humalog in association and dissociation kinetics to insulin receptor isomers within the assay conditions. The calculated ratios were similar. Thus, SAR342434 can be considered similar to Humalog EU in the IR-B and IR-A binding.

For the insulin receptor autophosphorylation (activation), and metabolic activities (inhibition of lipolysis, stimulation of glucose uptake,regulation of glucose 6-phosphatase gene) and binding to and activation of the IGF-1R and mitogenic activity, SAR342434 and Humalog can be considered similar.

Toxicology studies usually are not required for insulin biosimilar applications. Nevertheless, the applicant submitted two 1-month studies in rats, one comparing SAR342434 with Humalog from EU and one comparing SAR342434 with Humalog from US. Furthermore, local tolerance was studied in rabbits.

Studies of single dose toxicity, genetic toxicity, carcinogenicity and reproductive toxicity are not required for insulin biosimilars and were not submitted by the applicant.

Rats received SAR342434 or Humalog 5, 25 or 100 U/kg/administration by subcutaneous injection twice daily for 1 month. Maximum daily dose tested was 200 U/kg/day which was equivalent to the dose level used with the previous studies of insulin lispro (reference medicinal product).

There were no unexpected toxicity findings in the rats and rabbits related to the SAR342434 or Humalog. The increases in body weight, body weight gain, food consumption, glucose and phosphorus, and evidence of hypoglycaemia linked to either the direct or indirect pharmacological actions to the administration of insulin were noted in the repeated dose toxicity studies.

Rabbits received SAR342434 or Humalog EU with subcutaneous (0.1 ml, 100 U/ml (3.5 mg/ml), SC), intravenous (0.5 ml, IV), paravenous (0.1 ml, PV) or intramuscular (0.5 ml, IM) routes. Each rabbit was dosed either by the combination of the IM and the PV routes or the IV and the SC routes.

Injection site findings included subcutaneous inflammation, haemorrhage, necrosis and fibrosis in rats and erythema, oedema, hematoma and eschar/ulcer in rabbits after subcutaneous administration. The local tolerance findings in rabbits could be procedural or treatment/drug – related or a chance finding (small scale study). However, no significant differences were observed between the SAR342434 and Humalog treated animals in their injection site reactions.

There were no significant differences on pharmacokinetic/toxicokinetic profiles between SAR342434 and Humalog. At day 29 the C_{max} and AUC_{0-8h} exposure values for Humalog EU were slightly higher (C_{max} 1.7 –fold, AUC_{0-8h} 1.4 – 1.2 fold higher) than those for SAR342434 at 200 U/kg/day dose group animals, whilst some variation in the values was also noted. However, as there were no differences noted in the human PK data between SAR342434 and Humalog (see section 2.4.2), these findings in rats were not considered to be of clinical relevance.

Overall, no safety findings were identified in the nonclinical SAR342434 studies which could be considered of significant clinical relevance.

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 lispro Sanofi can be considered similar to the reference product Humalog 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 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

	PDY12704 Euglycemic clamp study (PK/PD)	EFC12619 Efficacy/safety Phase 3 study	EFC13403 Efficacy/safety Phase 3 study	PDY13502 Safety study
Design	3x1 day cross-over study	Randomised, active-controlled, open-label, parallel group study	Randomised, active-controlled, open-label, parallel group study	Randomised, active-controlled, open-label, 2x4 weeks cross-over study
Population	Patients with **T1DM**	Patients with **T1DM** on Lantus in combination with mealtime insulin analogue for at least 6 months prior to the study	Patients with **T2DM** on Lantus in combination with mealtime insulin analogue for at least 6 months prior to the study	Patients with **T1DM** on Continuous Subcutaneous Insulin Infusion (CSII)
Comparator and regions	• Humalog US • Humalog EU	• Humalog US • Humalog EU	• Humalog US • Humalog EU	• Humalog US
Randomisation	1:1:1	1:1	1:1	1:1
Route of administration and injection device for IMP	SC injection syringes	SC injection before each main meal or snack; or immediately after meal intake (if allowed per local label) SAR342434: SoloStar Humalog: KwikPen	SC injection before each main meal or snack; or immediately after meal intake (if allowed per local label) SAR342434: SoloStar Humalog: KwikPen	External pump for continuous SCII (Medtronic with 3 mL reservoir or Animas Vibe or OneTouch Ping pump)
Objectives	PK and PD	Efficacy and safety	Efficacy and safety	Safety
Primary endpoint	• PK: AUC, AUC_{last} $C_{max,}$ • PD: GIR-AUC_{0-12}	HbA1c (%), change from baseline to Week 26	HbA1c (%), change from baseline to Week 26	Incidence of infusion set occlusions defined as failure to correct hyperglycemia (plasma glucose ≥300 mg/dL) by insulin bolus via the insulin pump
Number of patients randomized	N=30	SAR342434: N=253 Humalog: N=254	SAR342434: N=253 Humalog: N=252	N=27
Duration of treatment	3x1 day	6 months (main study period) 6 months comparative safety extension period	6 months	2x4 weeks

T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; PK: pharmacokinetic; PD: pharmacodynamics; SC: subcutaneous; CSII: continuous subcutaneous insulin infusion; IMP: investigational medicinal product; HbA1c: glycated hemoglobin; AUC: area under the concentration versus time curve extrapolated to infinity; AUClast: area under the concentration versus time curve from 0 to time of last concentration above the limit of quantification; Cmax: maximum observed concentration; GIR-AUC0-12: area under the body weight standardized glucose infusion rate versus time curve from 0 to 12 hours post-IMP administration

2.4.2. Pharmacokinetics

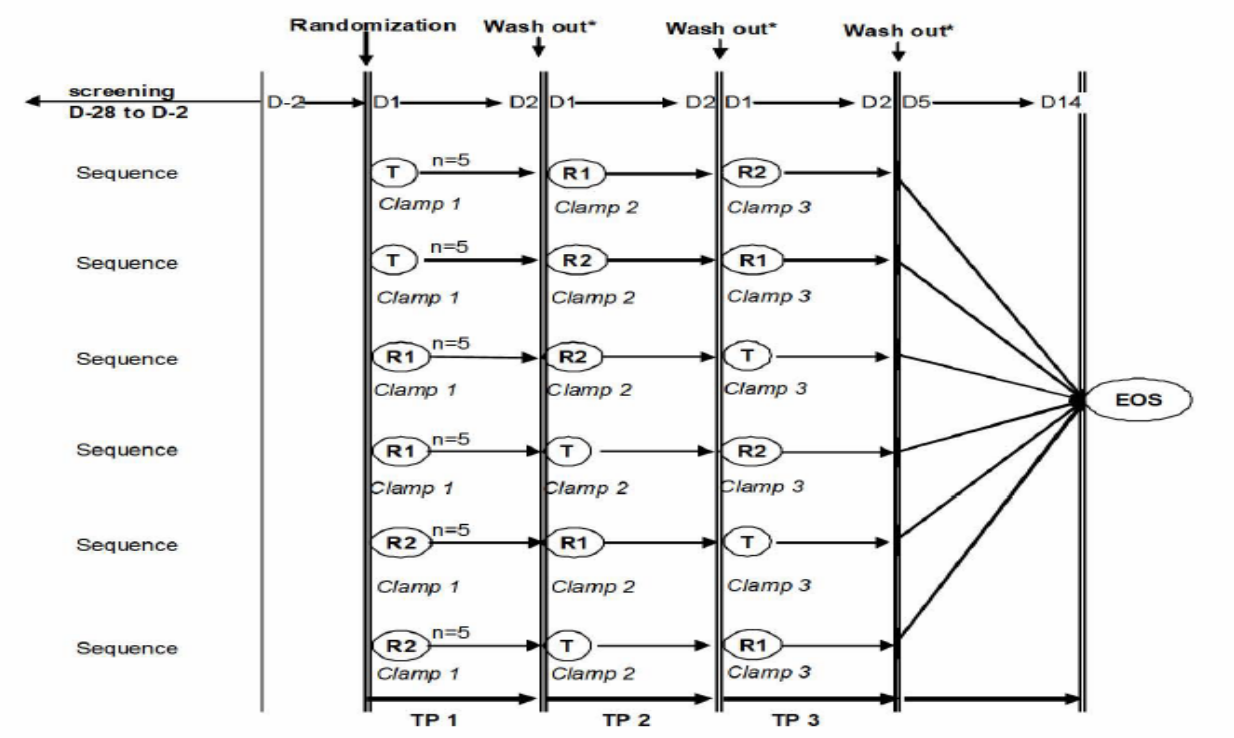
Study PDY12704

This was a single-centre, double-blind, randomized, 3-way cross-over euglycaemic clamp study conducted under fasting conditions in patients with type 1 diabetes mellitus (T1DM). The study compared the PK and PD of SAR342434 (T) to Humalog 100 U/mL registered in the US (R1; Humalog

US) and Humalog 100 U/mL registered in the EU (R2; Humalog EU), as well as the PK and PD between Humalog US and Humalog EU.

The 3 treatments were administered as single dose injections of 0.3 U/kg, in a crossover manner in 3 treatment periods with 6 treatment sequences, as illustrated in **Figure 3**. Plasma samples for insulin lispro concentrations were collected for 12 hours post dose.

Figure 3. Design of study PDY12704



T=SAR342434; **R1**=Humalog US; **R2**=Humalog EU; **TP**=Treatment Period; **EOS**=End of Study;
***** wash-out period 5 to 18 days (preferentially 7 days).

An LC-MS/MS assay was developed for quantitative determination of insulin lispro in human plasma samples. The assay was validated over the concentration range of 100.00-8000.00 pg/mL.

The primary PK parameters were log-transformed before statistical analyses. A linear mixed effects model was used to obtain estimates and the 90% confidence interval (CI) of the difference between treatment means and then converted to ratio of geometric means by the antilog transformation.

Bioequivalence was concluded if the 90% CI for the treatment ratios (T/R1 and T/R2) was entirely contained within 0.80 to 1.25.

A total of 30 subjects were randomized and treated, with 28 subjects completing all 3 treatment periods. For one subject data was available only for treatment period with SAR342434, and for another subject only for treatment periods with Humalog US and Humalog EU. Thus, PK parameters for 29 plasma concentration versus time profiles were obtained for each treatment and were included in statistical analyses in accordance with the statistical analysis plan. Supplemental statistical analyses for the primary PK and PD parameters were performed, excluding one subject who was not compliant with study protocol. The results matched closely the original results presented below.

Mean plasma concentration versus time profiles for SAR342434, Humalog US, and Humalog EU are presented in **Figure 4** and the results of the relative bioavailability analyses are summarised in **Table 5.**

Figure 4. Mean (+SD) plasma concentration vs. time profiles for SAR342434, Humalog US, and Humalog EU in study PDY12704

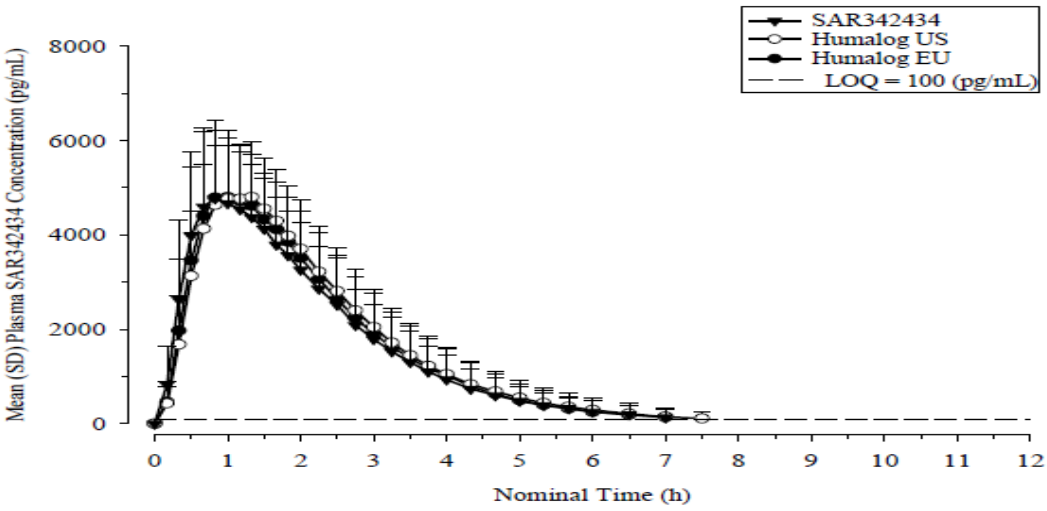


Table 5. Relative bioavailability analysis of INS-C_{max}, INS-AUC_{last}, and INS-AUC for SAR342434 vs. Humalog US and Humalog EU, and Humalog US vs. Humalog EU in Study PDY12704

Parameter	Treatment ratio	Estimate	90% CI
INS-C_{max} (pg/mL)	SAR342434 vs Humalog US	0.97	(0.89 to 1.05)
	SAR342434 vs Humalog EU	0.96	(0.89 to 1.04)
	Humalog US vs Humalog EU	0.99	(0.94 to 1.03)
INS-AUC_{last} (pg.h/mL)	SAR342434 vs Humalog US	0.95	(0.91 to 0.99)
	SAR342434 vs Humalog EU	0.97	(0.94 to 1.01)
	Humalog US vs Humalog EU	1.03	(1.00 to 1.05)
INS-AUC (pg.h/mL)	SAR342434 vs Humalog US	0.95	(0.92 to 0.99)
	SAR342434 vs Humalog EU	0.97	(0.94 to 1.00)
	Humalog US vs Humalog EU	1.02	(1.00 to 1.05)

2.4.3. Pharmacodynamics

Mechanism of action

Insulin lispro, 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.

Further effects induced by insulin include e.g. increase in lipid synthesis and amino acid uptake, decrease in lipolysis and proteolysis, relaxation of arterial walls, increase in potassium uptake etc.

Primary and Secondary pharmacology

The PD effect of SAR342434 vs. was evaluated using the euglycaemic clamp technique in study PDY12704 which has been described in Section 2.4.2 of this report. During the clamp, the blood glucose concentration, the glucose infusion rate (GIR), and the amount of glucose needed to keep a subject's blood glucose concentration at its target level were continuously measured and recorded using the Biostator device (continuous glucose monitoring system, Life Sciences Instruments, Elkhart, IN, US). The target blood glucose level was 5.5 mmol/L (100 mg/dL). The study was conducted under fasting conditions.

The Biostator determined blood glucose levels in 1-minute intervals and adjusted the body weight standardized glucose infusion rate (GIR) in response to changes in blood glucose using a predefined algorithm. During the clamp, arterialized venous blood glucose concentrations, which reflected the supply for total glucose utilization of all tissues, as well as GIRs, were continuously monitored.

The clamp quality, assessed by the individual CV% of blood glucose over the clamp duration (from time 0 to the end of euglycaemia), was reliably maintained with reasonable variability [median CV values of 6.80%, 6.60%, and 6.20% for SAR342434, Humalog US, and Humalog EU, respectively].

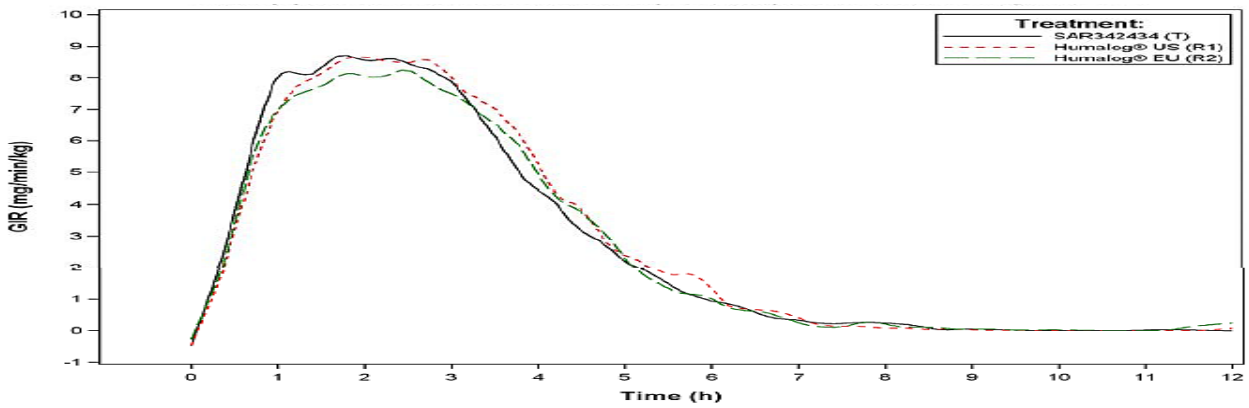
Due to noise in the GIR adjustment, the derivation of GIR_{max} was based upon a locally weighted regression smoothing technique for the raw body weight standardized GIR data.

Body weight standardized GIR vs. time curve from 0 to 12 hours (GIR-AUC_{0-12}) was the primary PD endpoint specified in the study protocol. In accordance with Guideline EMEA/CHMP/BMWP/32775/2005_Rev.1 in the evaluation of this application, GIR_{max} was also considered a primary PD endpoint.

Treatment ratios with 90% and 95% confidence intervals for GIR-AUC_{0-12} and GIR_{max} were calculated in accordance with the statistical analysis plan using similar statistical methodology as was used for primary PK parameters.

Mean smoothed GIR profiles are displayed in **Figure 5**.

Figure 5. Overlay plots of mean smoothed GIR profiles in study PDY12704



Point estimates for between-treatment GIR-AUC$_{0\text{-}12}$ and GIR$_{max}$ ratios and the corresponding 90% and 95% CIs are provided in **Table 6**.

Table 6. Comparability of GIR-AUC$_{0\text{-}12}$ and GIR$_{max}$ for SAR342434 vs. Humalog US and Humalog EU, and Humalog US vs. Humalog EU in study PDY12704

Parameter	Treatment ratio	Estimate	90% CI	95% CI
GIR-AUC$_{0\text{-}12h}$ (mg/kg)	SAR342434 vs Humalog US	1.00	(0.94 to 1.07)	(0.93 to 1.08)
	SAR342434 vs Humalog EU	1.06	(0.97 to 1.15)	(0.95 to 1.17)
	Humalog US vs Humalog EU	1.05	(0.98 to 1.14)	(0.96 to 1.15)
GIR$_{max}$ (mg/kg/min)	SAR342434 vs Humalog US	1.04	(0.98 to 1.10)	(0.96 to 1.12)
	SAR342434 vs Humalog EU	1.07	(0.99 to 1.14)	(0.98 to 1.16)
	Humalog US vs Humalog EU	1.03	(0.95 to 1.10)	(0.94 to 1.12)

GIR = body weight standardized glucose infusion rate. GIR$_{max}$ is based on smoothed GIR profiles

The GIR-AUCs for time intervals of 0 to 2 hours (GIR-AUC$_{0\text{-}2}$) and 4 to 12 hours (GIR-AUC$_{4\text{-}12}$) were calculated as secondary endpoints and are presented in **Table 7.**

Table 7. Point estimates of treatment ratio of GIR-AUC0-2 and GIR-AUC4-12 with 90% and 95% confidence intervals for SAR342434 vs. Humalog US and Humalog EU, and Humalog US vs. Humalog EU in study PDY12704

Parameter	Treatment ratio	Estimate	90% CI	95% CI
GIR-AUC$_{0\text{-}2h}$ (mg/kg)	SAR342434 vs Humalog US	1.13	(1.05 to 1.21)	(1.04 to 1.23)
	SAR342434 vs Humalog EU	1.13	(1.02 to 1.27)	(0.99 to 1.29)
	Humalog US vs Humalog EU	1.01	(0.90 to 1.12)	(0.88 to 1.15)
GIR-AUC$_{4\text{-}12h}$ (mg/kg)	SAR342434 vs Humalog US	0.81	(0.61 to 1.06)	(0.58 to 1.12)
	SAR342434 vs Humalog EU	0.94	(0.72 to 1.24)	(0.68 to 1.31)
	Humalog US vs Humalog EU	1.17	(0.92 to 1.48)	(0.88 to 1.55)

Time to GIR onset [mean (SD)] was 0.27 (0.15) hours, 0.35 (0.17) hours, and 0.35 (0.22) hours for SAR342434, Humalog US, and Humalog EU, respectively. GIR-t_{max} [mean (SD)] was 2.07 (0.78) hours, 2.30 (0.83) hours, and 2.37 (0.85) hours for SAR342434, Humalog US, and Humalog EU, respectively.

2.4.4. Discussion on clinical pharmacology

Design of the clamp study PDY12704, including blinding, population (patients with T1DM), insulin dosage, pre-study and within-study fasting, target blood glucose level, and duration of clamp, were 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).

There was some deviation from the *Guideline* with regards to the selected primary endpoints of the study. In assessment of the current application the following were considered as primary endpoints:

- PK: $AUC_{0\text{-last}}$ and C_{max}
- PD: GIR-$AUC_{0\text{-}12}$ and GIR_{max}

in accordance with the Guideline.

The 12-hour study sufficiently covered the PK profile of insulin lispro: only 4 subjects had quantifiable concentrations (>100 pg/mL) at 12 hours post dose. The PK parameters were calculated using conventional noncompartmental analysis, and body weight standardised glucose infusion rate is the conventional PD marker in insulin clamp studies. Appropriately pre-defined smoothing technique (LOESS, factor 0.06) was used for GIR_{max} and several secondary PD endpoints. This is in accordance with the Guideline and was considered acceptable.

Pharmacokinetics:

Mean plasma concentration vs. time curves of SAR342434 and Humalog EU (and Humalog US) were comparable. The treatment ratios and 90% CIs for PK parameters were calculated in accordance with the statistical analysis plan and using acceptable methodology, and pre-defined biosimilar comparability limits (0.80 to 1.25) are acceptable.

The point estimates [90% CIs] of treatment ratio for SAR342434 vs. Humalog EU for the primary PK parameters INS-C_{max} and INS-AUC_{last} were 0.96 [0.89 to 1.04] and 0.97 [0.94 to 1.01], respectively. The results indicate similar pharmacokinetics between SAR342434 vs. Humalog EU. The results for secondary PK endpoints support this conclusion. For INS-AUC, the ratio was 0.97 [0.94 to 1.00].

Pharmacodynamics:

The variability of blood glucose level during the clamp was acceptable. The point estimates [95% CIs] of treatment ratio for SAR342434 vs. Humalog EU for the primary PD parameters GIR-$AUC_{0\text{-}12h}$ and GIR_{max} were 1.06 [0.95 to 1.17] and 1.07 [0.98 to 1.16], respectively. The results indicate similar pharmacodynamic effect between SAR342434 vs. Humalog EU. In addition, similar pharmacodynamic effect between SAR342434 vs. Humalog US was demonstrated for the primary PD parameters.

Regarding secondary PD endpoints, the point estimates [95% CIs] of treatment ratio for SAR342434 vs. Humalog EU 95% were 1.13 [0.99-1.29] and 0.94 [0.68-1.31] for GIR-$AUC_{0\text{-}2}$ and GIR-$AUC_{4\text{-}12}$, respectively, i.e. outside the equivalence margin (0.80 to 1.25). However, this was not considered to

negatively impact on the similarity comparability, as the primary PD endpoints for rapid- and short-acting insulins as defined in Guideline EMEA/CHMP/BMWP/32775/2005_Rev. 1, demonstrated similar pharmacodynamic effect between SAR342434 and Humalog EU.

2.4.5. Conclusions on clinical pharmacology

Results from Study PDY12704 demonstrated similarity between Insulin lispro Sanofi (SAR342434) and Humalog.

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 lispro Sanofi are identical to those approved for Humalog.

2.5.2. Main studies

Study EFC12619 (Sorella-1)

A 6-month, Randomized, Open-label, Parallel-group Comparison of SAR342434 to Humalog in Adult Patients With Type 1 Diabetes Mellitus Also Using Insulin Glargine, with a 6-month Safety Extension Period

Methods

Study Participants

Inclusion criteria

- Patients with T1DM diagnosed for at least 12 months and treated with Lantus and Humalog/Liprolog (as per amendment 2) or NovoLog/NovoRapid (at least 3 times daily before each meal) in the 6 months prior to the screening visit.
- Signed written informed consent.

Exclusion criteria (selection)

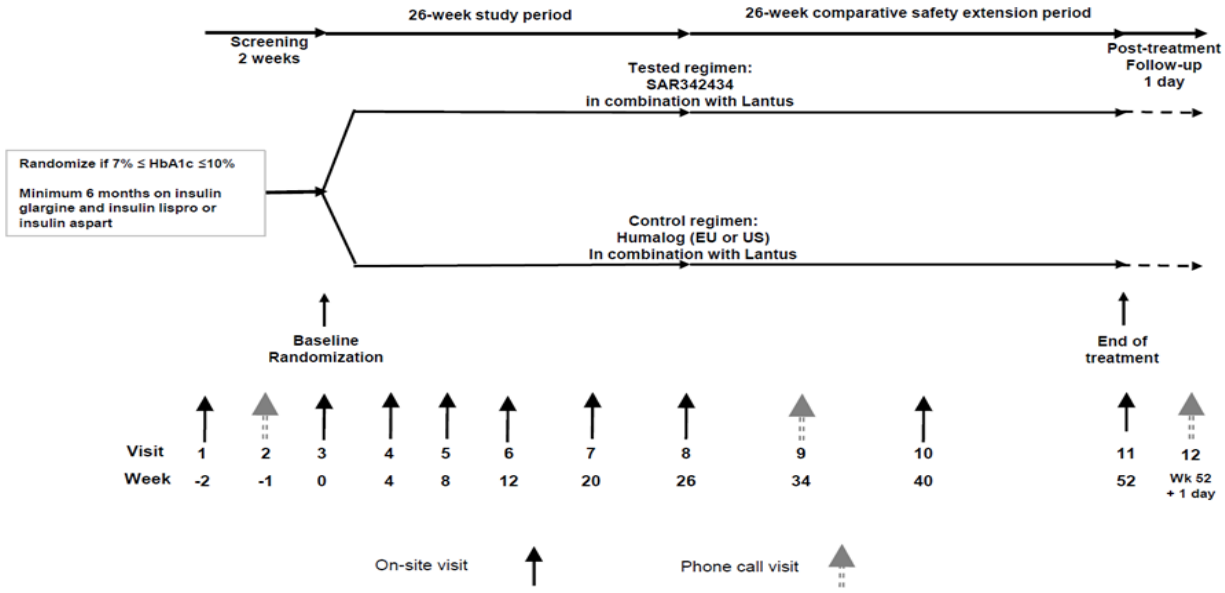
- Male or female; age under legal age of adulthood at screening visit.
- HbA1c <7% or >10% at screening.
- Diabetes other than T1DM.
- Status post pancreatectomy.
- Status post pancreas and/or islet cell transplantation.
- Less than 1 year on continuous insulin treatment.
- Use of insulin pump in the last 6 months before screening visit.

- Use of glucose lowering agents other than insulin including use of non-insulin injectable peptides in the last 6 months prior to screening.
- Any contraindication to use of Lantus and/or Humalog as defined in the national product labels.
- Pregnancy and lactation.
- Women of child bearing potential (premenopausal, not surgically sterile for at least 3 months prior to the time of screening) not using highly-effective (ie, with low failure rate <1% per year) method(s) of birth control throughout the study and/or unwilling to be tested for pregnancy.

Treatments

The study design is presented in **Figure 6**.

Figure 6. Study design, EFC12619



SAR342434 was supplied as a 100 U/mL solution for SC injection in 3 mL cartridges in the SoloSTAR disposable prefilled pen, allowing a maximum dose of SAR342434 per injection of 80 units and minimum dose of 1 unit. Humalog was supplied as a 100 U/mL insulin solution for subcutaneous injection in the Humalog KwikPen disposable prefilled pen, allowing a maximum dose of the Humalog of 60 units and minimum dose of 1 unit.

Patients in both treatment groups continued with their mandatory background basal insulin therapy: Lantus, injected SC once daily, which was considered to be NIMP. Lantus was self-administered by SC injection once daily at the same time either at bedtime or in the morning, consistent with the local label.

Any other glucose-lowering agents were prohibited.

Objectives

Primary objectives

The primary objective of this study was to demonstrate non-inferiority of SAR342434 versus Humalog in terms of change in HbA1c from baseline to Week 26 in patients with T1DM also using Lantus.

Secondary objectives

The secondary objectives were:

- To assess the immunogenicity of SAR342434 and Humalog in terms of positive/negative status and antibody titers at baseline and during the course of the study (as per protocol amendment 1)
- To assess the relationship of anti-insulin antibodies with efficacy and safety including during the safety extension (Week 52)
- To assess the efficacy of SAR342434 and Humalog in terms of proportion of patients reaching target HbA1c < 7%, Fasting Plasma Glucose (FPG) and SMPG profiles and insulin dose (proportion of patients reaching target HbA1c <7% was specified in protocol amendment 1).
- To assess safety of SAR342434 and Humalog.

Outcomes/endpoints

The primary efficacy variable was the change in HbA1c from baseline (scheduled at Day 1) to Week 26 (Month 6) which is defined as: HbA1c value at Week 26 - HbA1c value at baseline (%).

Results for the primary efficacy variable were also presented in mmol/mol.

The secondary efficacy endpoints were:

- Percentage of HbA1c responders (patients with HbA1c <7%) at Week 26
- Change in FPG (mmol/L) from baseline to Week 26;
- Change in the mean 24-hour plasma glucose concentration (mmol/L) from baseline to Week 26 based on the 7-point SMPG profiles;
- Change in postprandial plasma glucose excursions (mmol/L) from baseline to Week 26 based on the 7-point SMPG profiles (difference between 2 hour postprandial and pre-prandial plasma glucose values at breakfast, lunch and dinner).

Other secondary efficacy endpoints were:

- Change in 7-point SMPG profiles per time-point from baseline to Week 26;
- Change in 3-point SMPG profiles per time-point from baseline to Week 26.

Sample size

The sample size calculation was performed based on the primary endpoint, change in HbA1c from baseline to endpoint (Week 26).

A sample size of 480 patients (240 patients per arm) was considered sufficient to ensure that the upper bound of the 2-sided 95% confidence interval (CI) for the adjusted mean difference between SAR342434 and Humalog would not exceed 0.3% HbA1c with at least 90% power. This calculation assumed a common standard deviation (SD) of 1.0% and a true difference in HbA1c between the treatment groups of zero.

Randomisation

The patients were randomised to either SAR342434 or Humalog (1:1) after the screening period, at baseline of the 26-week study period. Randomization was stratified according to the patients screening HbA1c (<8.0%; ≥8.0%), prior use of Humalog (Y/N) and also geographical region (Non-Japan, Japan). Interactive voice response system (IVRS) or interactive web response system (IWRS) was used for randomisation.

Blinding (masking)

Blinding on patient and investigator level was not feasible due to distinguishable pre-filled pen devices. Investigators were instructed to report any information relating to IMP without indicating to which open-label treatment the patient was assigned. The assessment of outcomes at sponsor level was blinded to treatment until database lock. HbA1c, FPG, and AIA were determined in central laboratories blinded to the treatment received.

Statistical methods

According to the statistical plan submitted, non-inferiority would be demonstrated if the upper bound of the two-sided 95% CI of the difference between SAR342434 and Humalog on ITT population was <0.3%.

Following a protocol amendment, the inverse non-inferiority of Humalog over SAR342434 would be demonstrated using a hierarchical step-down testing procedure, if the lower bound of the 2-sided 95% CI of the difference between SAR342434 and Humalog in the ITT population was above 0.3%.

For the primary endpoint, analysis was performed using a mixed-effect model for repeated measures (MMRM) approach. The model included the fixed categorical effects of randomisation strata of screening HbA1c (<8.0, ≥8.0%), prior use of Humalog (Yes, No), geographical region (Japan, Non-Japan); treatment group (SAR342434, Humalog), visit (Week 12, Week 26), and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline HbA1c value and baseline HbA1c value-by-visit interaction.

Multiple sensitivity analyses for handling of missing data were performed on the ITT population. These analyses involved a penalized multiple imputation approach, a tipping point analysis and analyses to explore the missing data frequency and pattern.

All continuous secondary endpoints were analysed using a similar MMRM model as the primary endpoint.

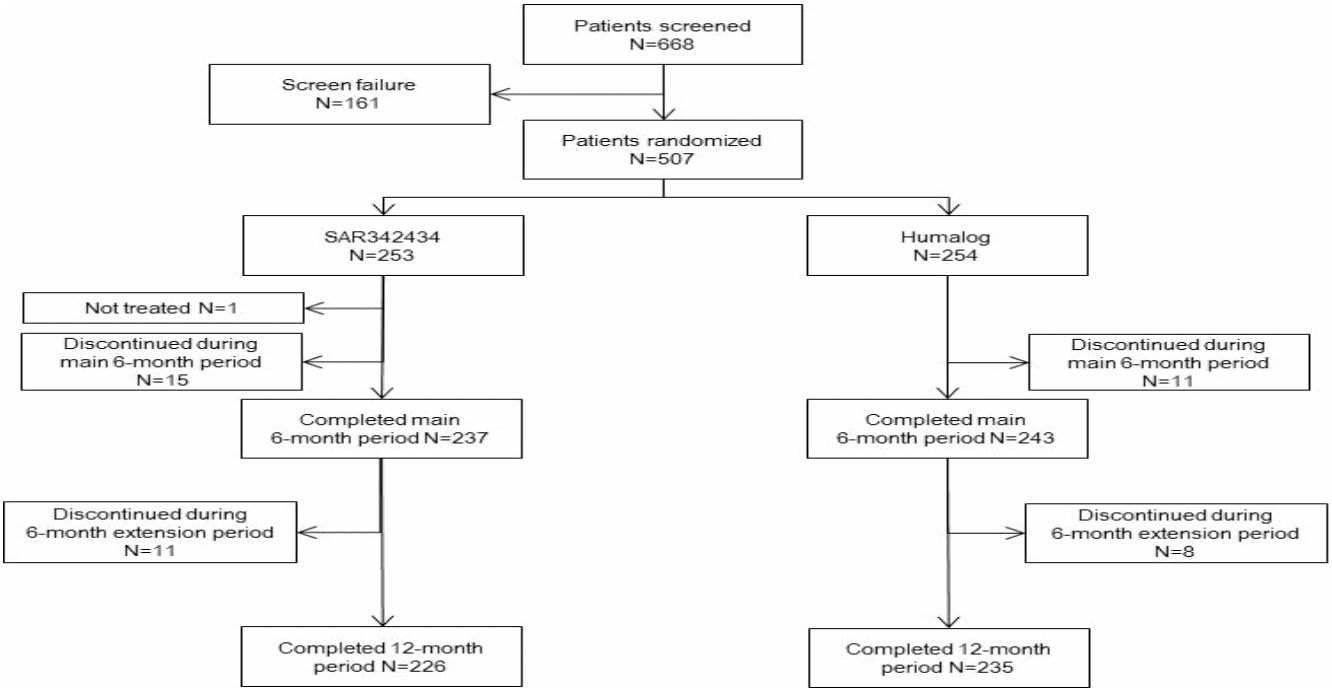
All categorical secondary endpoints were analysed by using logistic regression stratified by randomization strata of screening HbA1c, prior use Humalog, and geographical region (Non-Japan; Japan).

Safety analyses were descriptive and performed on the safety population: all patients randomized and exposed to at least one dose of IMP, regardless of the amount of treatment administered.

Results

Participant flow

Figure 7. Patient disposition in study EFC12619



Among the 254 patients randomized to Humalog, 140 (55.1%) were randomized in sites using Humalog US, and 114 (44.9%) were randomized in sites using Humalog EU.

Recruitment

The study was initiated on 11 November 2014 (first patient enrolled) and was completed on 1 July 2016. A total of 89 study centres across 8 countries worldwide enrolled patients.

Conduct of the study

The protocol was amended 2 times mainly to clarify inclusion and exclusion criteria and the monitoring of patients with elevated AIA titres and to introduce some changes to the statistical analysis plan.

Major or critical protocol deviations potentially impacting efficacy analyses were reported in few patients in both treatment groups (SAR342434: 9 patients [3.6%]; Humalog: 8 patients [3.1%]). In both groups, the most frequently reported deviation was the absence of post-baseline HbA1c value available for analysis. One patient in the SAR342434 group was included in the study with having diabetes other than T1DM.

Baseline data

Baseline demographic and patient characteristics are summarised in **Table 8.**

Table 8. Demographics and patient characteristics at baseline in study EFC12619

	SAR342434 (N=253)	Humalog (N=254)	All (N=507)
Age (years)			
Number	253	254	507
Mean (SD)	43.3 (14.5)	42.6 (13.9)	43.0 (14.2)
Median	43.0	42.0	42.0
Min : Max	18 : 83	18 : 84	18 : 84
Age group (years) [n(%)]			
Number	253	254	507
<65	226 (89.3%)	237 (93.3%)	463 (91.3%)
≥65 to <75	25 (9.9%)	16 (6.3%)	41 (8.1%)
≥75	2 (0.8%)	1 (0.4%)	3 (0.6%)
Gender [n(%)]			
Number	253	254	507
Male	149 (58.9%)	153 (60.2%)	302 (59.6%)
Female	104 (41.1%)	101 (39.8%)	205 (40.4%)
Race [n(%)]			
Number	253	254	507
Caucasian/White	202 (79.8%)	214 (84.3%)	416 (82.1%)
Black	16 (6.3%)	8 (3.1%)	24 (4.7%)
Asian/Oriental	32 (12.6%)	31 (12.2%)	63 (12.4%)
Other	3 (1.2%)	1 (0.4%)	4 (0.8%)
Ethnicity [n(%)]			
Number	253	254	507
Hispanic	17 (6.7%)	10 (3.9%)	27 (5.3%)
Not Hispanic	236 (93.3%)	244 (96.1%)	480 (94.7%)
Regions [n(%)]			
Number	253	254	507
United States	108 (42.7%)	110 (43.3%)	218 (43.0%)
Western Europe	46 (18.2%)	26 (10.2%)	72 (14.2%)
Eastern Europe	68 (26.9%)	88 (34.6%)	156 (30.8%)
Rest of the World	31 (12.3%)	30 (11.8%)	61 (12.0%)

Region-approved Humalog [n(%)]			
Number	253	254	507
US-approved Humalog	139 (54.9%)	140 (55.1%)	279 (55.0%)
EU-approved Humalog	114 (45.1%)	114 (44.9%)	228 (45.0%)
Baseline weight (kg)			
Number	253	254	507
Mean (SD)	77.7 (14.8)	76.7 (16.8)	77.2 (15.8)
Median	77.0	75.5	76.4
Min : Max	44 : 117	40 : 130	40 : 130
Baseline BMI (kg/m^2)			
Number	253	254	507
Mean (SD)	26.2 (4.0)	25.8 (4.1)	26.0 (4.1)
Median	25.6	25.2	25.5
Min : Max	17 : 35	16 : 35	16 : 35
Baseline BMI categories (kg/m^2) [n(%)]			
Number	253	254	507
<25	107 (42.3%)	121 (47.6%)	228 (45.0%)
≥25 to <30	99 (39.1%)	88 (34.6%)	187 (36.9%)
≥30	47 (18.6%)	45 (17.7%)	92 (18.1%)
Baseline estimated GFR ($mL/min/1.73m^2$)			
Number	253	254	507
Mean (SD)	90.37 (22.10)	90.82 (19.15)	90.59 (20.65)
Median	89.34	89.78	89.49
Min : Max	36.1 : 187.7	36.5 : 148.4	36.1 : 187.7
Baseline estimated GFR categories ($mL/min/1.73\ m^2$) [n(%)]			
Number	253	254	507
≥90	123 (48.6%)	124 (48.8%)	247 (48.7%)
≥60 to <90	111 (43.9%)	115 (45.3%)	226 (44.6%)
≥30 to <60	19 (7.5%)	15 (5.9%)	34 (6.7%)
<30	0	0	0
Randomization strata of screening HbA1c categories (%) [n(%)]			
Number	253	254	507
<8	99 (39.1%)	99 (39.0%)	198 (39.1%)
≥8	154 (60.9%)	155 (61.0%)	309 (60.9%)

Disease characteristics of patients are summarised in **Table 9**.

Table 9. Disease characteristics of patients at baseline in study EFC12619

	SAR342434 (N=253)	Humalog (N=254)	All (N=507)
Fasting C-peptide categories (nmol/L) at randomization [n(%)]			
Number	250	244	494
<0.023	192 (76.8%)	195 (79.9%)	387 (78.3%)
≥0.023 to <0.42	57 (22.8%)	45 (18.4%)	102 (20.6%)
≥0.42	1 (0.4%)	4 (1.6%)	5 (1.0%)
Duration of T1DM (years)			
Number	253	254	507
Mean (SD)	19.53 (12.63)	18.57 (11.99)	19.05 (12.31)
Median	16.40	16.30	16.40
Min : Max	1.3 : 60.2	1.1 : 52.0	1.1 : 60.2
Category of duration of T1DM (years) [n(%)]			
Number	253	254	507
<10	63 (24.9%)	65 (25.6%)	128 (25.2%)
≥10	190 (75.1%)	189 (74.4%)	379 (74.8%)
Age at onset of T1DM (years)			
Number	253	254	507
Mean (SD)	24.2 (14.1)	24.6 (14.2)	24.4 (14.1)
Median	21.4	22.0	22.0
Min : Max	2 : 81	0 : 65	0 : 81
Duration of basal bolus insulin treatment (years)			
Number	242	249	491
Mean (SD)	16.55 (11.08)	15.92 (10.47)	16.23 (10.77)
Median	13.80	14.30	14.10
Min : Max	1.0 : 52.3	1.1 : 51.1	1.0 : 52.3
Duration of mealtime insulin treatment in patient life (years)			
Number	243	248	491
Mean (SD)	16.47 (10.81)	16.30 (10.53)	16.38 (10.66)
Median	13.90	14.90	14.30
Min : Max	0.5 : 52.3	1.1 : 52.0	0.5 : 52.3
Previous basal insulin type [n(%)]			
Number	253	254	507
Insulin glargine	253 (100%)	254 (100%)	507 (100%)

Duration of insulin glargine treatment (years)			
Number	253	254	507
Mean (SD)	7.12 (6.48)	6.68 (5.91)	6.90 (6.20)
Median	5.90	5.20	5.40
Min : Max	0.5 : 43.4	0.5 : 35.7	0.5 : 43.4
Previous mealtime insulin type [n(%)]			
Number	253	254	507
Humalog/Liprolog	155 (61.3%)	152 (59.8%)	307 (60.6%)
NovoLog/NovoRapid	95 (37.5%)	95 (37.4%)	190 (37.5%)
Both Humalog/Liprolog and NovoLog/NovoRapid	3 (1.2%)	7 (2.8%)	10 (2.0%)
Duration of previous treatment with Humalog/Liprolog (years)			
Number	157	158	315
Mean (SD)	7.91 (6.86)	7.92 (7.05)	7.91 (6.94)
Median	6.20	5.95	6.10
Min : Max	0.1 : 39.2	0.2 : 35.7	0.1 : 39.2
Duration of previous treatment with NovoLog/NovoRapid (years)			
Number	98	102	200
Mean (SD)	7.14 (6.39)	6.26 (5.19)	6.69 (5.81)
Median	5.40	5.10	5.30
Min : Max	0.2 : 38.0	0.1 : 20.1	0.1 : 38.0

Concomitant antidiabetic medications

A similar percentage of patients, 16.2% in the SAR342434 group and 17.7% in the Humalog group, took concomitant antidiabetic medications other than the IMP or the NIMP which in most cases were other insulin products.

Numbers analysed

All randomized patients were included in the ITT population for the efficacy analyses. Of the 507 randomized patients, 1 patient in the SAR342434 group did not receive the IMP and was not included in the safety population.

Table 10. Data sets analysed in study EFC12619

	SAR342434	Humalog	All
Randomized population	253 (100%)	254 (100%)	507 (100%)
Efficacy populations			
Intent-to-Treat (ITT)	253 (100%)	254 (100%)	507 (100%)
Safety population	252	254	506
Anti-insulin antibody population	247	252	499

Outcomes and estimation

The primary efficacy analysis results are summarised in **Table11**.

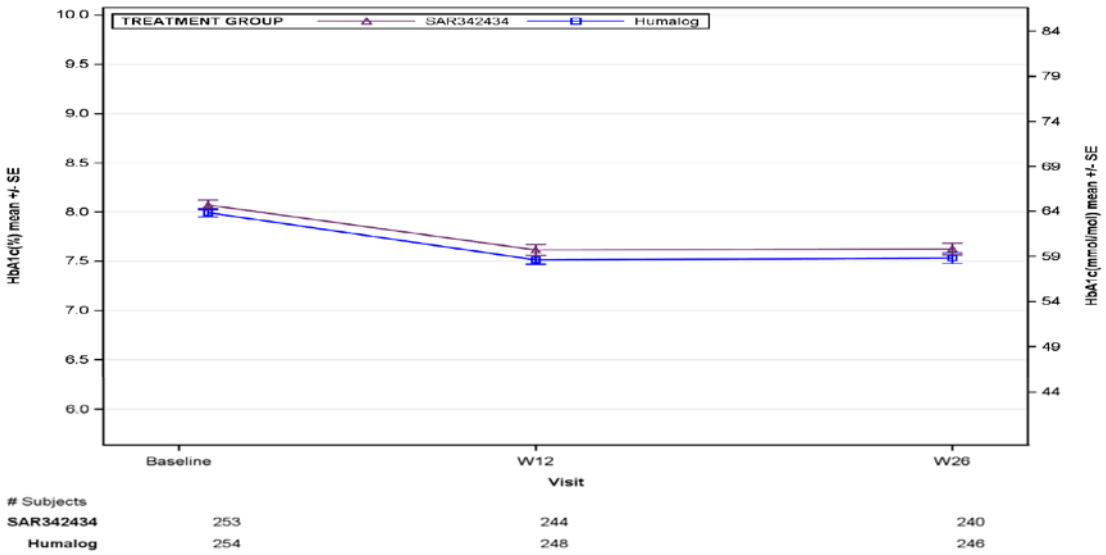
Table 11. Primary efficacy endpoint analysis in study EFC12619 - summary of change in HbA1c (%) form baseline to Week 26 using MMRM analysis (ITT population)

HbA1c (%)	SAR342434 (N=253)	Humalog (N=254)
Baseline		
Number	247	249
Mean (SD)	8.08 (0.78)	7.99 (0.64)
Median	8.00	7.90
Min : Max	5.4 : 10.5	6.7 : 9.7
Week 26		
Number	240	246
Mean (SD)	7.62 (0.92)	7.53 (0.87)
Median	7.60	7.50
Min : Max	5.5 : 11.7	5.8 : 13.8
Change from baseline to Week 26		
Number	240	246
Mean (SD)	-0.44 (0.81)	-0.46 (0.88)
Median	-0.40	-0.50
Min : Max	-2.6 : 2.8	-2.8 : 6.4
LS Mean (SE)[a]	-0.42 (0.051)	-0.47 (0.050)
95% CI	(-0.517 to -0.318)	(-0.573 to -0.376)
LS Mean difference (SE) vs Humalog[a]	0.06 (0.071)	
95% CI	(-0.084 to 0.197)	

MMRM; Mixed-effect model for repeated measures

The plot of mean HbA1c values from baseline to Week 26 by visit is provided in **Figure 8**.

Figure 8. HbA1c (% and mmol/mol) - Mean (+/- SE) by visit during the main 6-month period – ITT population – EFC12619



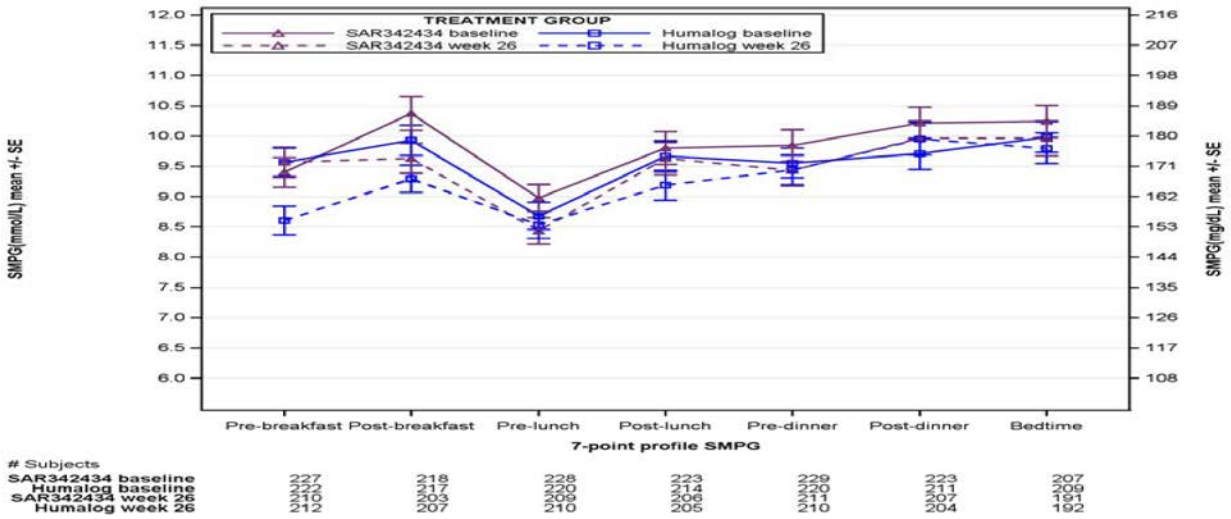
Secondary efficacy endpoints

Secondary endpoints included the percentage of HbA1c responders 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 12** and **Figure 9**).

Table 12. Summary of secondary efficacy endpoints in study EFC12619

	SAR342434 (N=253)	Humalog (N=254)
Responders HbA1c <7% at Week 26		
n (%)	57 (22.5%)	55 (21.7%)
FPG (mmol/L)		
Number	240	242
Baseline - Mean (SD)	10.13 (4.40)	10.06 (4.10)
LS Mean change (SE)[a]	-0.46 (0.248)	-0.62 (0.248)
LS Mean diff vs. Humalog [a] [95% CI]	0.15 [-0.537 to 0.841]	
Postprandial plasma glucose excursions (mmol/L)		
At breakfast		
Number at baseline	205	198
Baseline - Mean (SD)	0.79 (4.66)	0.34 (4.25)
Month 6 – Mean (SD)	0.10 (3.80)	0.77 (4.23)
LS Mean change (SE) [a]	-0.46 (0.297)	0.19 (0.297)
LS Mean diff. vs. Humalog [a] [95% CI]	-0.64 [-1.469 to 0.184]	
At lunch		
Number at baseline	207	193
Baseline - Mean (SD)	0.94 (4.49)	0.91 (4.05)
Month 6 – Mean (SD)	1.08 (4.17)	0.66 (4.01)
LS Mean change (SE) [a]	0.14 (0.298)	-0.26 (0.309)
LS Mean diff vs. Humalog [a] [95% CI]	0.40 [-0.443 to 1.245]	
At dinner		
Number at baseline	208	190
Baseline - Mean (SD)	0.40 (4.48)	0.06 (4.01)
Month 6 – Mean (SD)	0.63 (4.12)	0.71 (4.45)
LS Mean change (SE) [a]	0.48 (0.308)	0.56 (0.324)
LS Mean diff. vs. Humalog [a] [95% CI]	-0.07 [-0.953 to 0.804]	

Figure 9. 7-point SMPG profile (mmol/L and mg/dL) - Mean (+/- SE) at baseline and Week 26 per time point (ITT population) – EFC12619



Study EFC13403

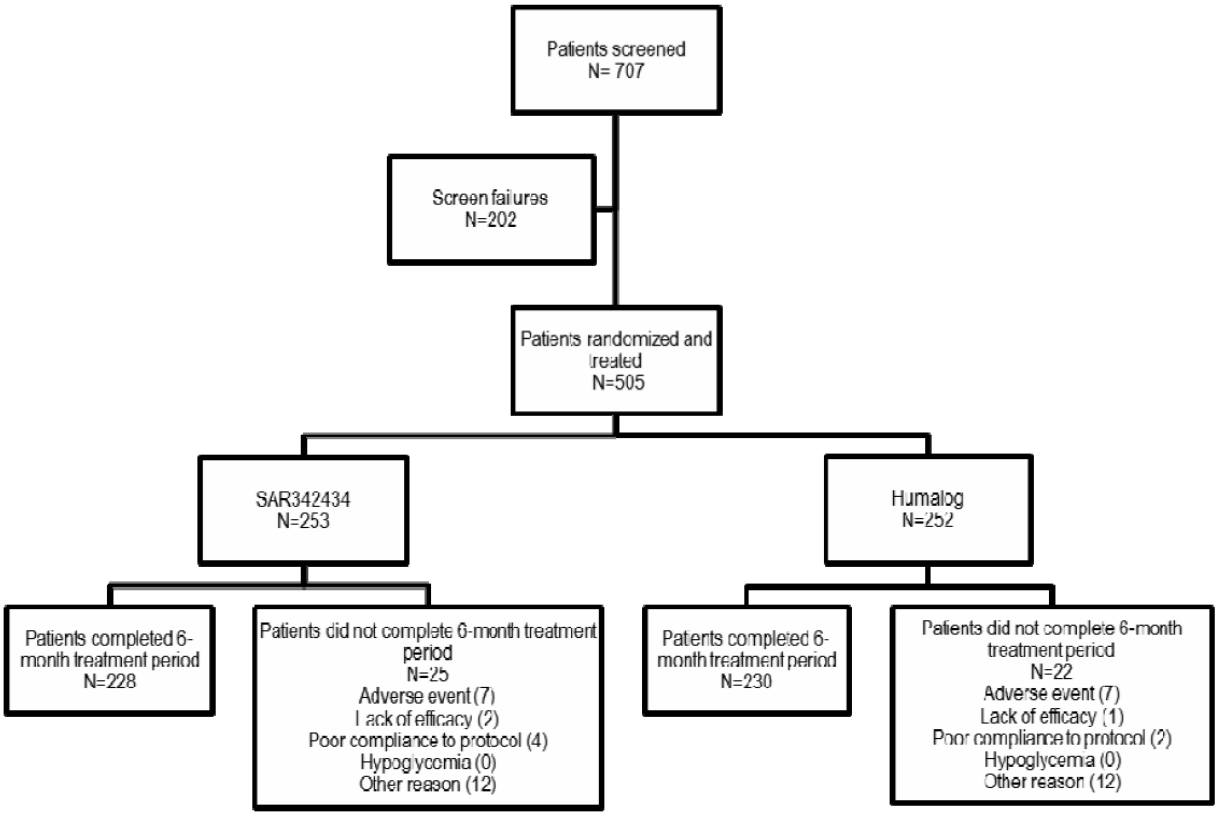
This was similar to EFC12619, in terms of design, duration andf endpoints investigated, but included patients with T2DM.

Therefore only the results from this study are presented in the following sections of this report.

Results

Participant flow

Figure 10. Patient disposition in study EFC13403



Among the 252 patients randomized to Humalog, 120 (47.6%) were randomized in sites using Humalog US, and 132 (52.4%) were randomized in sites using Humalog EU.

Recruitment

The study was initiated on 14 January 2015 (first patient enrolled) and was completed on 16 February 2016. A total of 99 study centres across 12 countries worldwide enrolled patients.

Conduct of the study

The protocol was amended 1 time mainly to clarify monitoring of patients with elevated AIA titres.

The only major or critical deviation potentially impacting the efficacy analyses that was identified during the treatment period was the absence of post-baseline HbA1c value available for analysis; it

was reported in few patients in both treatment groups (SAR342434: 14 patients [5.5%]; Humalog: 6 patients [2.4%]) who discontinued the treatment before the first HbA1c measurement at Week 12.

Baseline data

Baseline demographic and patient characteristics are summarised in **Table 13**.

Table 13. Demographics and patient characteristics at baseline in study EFC13403

	SAR342434 (N=253)	Humalog (N=252)	All (N=505)
Age (years)			
Number	253	252	505
Mean (SD)	62.1 (9.4)	62.8 (8.9)	62.5 (9.1)
Median	63.0	64.0	63.0
Min : Max	35 : 88	38 : 86	35 : 88
Age group (years) [n(%)]			
Number	253	252	505
<65	144 (56.9%)	137 (54.4%)	281 (55.6%)
≥65 to <75	89 (35.2%)	93 (36.9%)	182 (36.0%)
≥75	20 (7.9%)	22 (8.7%)	42 (8.3%)
Gender [n(%)]			
Number	253	252	505
Male	136 (53.8%)	132 (52.4%)	268 (53.1%)
Female	117 (46.2%)	120 (47.6%)	237 (46.9%)
Race [n(%)]			
Number	253	252	505
Caucasian/White	228 (90.1%)	218 (86.5%)	446 (88.3%)
Black	14 (5.5%)	17 (6.7%)	31 (6.1%)
Asian/Oriental	11 (4.3%)	16 (6.3%)	27 (5.3%)
Other	0	1 (0.4%)	1 (0.2%)
Ethnicity [n(%)]			
Number	253	252	505
Hispanic	43 (17.0%)	47 (18.7%)	90 (17.8%)
Not Hispanic	210 (83.0%)	205 (81.3%)	415 (82.2%)
Regions [n(%)]			
Number	253	252	505
United States	122 (48.2%)	120 (47.6%)	242 (47.9%)
Western Europe	32 (12.6%)	37 (14.7%)	69 (13.7%)
Eastern Europe	67 (26.5%)	58 (23.0%)	125 (24.8%)
Rest of the World	32 (12.6%)	37 (14.7%)	69 (13.7%)

Baseline weight (kg)			
Number	253	252	505
Mean (SD)	92.2 (17.5)	91.2 (17.4)	91.7 (17.4)
Median	91.1	90.7	91.0
Min : Max	52 : 138	53 : 149	52 : 149
Baseline BMI (kg/m^2)			
Number	253	252	505
Mean (SD)	32.3 (4.8)	32.1 (4.8)	32.2 (4.8)
Median	32.3	32.2	32.3
Min : Max	20 : 45	21 : 42	20 : 45
Baseline BMI categories (kg/m^2) [n(%)]			
Number	253	252	505
<25	17 (6.7%)	18 (7.1%)	35 (6.9%)
≥25 to <30	62 (24.5%)	72 (28.6%)	134 (26.5%)
≥30	174 (68.8%)	162 (64.3%)	336 (66.5%)
Baseline estimated GFR ($mL/min/1.73m^2$)			
Number	253	252	505
Mean (SD)	77.29 (22.89)	78.48 (23.66)	77.89 (23.26)
Median	77.10	77.57	77.37
Min : Max	28.0 : 141.1	26.7 : 228.6	26.7 : 228.6
Baseline estimated GFR categories ($mL/min/1.73\ m^2$) [n(%)]			
Number	253	252	505
≥90	69 (27.3%)	67 (26.6%)	136 (26.9%)
≥60 to <90	130 (51.4%)	135 (53.6%)	265 (52.5%)
≥30 to <60	51 (20.2%)	49 (19.4%)	100 (19.8%)
<30	3 (1.2%)	1 (0.4%)	4 (0.8%)

Disease characteristics of patients are summarised in **Table 14**.

Table 14. Disease characteristics of patients at baseline in study EFC13403

	SAR342434 (N=253)	**Humalog (N=252)**	**All (N=505)**
Duration of T2DM (years)			
Number	253	252	505
Mean (SD)	16.60 (7.93)	17.52 (8.67)	17.06 (8.31)
Median	16.00	16.35	16.30
Min : Max	1.2 : 45.4	1.1 : 45.4	1.1 : 45.4
Category of duration of T2DM (years) [n(%)]			
Number	253	252	505
<10	50 (19.8%)	47 (18.7%)	97 (19.2%)
≥10	203 (80.2%)	205 (81.3%)	408 (80.8%)
Age at onset of T2DM (years)			
Number	253	252	505
Mean (SD)	46.0 (10.1)	45.8 (10.2)	45.9 (10.1)
Median	46.0	46.0	46.0
Min : Max	21 : 87	20 : 74	20 : 87

Duration of basal bolus insulin treatment (years)			
Number	247	243	490
Mean (SD)	7.10 (5.67)	7.99 (6.76)	7.54 (6.24)
Median	5.60	6.20	5.85
Min : Max	0.5 : 36.4	0.5 : 38.5	0.5 : 38.5
Duration of mealtime insulin treatment in patient life (years)			
Number	250	247	497
Mean (SD)	6.43 (5.54)	7.17 (6.33)	6.80 (5.95)
Median	5.20	5.30	5.20
Min : Max	0.5 : 35.4	0.5 : 35.5	0.5 : 35.5
Previous basal insulin type [n(%)]			
Number	253	252	505
Insulin glargine	253 (100%)	251 (99.6%)	504 (99.8%)
Duration of insulin glargine treatment (years)			
Number	253	251	504
Mean (SD)	5.75 (4.62)	5.97 (4.69)	5.86 (4.65)
Median	4.60	4.60	4.60
Min : Max	0.5 : 21.4	0.5 : 23.3	0.5 : 23.3
Previous mealtime insulin type [n(%)]			
Number	253	251	504
Humalog/Liprolog	133(52.6%)	126(50.2%)	259(51.4%)
NovoLog/NovoRapid	119(47.0%)	124(49.4%)	243(48.2%)
Both Humalog/Liprolog and NovoLog/NovoRapid	1(0.4%)	1(0.4%)	2(0.4%)
Duration of previous treatment with Humalog/Liprolog (years)			
Number	134	127	261
Mean (SD)	5.36 (5.29)	4.64 (4.55)	5.01 (4.95)
Median	3.35	2.70	3.20
Min : Max	0.5 : 25.4	0.1 : 20.3	0.1 : 25.4

Concomitant antidiabetic medications

A similar percentage of patients, 61.3% in the SAR342434 group and 67.1% in the Humalog group, took concomitant antidiabetic medications other than the IMP or the NIMP.

Numbers analysed

All randomized patients (505) were included in the ITT population for the efficacy analyses; all randomised patients received the IMP and were included in the safety population.

Table 15. Data sets analysed in study EFC13403

	SAR342434	Humalog	All
Randomized population	253 (100%)	252 (100%)	505 (100%)
Efficacy populations			
Intent-to-Treat (ITT)	253 (100%)	252 (100%)	505 (100%)
Safety population	253	252	505
Anti-insulin antibody population	245	248	493

Outcomes and estimation

The primary efficacy analysis results are summarised in **Table 16**.

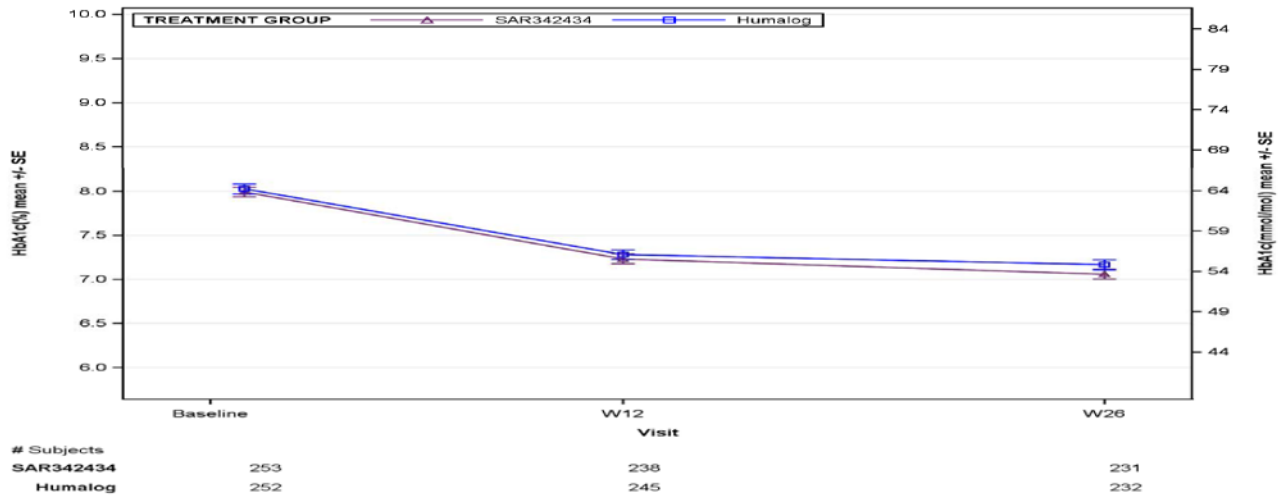
Table 16. Primary efficacy endpoint analysis in study EFC13403 - summary of change in HbA1c (%) form baseline to week 26 using MMRM analysis (ITT population)

HbA1c (%)	SAR342434 (N=253)	Humalog (N=252)
Baseline		
Number	239	246
Mean (SD)	8.00 (0.86)	8.03 (0.91)
Median	8.00	8.00
Min : Max	6.3 : 10.2	5.6 : 11.2
Week 26		
Number	231	232
Mean (SD)	7.06 (0.85)	7.16 (0.88)
Median	7.00	7.05
Min : Max	5.5 : 10.8	5.3 : 10.1
Change from baseline to Week 26		
Number	231	232
Mean (SD)	-0.93 (0.97)	-0.88 (0.84)
Median	-0.90	-0.80
Min : Max	-3.9 : 2.7	-3.5 : 1.7
LS Mean (SE)[a]	-0.92 (0.051)	-0.85 (0.051)
95% CI	(-1.023 to -0.823)	(-0.948 to -0.750)
LS Mean difference (SE) vs Humalog[a]	-0.07 (0.072)	
95% CI	(-0.215 to 0.067)	

MMRM; Mixed-effect model for repeated measures

The plot of mean HbA1c values from baseline to Week 26 by visit is provided in **Figure 11**.

Figure 11. HbA1c (% and mmol/mol) - Mean (+/- SE) by visit during the main 6-month period – ITT population – EFC13403



Secondary efficacy endpoints

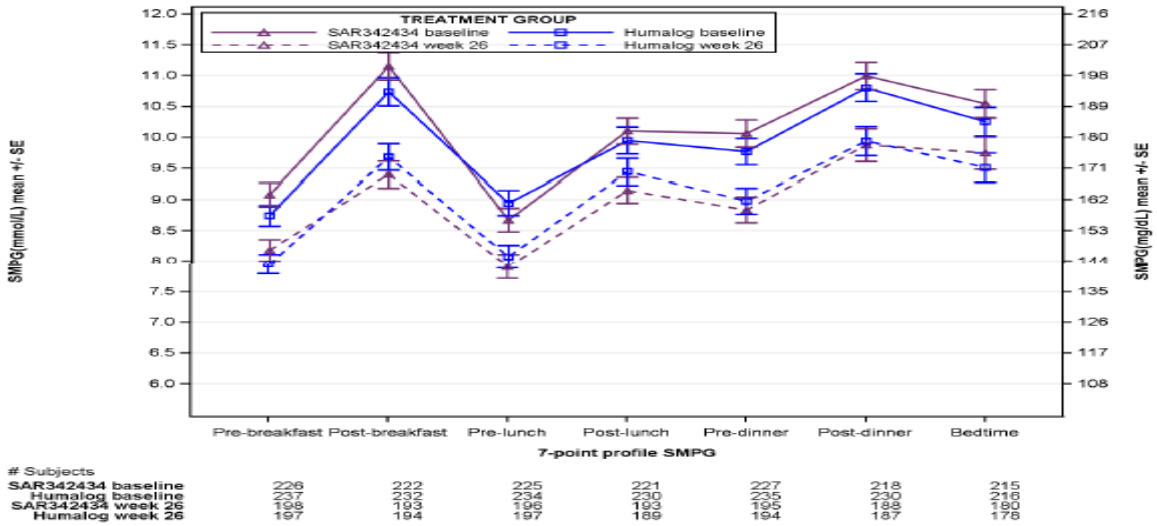
Secondary endpoints included the percentage of HbA1c responders as well as change from baseline to Week 26 in FPG, mean 24-hour plasma glucose concentration, glucose excursions and 7-point SMPG profiles **(Table 17** and **Figure 12**).

Table 17. Summary of secondary efficacy endpoints in study EFC13403

Responders HbA1c <7% at Week 26 n (%)	**SAR342434 (N=253)**	**Humalog (N=252)**
FPG (mmol/L)		
Number	107 (42.3%)	102 (40.5%)
Baseline - Mean (SD)	228 8.35 (2.67)	235 8.18 (2.80)
LS Mean change (SE)[a]	-0.62 (0.176)	-0.67 (0.176)
LS Mean diff vs. Humalog [a] [95% CI]	0.06 [-0.430 to 0.547]	
Postprandial plasma glucose excursions (mmol/L)		
At breakfast		
Number at baseline	194	204
Baseline - Mean (SD)	1.96 (3.27)	1.82 (3.46)
Month 6 – Mean (SD)	1.30 (3.17)	1.77 (3.14)
LS Mean change (SE) [a]	-0.72 (0.236)	-0.23 (0.228)
LS Mean diff. vs. Humalog [a] [95% CI]	-0.48 [-1.127 to 0.164]	
At lunch		
Number at baseline	195	200
Baseline - Mean (SD)	1.71 (3.36)	1.11 (3.68)
Month 6 – Mean (SD)	1.42 (3.52)	1.33 (3.26)
LS Mean change (SE) [a]	0.06 (0.255)	0.11 (0.250)
LS Mean diff vs. Humalog [a] [95% CI]	-0.05 [-0.749 to 0.655]	
At dinner		
Number at baseline	190	193
Baseline - Mean (SD)	1.00 (3.23)	1.08 (3.40)
Month 6 – Mean (SD)	1.11 (3.47)	0.94 (3.36)
LS Mean change (SE) [a]	0.11 (0.264)	-0.10 (0.264)
LS Mean diff. vs. Humalog [a] [95% CI]	0.21 [-0.525 to 0.945]	

]

Figure 12. 7-point SMPG profile (mmol/L and mg/dL) - Mean (+/- SE) at baseline and Week 26 per time point (ITT population) – EFC13403



Summary of main studies

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

Table 18. Summary of efficacy for trial EFC12619

Title: Six-month, Randomized, Open-label, Parallel-group Comparison of SAR342434 to Humalog® in Adult Patients With Type 1 Diabetes Mellitus Also Using Insulin Glargine, with a 6-month Safety Extension Period (N=507)			
Study identifier	EFC12619		
Design	Randomized (1:1), open-label, 2-arm parallel group, multicentre study. The total study duration per patient was 2 weeks of screening + 52 weeks of treatment + 1 day safety follow-up.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 weeks 2 weeks 26 weeks safety extension period
Hypothesis	Non-inferiority (margin of 0.3% HbA1c on primary end point)		
Treatments groups	SAR342434 in combination with Lantus		SAR342434 100 U/ml, self-administrated SC, immediately before food intake, 6 months, N=253, randomized
	Humalog in combination with Lantus [US-Humalog (US and Japan) or EU-Humalog (France, Germany, Hungary, Poland, Spain, Russia)]		Humalog 100 U/ml, self-administrated SC, immediately before food intake, 6 months, N=254, randomized
Endpoints and definitions	Primary end point	**Change in HbA1c (%-units)**	Change in HbA1c (%-units) from baseline to Week 26
	Secondary end point	**HbA1c <7%**	Percentage of HbA1c responders (patients with HbA1c <7%) at Week 26
	Secondary end point	**Change in FPG (mmol/L)**	Change in FPG (fasting plasma glucose mmol/L) from baseline to Week 26
	Secondary end point	**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 profiles

	Secondary end point	**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 (difference between 2 hour postprandial and pre-prandial plasma glucose values at **breakfast, lunch and dinner**).
Database lock	The database for study EFC12619 was locked on 03 February 2016 (26-week treatment period; results in this table) and on 20 July 2016 (52-week, incl. 6-month safety extension period; results not included in this table).		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT population, week 26		
Descriptive statistics and estimate variability	Treatment group	SAR342434	Humalog
	Number of subject	n=253	n=254
	Primary endpoint **Change in HbA1c (% units)**	n=240	n=246
	Mean SD Median Min/Max	-0.44 0.81 -0.40 -2.6 : 2.8	-0.46 0.88 -0.50 -2.8 : 6.4
	Secondary endpoint Proportion of subjects with **HbA1c <7%**	n=253 22.5% (57)	n=254 21.7% (55)
	Secondary endpoint **Change in FPG (mmol/L)**	n=234	n=235
	Mean SD Median Min/Max	-0.41 4.54 -0.65 -17.3 : 11.5	-0.55 5.24 -0.40 -16.4 : 16.3

	Secondary endpoint **Change in mean 24-hour plasma glucose (mmol/L)**	n=198	n=190
	Mean SD Median Min/Max	-0.27 2.53 -0.46 -8.0 : 7.4	-0.41 2.39 -0.53 -7.0 : 8.4
	Secondary endpoint **Change in PPG excursion - breakfast**	n=181	n=181
	Mean SD Median Min/Max	-0.54 5.58 -0.25 -20.0 : 23.2	0.47 5.61 0.36 -14.7 : 12.7
	Secondary endpoint **Change in PPG excursion - lunch**	n=185	n=172
	Mean SD Median Min/Max	0.14 5.23 0.07 -21.7 : 11.6	-0.25 5.41 -0.08 -15.0 : 18.7
	Secondary endpoint **Change in PPG excursion - dinner**	n=190	n=171
	Mean SD Median Min/Max	0.09 5.41 -0.28 -14.2 : 15.7	0.45 5.78 0.65 -18.2 : 15.1
Effect estimate per comparison	Primary endpoint **Difference in change in HbA1c (%-units)**	Comparison groups	SAR342434 - Humalog
		LS Mean difference vs. Humalog	0.06
		95% CI	[-0.084, 0.197]
		P-value	0.4270
	Secondary endpoint **Proportion of subjects with HbA1c <7%**	Comparison groups	SAR342434 - Humalog
		OR (Odds Ratio)	1.06
		95% CI	[0.685, 1.632]

		P-value	ND*
	Secondary endpoint **Difference in change in FPG (mmol/L)**	Comparison groups	SAR342434 - Humalog
		LS Mean difference vs. Humalog	0.15
		95% CI	[-0.537, 0.841]
		P-value	ND*
	Secondary endpoint **Difference in change in 24-hour plasma glucose**	Comparison groups	SAR342434 - Humalog
		LS Mean difference vs. Humalog	0.25
		95% CI	[-0.153, 0.660]
		P-value	ND*
	Secondary endpoint **Difference in change in PPG excursion - breakfast**	Comparison groups	SAR342434 - Humalog
		LS Mean difference vs. Humalog	-0.64
		95% CI	[-1.469, 0.184]
		P-value	ND*
	Secondary endpoint **Difference in change in PPG excursion - lunch**	Comparison groups	SAR342434 - Humalog
		LS Mean difference vs. Humalog	0.40
		95% CI	[-0.443, 1.245]
		P-value	ND*
	Secondary endpoint **Difference in change in PPG excursion - dinner**	Comparison groups	SAR342434 - Humalog
		LS Mean difference vs. Humalog	-0.07
		95% CI	[-0.953, 0.804]
		P-value	ND*
Notes	*ND = Not done. P-values not calculated for secondary endpoints.		

Table 19. Summary of Efficacy for trial EFC13403

Title: Six-month, Randomized, Open-label, Parallel-group Comparison of the Insulin Analog SAR342434 to Humalog in Adult Patients With Type 2 Diabetes Mellitus also Using Insulin Glargine (EFC13403;SORELLA 2)			
Study identifier	EFC13403		
Design	Randomized (1:1), open-label, active-controlled, 2-arm parallel-group multicentre trial. The total study duration per patient was 2 weeks of screening + 52 weeks of treatment + 1 day safety follow-up.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 weeks 2 weeks 26 weeks safety extension period
Hypothesis	Non-inferiority		
Treatments groups	SAR342434 in combination with Lantus		SAR342434 100 U/ml, self-administrated SC, immediately before food intake, 6 months, N=253, randomized
	Humalog in combination with Lantus [US-Humalog (US and Japan) or EU-Humalog (France, Germany, Hungary, Poland, Spain, Russia)]		Humalog 100 U/ml, self-administrated SC, immediately before food intake, 6 months, N=252, randomized
Endpoints and definitions	Primary end point	**Change in HbA1c (%-units)**	Change in HbA1c (%-units) from baseline to Week 26
	Secondary end point	**Proportion of subjects with HbA1c <7%**	Percentage of HbA1c responders (patients with HbA1c <7%) at Week 26
	Secondary end point	**Proportion of subjects with HbA1c ≤6.5%**	Percentage of HbA1c responders (patients with HbA1c ≤6.5%) at Week 26
	Secondary end point	**Change in FPG (mmol/L)**	Change in FPG (fasting plasma glucose mmol/L) from baseline to Week 26
	Secondary end point	**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 profiles
	Secondary end point	**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 (difference between 2 hour postprandial and pre-prandial plasma glucose values at **breakfast, lunch and dinner**).
Database lock	11 April 2016.		
Analysis description	**Primary Analysis**		
Analysis population and time point	ITT population, week 26		

description			
Descriptive statistics and estimate variability	Treatment group	SAR342434	Humalog
	Number of subject	n=253	n=252
	Primary endpoint **Change in HbA1c(% units)**	n=231	n=232
	Mean SD Median Min/Max	–0.93 0.97 –0.90 –3.9 : 2.7	–0.88 0.84 -0.80 –3.5 : 1.7
	Secondary endpoint **Proportion of subjects with HbA1c <7%**	n=253 42.3% (107)	n=252 40.5% (102)
	Secondary endpoint **Proportion of subjects with HbA1c ≤6.5%**	n=253 27.3% (69)	n=252 24.2% (61)
	Secondary endpoint **Change in FPG (mmol/L)**	n=220	n=220
	Mean SD Median Min/Max	–0.65 2.92 –0.64 –8.9 : 15.1	–0.60 3.34 –0.42 –10.8 : 13.7
	Secondary endpoint **Change in mean 24-hour plasma glucose (mmol/L)**	n=180	n=189
	Mean SD Median Min/Max	–1.06 2.65 –1.01 –7.9 : 12.6	–0.85 1.98 –0.55 –7.2 : 4.1
	Secondary endpoint **Change in PPG excursion - breakfast**	n=171	n=184
	Mean SD Median Min/Max	–0.72 4.18 –0.89 –11.9 : 12.7	–0.14 3.93 –0.26 –11.8 : 12.1

	Secondary endpoint **Change in PPG excursion - lunch**	n=170	n=174
	Mean SD Median Min/Max	–0.38 4.36 –0.44 –13.6 : 19.3	0.10 4.32 0.04 –12.2 : 20.6
	Secondary endpoint **Change in PPG excursion - dinner**	n=167	n=168
	Mean SD Median Min/Max	0.14 4.37 –0.47 –11.4 : 16.5	–0.35 4.56 –0.04 –11.5 : 12.6
Effect estimate per comparison	Primary endpoint **Difference in change in HbA1c (%-units)**	Comparison groups	SAR342434 - Humalog
		LS Mean difference vs. Humalog	–0.07
		95% CI	[–0.215, 0.067]
		P-value	0.3039
	Secondary endpoint **Proportion of subjects with HbA1c <7%**	Comparison groups	SAR342434 - Humalog
		OR (Odds Ratio)	1.08
		95% CI	[0.748, 1.566]
		P-value	ND*
	Secondary endpoint **Proportion of subjects with HbA1c ≤6.5%**	Comparison groups	SAR342434 - Humalog
		OR (Odds Ratio)	1.19
		95% CI	[0.783, 1.803]
		P-value	ND*
	Secondary endpoint **Difference in change in FPG (mmol/L)**	Comparison groups	SAR342434 - Humalog
		LS Mean difference vs. Humalog	0.06
		95% CI	[–0.430, 0.547]
		P-value	ND*
	Secondary endpoint **Difference in change in 24-hour plasma glucose**	Comparison groups	SAR342434 - Humalog
		LS Mean difference vs. Humalog	–0.09
		95% CI	[–0.464, 0.287]

		P-value	ND*
	Secondary endpoint **Difference in change in PPG excursion - breakfast**	Comparison groups	SAR342434 - Humalog
		LS Mean difference vs. Humalog	–0.48
		95% CI	[–1.127, 0.164]
		P-value	ND*
	Secondary endpoint **Difference in change in PPG excursion - lunch**	Comparison groups	SAR342434 - Humalog
		LS Mean difference vs. Humalog	–0.05
		95% CI	[–0.749, 0.655]
		P-value	ND*
	Secondary endpoint **Difference in change in PPG excursion - dinner**	Comparison groups	SAR342434 - Humalog
		LS Mean difference vs. Humalog	0.21
		95% CI	[–0.525, 0.945]
		P-value	ND*
Notes	*ND = Not done. P-values not calculated for secondary endpoints.		
		LS Mean difference vs. Humalog	–0.48
		95% CI	[–1.127, 0.164]
		P-value	ND*
	Secondary endpoint **Difference in change in PPG excursion - lunch**	Comparison groups	SAR342434 - Humalog
		LS Mean difference vs. Humalog	–0.05
		95% CI	[–0.749, 0.655]
		P-value	ND*
	Secondary endpoint **Difference in change in PPG excursion - dinner**	Comparison groups	SAR342434 - Humalog
		LS Mean difference vs. Humalog	0.21
		95% CI	[–0.525, 0.945]
Notes	*ND = Not done. P-values not calculated for secondary endpoints.		

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy profile of SAR342434 was compared with the reference product Humalog based on 26-week data from two phase III clinical trials, one in subjects with T1DM (EFC12619) and one in subjects with T2DM (EFC13403). Both studies were multinational, randomised, open-label, 2-parallel group efficacy studies and a total of 1012 patients were randomized. Insulin glargine 100 U/mL (Lantus) was used as the mandatory basal insulin therapy throughout both studies.

The data from the efficacy and safety studies included in the submission were collected in 15 countries worldwide. Global standards were followed for study design, choice of comparator and study conduct. The comparator was Humalog EU (for patients enrolled in Europe, Turkey, Korea, Argentina, Chile and Colombia) or Humalog US (for patients enrolled in US and Japan). As similarity of PK exposure and PD activity between Humalog products from both regions has been established in study PDY12704, this was considered appropriate.

The primary efficacy endpoint, reduction of HbA1c from baseline after 26 weeks, and the secondary efficacy endpoints, i.e. fasting plasma glucose (FPG) and SMPG profiles, the proportion of subjects achieving glycaemic goals, and changes in insulin dose are typically used in studies of anti-hyperglycaemic medications.

Both studies were conducted open-label: subjects and investigators were aware of subject treatment assignments; however, HbA1c, FPG and AIA were determined in central laboratories blinded to the treatment received. In addition, at Sponsor level, the unblinded treatment group allocation variable was included in the clinical study database only at time of 6-month database lock, to perform the corresponding final analyses. Summary results by treatment arm were therefore not available to anyone before the last patient end of main 6-month period and corresponding database lock. The open-label setting on patient and investigator level might have biased results by affecting patient counselling or other non-pharmaceutical aspects in the treatment of study subjects according to study arm. For safety assessment and comparison with the reference product, it is considered appropriate to use the prefilled pen device intended for marketing authorisation. Even if non-blinding on the patient/ investigator-level might affect efficacy and safety, or assessment thereof by the investigators, the open-label design is not expected to affect the crucial issue of immunogenicity assessment.

The study subjects chosen for both efficacy and safety studies were representative of target populations for prandial insulin. The ethnic profile is considered sufficiently representative of European population. Studies were conducted only in adults, which is acceptable, as for a biosimilar no studies in special populations are required.

Allowing only one type of basal insulin is appropriate to reduce confounding by basal insulin effect on efficacy and safety endpoints. As the efficacy and safety studies included patients having previously used as bolus insulin either insulin lispro or insulin aspart, the studies yield clinical information on changing from these insulins to SAR342434. Therefore, study results may help clinicians when they consider changing the bolus insulin from one rapid-acting to another in clinical practice.

Overall, the conduct of both studies was acceptable and there were no notable findings that could have impacted the robustness of clinical findings and conclusions.

Efficacy data and additional analyses

Patient demographics and disease characteristics were well balanced across treatment arms in both efficacy and safety studies. Non-inferiority in the primary objective, change in HbA1c, was

demonstrated as the upper bound of the 2 sided 95% CI of the difference between SAR342434 and Humalog was below the pre-specified non-inferiority margin of 0.3% in both studies.

In study EFC12619, the observed LS mean change in HbA1c from baseline to Week 26 in the SAR342434 group was –0.42% and the Humalog group –0.47% The LS mean difference between the SAR342434 and the Humalog group was 0.06% (95% CI: –0.084 to 0.197). In study EFC13403, mean HbA1c decreased similarly from baseline to Week 26 in the SAR342434 group (LS mean change –0.92%) and the Humalog group (–0.85%). The LS mean difference between the SAR342434 and the Humalog group was –0.07% (95%CI: –0.215 to 0.067). The inverse non-inferiority of Humalog over SAR342434 was also demonstrated in both studies as the lower bound of the 2 sided 95% CI of the difference between SAR342434 and Humalog was above –0.3% (95% CI: –0.215 to 0.067).

Secondary efficacy endpoint results were comparable in both efficacy and safety studies with one exception: self-monitored pre-breakfast glucose values at Week 26 in study EFC12619 were higher for SAR342434 than Humalog, as the self-monitored pre-breakfast values for SAR342434 increased and for Humalog decreased over time. The difference in morning SMPG was reflected also in a difference in post-breakfast glucose excursion, as the post-breakfast SMPG values were similar in both arms. Potentially the patients injected more prandial insulin or ingested fewer carbohydrates at breakfast in the SAR342434 arm to correct for the elevated fasting glucose than the patients on Humalog, who had a lower morning level of glucose. The difference on pre-breakfast values is not considered relevant for defining biosimilarity, as the pre-breakfast values do not depend on prandial insulin but rather on basal insulin and/or evening snack. Furthermore, the more accurate laboratory-measured FPG was on similar level. For all other time points, the confidence intervals for mean glucose values at baseline and at endpoint and for the change in glucose level over 26 weeks overlapped. Overall, the SMPG curves were similar.

At all other time points of the SMPG profile showed similar glucose levels, and in study EFC13403 also the morning SMPG levels were similar. This small difference observed only in the T1DM study is considered a chance finding.

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 two large 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 Type 1 and 2 DM.

This data is considered supportive in establishing biosimilarity. Both studies, demonstrated that SAR342434 is non-inferior to Humalog in improvement of glycaemic control by Week 26 and therefore provided strong supportive evidence about the comparability/ biosimilarity of the two products. The 12-month results of study EFC12619 further supported similar clinical efficacy of SAR342434 and Humalog in T1DM subjects.

2.6. Clinical safety

Clinical safety was assessed in one Phase 1 PK/PD euglycaemic clamp study for T1DM (PD12704), two efficacy and safety studies for T1DM (EFC12619) and T2DM (EFC13403) and a safety study using an external insulin pump for T1DM (PDY13502).

Since the main long-term safety (and efficacy) Phase III studies (EFC12619 and EFC13403) have a similar design (multinational, randomized, open-label, parallel group, controlled 6-month) safety and efficacy comparisons of SAR342434 and Humalog data were also pooled across these studies to gather a safety assessment of SAR342434 versus Humalog in the combined population of T1DM and T2DM patients. Hypoglycaemia results were not pooled across studies because of the differences in the underlying risk of hypoglycaemia. Furthermore, study EFC12619 has a 6-month comparative safety extension period.

In the safety study using external insulin pump (PDY13502**,** T1DM) the main safety parameter, frequency distributions by treatment (SAR342434 versus US approved Humalog) were provided for number and percentage of patients with at least one infusion set occlusion and also for the number of infusion set occlusion events.

Patient exposure

In clinical studies, over 1000 subjects with T1DM or T2DM received treatment with SAR342434 or Humalog (the total number of patients receiving SAR342434 being 553 patients). In addition, the mean duration of exposure to SAR342434 vs. Humalog was comparable. Overall there were 233 T1DM patients and 221 T2DM patients exposed to SAR342434 for > 6 months.

Adverse events

The results for treatment emergent adverse events (TEAEs) and severe TEAEs are presented in **Tables 20** and **21**.

Table 20. Overview of treatment emergent adverse events during the on-treatment period in Phase III studies

	EFC12619 (T1DM)		**EFC13403 (T2DM)**	
n(%)	**SAR342434 (N=252)**	**Humalog (N=254)**	**SAR342434 (N=253)**	**Humalog (N=252)**
Patients with any TEAE	108 (42.9%)	106 (41.7%)	118 (46.6%)	108 (42.9%)
Patients with any treatment emergent SAE	8 (3.2%)	14 (5.5%)	14 (5.5%)	27 (10.7%)
Patients with any TEAE leading to death	1 (0.4%)	0	1 (0.4%)	2 (0.8%)
Patients with any TEAE leading to permanent IMP discontinuation	1 (0.4%)	1 (0.4%)	7 (2.8%)	6 (2.4%)

Table 21. Summary of severe TEAEs by preferred term in 2 or more patients in Phase III studies

Preferred term	**Study EFC12619 (T1DM)**		**Study EFC13403 (T2DM)**	
	SAR342434 (N=252) n (%)	**Humalog (N=254) n (%)**	**SAR342434 (N=252) n (%)**	**Humalog (N=253) n (%)**
Any class	7 (2.8%)	10 (3.9%)	11 (4.3%)	20 (7.9%)
Hypoglycaemic unconsciousness	2 (0.8%)	3 (1.2%)	2 (0.8%)	0
Hypoglycaemia	0	2 (0.8%)	0	2 (0.8%)
Diabetic ketoacidosis	0	2 (0.8%)	0	1 (0.4%)

Preferred term	Study EFC12619 (T1DM)		Study EFC13403 (T2DM)	
	SAR342434 (N=252) n (%)	Humalog (N=254) n (%)	SAR342434 (N=252) n (%)	Humalog (N=253) n (%)
Atrial fibrillation	0	0	0	2 (0.8%)

Based on the pooled data of Phase III studies, the percentage of patients with any TEAEs was in the SAR342434 group (44.8%) and Humalog group (42.3%). Events with severe intensity were reported in 3.6% of the patients treated with SAR342434 and in 5.9% of the patients treated with Humalog. Further, TEAEs related to IMP were reported in 22 (4.4%) SAR342434 treated patients and in 15 (3.0%) in Humalog treated patients; the most frequently reported were general disorders and administration site conditions (SAR3424341 group 1.4% and Humalog group 0.6%) and injury, poisoning and procedural complications (SAR342434 group 0.8% and Humalog group 1.2%).

PDY12704 (T1DM)

Treatment-emergent adverse events were reported in 6/29 subjects following administration of SAR342434, 6/29 subjects following administration of Humalog US-approved, and 3 out of 29 subjects following administration of Humalog EU-approved. Altogether 5 (17.2%) subjects reported 5 AEs of headache following administration of SAR342434, 4 (13.8%) subjects reported 4 AEs following administration of Humalog US and 2 (6.9%) subjects reported 2 AEs of headache following administration of Humalog EU. None of the TEAEs were severe.

PDY13502 (T1DM)

Altogether three (12%) SAR342434-treated patients and four (14.8%) Humalog-treated patients reported at least one TEAE. The most frequently reported TEAEs at the HLT level were upper respiratory tract infections (4% for SAR342434 versus 7.4% for Humalog) and potassium imbalance (none in SAR342434 group versus 7.4% patients in Humalog group). No patient in the SAR342434 group reported any TEAE related to IMP.

The number of patients who had at least one infusion set occlusion during the on-treatment period, defined as failure to correct hyperglycaemia by insulin bolus via the insulin pump (excluding pump malfunction) was 6/25 (24%) in the SAR342434 group and 4/27 (14.8%) in the Humalog group (risk estimate of 22.5% versus 14.6% respectively) with a risk difference for SAR342434 versus Humalog of 7.9% (95% CI [-1.90% to 17.73%]).

Serious adverse event / deaths / other significant events

Serious TEAEs were reported in 8 subjects (3.2%) in the SAR342434 group and in 14 subjects (5.5%) in the Humalog group (5.5%) in study EFC12619 (T1DM). The reported serious TEAE were hypoglycaemia in one patient (0.4%) in SAR342434 group and 2 patients (0.8%) in Humalog group. In addition, hypoglycaemic unconsciousness was reported in SAR342434 group (0.8%; 2 patients with each 1 event) and in Humalog group (1.6%; 4 patients with each 1 event).

Serious TEAEs were reported in 14 subjects (5.5 %) in the SAR342434 group and 27 subjects (10.7%) in the Humalog group in EFC13403 study (T2DM). There were events from the cardiac disorders SOC in the Humalog group (11 patients [4.4%]) and in the SAR342434 group (3 patients [1.2%]). The reported serious TEAE were angina pectoris in Humalog group 1.2% (3 patients) and cardiac failure congestive in SAR342434 group in 0.4% of patients (1 patient) and in Humalog group 0.8% (2

patients). Severe hypoglycaemia was reported as an SAE in 2 patients (0.8%) in both treatment groups: SAR34234 group as hypoglycaemia and Humalog group as hypoglycaemia unconsciousness

Moreover, in PDY13502 (T1DM) study one patient (3.7%) in the Humalog group experienced 3 treatment-emergent SAEs: cardiorespiratory arrest, hypoglycaemia and accidental overdose with fatal outcome.

Altogether five on-treatment deaths were reported. In EFC12619 (T1DM) study one death was reported in the SAR342434 group and not considered related to IMP.

Three deaths were reported in EFC13403 (T2DM) study: one patient in the SAR342434 group and 2 patients in the Humalog group. None of these deaths were considered related either to the IMP or to Humalog.

Adverse Events of special interest

Hypoglycaemia

Hypoglycaemia was reported as an SAE only if it was associated with clinical symptoms such as seizure, unconsciousness or coma or SAE criteria were met. The threshold of plasma glucose ≤3.9 mmol/L (70 mg/dL) was defined as hypoglycaemia.

The incidence of hypoglycaemia and number of hypoglycaemic events and rate per patient-year in both Phase III studies are summarised in **Tables 22** and **23**.

Table 22. Number (%) of patients with at least one hypoglycaemia during the 6-month on-treatment period in Phase III studies

	EFC12619 (T1DM)		EFC13403 (T2DM)	
	SAR342434 (N=252)	Humalog (N=254)	SAR342434 (N=253)	Humalog (N=252)
Any hypoglycaemia	249 (98.8%)	253 (99.6%)	173 (68.4%)	188 (74.6%)
Severe hypoglycaemia	20 (7.9%)	19 (7.5%)	6 (2.4%)	4 (1.6%)
Documented symptomatic hypoglycaemia				
≤3.9 mmol/L (70 mg/dL)	214 (84.9%)	225 (88.6%)	152 (60.1%)	167 (66.3%)
<3.0 mmol/L (54 mg/dL)	159 (63.1%)	177 (69.7%)	73 (28.9%)	69 (27.4%)
Asymptomatic hypoglycaemia				
≤3.9 mmol/L (70 mg/dL)	238 (94.4%)	241 (94.9%)	89 (35.2%)	94 (37.3%)
<3.0 mmol/L (54 mg/dL)	167 (66.3%)	180 (70.9%)	26 (10.3%)	32 (12.7%)
Severe and/or confirmed hypoglycaemia				
≤3.9 mmol/L (70 mg/dL)	247 (98.0%)	253 (99.6%)	169 (66.8%)	183 (72.6%)
<3.0 mmol/L (54 mg/dL)	216 (85.7%)	227 (89.4%)	89 (35.2%)	84 (33.3%)
Probable symptomatic hypoglycaemia	26 (10.3%)	24 (9.4%)	9 (3.6%)	16 (6.3%)
Relative hypoglycaemia				
>3.9 mmol/L (70 mg/dL)	16 (6.3%)	17 (6.7%)	22 (8.7%)	33 (13.1%)

Table 23. Number of hypoglycaemic events and rate per patient-year in Phase III studies

Type of hypoglycemia Number of events (rate per patient-year)	EFC12619 (T1DM)		EFC13403 (T2DM)	
	SAR342434 (N=252)	Humalog (N=254)	SAR342434 (N=253)	Humalog (N=252)
Total patient years	122.77	125.77	118.69	121.23
Any hypoglycemia	12097 (98.53)	12779 (101.61)	1992 (16.78)	2254 (18.59)
Severe hypoglycemia	148 (1.21)	39 (0.31)	9 (0.08)	4 (0.03)
Documented symptomatic hypoglycemia				
≤3.9 mmol/L (70 mg/dL)	4348 (35.42)	4729 (37.60)	1345 (11.33)	1478 (12.19)
<3.0 mmol/L (54 mg/dL)	889 (7.24)	1016 (8.08)	193 (1.63)	196 (1.62)
Asymptomatic hypoglycemia				
≤3.9 mmol/L (70 mg/dL)	7333 (59.73)	7757 (61.68)	409 (3.45)	598 (4.93)
<3.0 mmol/L (54 mg/dL)	1172 (9.55)	1354 (10.77)	47 (0.40)	66 (0.54)
Severe and/or confirmed hypoglycemia[a]				
≤3.9 mmol/L (70 mg/dL)	11863 (96.63)	12550 (99.79)	1907 (16.07)	2154 (17.77)
<3.0 mmol/L (54 mg/dL)	2215 (18.04)	2410 (19.16)	271 (2.28)	277 (2.28)

Studies included: main 6-month treatment period of EFC12619 and EFC13403

a Severe and/or confirmed hypoglycemia= severe and/or confirmed by plasma glucose <=3.9 mmol/L (70 mg/dL) (resp. <3.0 mmol/L [54 mg/dL])

In study PDY13502 (T1DM) Hypoglycaemia occurred in 21 (84%) patients when taking SAR342434 and in 23 (85.2%) patients taking Humalog. There were no reports of severe hypoglycaemia.

Injection site reactions

In study EFC12619 the percentage of patients experiencing injection site reactions during the on-treatment period was in the SAR342434 group 1.2% (3 patients) and in Humalog group 0.8% (2 patients). None of the events were considered as serious. Altogether three injection site reaction in SAR342434 group and two in Humalog group was considered as related to IMP.

In study EFC13403 the percentage of patients experiencing injection site reactions during the on-treatment period was in the SAR342434 group 0.4% (1 patient) and in Humalog group 1.6% (4 patients). None were considered as serious. Moreover, one injection site reaction was considered as related to SAR342434 and 3 reactions related to Humalog.

In study PDY13502 one patient in the SAR342434 group and no patients in the Humalog group experienced an injection site reaction.

Hypersensitivity reactions

EFC12619 (T1DM)

Hypersensitivity reactions were reported in 13 patients (5.2%) in the SAR342434 and 10 patients (3.9%) in the Humalog group.

Hypersensitivity reaction was considered by the investigator as related to IMP in 1 patient in the SAR342434 group (hypersensitivity) versus none in the Humalog group. None of the events were

considered as serious. Further, all resolved while treatment was ongoing with the exception of 2 events in each treatment group (SAR342434 group: 1 event of asthma that was 'not recovered but stabilized' and 1 event of conjunctivitis allergic that was recovering/resolving; Humalog group: 1 event of rhinitis allergic and 1 event of eosinophil count increased that were not resolved).

Altogether, 8 events (SAR342434 group 5 events and Humalog group 3 events) were adjudicated by the ARAC: none of the 5 events in the SAR342434 group were adjudicated to be an allergic reaction. However, in the Humalog group, 1 of the 3 events was adjudicated to be an allergic reaction (urticaria): not related to IMP and mild in intensity.

EFC13403 (T2DM)

Hypersensitivity reactions were reported in 10 patients (4.0%) in the SAR342434 and 9 patients (3.6%) in the Humalog group.

One event in the SAR342434 group (respiratory failure during a brain surgery) was reported as SAE and not related to IMP. None of hypersensitivity reactions led to IMP discontinuation and most events were mild or moderate in intensity. Hypersensitivity reactions that were considered by the investigator as related to IMP was reported in 1 patient in the SAR342434 group (pruritus) and 1 patient in the Humalog group (erythema).

Among events of hypersensitivity reactions, 4 events in 4 patients in the SAR342434 group and 3 events in 2 patients in the Humalog group were adjudicated by the ARAC as allergic reactions. Those events in the SAR342434 group (seasonal allergy, dermatitis contact, allergy to arthropod bite and rhinitis allergic) were all mild as intensity and assessed not related to the IMP. The 2 events of hypersensitivity (both pruritus) in one patient in the Humalog group were both mild in intensity and assessed possibly related to the study medication. Thus, the event of mouth swelling was considered as moderate in intensity and not related to the study medication.

Laboratory findings

Haematology (haemoglobin, platelet count, white blood cell count with differential count) and clinical chemistry parameters (lipid parameters, electrolytes, renal and liver function) were analysed and no meaningful differences between SAR342434 and Humalog were revealed.

Immunological events

The immunogenicity of SAR342434 and Humalog was compared regarding formation of AIA; potential effects of AIA on efficacy (i.e. effects on glycaemic endpoints and/or insulin doses); and potential effects of AIA on safety, especially hypoglycaemic events and hypersensitivity reactions.

Anti-insulin antibodies (AIA) were measured in the pivotal PK/PD study (insulin clamp study, PDY12704) at screening and again at the end of the study. However, as the assay used to detect AIAs in this study was not validated these results are of limited significance in assessing the immunogenicity of the product.

No AIA determinations occurred in the supportive study PDY13502 comparing the biosimilar and reference product used as continuous subcutaneous insulin infusion.

Studies EFC12619 and EFC23403

In EFC12619, blood samples for AIA were taken at V3 (Day 1, baseline), V4 (Week 4), V6 (Week 12), V8 (Week 26; endpoint), V10 (Week 40) and V11 (Week 52, end of the safety extension period of the study).

In EFC13403, AIA samples were collected at V3 (Day 1, baseline), V4 (Week 4), V6 (week 12), and V8 (Week 26, end of study).

AIA were determined in a blinded fashion at a centralized laboratory.

The anti-insulin antibody population was defined as all patients from the safety population with at least one AIA sample available for analysis during the main 6-month on-treatment period. An AIA sample was considered as available for analysis if the sample was collected during the main 6-month on-treatment period and at least 8 hours after the last administration of mealtime insulin. Results were expressed in titres (1/dil).

Based on the pre-existing AIA and recent recommendations for the reporting of clinical immunogenicity, the analysis of AIA data focused on the change in AIA response observed following the IMP administration using the following definitions:

- *Patients with treatment-induced AIAs* were defined as patients with AIAs that developed *de novo* (seroconversion) following the IMP administration (defined as patients with at least one positive AIA sample at any time during the on-treatment period, in those patients without pre-existing AIA or with missing baseline sample).
- *Patients with treatment-boosted AIAs* were defined as patients with pre-existing AIAs that were boosted to a significant higher titre following the IMP administration (defined as patients with at least one AIA sample with at least a 4-fold increase in titres compared to baseline value at any time during the on-treatment period, in those patients with pre-existing AIA).
- *Patients with treatment-emergent AIA* (Yes, No) were derived as follows:
    - *Patients with treatment-emergent AIAs* (AIA incidence) were defined as patients with treatment-induced or treatment-boosted AIAs.
    - *Patients without treatment-emergent AIAs* were defined as patients with neither treatment-induced nor treatment-boosted AIAs.
    - *Inconclusive patients* (patients who could not irrefutably be classified as patients without treatment-emergent AIAs were not included in the above categories and were listed separately.

For patients with treatment-induced and treatment-boosted AIAs, the peak titre was defined as the maximal titre observed during the on-treatment period and the kinetics of AIA response was further classified as follows:

- *Transient AIA response*, defined as a response detected only at one sampling time point during the on-treatment period (excluding the last sampling time point); or response detected at two or more sampling time points during the on-treatment period, where the first and last AIA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the patient's last sampling time point is AIA-negative.
- *Persistent AIA response*, defined as a response detected at two or more sampling time points during the on-treatment period, where the first and last AIA-positive on-treatment sample (irrespective of any negative samples in between) are separated by at least 16 weeks; or response detected in the last two sampling time points, irrespective of the time period in between.
- *Indeterminate AIA response*, defined as a response where only the last sampling time point is positive and all previous samples are negative.

Anti-insulin antibody response in Studies EFC12619 (T1DM) and EFC13403 (T2DM)

At baseline, close to half of T1DM subjects participating in study EFC12619 and one fourth of T2DM subjects participating in study EFC13403 were AIA-positive.

The changes in AIA over the 6-month controlled periods of the two studies are presented in **Table 24**.

Table 24. Anti-insulin antibody data – Summary of AIA response during the main 6-month on-treatment period – Anti-insulin antibody population

	EFC12619 (T1DM)		EFC13403 (T2DM)	
Patients	**SAR342434 (N=247)**	**Humalog (N=252)**	**SAR342434 (N=245)**	**Humalog (N=248)**
AIA positive at baseline, n(%)	117/247 (47.4%)	124/252 (49.2%)	60/245 (24.5%)	63/248 (25.4%)
Median titer (1/dil)	4.00	4.00	4.00	4.00
Q1 : Q3	2.00 : 16.00	2.00 : 8.00	2.00 : 8.00	2.00 : 16.00
Treatment boosted AIA n(%)	14/117 (12.0%)	18/124 (14.5%)	12/60 (20.0%)	8/63 (12.7%)
Median peak titer [a] (1/dil)	16.00	24.00	12.00	16.00
Q1 : Q3	8.00 : 64.00	8.00 : 32.00	8.00 : 32.00	8.00 : 32.00
Transient AIA response n(%)	2/14 (14.3%)	0/18	0/12	0/8
Persistent AIA response n(%)	12/14 (85.7%)	18/18 (100%)	12/12 (100%)	8/8 (100%)
Indeterminate AIA response n(%)	0/14	0/18	0/12	0/8
AIA negative or missing at baseline, n(%)	130/247 (52.6%)	128/252 (50.8%)	185/245 (75.5%)	185/248 (74.6%)
Treatment induced AIA n(%)	29/130 (22.3%)	26/128 (20.3%)	34/185 (18.4%)	28/185 (15.1%)
Median peak titer [a] (1/dil)	2.00	2.00	2.00	2.00
Q1 : Q3	1.00 : 4.00	1.00 : 4.00	1.00 : 8.00	1.00 : 4.00
Transient AIA response n(%)	9/29 (31.0%)	7/26 (26.9%)	8/34 (23.5%)	8/28 (28.6%)
Persistent AIA response n(%)	12/29 (41.4%)	13/26 (50.0%)	15/34 (44.1%)	10/28 (35.7%)
Indeterminate AIA response n(%)	8/29 (27.6%)	6/26 (23.1%)	11/34 (32.4%)	10/28 (35.7%)
Patients with ≥1 positive AIA sample (prevalence) [b], n(%)	146/247 (59.1%)	150/252 (59.5%)	94/245 (38.4%)	91/248 (36.7%)
Patients with treatment-emergent AIA (incidence) [c], n(%)	43/247 (17.4%)	44/252 (17.5%)	46/245 (18.8%)	36/248 (14.5%)
Patients without treatment-emergent AIA, n(%)	204/247 (82.6%)	208/252 (82.5%)	199/245 (81.2%)	211/248 (85.1%)
Inconclusive patients, n(%)	0/247	0/252	0/245	1/248 (0.4%)

Studies included: main 6-month treatment period of EFC12619 and EFC13403
AIA: Anti-insulin antibody
a Maximal titer measured during the 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)

The majority of AIAs both in the SAR342434 and the Humalog arms of the study showed cross-reactivity with human insulin (88.2% and 90.9%), insulin glargine (83.8% and 86.4%), and insulin glargine metabolite M1(70.6% and 72.7%).

AIAs in subgroups defined by screening and baseline factors of patients (age, gender, race, ethnicity, baseline BMI, baseline eGFR, duration of diabetes, prior use of Humalog, randomization stratum of screening HbA1c), or by sites in different geographical regions, showed no consistent trends suggesting heterogeneity (data not shown).

When subgroups using US-approved Humalog and EU-approved Humalog were analysed separately, it was found out that in the subgroup of US-approved Humalog treatment boosted AIAs occurred more frequently with the biosimilar (SAR342434 29.6%; Humalog US 13.3%), whereas in the subgroup of EU-approved Humalog the difference was due to patients with treatment induced AIAs (SAR342434 18.1%; Humalog EU 12.4%).

The percentages of patients positive for AIA slightly increased during the 6-month on-treatment period similarly in both treatment groups. At Week 26, 30.8% of the patients in the SAR342434 group and 29.2% in the Humalog group were AIA positive. The median AIA titres were similar in both treatment groups (4.00) and remained unchanged over time, with a maximum interquartile range during the 6-month on-treatment period of 2.00 to 16.00 in both group. Maximum titres (in both groups 256) were found in the SAR342434 group at baseline, in the Humalog group at Week 4.

In study EFC13403, in the subgroup of patients having used Humalog in the 6 months prior to the study, ie., switching from commercial Humalog to SAR342434 or the comparator Humalog, similar percentages of patients in the SAR342434 group (31/130; 23.8%) and Humalog group (27/126 ;

21.4%) were AIA positive at baseline. In this subgroup, treatment-emergent AIAs were found in similar percentages of SAR342434 (21/130; 16.2%) and Humalog treated patients (19/126; 15.1%).

In study EFC12619 similar percentages of patients in both treatment groups were positive for AIA at baseline (SAR342434: 47.6%; Humalog: 49.2%). The percentages of patients with a treatment-emergent AIA response (i.e., treatment-boosted or treatment-induced AIAs) during the 12-month on-treatment period were similar in both groups (incidence, SAR342434: 56/248 [22.6%]; Humalog: 61/252 [24.2%]):

- Treatment-boosted AIAs were found in less SAR342434 treated patients (19/118 [16.1%) than in Humalog treated patients (26/124 [21.0%]). The median peak titre was 16.00 in both treatment groups.

- Treatment-induced AIAs were found in similar percentages of SAR342434 treated patients (37/130 [28.5%]) and Humalog treated patients (35/128 [27.3%]). The median peak titre was 2.00 in both treatment groups.

Similar percentages of patients in the SAR342434 group (155/248; 62.5%) and in the Humalog group (159/252; 63.1%) were positive for AIA at least at one time-point between baseline and Week 52. Treatment-emergent AIA at the last on treatment value were comparable in both treatment groups (SAR342434: 10.2%; Humalog: 13.5%).

Additional analyses were performed to further clarify the AIA response for studies EFC12619 (12 months) and EFC13403, using for the calculations titres (unit: 1/dil) as continuous variable without applying any titre threshold. In these analyses, increased titres of AIA (i.e. treatment-boosted AIA) occurred in 42.4 % of AIA positive T1DM patients administered SAR342434 and in 52.4% of those administered Humalog. Occurrence of AIA in T1DM patients that were AIA-negative at baseline, i.e. treatment-induced AIA, was 28.5% in patients administered SAR342434 and 27.3% in patients administered Humalog.

For T2DM subjects, the difference in AIA response in study EFC13403 was found to be smaller when no titre threshold was applied in the calculations than in the original calculations. In T2DM patients who were AIA-positive at baseline, an increase of AIA titres (treatment-boosted AIA) occurred in 40.0% of patients in the SAR342434 arm of the study and in 34.9% in the Humalog arm of the study. In patients who were AIA-negative at baseline, the occurrence of AIA (treatment-induced AIA) was 18.4% in subjects administered SAR342434 arm and 15.1% in subjects administered Humalog.

Impact of anti-insulin antibodies on glycaemic efficacy in Studies EFC12619 (T1DM) and EFC13403 (T2DM)

No relationship between AIA levels and glycaemic efficacy was seen in studies EFC12619 and EFC13403. Scatterplots were provided in the submission to identify any individuals with high AIA. These subjects had a similar change in HbA1c as the study participants in general.

No differences were noted between study arms in glycaemic endpoints when analysing the subgroups with and without treatment-emergent AIA.

The primary endpoint, change in HbA1c during the 6-month controlled study period, was similar in both study arms in both phase III efficacy/safety trials regardless of treatment-emergent AIA.

Impact of anti-insulin antibodies on insulin dose in Studies EFC12619 (T1DM) and EFC13403 (T2DM)

In study EFC12619 (T1DM), changes in the basal insulin dose from baseline to Week 26 were slightly (about 0.01 to 0.02 U/kg) higher in both treatment groups in patients with treatment-emergent AIA than in patients without treatment-emergent AIA; however, no difference was noted between subjects administered SAR342434 and subjects administered Humalog. One patient in the SAR342434 group with treatment-emergent AIA (treatment induced) was reported with an increase from baseline of 324 U (5.83 U/kg) at Week 20 and 210 U (3.98 U/kg) at Week 26, resulting in a higher mean daily dose in patients treated with SAR342434 than in those treated with Humalog; but this was confirmed to be data entry error. Changes in the doses of both lispro insulin products from baseline to week 26 were small and not related to treatment-emergent AIA.

In study EFC13403 (T2DM), changes from baseline to Week 26 in daily doses of prandial insulin lispro and basal insulin glargine were similar between the SAR342434 and Humalog arms of the study both in the subgroup with treatment-emergent AIA and in the subgroup without treatment-emergent AIA. Treatment-emergent AIA were overall not related to evolution of insulin doses during the 6 months of the study.

The 12-month data from study EFC12619 showed no relationship between the individual maximal AIA titres or titres at Week 52 and the change in total insulin dose from baseline to Week 52, regardless of treatment-emergent AIA status.

Impact of anti-insulin antibodies on safety

Hypoglycaemia

Forest plot graphs were given for the number of patients with at least one hypoglycaemia during the on-treatment period, stratified for each category of hypoglycaemia, and according to AIA status (yes/no), and no differences between the SAR342434 group and the Humalog group were seen (Data not shown).

In the 12-month results of study EC12619, no differences in hypoglycaemic events were seen between study arms regardless of AIA status.

Injection site and hypersensitivity reactions

During the 6-month treatment periods of both safety studies, similar percentages of patients reported injection site and hypersensitivity reactions in both treatment groups (**Table 25**). None of the hypersensitivity reactions led to permanent IMP discontinuation.

Table 25. Number (%) of patients with hypersensitivity reactions and injection site reactions by treatment-emergent AIA during the 6-month on-treatment period in study EFC12619 and study EFC13403 – Anti-insulin antibody population

	EFC12619 (T1DM)		EFC13403 (T2DM)	
Preferred term n(%)	SAR342434 (N=252)	Humalog (N=254)	SAR342434 (N=253)	Humalog (N=252)
Any injection site reaction	3 (1.2%)	2 (0.8%)	1 (0.4%)	4 (1.6%)
Any hypersensitivity reactions	13 (5.2%)	10 (3.9%)	10 (4.0%)	9 (3.6%)

Studies included: main 6-month treatment period of EFC12619 and EFC13403

n (%) = number and percentage of patients with at least one TEAE linked to injection site or hypersensitivity reaction

All these events were of mild intensity and resolved while treatment was ongoing.

One event in the SAR342434 group was reported as a SAE (respiratory failure during biopsy of a gliosis; not related to IMP). Events were considered by the Investigator as related to SAR342434 in 1 patient with T1DM (hypersensitivity) and 1 patient with T2DM (pruritus) and related to Humalog in 1 patient with T2DM (erythema).

2.6.1. Discussion on clinical safety

The two efficacy and safety studies, EFC12619 in T1DM (N = 507) and EFC13403 in T2DM (N = 505), provide a sufficient data base to establish the safety profile of Insulin lispro Sanofi.

No relevant differences were observed between SAR342434 and Humalog in patients with any AEs, TEAEs, treatment emergent SAEs, TEAEs leading to death or TEAEs leading to permanent IMP discontinuation.

In T2DM patients, TEAE incidence was slightly higher in SAR342434 treated patients compared with Humalog treated patients. However, there were more TEAEs in the infections and infestations SOC in SAR342434 treated patients and within the SOC, nasopharyngitis was the most frequently reported PT in this patient population. This difference in occurrence of infections and specifically nasopharyngitis cannot be addressed to glycaemic control as there was no difference between study arms in glycaemia. Thus, this numerical difference is small, and is most likely due to random fluctuation and unlikely related to the IMP.

In the two efficacy and safety studies, the percentage of patients with at least one hypoglycaemia reported at any time of the day was similar between the SAR342434 and Humalog groups. The number of hypoglycaemic events (rate per patient-year) was higher in SAR342434 group in both Phase III studies. However, this imbalance is explained by one patient in both studies. No difference in hypoglycaemia risk between SAR342434 and Humalog was identified in any other subgroup analyses.

In the short-term studies (PDY12704 and PDY13502) no relevant safety differences were detected, apart from difference in the proportion of patients with at least one infusion set occlusion in the insulin pump study (24% in SAR342434 and 14.8% in the Humalog groups). The Applicant confirmed that the difference was due to only two subjects in the SAR342434 group. The difference is not regarded as clinically relevant.

Thus, when assessing the safety according to occurrence of AEs, TEAEs, SAEs, TEAEs leading to IMP discontinuation and death, in addition to hypoglycaemia, injection site and hypersensitivity reactions, no differences could be seen between SAR342434 and Humalog.

Injection site reactions were rare and there were no relevant differences between SAR342434 and Humalog groups. Further, during the 6-month treatment period of both Phase III studies, very similar percentages of patients reported mild or moderate hypersensitivity reactions.

One of the main focuses of safety assessment of a biosimilar product is based on immunogenicity. Anti-insulin antibodies and their potential effects on efficacy and safety were evaluated in the two efficacy and safety clinical studies in patients with T1DM and patients with T2DM. At baseline almost 50% of T1DM patients and 25% of T2DM patients were AIA positive.

The determination of the clinical significance of AIA in the investigated patient population was difficult due to the abundant pre-existing AIA that cross-react with SAR342434 and because of the concomitant basal insulin that cross-reacted in the anti-insulin antibody assay. Most of the AIA-positive patients were positive already at baseline. The Applicant classified the AIA responses as treatment-induced and treatment-boosted. Together, these subgroups form the group "treatment emergent" AIA-responder which was considered acceptable considering the difficulties in reliably detecting SAR342434-specific antibodies.

In study EFC12619, no relevant differences between study arms were noted in either treatment-boosted or treatment-induced AIA. The total proportion of subjects with treatment-emergent AIA was comparable: 17.4% in the SAR342434 group and 17.5% in the Humalog group. In the SAR342434 and Humalog groups, 89.7% and 91.1% of AIA were cross-reactive with insulin glargine, 88.0% and 90.3% cross-reactive with human insulin, and 74.1% and 71.9% cross-reactive with insulin glargine metabolite M1 (desArg, Arg(B31,B32)-insulin glargine).

In study EFC13403, the percentages of patients with a treatment-emergent AIA response (i.e., treatment-boosted or treatment-induced AIAs) during the 6-month on-treatment period was higher in the SAR342434 group (46/245; 18.8%) compared with the Humalog group (36/248; 14.5%). This difference was caused by more patients with SAR342434 than patients with Humalog with treatment boosted as well as treatment induced AIAs:

- *Treatment-boosted AIAs* were found in 12/60 (20.0%) patients in the SAR342434 group and 8/63 (12.7%) in the Humalog group. The median peak titre was 12.00 in the SAR342434 group and 16.00 in the Humalog group
- *Treatment-induced AIAs* were found in 34/185 (18.4%) patients in the SAR342434 group and 28/185 (15.1%) patients in the Humalog group. The median peak titre was 2.00 in both treatment groups.

In T1DM patients, no difference was found in the incidence of treatment emergent AIA between the treatment groups. In T2DM patients the incidence was slightly higher in the SAR342434 group (18.8%) compared with the Humalog group (14.5%); patients with treatment boosted (20% and 12.7% in the SAR342434 and Humalog groups, respectively) and treatment induced (18.4% and 15.1%), respectively) AIAs have both contributed to this small imbalance. Over the 6-month period in both studies AIA titres were comparable between treatment groups and remained relatively low. No relevant differences were found between patients with treatment-emergent AIAs and those without treatment-emergent AIAs regarding efficacy (change in HbA1c), insulin dosage, occurrence of hypoglycaemia, injection site reactions, hypersensitivity events and general AEs.

Moreover, the 12-month (6 month controlled period and 6-month safety extension period) results in EFC12619 confirmed similar safety of SAR342434 and Humalog in T1DM subjects.

Contrary to regulatory guidance for biosimilar products, the Applicant did not measure neutralizing antibodies. The Applicant justified this deviation from the biosimilar guideline by stating that glycaemic efficacy and effects on insulin dose are reliable indicators of neutralizing potency of antibodies. This was accepted, as the clinical study results showed no difference in efficacy between SAR342434 and Humalog in T21DM and T2DM subjects.

2.6.2. Conclusions on the clinical safety

The size of the safety database and duration of exposure is considered appropriate for the evaluation of the general safety profile of Insulin lispro Sanofi. Safety and tolerability of Insulin lispro Sanofi and Humalog seem to be comparable and thus support biosimilarity of these two products.

With regard to immunogenicity, the differences in the AIA response between SARS342434 and Humalog were small and inconsistent. Treatment-emergent AIA did not affect efficacy or safety endpoints in either T1DM or T2DM subjects.

In conclusion, the safety profile of Insulin lispro Sanofi is acceptable and not different to that of Humalog.

2.7. Risk Management Plan

Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 26. Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Hypoglycaemia • Hypersensitivity • Oedema leading to congestive heart failure when insulin lispro is used concomitantly with thiazolidinediones
Important potential risks	• Medication errors due to insulin mix-up (bolus or wrong basal insulin) and potential misuse of the pen • Antigenicity • Neoplasms
Missing information	• None

Pharmacovigilance plan

No studies are planned with Insulin lispro Sanofi.

Risk minimisation measures

Table 27. Summary table of risk minimisation measures

Safety concerns	Routine risk minimisation activities	Additional risk minimisation activities
Important identified risks		
Hypoglycaemia	Education and information to HCPs and patients through SmPC and PL.	None

	SmPC: Section 4.3: Contraindication Section 4.4: Special warnings and precautions for use Section 4.5: Interaction with other medicinal products and other forms of interaction Section 4.7: Effects on ability to drive and use machine Section 4.8: Undesirable effects Section 4.9: Overdose **PL:** Section 2: What do you need to know before you use Insulin lispro Sanofi -Do Not use Insulin lispro Sanofi Section 2: What do you need to know before you use Insulin lispro Sanofi - Warnings and precautions Section 3: How to use Insulin lispro Sanofi Section 4: Possible side effects - Common problems of diabetes Prescription only medicine.	
Hypersensitivity	Education and information to HCPs and patients through SmPC and PL. **SmPC:** Section 4.3: Contraindications Section 4.8: Undesirable effects **PL:** Section 2: What do you need to know before you use Insulin lispro Sanofi - Do not use Insulin lispro Sanofi Section 4: Possible side effects Prescription only medicine.	None
Oedema leading to congestive heart failure when insulin lispro is used concomitantly with thiazolidinediones	Education and information to HCPs and patients through SmPC and PL. **SmPC:** Section 4.4: Special warning and precautions for use **PL:** Section 2: What do you need to know before you use Insulin lispro Sanofi - Warnings and precautions Prescription only medicine.	None
Important potential risks		
Medication errors due to insulin mix-up (bolus or wrong basal insulin) and potential misuse	Education and information to HCPs and patients through SmPC and PL. **SmPC:** Section 4.2: Posology and method of administration Section 4.4 Special warnings and precautions for use Section 6.2: Incompatibilities	None

of the pen	Section 6.6: Special precautions for disposal and other handling **PL:** Section 2: What do you need to know before you use Insulin lispro Sanofi - Warnings and precautions Section 3: How to use Insulin lispro Sanofi Prescription only medicine.	
Antigenicity	Prescription only medicine.	None
Neoplasms	Prescription only medicine.	None
Missing information		
None	Not applicable	Not applicable

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Humalog package leaflet (for package leaflet content) and to Toujeo full user testing (for package leaflet layout). The bridging report 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 lispro Sanofi (insulin lispro) is included in the additional monitoring list as a new biological product.

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. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Insulin lispro Sanofi (SAR342434) is an insulin lispro that has developed by the applicant as a biosimilar. The EU reference product Humalog is indicated for the treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Humalog is also indicated for the initial stabilisation of diabetes mellitus. The applicant is seeking approval for the same indications as those approved for Humalog.

3.1.2. Available therapies and unmet medical need

In addition to insulin lispro, there are other rapid-acting insulins available such as insulin glulisine and insulin aspart.

The reason for the development of a biosimilar product is not to fulfil an unmet medical need but to offer an alternative to the reference product.

3.1.3. Main clinical studies

The pivotal study was PDY12704, a single-centre, double-blind, randomized, 3-way cross-over euglycaemic clamp study conducted under fasting conditions in 30 patients with type 1 diabetes mellitus (T1DM). The study compared the PK and PD of SAR342434 to Humalog 100 U/mL registered in the US and Humalog 100 U/mL registered in the EU, as well as the PK and PD between Humalog US and Humalog EU. This clamp study was considered pivotal for the demonstration of similar efficacy.

Further supportive information for demonstration of biosimilarity between Insulin lispro Sanofi and Humalog was provided by two multinational, open-label, randomized, controlled Phase III studies in patients with T1DM (EFC12619) or patients with T2DM (EFC13403), with approximately 250 patients in each study arm in both studies. Both studies were 6-month parallel-group studies. The study in T1DM patients has additionally a 6-month safety extension period. The purpose of these studies was to compare efficacy and safety of SAR342434 to that of Humalog in a broad spectrum of diabetes population. As these studies are not formal requirements according to the CHMP Guideline on similar medicinal products containing recombinant human insulin, they are only considered as supportive for efficacy, and the specific focus of these studies is on the comparison of immunogenicity.

3.2. Favourable effects

From a Quality perspective, the applicant performed an extensive biosimilarity exercise with considerable number of batches using a statistical approach for setting similarity ranges. Relevant attributes for the biosimilarity studies for the comparison of Insulin lispro Sanofi to both EU and US Humalog products were chosen. The overall conclusion of this exercise indicates that the products could be regarded as similar in terms of quality characteristics.

From a non-clinical perspective similarity was overall demonstrated between SAR342434 and Humalog based on data from a set of *in vitro* bioassays. More specifically similarity between the two products

was shown fort insulin receptor binding, kinetics and activation, metabolic activities (inhibition of lipolysis, stimulation of glucose uptake, and regulation of glucose 6-phosphatase gene expression) and binding to and activation of the IGF-1R and mitogenic activity were demonstrated. In addition, the toxicology/toxicokinetic studies also showed comparable results for both, SAR342434 and Humalog.

From a clinical perspective, in the pivotal Phase 1 PK/PD study in patients with T1DM the point estimates [90% CIs] of treatment ratio for SAR342434 vs. Humalog EU for the primary PK parameters INS-C_{max} and INS-AUC_{last} were 0.96 [0.88 to 1.04] and 0.97 [0.94 to 1.00], respectively, indicating similar pharmacokinetics between SAR342434 vs. Humalog EU. The results for secondary PK endpoints also supported this conclusion. For INS-AUC, the ratio was 0.97 [0.94 to 1.00]. The point estimates [95% CIs] of treatment ratio for SAR342434 vs. Humalog EU for the primary PD parameters GIR-AUC_{0-12h} and GIR_{max} were 1.06 [0.95 to 1.16] and 1.07 [0.98 to 1.17], respectively, indicating similar pharmacodynamic effect between SAR342434 vs. Humalog EU.

In the Phase III studies non-inferiority in change in HbA1c was demonstrated as the upper bound of the 2 sided 95% CI of the difference between SAR342434 and Humalog was below the pre-specified non-inferiority margin of 0.3% in both studies: in study EFC12619, the observed LS mean change in HbA1c from baseline to Week 26 in the SAR342434 group was –0.42% and the Humalog group –0.47%. The LS mean difference between the SAR342434 and the Humalog group was 0.06% (95% CI: –0.084 to 0.197). In study EFC13403, mean HbA1c decreased similarly from baseline to Week 26 in the SAR342434 group (LS mean change –0.92%) and the Humalog group (–0.85%). The LS mean difference between the SAR342434 and the Humalog group was –0.07% (95%CI: –0.215 to 0.067). The inverse non-inferiority of Humalog over SAR342434 was also demonstrated in both studies as the lower bound of the 2 sided 95% CI of the difference between SAR342434 and Humalog was above –0.3% (95% CI: –0.215 to 0.067).

Also the results for secondary efficacy endpoints including fasting plasma glucose (FPG) and SMPG profiles, the proportion of subjects achieving glycaemic goals, and changes in insulin dose were overall similar for SAR342434 and Humalog in both studies.

3.3. Uncertainties and limitations about favourable effects

From the quality point of view it was noted that the glass syringe material used in the stability batches differing from that intended for the market. The applicant has initiated stability studies with a sufficient number of drug product batches in the glass syringes intended for marketing and has provided confirmation that the CHMP will be informed in case of any unexpected trends or out of specification results during these stability studies.

In the non-clinical evaluation, at day 29 ~1.7 –fold higher C_{max} and ~1.4 – 1.2 fold higher AUC_{0-8h} values were reported for Humalog EU –treated animals than those of SAR342434 –treated animals at 200 U/kg/day dose group rats. However, these findings are considered not to be of a clinical relevance as there were no differences noted in the human pharmacodynamics and pharmacokinetic data between SAR342434 and Humalog.

From the clinical perspective_secondary PD endpoints GIR-AUC_{0-2} and GIR-AUC_{4-12}, the point estimates [95% CIs] of treatment ratio for SAR342434 vs. Humalog EU 95% were 1.13 [0.99-1.29] and 0.94 [0.68-1.31], respectively, i.e. marginally outside the equivalence margin (0.80 to 1.25). This was not pursued further because GIR-AUC_{0-12h} and GIR_{max}, which are defined as the primary PD endpoints for rapid- and short-acting insulins in Guideline EMEA/CHMP/BMWP/32775/2005_Rev. 1, demonstrated similar pharmacodynamic effect between SAR342434 and Humalog EU in study PDY12704.

3.4. Unfavourable effects

There were no relevant differences in the overall rate of TEAEs, SAEs, treatment discontinuations due to AEs, laboratory findings, hypoglycaemic events, injection site nor hypersensitivity reactions between the treatment groups in any of the studies. The adverse events captured mirrored those already described in the SmPC for Humalog.

The main safety concerns with all insulin-containing products are hypoglycaemia, and hypersensitivity reactions and the incidences of these events were similar between the treatment arms in the clinical trials. In T1DM patients, the percentage of patients reporting at least one severe hypoglycaemia was 7.9% in the SAR342434 group and 7.5% in the Humalog group; the corresponding figures for T2DM patients were 2.4% in the SAR342434 group and 1.6% in the Humalog group.

Hypersensitivity reactions were reported in 13 T1DM patients (5.2%) in the SAR342434 and 10 patients (3.9%) in the Humalog group, and in 10 T2DM patients (4.0%) in the SAR342434 and 9 patients (3.6%) in the Humalog group.

In terms of antigenicity, at baseline, close to 50% of T1DM patients and about 25% of T2DM patients were AIA positive. Over the 6-month period in both studies, AIA titres remained relatively low in both treatment groups. The proportion of patients with treatment-emergent AIA (including incidence of AIA in previously AIA-negative subjects and increase in titres of pre-existing AIA) was similar in T1DM patients regardless of study arm. Similarly, no difference between occurrence of AIA was noted between study arms during the 6-month safety extension of study EFC12619 (T1DM) when the analyses were performed using a threshold of at least 4-fold increase in AIA titre. Recalculations performed without applying any titre threshold demonstrated overall small differences in AIA response between the originator and SAR342434. In T2DM subjects, the incidence and increase in AIA was slightly higher with SAR342434, whereas in T1DM patients slightly lower with SAR342434 than with Humalog.

No relevant differences were found between patients with treatment-emergent AIAs and those without treatment-emergent AIAs regarding efficacy, insulin doses, occurrence of hypoglycaemia, injection site reactions, hypersensitivity events and general AEs.

The 12-month results (6 month efficacy/safety period and 6-month safety extension) of study EFC12619 further support similar clinical safety of SAR342434 and Humalog in T1DM subjects.

3.5. Uncertainties and limitations about unfavourable effects

The number of severe hypoglycaemic events (rate per patient-year) was higher in SAR342434 group in both Phase III studies. However, this imbalance is explained by a single patient in both studies. Furthermore, the overall incidence of hypoglycaemic events was comparable between SAR342434 and Humalog groups.

In T2DM patients, TEAE incidence with infections and infestations and within this SOC, nasopharyngitis, was slightly higher in SAR342434 treated patients compared with Humalog treated patients. However, the numerical difference is small, and is most likely due to random fluctuation and unlikely related to the IMP.

Despite regulatory guidance for biosimilar products, the applicant did not measure neutralizing antibodies. This was justified on the basis that the clinical effects in the Phase 3 studies, i.e. insulin doses and glycaemic endpoints, were adequate to assess a potential neutralizing capacity of the AIAs.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The applicant provided a thorough comparative exercise in terms of quality, efficacy and safety parameters in order to support this biosimilar application.

3.6.2. Balance of benefits and risks

When evaluating a biosimilar application, it is of importance that all parts of the comparability exercise point in the same direction, which is the case here.

Demonstration of structural and functional similarity is the foundation of any biosimilar development. Analytical results from comprehensive biosimilarity testing indicate that the products could be regarded as similar.

From a non-clinical perspective similarity of SAR342434 and Humalog has been shown in terms of in vitro functionality and of toxicological, toxicokinetic and local tolerance profiles.

From the clinical point of view the demonstrated PK/PD similarity by the euglycaemic clamp study (PDY12704) is considered key for concluding similar efficacy.

Demonstration of similar glycaemic control with similar insulin doses within the Phase III studies supports the favourable outcome of the pivotal clamp study. In addition, no relevant differences were noted in the incidence of adverse events, including hypoglycaemic events.

As biosimilarity in terms of quality, non-clinical, clinical PK and PD, safety and efficacy has been demonstrated, the benefit-risk balance for Insulin lispro Sanofi is considered positive.

3.7. Conclusions

The overall B/R of Insulin lispro Sanofi is positive.

4. Recommendations

Outcome

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

"*Treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Insulin lispro Sanofi is also indicated for the initial stabilisation of diabetes mellitus*."

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.

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.