24 February 2022
EMA/165165/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Truvelog Mix 30

International non-proprietary name/Common name: insulin aspart

Procedure No. EMEA/H/C/005635/0000

Note

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

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Administrative information

Name of the medicinal product:	Truvelog Mix 30
Applicant:	sanofi-aventis groupe 54 rue La Boetie 75008 Paris FRANCE
Active substance:	Insulin aspart
International Non-proprietary Name/Common Name:	insulin aspart
Pharmaco-therapeutic group (ATC Code):	insulins and analogues, insulins and analogues for injection, intermediate- or long-acting combined with fast-acting (A10AD05)
Therapeutic indication(s):	Truvelog Mix 30 is indicated for treatment of diabetes mellitus in adults, adolescents and children aged 10 years and above.
Pharmaceutical form(s):	Suspension for injection
Strength(s):	100 U/ml
Route(s) of administration:	Subcutaneous use
Packaging:	cartridge (glass) in pre-filled pen (SoloStar) and cartridge (glass)
Package size(s):	1 pre-filled pen, 10 cartridges, 10 pre-filled pens, 5 cartridges and 5 pre-filled pens

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List of abbreviations

ADA:	American Diabetes Association
AE:	adverse event
AIA:	anti-insulin aspart antibody
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AS:	active substance
ATC:	anatomical therapeutic chemical
BG:	blood glucose
BMI:	body mass index
CCI:	container closure integrity
CF:	correction factor
CLB:	competitive ligand binding assay
CHMP:	Committee for Medicinal Products for Human Use
CHO:	Chinese hamster ovary
CI:	confidence interval
COVID-19:	Coronavirus Disease 2019
CQA:	Critical Quality Attribute
CSR:	clinical study report
CV:	coefficient of variation
DNA:	deoxyribonucleic acid
DTP:	direct-to-patient
EC50	half maximal effective concentration
eCRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
EMA:	European Medicines Agency
EOS:	end-of-study
EOT:	end-of-treatment
EU:	European Union
FDA:	Food and Drug Administration
FP:	finished product

FPG:	fasting plasma glucose
GCP:	good clinical practice
GMP:	good manufacturing practice
GIR_{max}:	maximum smoothed body weight standardised glucose infusion rate
GIR-t_{max}:	time to GIRmax
GLP:	good laboratory practice
GLP-1:	glucagon-like peptide-1
Glut-4:	glucose transporter 4
G6PC:	glucose 6-phosphatase
GSPRs:	general safety and performance requirements
HbA_{1c}:	glycated haemoglobin A1c
HiPC:	high positive control
IC50	half maximal inhibitory concentration
IGF-1R	insulin-like growth factor-1 receptor
IMP:	investigational medicinal product
INS-AUC_{0-4h}:	area under the plasma concentration versus time curve over the dosing interval 0-4 hours
INS-AUC_{4-12h}:	area under the concentration versus time curve over the dosing interval 4-12h
INS-AUC_{last}:	area under the concentration versus time curve from 0 to the corresponding to the last concentration above the limit of quantification
INS-C_{max}:	maximum observed concentration
IPCs	in-process controls
IR-A	insulin receptor, subtype A
IR-B	insulin receptor, subtype B
IRT:	interactive response technology
ITT:	intent-to-treat
K_2EDTA:	ethylenediaminetetraacetic acid dipotassium saltMDI: multiple daily injection
LC-MS/MS	liquid chromatography/tandem mass spectrometry
LoPC	low positive control
MAR:	missing at random
MCB:	master cell bank
MCF-7	Michigan Cancer Foundation, cell type 7 (human breast adenocarcinoma cell line)

MDRD:	modification of diet in renal disease
MedDRA:	Medical Dictionary for Regulatory Activities
MEF:	Mouse embryonic fibroblast
MSD:	mesoscale discovery
NAb:	neutralizing anti-insulin aspart antibody
NPH:	Neutral Protamine Hagedorn
OAD:	oral antidiabetic drug
PD:	pharmacodynamic
PK:	pharmacokinetic
PP:	per-protocol
PPQ:	process performance qualification
PT:	preferred term
R:	reference product
RIPA:	radioimmunoprecipitation assay
ROW:	rest of the world
RT:	retention time
SAE:	serious adverse event
SAP	statistical analysis plan
SC:	subcutaneous
SCP:	screening cut-point
SD:	standard deviation
SMPG:	self-monitored plasma glucose
SOC:	system organ class
SPA	scintillation proximity assay
SmPC:	summary of product characteristics
SPR:	surface Plasmon Resonance
T1DM:	type 1 diabetes mellitus
T2DM:	type 2 diabetes mellitus
TEAE:	treatment-emergent adverse event
T:	Test product
TP:	Treatment period

US:	United States
WCB:	working cell bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant sanofi-aventis groupe submitted on 28 April 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Truvelog Mix 30, 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:

Truvelog Mix 30 is indicated for treatment of diabetes mellitus in adults, adolescents and children aged 10 years and above.

1.2. Legal basis, dossier content

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, a clinical bioequivalent study with the reference medicinal product NovoMix 30 and with appropriate own applicant's non-clinical and clinical data.

The chosen reference product is: NovoMix 30

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

- Product name, strength, pharmaceutical form: NovoMix 30, 100 U/ml, Suspension for injection
- Marketing authorisation holder: Novo Nordisk A/S
- Date of authorisation: 01-08-2000
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/00/142

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

- Product name, strength, pharmaceutical form: NovoMix 30, 100 U/ml, Suspension for injection
- Marketing authorisation holder: Novo Nordisk A/S
- Date of authorisation: 01-08-2000
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/00/142

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

- Product name, strength, pharmaceutical form: NovoMix 30, 100 U/ml, Suspension for injection

- Marketing authorisation holder: Novo Nordisk A/S
- Date of authorisation: 01-08-2000
- Marketing authorisation granted by:
  - Union
  - (Union) Marketing authorisation number(s): EU/1/00/142
- Bioavailability study number(s): Study PDY15084

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

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

Date	Reference	SAWP co-ordinators
24 May 2012	EMEA/H/SA/2316/1/2012/III	Dr Kolbeinn Gudmundsson and Dr Christoph Unkrig
23 March 2017	EMEA/H/SA/2316/1/FU/1/2017/III	Dr Amany N. El-Gazayerly and Dr Armin Koch
26 April 2019	EMEA/H/SA/2316/1/FU/3/2019/I	Dr Stephan Lehr and Dr Kolbeinn Gudmundsson

Scientific Advice

The applicant received Scientific Advice on three occasions as mentioned in the table above for the development of Truvelog Mix 30 for the treatment of Type 1 and Type 2 Diabetes Mellitus. The Scientific Advice pertained to the following Quality, Pre-Clinical and Clinical aspects:

- Physico-chemical comparability exercise of the drug substance and drug product vs. reference medicinal product
- Isolation of Insulin Aspart drug substance for quality comparison
- Drug product comparability based on structure elucidation and impurity profile comparison
- Stress and stability testing strategy

- Number of batches to be used for demonstration of similarity and stability
- Analytical characterisation of protamine component
- Bracketing approach for the manufacture of process evaluation batches also used for primary stability evaluation
- Pen differentiation study
- General non-clinical strategy
- Design of hyperinsulinaemic euglycaemic clamp studies in subjects with Type 1 Diabetes Mellitus to demonstrate bioequivalence, confirmation on the adequacy of the study designs after update of EMA Note for Guidance
- Design of safety and efficacy studies including immunogenicity characterisation: patient population, endpoints, statistical analyses, anti-insulin aspart assay
- Patient exposure and safety database

1.6. Steps taken for the assessment of the product

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

Rapporteur: Martina Weise Co-Rapporteur: Kirstine Moll Harboe

The application was received by the EMA on	28 April 2021
The procedure started on	20 May 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 August 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	23 August 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	19 August 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	16 September 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 November 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	23 December 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 January 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	27 January 2022
The applicant submitted the responses to the CHMP List of Outstanding	1 February 2022

Issues on	
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	9 February 2022
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 Truvelog Mix 30 on	24 February 2022
The CHMP adopted a report on similarity of Truvelog Mix 30 with Amglidia on (see Appendix on similarity)	24 February 2022

2. Scientific discussion

2.1. About the product

Truvelog Mix 30 suspension for injection is a biosimilar medicinal product to NovoMix 30.

Insulin aspart is a human insulin analogue produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* as the production organism.

The biphasic insulin analogue preparation (also referred to as SAR341402 Mix 70/30) contains a mixture of 70% protamine-crystallised insulin aspart (intermediate-acting) and 30% soluble insulin aspart (rapid-acting) allowing a biphasic action profile. The insulin aspart in the soluble phase of Truvelog Mix 30 (30% of the total insulin) is absorbed more rapidly from the subcutaneous layer than the soluble insulin component of biphasic human insulin. The remaining 70% of insulin is in crystalline form as protamine-crystallised insulin aspart; this has a prolonged absorption profile similar to human NPH insulin.

Truvelog Mix 30 is indicated for treatment of diabetes mellitus in adults, adolescents and children aged 10 years and above.

The blood glucose lowering effect of insulin aspart is due to the facilitated uptake of glucose following binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

2.2. Type of Application and aspects on development

Truvelog Mix 30 has been developed as a biosimilar of the EU reference medicinal product NovoMix 30.

The quality development is performed as required for new biotechnology-derived drugs and covers the relevant information on drug substance and drug product manufacture, control, specifications, and stability evaluation.

The clinical development programme of Truvelog Mix 30 suspension for injection includes the following studies:

- **PDY15084** study - Comparison of PK, PD and initial tolerability of Truvelog Mix 30 to NovoLog Mix 70/30, NovoMix 30 and SAR341402 rapid-acting solution using the euglycaemic clamp technique, in participants with Type 1 diabetes mellitus (T1DM) conducted in 2 cohorts;
- **EFC15082** Phase 3 study conducted in patients with type 2 diabetes mellitus (T2DM) or T1DM, to compare the efficacy, safety and immunogenicity of Truvelog Mix 30 to NovoMix 30.

Compliance with CHMP guidance

The following guidelines were taken into account during the development programme:

- Guideline on nonclinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues. EMEA/CHMP/BMWP/32775/2005 Rev.1.
- Guideline on similar biological medicinal products. Committee for Medicinal Products for Human Use (CHMP). 23 October 2014. CHMP/437/04 Rev.1.
- Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. Draft 29 January 2018.CPMP/EWP/1080/00 Rev.2.
- Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins - Draft. EMEA/CHMP/BMWP/14327/2006 Rev. 1.

Scientific Advice

The applicant sought CHMP scientific advice in 2012 on the clinical development programme and follow-up scientific advices in 2017 and in 2019 (see above). The CHMP agreed on the design of the PK/PD study – a single-dose, cross-over PK/PD hyperinsulinaemic euglycaemic clamp study in subjects with Type 1 diabetes mellitus in two sequential cohorts to demonstrate similarity in exposure and activity of Truvelog Mix 30 to NovoMix 30 and NovoLog Mix 70/30. Moreover, the study design EFC15082 comparing efficacy and safety of Truvelog Mix 30 and NovoMix 30/NovoLog Mix 70/30 in T1DM patients and T2DM patients has been discussed.

2.3. Quality aspects

2.3.1. Introduction

Truvelog Mix 30 suspension for injection has been developed as a similar biological product to NovoMix 30 (EMEA/H/C/000308).

Truvelog Mix 30 is a subcutaneous injection presented as a suspension for injection in a cartridge or disposable pre-filled pen, containing 100 units/mL (3.5 mg/mL) of insulin aspart as active substance. It is a biphasic suspension of 30% soluble insulin aspart and 70% protamine-crystallised insulin aspart, both produced in *Escherichia coli* by recombinant DNA technology.

Other ingredients are: glycerol, phenol, metacresol, zinc chloride, disodium hydrogen phosphate heptahydrate, sodium chloride, protamine sulfate, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), and water for injections.

The cartridge consists of type 1 colourless glass with a grey plunger (bromobutyl rubber) and a flanged cap (aluminium) with a sealing disk (laminate of isoprene and bromobutyl rubber). The cartridge contains steel

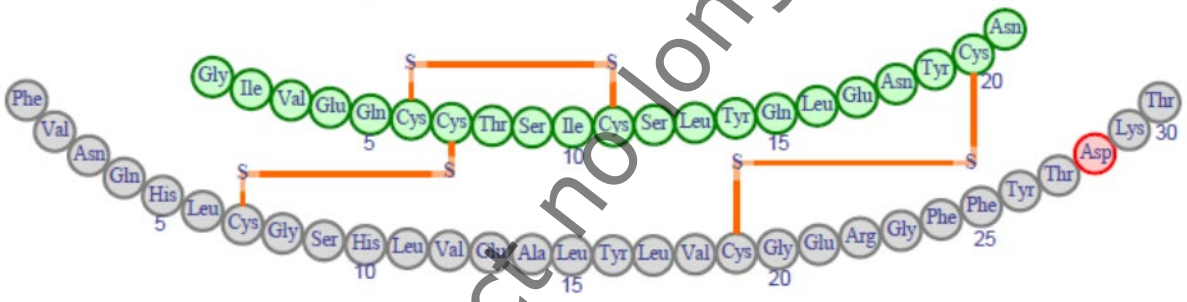
balls to facilitate resuspension. Each cartridge contains 3 mL of suspension. The cartridge can be used with a marketed reusable pen injector, or irreversibly assembled into a disposable pen injector (SoloStar).

2.3.2. Active Substance

2.3.2.1. General information

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

Figure 1 – Schematic amino acid sequence



2.3.2.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls

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

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

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

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

The AS manufacturing process is described in sufficient detail. A narrative description of each step is provided, including ranges of process parameters and in-process-controls (IPCs). Composition, preparation, sterilisation, and storage of culture media are indicated. The active substance manufacturing process is considered acceptable.

Control of materials

No materials of human or animal origin are used in the manufacturing process of insulin aspart. Quality agreements are in place with all suppliers to ensure consistent quality of raw materials. Relevant compendial specifications (current editions of Ph. Eur.) are applied to raw materials. Specifications for non-compendial materials are defined in the dossier.

The history and development of the expression system are clearly presented.

The cell bank system is characterised in line with ICH Q5B and ICH Q5D guidance. Testing panels of the cell banks are considered sufficient to ensure their quality. The stability of the production cell line has been demonstrated. These cell banks were tested for genetic integrity and consistency of production. These tests confirmed the expected genetic characteristics of the cell line and demonstrate genetic stability.

Adequate protocols for stability monitoring of the MCB and the current WCB have been provided. Results are satisfactory. Specifications for release and stability monitoring of new WCBs are considered adequate. Adequate protocols for the establishment of new WCBs are provided.

Control of critical steps and intermediates

During the insulin aspart manufacturing process, the quality of the product is ensured by maintaining process conditions within predetermined ranges and by IPCs. The criticality of parameters is based on the applicant´s risk assessment of the process in order to ensure adequate process performance and product quality attributes falling within the established ranges. The classification is transparent and comprehensive. The set of IPCs are logical and adequately justified. At three stages (step 10, 13 and 14) of the manufacturing process batches may be pooled. The sub-batches are tested in order to ensure their quality before being pooled. Overall the critical process parameters and in-process tests are considered adequate.

Process validation and/or evaluation

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

Clearance of process- and product-related impurities has been adequately addressed. The residual level of impurities at different stages of the manufacturing process has been determined to provide relevant information on the clearance capability of the manufacturing process.
For intermediates of the downstream process, hold time studies were performed to validate the proposed hold times. Microbiological purity and product purity/impurity have been evaluated. Acceptable

microbiological and physico-chemical stability of the process intermediates over the proposed holding time could be observed and based on that, the proposed hold times are considered sufficiently justified.

The applicant proposes a concurrent column lifetime validation approach. The provided criteria and frequency of evaluation are satisfactory. Column lifetime validation is considered addressed in an acceptable manner.

Manufacturing process development

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

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

The first manufacturing process at pilot scale, was used to manufacture a finished product batch for early toxicology studies. The finished product batches used in clinical studies were manufactured using AS from production scale. Also, the finished product batches included in the analytical similarity exercise and the non-clinical *in-vitro* similarity studies with the reference product were manufactured using AS from production scale.

Comparability between AS batches is supported by a comparability exercise comprising release and extended characterisation. It can be concluded that comparability between batches has been adequately shown. Pilot scale batches can be considered supportive.

Characterisation

The structural elucidation and confirmation of insulin aspart have been carried out on insulin aspart manufactured by Sanofi. The batch investigated has been manufactured on a full scale and can be considered representative for the commercial AS.

Characterisation was performed using the following analytical techniques: mass spectrometry (MS), amino acid sequencing, peptide mapping, isoelectric point determination by capillary isoelectric focusing, ultraviolet (UV) / visible absorption spectrophotometry, circular dichroism (CD) spectroscopy, fourier transform infrared (FT-IR) absorption spectrophotometry, nuclear magnetic resonance (NMR) spectrometry and reversed phase chromatography. The studies cover primary, secondary, tertiary and higher order structural aspects. In the studies, comparisons were made with compendial (Ph.Eur., USP and JP) reference preparations. All studies supported the proposed structure. Biological methods are not part of the characterisation section. *In-vivo* and *in-vitro* biological testing are addressed in the biosimilarity studies.

Comprehensive analysis and discussion of the impurity profile of insulin aspart including degradation products are presented. Altogether, a clear picture is provided on the contribution of the individual amount of a product-related substance/ impurity or degradation product to the composition of the active substance.

Process-related impurities as HCP, DNA, residual enzymes, residual solvents and elemental impurities have been addressed and the low levels do not raise any concern. Specified impurities have been present in product studied in clinical studies.

2.3.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

For active substance, release and shelf-life specifications have been provided that comprise identity testing, assay by HPLC, related proteins determination by HPLC and high molecular weight impurities testing by HP-SEC. In addition, contents of sulphated ash, water and residuals of 1-propanol are tested at AS release and during stability. Endotoxins and microbial contamination are also controlled at AS release and during stability.

Adequate descriptions of the analytical methods including their system suitability criteria and validation have been provided. Acceptable data are presented to demonstrate the suitability of the proposed analytical procedures.

Batch analysis data are provided for batches representative of the commercial process. All results comply with the pre-defined acceptance criteria of the specification.

The proposed limits are either complying with the acceptance limits as defined in the Ph. Eur. Monograph insulin aspart or are even stricter.

The applicant has adopted the compendial standard as primary standard. Sufficient information is provided for the preparation of working reference standard currently used in the content assay and for identity.

Insulin aspart active substance is packaged in stainless steel lidded drums. Detailed information on the container closure system of the AS is provided.

2.3.2.4. Stability

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

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

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The finished product (FP) is a sterile suspension in a 3 mL cartridge intended for parenteral injection. The finished product is available as a sterile suspension for injection containing 3.50 mg/mL insulin aspart [equivalent to 100 U (units) of insulin per mL].

Each cartridge is filled with a nominal fill volume of 3 mL suspension for injection containing 300 U of insulin aspart. The cartridge has to be used with a pen injector and there are two presentations:

- The cartridge is irreversibly assembled into a disposable pen injector by Sanofi. The combination of pen injector and 3 mL cartridge (insulin aspart suspension pen injector) is a multiple-use disposable device used to dispense variable doses according to patients' needs.

- The cartridge can be used with a compatible reusable pen injector referenced in the product information (AllStar and AllStar Pro).

For each injection, a new sterile needle is needed (not included with the cartridge or pen injector). An overfill is applied to ensure that the labelled volume can actually be expelled from the cartridges.

The excipients are metacresol, phenol, glycerol, disodium hydrogen phosphate heptahydrate, sodium chloride, protamine sulphate, zinc chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and water for injections. No novel excipient is used in the formulation. Most excipients used for Truvelog Mix 30 are compendial and tested according to the Ph. Eur.

Pharmaceutical development

Formulation development was guided by the biosimilar approach, i.e. the components of the finished product were selected to achieve similarity to the reference product. Nevertheless, formulation studies were performed to evaluate e.g. the impact of phenol and metacresol on formation of crystals, impact of protamine and the influence of zinc concentration and pH range.

The selected concentrations for the preservatives are considered justified.

Manufacturing process development

The manufacturing process development was informed by prior knowledge gained from other insulin suspension manufacturing processes. The control strategy was developed based on risk assessments and the results of laboratory scale experiments. The entire process development is outlined transparently and the control strategy based on the development studies is considered well justified.

Only minor modifications were made in the manufacturing procedure / process controls to adapt the process to the batch sizes and to state-of-the-art equipment.

Container Closure System

The primary packaging system of the Truvelog Mix 30 finished product suspension consists of a glass cartridge, closed with a plunger stopper, and a disc seal. Steel balls are included in each cartridge to enable resuspension.

The glass used for the cartridge is compliant to Ph. Eur. The rubber materials used for commercial primary packaging are identical to those that have been tested during pharmaceutical development and found suitable.

Overall, compatibility of the FP solution with the primary packaging is considered demonstrated.

The disposable pen marketed in a fixed combination with Truvelog Mix 30 cartridges has been developed based on the SoloStar pen. Functionality of the disposable pen has been confirmed in studies with the insulin suspension in compliance to the current requirements. The disposable pen injector has been adequately described, the materials of construction stated, and biocompatibility of those parts that come into contact with the user investigated. The pen device does not come into contact with the FP solution. A notified body opinion on the disposable pen in combination with the Truvelog Mix 30 cartridge is provided in section 3.2.R, confirming full compliance with the relevant general safety and performance requirements (GSPRs).

Further, the product information for the cartridge presentation also refers to the re-usable pens AllStar and AllStar Pro provided separately. These pens are already used for other finished products containing 100 U/mL of insulin. The functionality tests of the cartridge according to ISO requirements were successfully performed,

supporting the general suitability of the cartridge for use with a pen device. EC certificates issued by the notified body covering the reusable pens AllStar and AllStar Pro, as well as EC declarations of conformity were provided by the applicant.

Microbiological Attributes

The finished product suspension is intended for multiple dosing, so that microbial preservation is required in line with current guidance. Preservative effectiveness was demonstrated, and container closure integrity (CCI) ensures maintenance of sterility throughout shelf-life.

Compatibility

No compatibility studies are necessary as the pen itself is not in contact with the product suspension, and the FP is not foreseen for any dilution or mix with other products.

Compatibility of the FP in the disposable pen has been investigated with a variety of injection needles, so that the general statement in the SmPC "Only use needles that are compatible for use with Truvelog Mix 30" without reference to particular needle configurations is included.

2.3.3.2. Manufacture of the product and process controls

Truvelog Mix 30 is manufactured, analytically tested, packed and released at different dedicated authorised sites. GMP compliance of all sites is confirmed by respective documents.

The finished product manufacturing process follows a two-step manufacturing concept – compounding of the insulin aspart premixed suspension for injection and filling into cartridges, followed by pen-assembly, if applicable.

The description of the finished product manufacturing process and its controls is acceptable. The control strategy is based on the process characterisation studies, where the impact of process parameters on critical quality attributes was evaluated. Critical and non-critical process parameters are stated, as well as critical and non-critical IPCs. Classification of the process parameters and IPCs is deemed acceptable.

Process Validation

Batches at scale have been executed to confirm that the finished product manufacturing process performs consistently. Several tests were performed in addition to the routine testing. All predefined acceptance criteria were met, and the resulting batches were compliant with the FP specification. Overall, the data show that the FP manufacturing process consistently delivers FP of the desired quality.

Shipping was successfully validated by simulated shipping studies under temperature-controlled conditions, evaluating the impact of shock and vibration. No negative impact on CQAs of the FP solution and container closer integrity could be detected.

2.3.3.3. Product specification, analytical procedures, batch analysis

The specifications are considered appropriate for the finished product control at release. Justifications for all specification limits have been provided. The finished product specification covers the relevant parameters.

Sufficient results of batch analyses of FP batches have been provided.

Reference Materials

The information on reference materials is satisfactory.

2.3.3.4. Stability of the product

The applicant proposes a 24-month shelf-life for the finished product, when stored at 2-8°C.

This claim is supported by the provided stability data.

In-use stability studies have been executed The results support the claimed in-use period of 28 days below 30°C.

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

2.3.3.5. Adventitious agents

For the manufacturing of the finished product no animal and/or human derived material is used. This applies to the active substance and all finished product excipients, except protamine sulphate.

Protamine sulphate is a purified mixture of simple protein principles obtained from the milt of salmon which has the property of neutralising heparins. For the manufacturing process of protamine sulphate, no materials of TSE-relevant animal species or cell culture derived products and additives are used. Therefore, protamine sulphate has no risks in terms of human virus infectious disease.

The finished product complies with the requirements of the note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev. 3).

2.3.3.6. GMO

Not applicable

2.3.3.7. Biosimilarity

As summarised in **Table 1**, comprehensive analytical comparability study was performed to evaluate similarity between Truvelog Mix 30 (six batches) and the EU reference product NovoMix 30.

Detailed analytical data of protamine sulphate are provided in the analytical similarity study, confirming similarity to protamine contained in the reference product.

The applicant's strategy to establish similarity of Truvelog Mix 30 with the EU reference product NovoMix 30 is endorsed. The attributes tested in the biosimilarity study cover all attributes relevant for the analytical

comparison. Justification is provided for attributes not included such as process related impurities and general pharmaceutical aspects which are covered by the control of finished product section.

The six Truvelog Mix 30 FP batches included in the analytical studies are considered sufficiently representative for the commercial product. Their age at the time of testing is generally lower compared to the age of the reference batches. The comparative stability and degradation studies indicate that only minor effects on quality attributes could have occurred upon storage of Truvelog Mix 30 and reference products.

Quantitative results for contents of insulin aspart, excipients and related substances/related impurities have been presented in clear graphs plotted in dependence of batch age. This graphical presentation enables satisfactory comparison of results.

Comprehensive comparative physico-chemical characterisation studies have been performed to establish structural similarity (primary, secondary, tertiary structure as well as higher-order structure) between Truvelog Mix 30 and NovoMix 30. The study design is considered sufficient to detect any possible difference in the structure of a relatively less complex protein molecule as insulin aspart. The number of FP batches chosen for each test seems appropriate to accommodate the expected variability and where relevant isolation of the API was performed and suitability of the isolation process have been investigated.

With respect to in vitro biological activity reference is made to studies performed with insulin aspart active substance and three batches each of NovoLog and NovoRapid (insulin aspart solution for injection). The applicant's view that in-vitro activity is determined by the properties of the active ingredient and the active ingredient insulin aspart is identical for both formulations – insulin aspart solution for injection and insulin aspart suspension for injection - is considered reasonable. Based on that the proposed similarity in biological activity is considered adequately demonstrated.

No major qualitative and quantitative differences are reported between Truvelog Mix 30 and the reference product. In particular, the following can be stated:

- Comparative results for assay insulin aspart and assay insulin aspart in supernatant are provided.

- The preservatives m-cresol and phenol are present in the same concentrations in Sanofi's product and the reference product.

Comparable cIEF electropherograms and SEC chromatograms are provided for the test and reference products. Proposed similarity with respect to high molecular weight proteins in Truvelog Mix 30 and NovoMix 30 is endorsed.

Summarising, detection and characterisation of impurities in Truvelog Mix 30 and NovoMix 30 have been adequately addressed and the reported similarity with respect to the qualitative and quantitative impurity pattern in Truvelog Mix 30 and NovoMix 30 is considered adequately demonstrated.

The pH, zinc content and protamine content of Truvelog Mix 30 batches are found comparable between the test and reference product. Also, in-depth characterisation of protamine using LC-MS and NMR techniques does not raise any concern with respect to comparability. Likewise, and with respect to resuspendability and sedimentation, comparable results can be found for the biosimilar and the reference product.

Crystal length of the biosimilar seems to be lower than in the reference products but still within the specified limit. Particle size distribution of Truvelog Mix 30 is in close agreement with the data of the reference product NovoMix 30. During the procedure, the applicant adequately provided further evidence demonstrating no significant difference in crystal length and particle size distribution between Truvelog Mix 30 and the reference product and their impact on the biosimilarity claim, to respond to a Major Objection. More

specifically the applicant presented particle size distribution for all batches in the biosimilarity exercise, which demonstrated the particle size data were in close agreement between the test product and the reference product. Additional in-use stability data (after resuspension and before administration) on particle size demonstrate a similar behaviour for the test product and the reference product. Optical microscopy data (crystal shape and crystal integrity as per Ph. Eur. and BP monographs) demonstrated compliance to the pharmacopoeial requirements both for test product and reference product. In addition, the similar resuspendability and sedimentation behaviour underlines that there is no impact to be expected for the delivery of the drug product to the patient. Based on the results, analytical similarity between Truvelog Mix 30 and NovoMix 30 could be firmly concluded.

The comparative in-use stability study is considered sufficiently well designed to demonstrate similarity of biosimilar with the reference product under the in-use conditions. The same is true for comparative stability and forced degradation studies. No major qualitative or quantitative differences in impurity profiles are observed. As confirmed in sensitive LC-MS studies, similar impurities are present in Truvelog Mix 30 and the reference product. Similar degradation profiles are also revealed in comparative side-by-side stability studies and thermal, hydrolytic and light stress studies.

Summarising the results for analytical comparability, the specifics of the test product and the reference product observed in particle size distribution and crystal length are considered negligible. Particle size distribution is found to be similar between test product and the reference product and crystal shape and crystal integrity is demonstrated compliant to the pharmacopoeial requirements. In addition, the similar resuspendability and sedimentation behaviour underlines that there is no impact to be expected for the delivery of the finished product to the patient. Based on the results, analytical similarity between Truvelog Mix 30 and NovoMix 30 can be firmly concluded.

Table 1: Summary of similarity assessment of the physico-chemical characteristics

Quality Attribute	Method	Test Item	Pur-pose	Acceptance criteria for similarity of Truvelog Mix 30 versus NovoMix 30 reference product	Results
Protein structure					
Primary Structure	MALDI-MS	Identity by Intact mass	AC	Identical masses for Truvelog Mix 30 and reference product NovoMix 30	Complies
		Reduced mass	AC	Identical masses for A- and B-chain	Complies
	MALDI-MS peptide map	Disulfide bonds	AC	Identical masses in MS/MS spectra	Complies
	N-terminal sequencing	N-terminal Edman degradation	AC	Identical amino acid sequence	Complies
Secondary Structure	Fourier transform infrared spectroscopy (FT-IR)		AC	Equivalent spectra	Complies
	Far UV CD spectroscopy		AC	Equivalent spectra	Complies

Quality Attribute	Method	Test Item	Pur-pose	Acceptance criteria for similarity of Truvelog Mix 30 versus NovoMix 30 reference product	Results
Tertiary Structure	Near UV CD spectroscopy		AC	Equivalent spectra	Complies
	NMR spectrometry (1H15N HSQC NMR)		AC	Equivalent spectra	Complies
Higher Order Structure	Dynamic light scattering (DLS)		AC	Equivalent size distribution	Complies
Biological activity [a]	In-vitro assay		AC	Equivalent biological activity	Complies
	Functional assays		AC	Comparable biological activity	Complies
Finished product quality attributes					
Potency	RP-HPLC	Assay insulin aspart (total)	RT	Statistical evaluation	Complies
		Assay insulin aspart in supernatant	RT	Statistical evaluation	Complies [b]
Content preservative	RP-HPLC	Content m-cresol	RT	Statistical evaluation	Complies
		Content phenol	RT	Statistical evaluation	Complies
Purity	RP-HPLC		RT	Statistical evaluation	Complies [c,d]
	Purity and pI by cIEF		AC	Equivalent electropherograms	Complies
High-molecular weight proteins, aggregates	HMWP Size-exclusion chromatography (SEC)		RT	Statistical evaluation	Complies [e]
pH	potentiometry		RT	Statistical evaluation	Complies
Zinc	AAS (total)		RT	Statistical evaluation	Complies
Impurity profile	HPLC-MS		AC	Equivalent impurity profile	Complies
Crystal properties	X-ray powder diffraction (XRPD)	Crystal phase	AC	Equivalent crystal phase and shape	Complies
	Microscopy		RT	Statistical evaluation	Complies
Particle size distribution	Laser granulometry		AC	Statistical evaluation	Complies [b]
Resuspendability	Resuspendability		RT	Equivalent Resuspendability	Complies

Quality Attribute	Method	Test Item	Pur-pose	Acceptance criteria for similarity of Truvelog Mix 30 versus NovoMix 30 reference product	Results
Sedimentation	Sedimentation		RT	Equivalent Sedimentation	Complies
Protamine	Content by RP-HPLC		RT	Statistical evaluation	Complies
	Characterisation by HPLC-MS		AC	Equivalent profile	Complies
Protamine / insulin aspart	Interaction of protamine/insulin aspart by NMR spectrometry		AC	Equivalent spectra	Complies
Comparative in-use studies					
Purity	RP-HPLC		RT	Equivalent impurity profile	Complies
High-molecular weight proteins, aggregates	HMWP Size-exclusion chromatography (SEC)		RT	Equivalent impurity profile	Complies
Impurity profile	HPLC-MS		AC	Equivalent impurity profile	Complies
Crystal properties	X-ray powder diffraction (XRPD)	Crystal phase	AC	Supportive information	Not applicable
	Microscopy		RT	Supportive information	Not applicable
Particle size distribution	Laser granulometry		AC	Supportive information	Not applicable
Potency	RP-HPLC	Assay insulin aspart (total and supernatant)	RT	Supportive information	Not applicable
Content preservative	RP-HPLC	Content m-cresol	RT	Supportive information	Not applicable
		Content phenol	RT	Supportive information	Not applicable
pH	potentiometry		RT	Supportive information	Not applicable
Resuspendability	Resuspendability		RT	Supportive information	Not applicable
Sedimentation	Sedimentation		RT	Supportive information	Not applicable
Protamine	Content by RP-HPLC		RT	Supportive information	Not applicable
	Characterisation by HPLC-MS		AC	Equivalent profile	Complies

Quality Attribute	Method	Test Item	Pur-pose	Acceptance criteria for similarity of Truvelog Mix 30 versus NovoMix 30 reference product	Results
Comparative stability and forced degradation studies - Long term and accelerated (temperature)					
Purity	RP-HPLC		RT	Equivalent impurity profile	Complies
High-molecular weight proteins, aggregates	HMWP Size-exclusion chromatography (SEC)		RT	Equivalent impurity profile	Complies
Impurity profile	HPLC-MS		AC	Equivalent impurity profile	Complies
Crystal properties	X-ray powder diffraction (XRPD)	Crystal phase	AC	Supportive information	Not applicable
	Microscopy		RT	Supportive information	Not applicable
Particle size distribution	Laser granulometry		AC	Supportive information	Not applicable
Potency	RP-HPLC	Assay insulin aspart (total and supernatant)	RT	Supportive information	Not applicable
Content preservative	RP-HPLC	Content m-cresol	RT	Supportive information	Not applicable
		Content phenol	RT	Supportive information	Not applicable
Resuspendability	Resuspendability		RT	Supportive information	Not applicable
Sedimentation	Sedimentation		RT	Supportive information	Not applicable
Protamine	Content by RP-HPLC		RT	Supportive information	Not applicable
	Characterisation by HPLC-MS		AC	Equivalent profile	Complies
Comparative stability and forced degradation studies - stress conditions, photostability					
Purity	RP-HPLC		RT	Equivalent impurity profile	Complies
High-molecular weight proteins, aggregates	HMWP Size-exclusion chromatography (SEC)		RT	Equivalent impurity profile	Complies
Impurity profile	HPLC-MS		AC	Equivalent impurity profile	Complies
Potency	RP-HPLC	Assay insulin aspart (total and supernatant)	RT	Supportive information	Not applicable

AC = Additional Characterisation
RT = Release Test on finished product
[a] Evaluated with solution for injection
[b] At least 4 out of 6 values of Truvelog Mix 30 are within the prediction interval of NovoMix 30
[c] At least 5 out of 6 values of Truvelog Mix 30 are within the prediction interval of NovoMix 30

[d] For 28B-isoAsp insulin aspart levels are slightly higher compared to NovoMix 30.
[e] All values of Truvelog Mix 30 are within the prediction interval for NovoMix 30 but slightly above the prediction interval for NovoLog Mix 70/30.

2.3.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The quality part of the dossier for Truvelog Mix 30 is of good quality. Two major objections were raised during the procedure: a first one on the differences observed in crystal length and particle size distribution between the test and the reference product and their potential impact on the biosimilarity claim, and a second one to request the applicant to provide a risk evaluation concerning the potential presence of nitrosamine impurities in the finished product applying the principles outlined in the notice "Information on nitrosamines for marketing authorisation holders (EMA/409815/2020)" and, in case of identified risk, perform confirmatory testing, and implement a control strategy to mitigate contamination with nitrosamines, as needed. Adequate responses were received to both MOs.

Active substance

The development, characterisation and manufacturing process of insulin aspart active substance have been adequately described and are overall considered appropriately controlled. Control of the active substance is deemed acceptable. Stability data were presented to support a 60-month shelf life at the proposed storage condition of -20°C±5°C, protected from light.

Finished product

The finished product is a suspension containing soluble insulin aspart and insulin aspart / protamine crystals in a defined ratio of 30/70. The manufacturing process of the finished product has been adequately described and is considered appropriately controlled. Pen assembly for the FP presentation in a fixed combination with a disposable pen is adequately described and controlled.

Control of the finished product is deemed acceptable.

The claimed shelf-life of 24 months at 2-8°C is supported by the stability data provided.

Biosimilarity

Based on the results for analytical comparability the specifics of the test product and the reference product observed in particle size distribution and crystal length are considered negligible. Particle size distribution is found to be similar between test product and the reference product and crystal shape and crystal integrity is demonstrated compliant to the pharmacopoeial requirements. In addition, the similar resuspendability and sedimentation behaviour underlines that there is no impact to be expected for the delivery of the finished product to the patient. Based on the results, analytical similarity between Truvelog Mix 30 and NovoMix 30 can be firmly concluded.

2.3.5. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take into account technical and scientific progress, the CHMP recommends the following:

1. The MAH should reconsider and re-evaluate acceptance limits of specific impurities and specification parameters of AS and FP when sufficient experience with commercial manufacturing has been gained.

2.4. Non-clinical aspects

2.4.1. Introduction

The *in vitro* and *in vivo* non-clinical development programme of Truvelog Mix 30 was performed with SAR341402 insulin aspart drug substance and reference medicinal products, EU NovoLog and US NovoRapid (insulin aspart solution for injection) which was agreed within a CHMP scientific advice procedure (Scientific Advice Letter EMEA/H/SA/2316/1/2012/III and Follow-up Scientific Advice Letter EMEA/H/SA/2316/1/FU/1/2017/III). Since the active ingredient insulin aspart is identical for both formulations – insulin aspart solution for injection and insulin aspart suspension for injection, it was reasonable to test biosimilarity between the references EU NovoRapid/US Novolog and test SAR341402.

2.4.2. Pharmacology

The applicant conducted a series of *in vitro* PD studies to demonstrate similarity between SAR341402 and EU and US reference medicinal products, NovoRapid and NovoLog, respectively. The binding affinities to IR-A and IR-B were analysed in a competitive binding assay using SPA technology, binding kinetics to IR-A, IR-B and IGF-1R were analysed by SPR technology. Receptor authophosphorylation activities were studied using Chinese hamster ovary (CHO) cells overexpressing human IR-A and IR-B, respectively, or mouse embryo fibroblasts (MEF) overexpressing human IGF-1R. The potency of metabolic activity was studied by inhibition of lipolysis in human adipocytes, by stimulation of glucose uptake in rat L6 myocytes overexpressing Glut4 transporter, and by inhibition of the Glucose-6-phosphatase (G6PC) expression in primary human hepatocytes. Thymidine incorporation into DNA of human MCF-7 adenocarcinoma cells was used to characterize the mitogenic activity of insulin analogues.

Four batches of Insulin aspart Sanofi (SAR341402 - three commercial batches and one Phase 3 clinical batch) and three batches each of NovoRapid and NovoLog were assessed in a comparative biological similarity assessment.

The weighted geometric means together with 95% confidence interval were calculated, first, per batch and, second, per compound. Data were also presented in tabular and graphical presentation of individual estimates of IC50s or EC50s by batch, including %CV based on the individual EC50/IC50 determinations as well as the number of determinations per batch. An equivalence statistical approach by compound (ratio of geometric means with 90% confidence interval) was used to compare the results from SAR341402 vs. NovoRapid, SAR341402 vs. NovoLog and NovoRapid vs. NovoLog.

In these comparative studies SAR341402 demonstrated visually comparable receptor binding affinities and binding kinetics as well as visually comparable metabolic and mitogenic activities compared to NovoLog and NovoRapid.

In addition, the biological activity of a product-related substance 28B-Succinimid-Ins-Aspart of SAR341402 was assessed in comparison to SAR341402 using an autophosphorylation of human IR-B assay. The ratio of mean EC50s with 90% confidence intervals showed 2.7 less potency of the 28B-succinimide insulin aspart compared to SAR341402.

Nonclinical studies on secondary pharmacodynamics, safety pharmacology, pharmacodynamic drug interactions and pharmacokinetics were not performed with SAR341402 or Truvelog Mix 30 as the applicant

relies on the Health Authority (HA) reviewer's findings of the reference product. This is adequate as such studies are not required for non-clinical testing of biosimilars.

2.4.3. Pharmacokinetics

Studies on non-clinical pharmacokinetics were not performed with SAR341402 or Truvelog Mix 30 . The applicant relies on the Agency's findings on the reference product. This is in line with the guidelines on biosimilarity and is accepted.

Toxicokinetic and anti-drug antibody evaluations were conducted as part of in a 1-month repeat-dose toxicity studies in rats with SAR341402, NovoRapid-EU and Novolog-US.

Liquid chromatography/tandem mass spectrometry (LC-MS/MS) method and a radioimmunoprecipitation assay (RIPA) were developed and validated in support of toxicokinetic evaluations in the 1-month repeat dose toxicity studies in rats.

The bioanalytical method LC-MS/MS used to determine the serum concentrations of insulin aspart in rat K_2EDTA plasma (DOS1496) is considered as successfully validated and suitable for intended use.

The immunoassay method (RIPA) used to screen rat K_2EDTA plasma for the presence of anti-SAR341402 antibodies (ADA) (DOS1502) is considered as properly set up and validated.

2.4.4. Toxicology

The toxicological development programme with SAR341402 consisted of two 1-month repeat-dose toxicity studies in rats and a local tolerability study in rabbits. No studies were performed with the Truvelog Mix 30 formulation. After dilution of the crystalline insulin aspart protamine suspension, the dissolved active substance is not expected to exhibit different pharmacological activity compared with the insulin aspart solution. Potential small differences on pharmacokinetic parameters do not justify additional animal testing and were assessed during clinical testing. All toxicology studies were conducted in compliance with GLP.

No relevant differences were found in repeat dose toxicological studies between proposed product SAR341402 and the reference product NovoRapid. SAR341402 was considered well tolerated following intravenous and paravenous administration, with a possible slight local irritation. SAR341402 was very well tolerated following intramuscular and subcutaneous administrations, without local irritation. However, *in vivo* toxicology data may be too insensitive for any conclusions on biosimilarity. According to the EMA guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (2015), toxicity studies could be regarded as unnecessary, and, in relation to the 3-R principles, should have been omitted.

2.4.5. Ecotoxicity/environmental risk assessment

As per the ERA Guideline, peptides and proteins can be exempted from ERA because they are unlikely to result in significant risk to the environment. The absence of ERA is acceptable.

2.4.6. Discussion on non-clinical aspects

The active substance is a natural substance, the use of which will not alter the concentration or distribution of

the substance in the environment. Therefore, insulin aspart is not expected to pose a risk to the environment.

Pharmacology

According to the Guideline on similar biological medicinal products (CHMP/437/04 Rev 1), the applicant submitted a comprehensive panel of *in vitro* studies comparing the Insulin Aspart SAR341402 with the reference products EU NovoRapid /US NovoLog. The applicant's justification for using Insulin Aspart SAR341402 in comparison to EU NovoRapid/US NovoLog in non-clinical comparability studies is considered acceptable from a non-clinical point of view.

The non-clinical *in vitro* pharmacological programme was developed in line with the recommendations of the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev 1) and 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). The applicant conducted complementary assays for similarity assessment of *in vitro* bioactivity between Insulin Aspart Sanofi and EU NovoRapid /US NovoLog including: competitive receptor binding assay for determination of IR-A and IR-B receptor binding affinity, surface plasmon resonance assay for determination of IR-A, IR-B and IGF-1R binding kinetics, InCell western assay to detect autophosphorylation of these receptors. IR- and IGF1R-mediated metabolic and mitogenic signalling profiles for Insulin Aspart Sanofi, NovoRapid and Novolog were shown through three different metabolic and one proliferation cell-based assays. Materials, methods and procedures were described in detail. The studies were performed on relevant test systems of biological source. The applied analytical procedures are acceptable. The number of repetitive experiments, measurement points and replicates per experiments were sufficient. The studies were performed with accepted methods with proven sensitivity.

Four batches for Insulin Aspart Sanofi (SAR341402, one clinical batch and three commercial-scale batches) and three batches for each reference medicinal product (three for NovoRapid and three for NovoLog) were compared in parallel within each experiment. The raw data for the analysis were presented.

The results (weighted geometric means of IC50s and EC50s with 95% CI; dose-response curves) demonstrated that the biological activity of the Insulin Aspart in SAR341402, NovoRapid and NovoLog were comparable in terms of IR-A and IR-B receptor binding and activation, the capability of receptor activated inhibition of lipolysis in human adipocytes, suppression of gluconeogenesis in hepatic cells and glucose uptake into myocytes, which are the primary mechanisms of action, as well as IGF-1R receptor activation and induction of proliferation of human adenocarcinoma cells. Similarity between the test and references was assessed per assay and was based on the supportive statistical analysis using an equivalence approach. For all the parameters tested, the 90% confidence intervals of the ratio of means between the test and references were within the defined acceptance criteria. The applicant has provided additional information on the statistical approach to assess biosimilarity with relevant details. As regards two batches from DIVT0112, DIVT0113 studies which were replaced from original investigation, the applicant already provided sufficient explanation with reasons for sample reanalysis during the procedure of the MA application submitted for Insulin Aspart Sanofi – rapid-acting solution for injection (EMA procedure number EMEA/H/C/005033, EPAR (EMA/CHMP/269410/2020) page 36/90). The strategy of similarity assessment is endorsed.

No secondary pharmacodynamic, safety and pharmacodynamic drug interactions studies were conducted. This is considered acceptable as such studies are not required for non-clinical testing of biosimilars.

Pharmacokinetics

An LC-MS/MS bioanalytical method was validated for the estimation of SAR341402 in K2EDTA rat plasma over the range 1.00 ng/mL to 500.00 ng/mL for the toxicokinetic study (DOS1469). The method met the acceptance criteria for parameters evaluated, demonstrating acceptable LC-MS/MS method performance for the analysis of SAR341402 in rat plasma samples over the concentration range 1 – 500 ng/ml.

The immunogenicity method for determination of Anti-SAR341402, Anti-Aspart US and Anti-Aspart EU Antibodies in rat plasma is considered to be successfully validated as the method met the acceptance criteria for parameters evaluated.

There are no distribution, metabolism, excretion or additional studies provided by the applicant and those studies are not needed for testing of biosimilars.

Toxicology

The applicant performed two 1-month repeat-dose toxicological animal studies to provide complementary information on biosimilarity for showing similarity between SAR341402 and the two reference products NovoRapid EU and NovoLog US. A local SC, IV, PV and IM tolerance study in male rabbits has been performed, where SAR341402 was compared with NovoRapid (EU) and control. No relevant differences were found in toxicological studies, however, *in vivo* data may be too insensitive for any conclusions on biosimilarity and are therefore not necessary according to the guideline. Truvelog Mix 30 was not tested in *in vitro* bioactivity assays nor in toxicology studies, because the toxicology profile of SAR341402, when tested as solution, is considered to be comparable; potential small differences on pharmacokinetic parameters do not justify additional animal testing.

The SmPC is in line with the one of the reference product and is thus acceptable.

2.4.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, Insulin Aspart Mix product (SAR341402 Mix) is accepted as biosimilar to the reference medicinal product NovoMix based on the comparability data between the Insulin Aspart (SAR341402) and reference medicinal product NovoRapid-EU/NovoLog-US.

No relevant differences between SAR341402 and the two reference products NovoRapid EU and NovoLog US were found in toxicological studies, however, *in vivo* data may be too insensitive for any conclusions on biosimilarity and are therefore not necessary according to the guideline.

As concerns the environmental risk assessment (ERA), the applicant's justification for non-submission of an ERA is considered acceptable as the active substance is a natural substance and its use will not alter the concentration or distribution of the substance in the environment. Therefore, insulin aspart is not expected to pose a risk to the environment.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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**

The clinical development programme of Truvelog Mix 30 suspension for injection includes the following studies:

- **PDY15084** study - Comparison of PK, PD and initial tolerability of Truvelog Mix 30 to NovoLog Mix 70/30, NovoMix 30 and SAR341402 rapid-acting solution using the euglycemic clamp technique, in participants with Type 1 diabetes mellitus (T1DM) conducted in 2 cohorts

- **EFC15082** Phase 3 study conducted in patients with type 2 diabetes mellitus (T2DM) or T1DM, to compare the efficacy, safety and immunogenicity of Truvelog Mix 30 to NovoMix 30.

Table 2 - Overview of completed clinical studies supporting Truvelog Mix 30 suspension registration.

	PDY15084 **Euglycemic clamp Phase 1 study (PK/PD)**	**EFC15082** **Efficacy/safety Phase 3 study**
Design	Randomised, double-blind, controlled, single dose, cross-over study in 2 cohorts Cohort 1: 3-period, 3-sequence Cohort 2: 2-period, 2-sequence	Randomised, active-controlled, open-label, parallel group study
Population	Patients with **T1DM**	Patients with **T2DM or T1DM** on at least twice daily premix insulin analogues for at least 3 months prior to the screening visit
Comparator	NovoMix 30 (Cohort 1) NovoLog Mix 70/30 (Cohort 1) SAR341402 solution (Cohort 2)	NovoMix 30
Randomisation	Cohort 1 - 1:1:1 between sequences Cohort 2 - 1:1 between sequences	1:1
Route of administration and injection device for IMP	SC injection Syringes	SC injection Truvelog Mix 30 : SoloStar® NovoMix 30: FlexPen®
Objectives	PK (primary) and PD (secondary) (euglycaemic clamp technique)	Efficacy, safety, and immunogenicity
Primary endpoint	Cohort 1: INS-AUC_{last}, INS-C_{max} Cohort 2: INS-AUC_{0-4h}, INS-AUC_{4-12h}, INS-C_{max}	HbA1c (%), change from baseline to Week 26
Safety	General safety	Immunogenicity and general safety

Number of participants randomised	N=52 (Cohort 1: 36; Cohort 2: 16)	Truvelog Mix 30 : N=204 (T2DM: 150, T1DM: 54) NovoMix 30: N=198 (T2DM: 147, T1DM: 51)
Duration of treatment	Cohort 1: 3x1 day Cohort 2: 2x1 day	26 weeks

T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; PD: pharmacodynamics; PK: pharmacokinetics; SC: subcutaneous; IMP: investigational medicinal product; HbA1c: glycated haemoglobin A1c; INS-AUC_{0-4h}: area under the concentration versus time curve extrapolated from 0 to 4 hours; INS-AUC_{4-12h}: area under the concentration versus time curve extrapolated from 4 to 12 hours; INS-AUC_{last}: area under the concentration versus time curve from 0 to time of last concentration above the limit of quantification; INS-C_{max}: maximum observed concentration

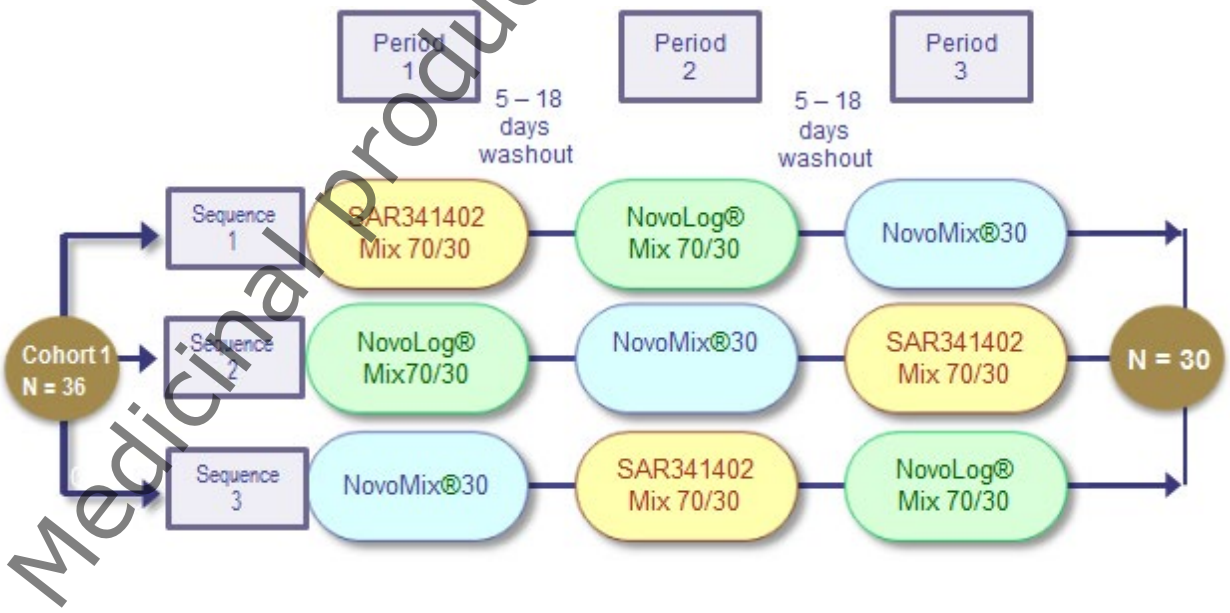
2.5.2. Clinical pharmacology

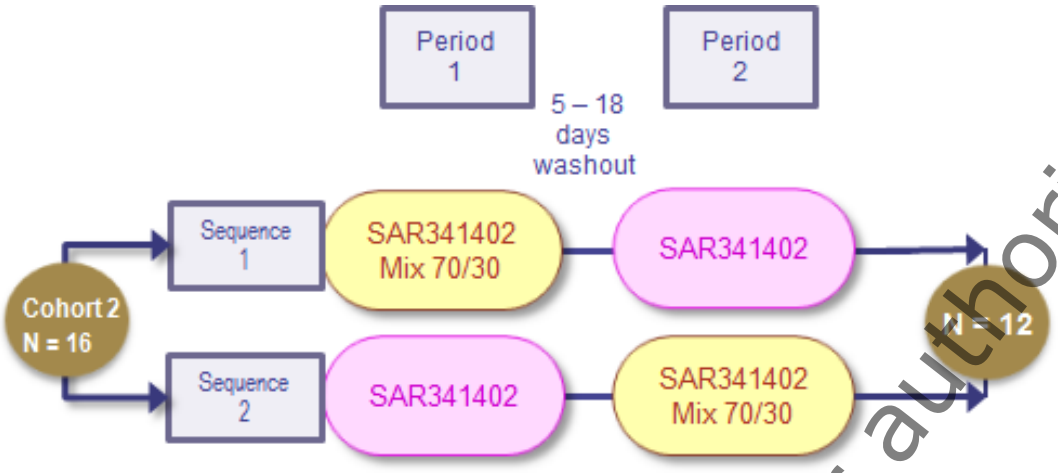
2.5.2.1. Pharmacokinetics

Study PDY15084

The comparative pharmacokinetics of Truvelog Mix 30 and the insulin aspart mix EU and US reference products NovoMix 30 and NovoLog Mix 70/30, respectively, were investigated in a randomised, double-blind, single-dose, 4-treatment, crossover study in 2 cohorts of participants with type 1 diabetes mellitus (T1DM). The development programme of Truvelog Mix 30 was planned worldwide; thus, study PDY15084 includes the US-reference product, NovoLog Mix 70/30.

Figure 2 – PDY15084 graphical study design.





The primary objective of this study was to demonstrate similarity in exposure of Truvelog Mix 30 to NovoLog Mix 70/30 and NovoMix 30 and to demonstrate distinctiveness in early and intermediate exposure of Truvelog Mix 30 compared to SAR341402 rapid-acting solution. The secondary objective was to demonstrate similarity in activity of Truvelog Mix 30 to NovoLog Mix 70/30 and NovoMix 30, distinctiveness in early and intermediate activity of Truvelog Mix 30 30 compared to SAR341402 rapid-acting solution, safety and tolerability of SAR341402 rapid-acting and Truvelog Mix 30 .

The study was conducted in patients with T1DM as most suitable population. Overall, a total of 52 patients were enrolled into the study and 48 patients completed the study. In Cohort 1, 36 patients were randomised and 34 patients completed all 3 study TPs. In Cohort 2, 16 patients were randomised and 14 patients completed both TPs.

A specific ultra-performance liquid chromatography method with tandem mass spectrometry detection (LC-MS/MS) and immunoaffinity purification was developed and validated for the analysis of SAR341402 in human EDTA K2 plasma. The analytical method was adequately validated and was proven to be precise, accurate and sensitive over the validated range. Selectivity, carry-over, calibration, accuracy, precision, dilution integrity, matrix effect and other stability investigations were all within acceptance limits.

The PK parameters were summarised for each cohort by descriptive statistic (such as mean, median, standard deviation (SD), standard error of the mean (SEM), coefficient of variance (CV %), minimum, and maximum for each treatment.

Cohort 1

Primary PK endpoints in Cohort 1 were:

• Maximum insulin concentration (INS-C_{max})

• Area under the insulin concentration time curve (INS-AUC_{last})

Secondary PK endpoints in Cohort 1 were:

• Area under the insulin concentration time curve from 0 to infinity (INS-AUC)

• Area under the insulin concentration time curve for fractional periods post administration (INS-AUC_{0-4H}, INS-AUC_{0-24H}, INS-AUC_{4-24H})

• Time to INS-C_{max} (INS-t_{max})

• Half-life (INS-$t_{1/2}$)

Cohort 2

Primary PK endpoints in Cohort 2 were:

• Area under the insulin concentration time curve from 0 to 4 hours post administration (INS-AUC_{0-4H})

• Area under the insulin concentration time curve from 4 to 12 hours post administration

(INS-AUC_{4-12H})

• Maximum insulin concentration (INS-C_{max})

Secondary PK endpoint in Cohort was:

• Time to C_{max} (INS-t_{max})

Study Results

Cohort 1

Primary pharmacokinetic variables:

The 90% confidence intervals (CIs) of the treatment ratios for the primary PK parameters, INS-C_{max} and INS-AUC_{last}, were entirely within the predefined acceptance range (0.80 to 1.25). While the CIs for INS-C_{max} were entirely within the predefined acceptance range, the value 1 was only included in the comparison of Truvelog Mix 30 and NovoMix 30, but not in the comparison versus NovoLog Mix 70/30.

The applicant justified the fact that the upper confidence limits for the ratios in INS-C_{max} do not cross value 1 by an experimental variability.

According to the applicant this result suggests a slight difference between Truvelog Mix 30 and the reference products in this study. INS-C_{max} is governed by the soluble fraction of insulin in Truvelog Mix 30 for which similarity was already shown in previous Study PDY12695.

Figure 3 - Study PDY15084: Cohort 1 - Mean (+SD) SAR341402 / insulin aspart plasma concentrations (pg/mL) following single dose SC administration of Truvelog Mix 30 , NovoLog Mix 70/30, and NovoMix 30 (linear scale).

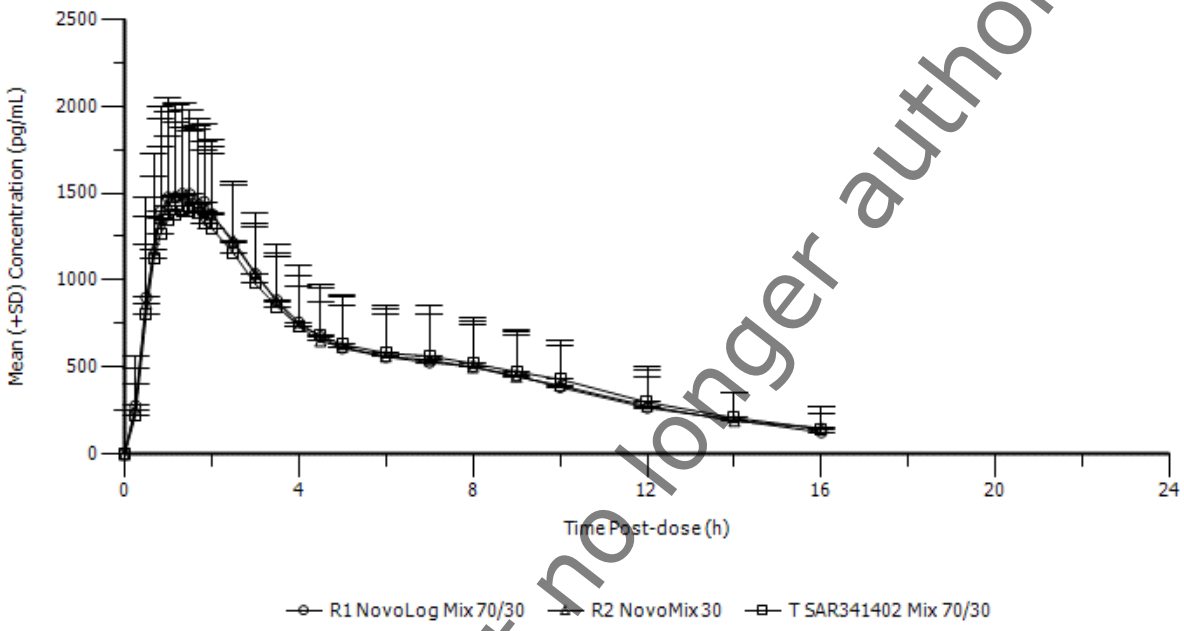


Table 3 - Study PDY15084: Cohort 1 - Treatment effect on INS-C_{max} and INS-AUC_{last} – Point estimates and 90% confidence intervals.

Treatment ratio	Parameter	Estimate	90% CI
Truvelog Mix 30 vs NovoLog Mix 70/30 (T/R1)	INS-C_{max}	0.91	(0.84 to 0.99)
Truvelog Mix 30 vs NovoMix 30 (T/R2)		0.92	(0.85 to 1.00)
Truvelog Mix 30 vs NovoLog Mix 70/30 (T/R1)	INS-AUC_{last}	1.00	(0.92 to 1.08)
Truvelog Mix 30 vs NovoMix 30 (T/R2)		0.99	(0.91 to 1.07)

Major deviations were reported for 2 patients in Cohort 1:

One patient received incorrect dose 21 U instead 22 U of R1 in TP1 and TP2 data for another patient (randomised to receive R1 in TP2 but received R2 in error) were excluded from the 'Main Analysis' descriptive and inferential statistics. An exploratory sensitivity analysis ('**Sensitivity Analysis-1'**) was performed to **include** the TP1 data (R1) and TP2 data (R2), respectively, and an additional exploratory analysis ('**Sensitivity Analysis-2**') excluded the TP1 data and TP2 data.

Table 4 - Study PDY15084 – Treatment effect on INS-C_{max} and INS-AUC_{last} – Point estimates and 90% confidence intervals (Cohort 1, Sensitivity Analysis – 1).

Treatment ratio	Parameter	Estimate	90% CI
Truvelog Mix 30 vs NovoLog Mix 70/30 (T/R1)	INS-C_{max}	0.91	(0.84 to 0.98)
Truvelog Mix 30 vs NovoMix 30 (T/R2)		0.92	(0.85 to 1.00)
NovoMix 30 vs NovoLog Mix 70/30 (R2/R1)		0.98	(0.91 to 1.07)
Truvelog Mix 30 vs NovoLog Mix 70/30 (T/R1)	INS-AUC_{last}	0.99	(0.91 to 1.07)
Truvelog Mix 30 vs NovoMix 30 (T/R2)		0.98	(0.90 to 1.06)
NovoMix 30 vs NovoLog Mix 70/30 (R2/R1)		1.01	(0.93 to 1.09)

Cohort 1, sensitivity analysis 1: profiles with major deviations included

Table 5 - Study PDY15084 – Treatment effect on INS-C_{max} and INS-AUC_{last} – Point estimates and 90% confidence intervals (Cohort 1, Sensitivity Analysis – 2).

Treatment ratio	Parameter	Estimate	90% CI
Truvelog Mix 30 vs NovoLog Mix 70/30 (T/R1)	INS-C_{max}	0.9088	(0.8371 to 0.9867)
Truvelog Mix 30 vs NovoMix 30 (T/R2)		0.9258	(0.8537 to 1.0040)
NovoMix 30 vs NovoLog Mix 70/30 (R2/R1)		0.9816	(0.9011 to 1.0694)
Truvelog Mix 30 vs NovoLog Mix 70/30 (T/R1)	INS-AUC_{last}	0.9960	(0.9184 to 1.0802)
Truvelog Mix 30 vs NovoMix 30 (T/R2)		0.9886	(0.9099 to 1.0742)
NovoMix 30 vs NovoLog Mix 70/30 (R2/R1)		1.0075	(0.9349 to 1.0857)

Cohort 1, sensitivity analysis 2: excluding outlier PK concentration

Secondary pharmacokinetic variables

The 90% CIs of all treatment ratios for secondary pharmacokinetics variables were within the range of 0.80 to 1.25. However, the CI for INS-AUC_{0-4h} in the comparison of Truvelog Mix 30 and NovoLog Mix 70/30 does not go beyond value 1. Point estimates for the pairwise treatment ratios for INS-AUC_{0-4h} are higher than the respective values for INS-C_{max}.

All 90% CIs of INS-AUC, INS-AUC_{0-24h}, and INS-AUC_{4-24h} included 1. The results for INS-AUC and INS-AUC_{0-24h} showed that the total exposure of Truvelog Mix 30 and the reference products is similar, and the results

for INS-AUC$_{4\text{-}24h}$ indicate that the exposure at later time points driven by crystalline insulin aspart in Truvelog Mix 30 and the reference products is also similar.

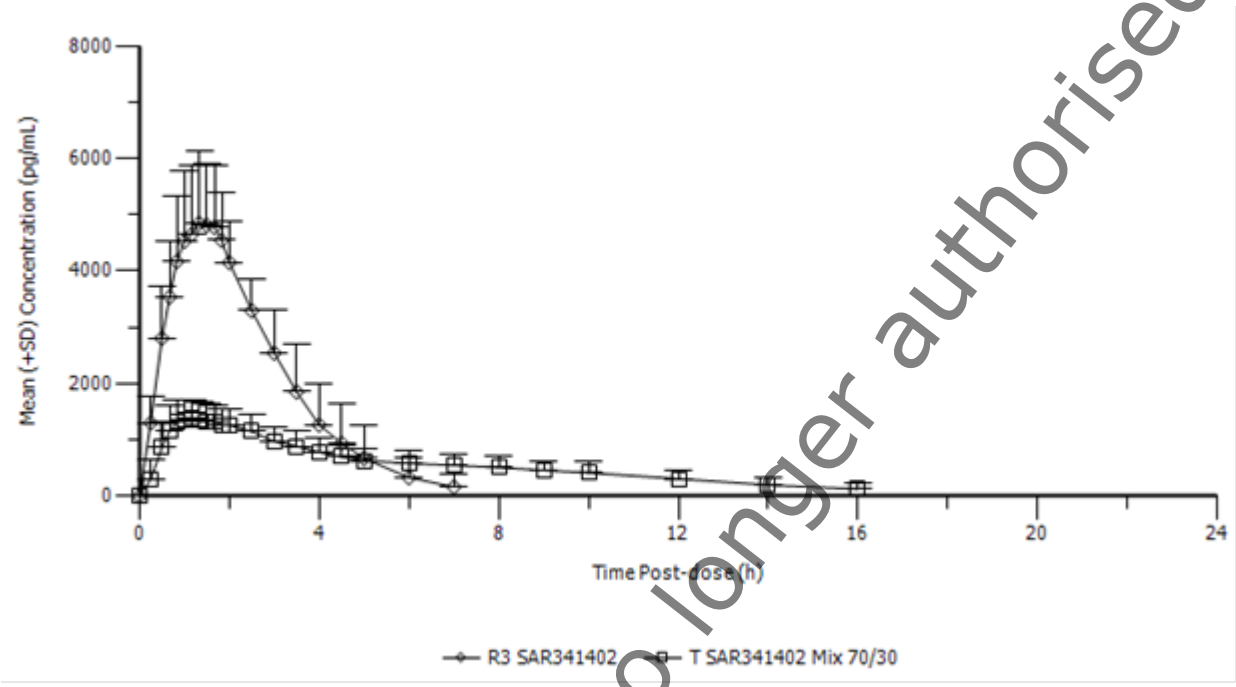
Table 6 - Study PDY15084: Cohort 1 - Treatment effect on INS-AUC, INS-AUC$_{0\text{-}24h}$, INS-AUC$_{0\text{-}4h}$, and INS-AUC$_{4\text{-}24h}$ – Point estimates and 90% confidence intervals.

Treatment ratio	Parameter	Estimate	90% CI
Truvelog Mix 30 vs NovoLog Mix 70/30 (T/R1)	INS-AUC	1.02	(0.95 to 1.09)
Truvelog Mix 30 vs NovoMix 30 (T/R2)		0.99	(0.92 to 1.07)
Truvelog Mix 30 vs NovoLog Mix 70/30 (T/R1)	INS-AUC$_{(0\text{-}24h)}$	1.00	(0.93 to 1.08)
Truvelog Mix 30 vs NovoMix 30 (T/R2)		0.98	(0.91 to 1.06)
Truvelog Mix 30 vs NovoLog Mix 70/30 (T/R1)	INS-AUC$_{(0\text{-}4h)}$	0.93	(0.86 to 1.00)
Truvelog Mix 30 vs NovoMix 30 (T/R2)		0.93	(0.86 to 1.01)
Truvelog Mix 30 vs NovoLog Mix 70/30 (T/R1)	INS-AUC$_{(4\text{-}24h)}$	1.07	(0.95 to 1.20)
Truvelog Mix 30 vs NovoMix 30 (T/R2)		1.04	(0.91 to 1.18)

Cohort 2:

The concentration-time profiles of the two SAR341402 products appear clearly different with a much flatter profile for Truvelog Mix 30 compared to SAR341402 rapid-acting solution.

Figure 4 - Study PDY15084: Cohort 2 - Mean (+SD) plasma concentrations of SAR341402 following single dose administration of Truvelog Mix 30 and SAR341402 rapid-acting solution (linear scale).



Primary pharmacokinetic variables:

For Cohort 2, the 95% CIs for the ratios of the geometric means (Truvelog Mix 30 versus SAR341402 rapid-acting solution) exclude the value 1.0 demonstrating statistically significant differences in early and intermediate PK parameters between SAR341402 rapid-acting solution and Truvelog Mix 30 . The p-values for treatment effect are below 0.001.

Table 7 - Study PDY15084: Cohort 2 - Treatment effect on INS-C_{max}, INS-AUC_{0-4h} and INS-AUC_{4-12h} – Point estimates and 95% confidence intervals.

Treatment ratio	Parameter	Estimate	95% CI
Truvelog Mix 30 vs SAR341402 solution (T/R3)	INS-C_{max}	0.29	(0.25 to 0.33)
	INS-AUC_{0-4h}	0.33	(0.29 to 0.36)
	INS-AUC_{4-12h}	2.89	(1.71 to 4.89)

Secondary pharmacokinetics endpoints in Cohort 2

The Hodges-Lehmann point estimate and 95% CIs of the median of the treatment difference in INS-t_{max} between T and R3 are presented in table below.

Table 8 - Treatment effect on INS-t_{max} - Point estimates and 95% confidence intervals (Cohort 2).

Exact Hodges-Lehmann		
Comparison	**Point estimate**	**95% confidence interval**
T vs. R3	0.2	(-0.2 ; 0.5)

T is Truvelog Mix 30 , and R3 is SAR341402 solution.

Post-hoc exploratory analysis of PK parameter for Cohort 1

The area under the plasma concentration versus time curve over the interval 0 to 12 hours after dosing (INS-AUC_{0-12H}) in Cohort 1 of study PDY15084 was calculated for SAR341402 and insulin aspart using the trapezoidal method.

A summary of INS-AUC_{0-12H} with descriptive statistics following single SC administrations of 0.3 U/kg of Truvelog Mix 30 (T), NovoLog Mix 70/30 (R1), and NovoMix 30 (R2) to participants with T1DM in Cohort 1 is presented in table below.

Table 9 - Study PDY15084: Cohort 1 - INS-AUC_{0-12H} of SAR341402 and insulin aspart following single-dose administration of Truvelog Mix 30 (T), NovoLog Mix 70/30 (R1) and NovoMix 30 (R2) in Cohort 1 (Main Analysis).

Mean ± SD (Geometric Mean) [CV%]	Plasma SAR341402 / insulin aspart		
	Truvelog Mix 30 (T)	NovoLog Mix 70/30 (R1)	NovoMix 30 (R2)
N	35	34	34
INS-AUC_{0-12H}	8180 ± 2850	8280 ± 2850	8250 ± 2560
(pg•h/ml)	(7710) [35]	(7870) [34]	(7900) [31]

Treatment ratios (T/R1, T/R2) were assessed for INS-AUC_{0-12H} with corresponding method as for the primary analysis. The corresponding exploratory analysis was also conducted for the R2/R1 ratio. Estimates with 90% CIs for the treatment ratios of geometric means were derived and are presented in table below.

Table 10 - Study PDY15084: Cohort 1 - Treatment ratios for INS-AUC_{0-12h} – Point estimates and 90% confidence intervals.

Treatment ratio	Parameter	Estimate	90% CI
Truvelog Mix 30 vs NovoLog Mix 70/30 (T/R1)	INS-$AUC_{(0-12h)}$	0.98	(0.89 to 1.06)
Truvelog Mix 30 vs NovoMix 30 (T/R2)		0.97	(0.89 to 1.06)
NovoMix 30 vs NovoLog Mix 70/30 (R2/R1)		1.01	(0.94 to 1.08)

Analysis is based on the analysis set of the primary analysis.

The 90% CIs of the treatment ratios for the additional PK parameter INS-AUC_{0-12H} are entirely within the range (0.80 to 1.25), supporting similar exposure also for the 0 to 12h interval after dosing.

2.5.2.2. Pharmacodynamics

The study PDY15084 was primarily designed as a PK study to demonstrate similarity of the biphasic preparation Truvelog Mix 30 with the reference products, NovoLog Mix 70/30, and NovoMix 30. The euglycemic clamp technology was used to measure PD effects as secondary objectives.

As was outlined by the applicant, the study was neither designed nor powered for treatment comparisons in PD parameters. The design of this study is described in the pharmacokinetic section. Statistical analyses on PD parameters were pre-specified as non-confirmative.

The following PD parameters were calculated from the GIR assessed during the clamp period, per patient and TP as secondary parameters:

• Cohort 1

- The area under the body weight standardised GIR time curve from 0 to 24 hours post administration (GIR-AUC_{0-24H})

- Maximum smoothed body weight standardised GIR (GIR_{max})

- Time to GIR_{max} (GIR-t_{max})

• Cohort 2

- The area under the body weight standardised GIR versus time curve from 0 to 4 hours post-administration (GIR-AUC_{0-4H})

- The area under the body weight standardised GIR versus time curve from 4 to 12 hours post-administration (GIR-$AUC4_{-12H}$)

- GIR_{max}

- GIR-t_{max}

For cohort 2, GIR-$AUC_{0\text{-}24H}$ was derived.

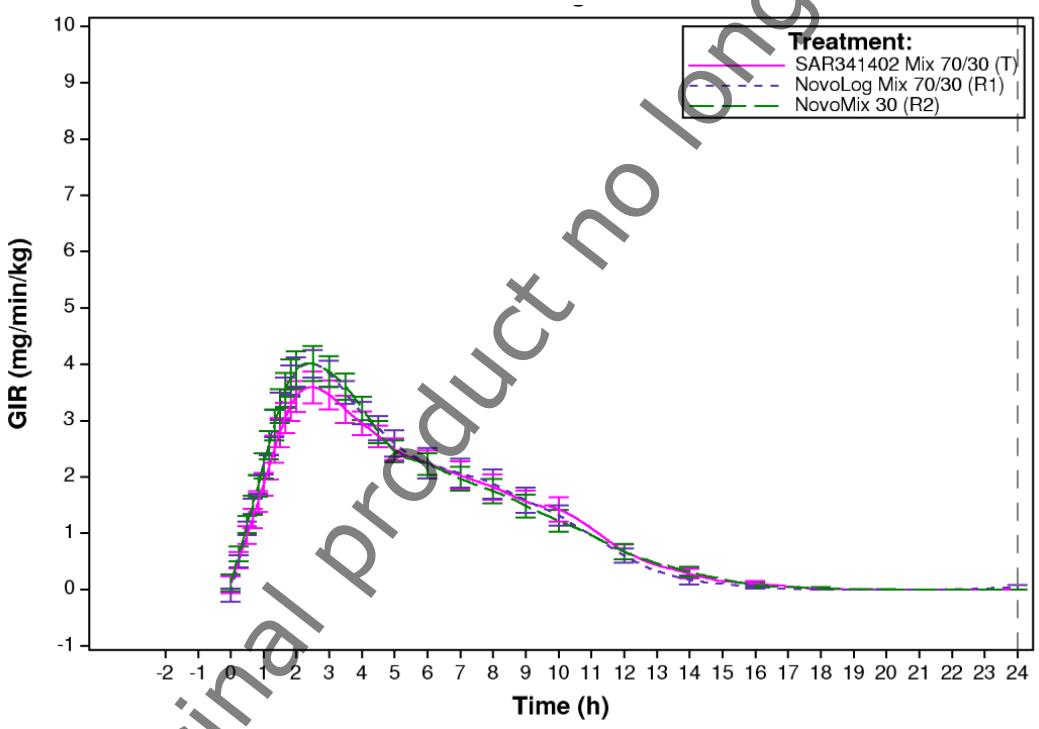
The derivation of GIR_{max}, the GIR-t_{max} and blood glucose levels was based upon a LOESS smoothing technique for the raw body weight standardised GIR data - smoothing factor of 15% was used (SAS, PROC LOESS, factor 0.15).

Pharmacodynamic results

Cohort 1

The mean smoothed body weight standardised GIR profiles (± SEM) of Truvelog Mix 30 , NovoLog Mix 70/30 and NovoMix 30 at 0.3 U/kg are shown in figure below. The onset and duration were similar with Truvelog Mix 30 reaching slightly lower peak average when compared to the NovoLog Mix 70/30 and NovoMix 30.

Figure 5 - Study PDY15084: Cohort 1 - Overlay plots of mean smoothed GIR profiles (+/-SEM) over time up to 24 hours after dosing.



GIR = body weight standardised Glucose Infusion Rate, LOESS smoothing using factor = 0.15

Point estimates for treatment ratios for GIR_{max} and GIR-$AUC_{0\text{-}24h}$, comparing Truvelog Mix 30 to NovoLog Mix 70/30 and NovoMix 30, and corresponding 95%CIs were calculated by the applicant.

For GIR_{max} and GIR-$AUC_{0\text{-}24h}$, the lower 95% confidence limits were ranging between 0.74 and 0.79 and the upper limits between 1.00 and 1.12.

Table 11 - Study PDY15084: Cohort 1 - Treatment ratios for GIR_{max} and GIR-AUC_{0-24h} - point estimates with 95% confidence intervals - profiles without major deviations - comparisons for test treatment.

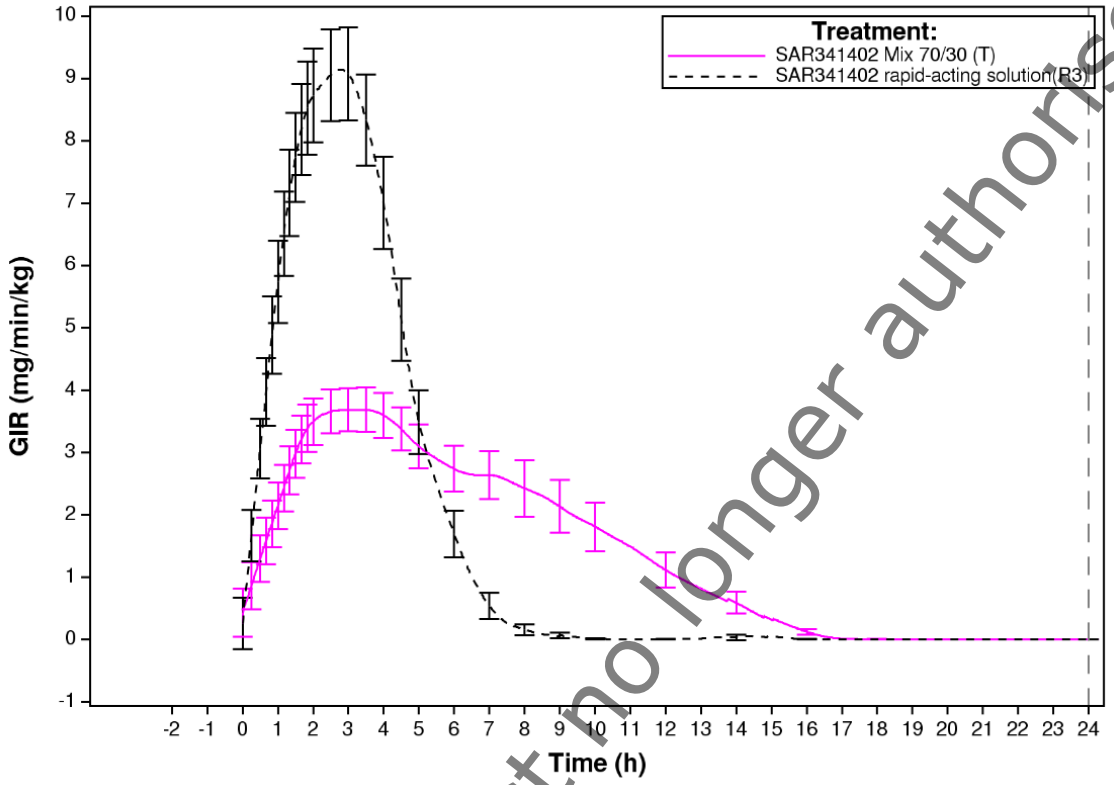
Treatment ratio	Parameter	Estimate	95% CI
Truvelog Mix 30 vs NovoLog Mix 70/30 (T/R1)	GIR_{max}	0.86	(0.74 to 1.00)
Truvelog Mix 30 vs NovoMix 30 (T/R2)		0.90	(0.75 to 1.07)
Truvelog Mix 30 vs NovoLog Mix 70/30 (T/R1)	GIR-AUC_{0-24h}	0.94	(0.79 to 1.12)
Truvelog Mix 30 vs NovoMix 30 (T/R2)		0.93	(0.77 to 1.12)

Sensitivity analyses including the PD profiles of patients with major deviations are presented by the applicant as well and results generally were similar to the results of the main analysis (95% CI for GIR_{max} 0.7568 – 1.0721 and 95% CI for GIR-AUC_{0-24h} 0.7703 to 1.1057 for T/R2).

Cohort 2

The mean smoothed body weight standardised GIR profiles of Truvelog Mix 30 and SAR341402 rapid-acting solution at 0.3 U/kg show clear differences (Figure below) with a clearly flatter profile for Truvelog Mix 30 .

Figure 6 - Study PDY15084: Cohort 2 - Overlay plots of mean smoothed GIR profiles (+/- SEM) over time up to 24 hours after dosing.



GIR = body weight standardised Glucose Infusion Rate, LOESS smoothing using factor = 0.15

The 95% CIs for the treatment ratios of the geometric means (Truvelog Mix 30 versus SAR341402 rapid-acting solution) for GIR_{max}, $GIR\text{-}AUC_{0\text{-}4h}$ and $GIR\text{-}AUC_{4\text{-}12h}$ exclude the value 1.0 demonstrating differences in early and intermediate PD parameters between SAR341402 rapid-acting solution and Truvelog Mix 30 .

Table 12 – Study PDY15084: Cohort 2 - Treatment ratios for GIR_{max}, $GIR\text{-}AUC_{0\text{-}4h}$, and $GIR\text{-}AUC_{4\text{-}12h}$- point estimates with 95% confidence intervals - profiles without major deviations.

Treatment ratio	Parameter	Estimate	95% CI
Truvelog Mix 30 vs SAR341402 solution (T/R3)	GIR_{max}	0.41	(0.34 to 0.48)
	$GIR\text{-}AUC_{0\text{-}4h}$	0.40	(0.32 to 0.49)
	$GIR\text{-}AUC_{4\text{-}12h}$	2.18	(1.19 to 4.02)

Performance of the clamp

For Cohort 1, the mean and median values for each clamp quality parameter were comparable between treatments. The small deviations for mean BG were reflected in median CV% of BG values of 4.40%, 4.50%, and 4.00% for T, R1, and R2, respectively, between start and end of euglycaemia. The difference between the mean BG and target value (control deviation) was generally small - 0.70, 0.70 and 0.60 mg/dL for T1, R1 and R2, respectively. The root square mean deviation of BG from clamp target level was 4.87, 4.70 and 4.56 mg/dL for T, R1 and R2, respectively.

Overall in Cohort 2, median CV% of BG values were 3.90% and 5.10% for T and R3, respectively. All other clamp parameters were comparable between treatments.

Explorative supplemental statistical PD analyses

Additional explorative analyses were conducted **post-hoc** to assess the difference in PD profiles.

In order to assess the relevance of the differences observed in GIR_{max}, in Cohort 1 of this study PDY15084, two additional PD parameters were derived:

- GIR-$AUC_{0\text{-}4h}$
- GIR-$AUC_{4\text{-}24h}$

Based on Cohort 1, when comparing Truvelog Mix 30 with references (R1, R2, R), the lower boundaries of 95% CIs were between 0.74 and 0.77 for GIR_{max} (mg/kg/min) and between 0.73 and 0.75 for GIR-$AUC_{0\text{-}4h}$ (mg/kg) . Upper 95% confidence limits were between 1.00 and 1.07 for GIR_{max} and between 1.01 and 1.06 for GIR-$AUC_{0\text{-}4h}$ (see table below).

Based on Cohort 1 when comparing Truvelog Mix 30 with references (R1, R2, R), for GIR-$AUC_{4\text{-}24h}$ (mg/kg) the point estimates for treatment ratios were close to 1.0, lower 95% confidence bounds are around 0.74 - 0.78 with upper bounds between 1.24 and 1.30 (Table 12). Nominal p-value for overall treatment effect is 0.949 for GIR-$AUC_{4\text{-}24h}$.

Table 13 - Study PDY15084: Cohort 1 - Treatment ratios for GIR_{max}, GIR-$AUC_{0\text{-}4h}$, and GIR-$AUC_{4\text{-}24h}$ - point estimates with 90% and 95% confidence intervals - profiles without major deviations.

Treatment ratio	Parameter	Estimate	90% CI	95% CI
SARmix/R1 (T/R1)	GIR_{max} (mg/kg/min)	0.86	(0.76 to 0.97)	(0.74 to 1.00)
SARmix/R2 (T/R2)		0.90	(0.77 to 1.04)	(0.75 to 1.07)
SARmix/R (T/R)		0.88	(0.78 to 0.98)	(0.77 to 1.01)
R2/R1		0.96	(0.83 to 1.12)	(0.80 to 1.15)
SARmix/R1 (T/R1)	GIR-$AUC_{(0\text{-}4h)}$ (mg/kg)	0.86	(0.75 to 0.99)	(0.73 to 1.02)
SARmix/R2 (T/R2)		0.88	(0.75 to 1.03)	(0.73 to 1.06)
SARmix/R (T/R)		0.87	(0.77 to 0.99)	(0.75 to 1.01)
R2/R1		0.98	(0.84 to 1.15)	(0.81 to 1.19)
SARmix/R1 (T/R1)	GIR-$AUC_{(4\text{-}24h)}$ (mg/kg)	1.01	(0.81 to 1.25)	(0.78 to 1.30)
SARmix/R2 (T/R2)		0.97	(0.77 to 1.21)	(0.74 to 1.27)
SARmix/R (T/R)		0.99	(0.81 to 1.20)	(0.78 to 1.24)
R2/R1		1.04	(0.84 to 1.29)	(0.80 to 1.35)

GIR denotes body weight standardised glucose infusion rate. GIR_{max} is based on smoothed GIR profiles.

SARmix and T denote Truvelog Mix 30 ; R1 denotes NovoLog Mix 70/30. R2 denotes NovoMix 30. R denotes equally weighted R1 and R2.

Analyses include all evaluable periods from the subjects in the PD population.

For the analyses on profiles pooled from Cohorts 1 and 2 when comparing Truvelog Mix 30 with references (R1, R2, R), for GIR_{max} and GIR-AUC_{0-4h} the lower boundaries of the 95% CIs were 0.77-0.79 and 0.75 – 0.78 respectively, with the point estimates close to 0.9. Unity is covered by all 95% CIs (see table below). Nominal p-values for overall treatment effect are 0.152 for GIR_{max} and 0.256 for GIR-AUC_{0-4h}.

For the analyses on profiles pooled from Cohorts 1 and 2 when comparing Truvelog Mix 30 with references (R1, R2, R), for GIR-AUC_{4-24h} the point estimates for treatment ratios were around 1.04 with all 95% confidence bounds between 0.83 and 1.30. Nominal p-value for overall treatment effect is 0.901 for GIR-AUC_{4-24h}.

Table 14 - Study PDY15084: Cohort 1 and 2 pooled - Treatment ratios for GIR_{max}, GIR-AUC_{0-4h}, and GIR-AUC_{4-24h}- point estimates with 90% and 95% confidence intervals - profiles without major deviations.

Treatment ratio	Parameter	Estimate	90% CI	95% CI
SARmix/R1 (T pooled/R1)	GIR_{max} (mg/kg/min)	0.88	(0.79 to 0.98)	(0.77 to 1.01)
SARmix/R2 (T pooled/R2)		0.91	(0.79 to 1.05)	(0.77 to 1.08)
SARmix/R (T pooled/R)		0.90	(0.81 to 0.99)	(0.79 to 1.01)
SARmix/R1 (T pooled/R1)	GIR-$AUC_{(0-4h)}$ (mg/kg)	0.89	(0.78 to 1.01)	(0.76 to 1.04)
SARmix/R2 (T pooled/R2)		0.90	(0.78 to 1.04)	(0.75 to 1.08)
SARmix/R (T pooled/R)		0.89	(0.80 to 1.00)	(0.78 to 1.02)
SARmix/R1 (T pooled/R1)	GIR-$AUC_{(4-24h)}$ (mg/kg)	1.06	(0.86 to 1.30)	(0.83 to 1.35)
SARmix/R2 (T pooled/R2)		1.02	(0.83 to 1.26)	(0.80 to 1.32)
SARmix/R (T pooled/R)		1.04	(0.87 to 1.24)	(0.84 to 1.29)

GIR denotes body weight standardised glucose infusion rate. GIRmax is based on smoothed GIR profiles.

SARmix and T denote Truvelog Mix 30 ; R1 denotes NovoLog Mix 70/30. R2 denotes NovoMix 30. R denotes equally weighted R1 and R2.

Analyses include all evaluable periods from the subjects in the PD population.

2.5.3. Discussion on clinical pharmacology

PK, PD and initial tolerability of Truvelog Mix 30 compared to NovoLog Mix 70/30 (US reference product), NovoMix 30 (EU reference product) and SAR341402 rapid-acting solution were investigated in a single-dose euglycemic clamp study in participants with Type 1 diabetes mellitus (T1DM). It was a randomised, double-blind cross-over study conducted in 2 cohorts. In general, the study design is adequate and 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). According to this guideline, in case a biosimilar manufacturer develops different preparations, e.g. short-acting, intermediate acting and biphasic preparations containing the same active ingredient, PD data are not needed for all of these preparations. This applies to the proposed product, as well. However, any PD data collected during PK studies should be presented.

To avoid any interference with endogenous insulin in PK/PD evaluations, the study was conducted in patients with T1DM as most suitable population. The study comprised of 4 treatments and was conducted in 2 cohort in order to reduce the burden to study participants implied with repeated lasting euglycemic clamp investigation. Cohort 1 was 3-treatments, 3-period and 3-sequence, and Cohort 2 was a 2-treatment, 2-period, 2-sequence cross-over study. Patients were exposed to each treatment once only. The insulin dose of 0.3 U/kg selected for this study is well characterised to provide euglycaemia in T1DM patients and has been readily investigated in other clamp studies with T1DM patients. Washout period between each IMP administration 5 to 18 days is acceptable.

A specific ultra-performance liquid chromatography method with tandem mass spectrometry detection (LC-MS/MS) and immunoaffinity purification was developed and validated for the analysis of SAR341402 in human EDTA K2 plasma. Analysis method for insulin aspart in plasma is adequately validated and was proven to be precise, accurate and sensitive over the validated range. Regarding the determination of insulin aspart in plasma samples obtained in clinical trial PDY15084, applicant was asked to provide a representative number of chromatograms and other raw data covering the whole concentration range for all standard and quality control samples and specimen analysed together in the respective run. The submitted data are acceptable.

To analyse anti-SAR341402 antibodies in human K_2 EDTA plasma, a validated radioimmunoprecipitation assay (RIPA) was used (DOH 1504). A competitive ligand binding assay (CLB) was validated for the evaluation of the neutralizing capacity of confirmed positive anti-insulin aspart antibodies in K2 EDTA plasma of type 2 and type 1 diabetic participants (DOH1500).

In the comparison of Truvelog Mix 30 and the EU reference product NovoMix 30, the 90% confidence intervals for the primary PK parameters INS-C_{max} and INS-AUC_{last} and for secondary parameters INS-AUC, INS-$AUC_{0\text{-}24h,}$ INS-$AUC_{(0\text{-}4h)}$ and INS-$AUC_{4\text{-}24h}$ were within the predefined acceptance limits of 0.80-1.25.

The standard dosing interval of Truvelog Mix 30 is twice daily, although the optimal administration for some patients could be once daily or three times daily as stated in the SmPC. Since the primary endpoint should be represented by an AUC of the time of a dosing interval (EMEA/CHMP/BMWP/32775/2005_Rev. 1), the applicant was also asked to provide calculation for PK parameter INS - $AUC_{0\text{-}12H}$. This exploratory analysis confirmed that the 90% CI for the treatment ratios for INS-$AUC_{0\text{-}12}$ of Truvelog Mix 30 vs. NovoMix 30 is within the range 0.80 – 1.25, supporting similar exposure for the interval 0-12 h after dosing.

In conclusion the study **PDY15084** demonstrated similarity for the primary PK endpoints between Truvelog Mix 30 and both reference products, NovoLog Mix 70/30 and NovoMix 30.

The PD effect of the different insulin aspart formulations was evaluated with the euglycemic clamp technique. As was outlined by the applicant, the study was neither designed nor powered for treatment comparisons in PD parameters.

The derivation of GIR_{max}, the time to GIR_{max} and blood glucose levels was based upon a LOESS smoothing technique for the raw body weight standardised GIR data and smoothing factor of 15% was used. This value for smoothing factor has been chosen based on previous experience with a smoothing factor for rapid acting insulin. Smoothing factor of 0.15 was expected to lead to interpretable GIR_{max} and still represent a conservative approach for the premix product.

The proven quality of the glucose clamp method is adequate.

The 95% confidence interval additionally presented for secondary parameter, GIR-AUC_{0-24h} treatment ratio for Truvelog Mix 30 vs NovoMix 30 in Cohort 1 ranged from 0.77 to 1.12 and for GIR_{max} from 0.75 to 1.07. Results of sensitivity analyses including the PD profiles of patients with major deviation were similar to the results of the main analysis.

To explore the difference in PD between the Truvelog Mix 30 and NovoLog Mix 70/30 and NovoMix 30 additional explorative statistical analyses were conducted by the applicant **post hoc**. The 95% CI for partial PD parameters - GIR-$AUC_{(0-4h)}$ treatment ratios for Truvelog Mix 30 vs. NovoMix 30 in Cohort 1 ranged from 0.73 to 1.06 and for GIR-$AUC_{(4-24h)}$ treatment ratios for Truvelog Mix 30 vs. NovoMix 30 in Cohort 1 ranged from 0.74 to 1.27.

The 95% CI for pooled GIR_{max} was in range 0.77 – 1.08 and the 95% CI for pooled GIR-$AUC_{(0-4h)}$ and GIR-$AUC_{(4-24h)}$ was in range 0.75 to 1.08 and 0.80 to 1.32 (pooled Truvelog Mix 30 vs. NovoMix 30), respectively.

The presented PD data suggest a difference between Truvelog Mix 30 and the NovoLog Mix 70/30 and NovoMix 30.

Relevance of these clinical findings and consequences of the observed differences in PD endpoints have been justified and discussed by the applicant during the procedure**.** It is agreed that the study PDY15084 demonstrated similarity of Truvelog Mix 30 to NovoMix 30 for the primary PK endpoints and these results were supported by post hoc analysis of the PK parameter INS-AUC_{0-12}. A minor deviation of Truvelog Mix 30 compared to NovoMix 30 in INS-C_{max} (however still within the bioequivalence range) has been amplified in PD. The study was not powered to formally demonstrate similarity for PD parameters. The chosen PD parameters as secondary parameters were in line 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), since the similarity of PK and PD profiles for the soluble-rapid acting insulin has been proved.

PD paramaters GIR_{max} and GIR-AUC_{0-4h} reflect the rapid-acting component of the premix products. The applicant justified the deviation observed for INS-C_{max} by the peculiarity of the clamp at the employed low dose of rapid acting insulin component (which represents only dose 0.09 U/kg from the whole administered dose 0.3 U/kg of the premix formulation), conferring greater variability in PD, rather than by a relevant true difference. Frequently used insulin doses in clamp studies are 0.3 to 0.4 U/ kg bodyweight for intermediate-acting insulins and the doses in the upper range usually produce a more reliable PD response, thereby reducing PD variability. The within-subject CV% are estimated for GIR_{max} and also for GIR-AUC_{0-4h}, as 33.0%

and 35.8% respectively, thus relatively large. This is expected for this premix formulation. Greater variability in PK of insulin premixes has been generally observed in comparison to the rapid acting insulins.

Since the close similarity in physicochemical and functional characteristics has been shown for the Truvelog Mix 30 and the reference insulin NovoMix 30, the issue related to the differences shown in PD parameters will be not pursued further.

The PK/PD profiles of Truvelog Mix 30 compared to SAR341402 rapid-acting solution for Cohort 2 showed a significant difference in exposure and activity, demonstrated as INS-C_{max}, INS-AUC_{0-4h} and INS-AUC_{4-12h}, GIR_{max}, GIR-AUC_{0-4H}, and GIR-AUC_{4-12H}. The treatment effect exceeded the target difference of 20% between these 2 formulations as requested by the FDA. The demonstration of >20% difference is not an EU requirement and therefore not relevant for the B/R assessment.

2.5.4. Conclusions on clinical pharmacology

In study PDY15084 similarity for the primary PK endpoints was demonstrated between Truvelog Mix 30 and both, NovoLog Mix 70/30 and NovoMix 30, with the 90% CIs falling within the predefined acceptance range (0.80 to 1.25). The available PD data suggested slight difference between Truvelog Mix 30 and NovoMix 30. The relevance of these clinical findings has been discussed by the applicant and justified by greater variability in PD and PK of insulin premixes in comparison to the rapid acting insulin, by low dose of rapid acting insulin component which represent only dose 0.09 U/kg from the whole administered dose 0.3 U/kg of the premix formulation. Moreover the study was not powered to demonstrate the similarity for PD parameters. Since the close similarity in physicochemical and functional characteristics has been shown for the Truvelog Mix 30 and the reference insulin NovoMix 30 and evaluation of PD parameters are not a strict requirement for a new biosimilar insulin formulation containing an active ingredient that is already licensed as part of another biosimilar insulin formulation, the issue related to the differences shown in PD parameters will be not pursued further.

2.5.5. Clinical efficacy

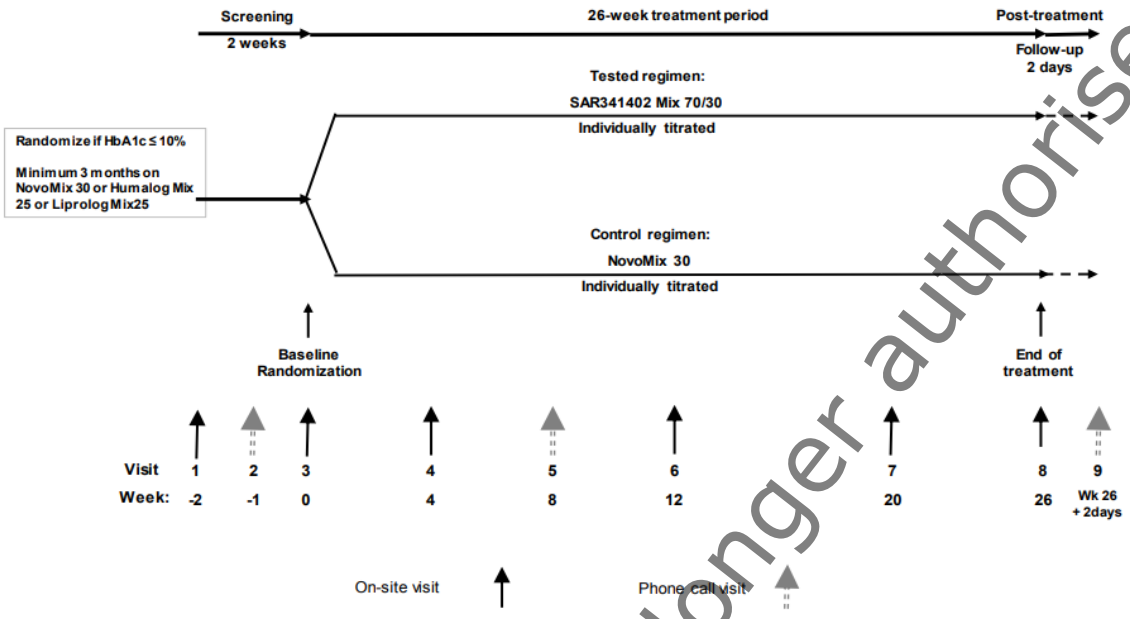
2.5.5.1. Main study

To support the efficacy, safety and immunogenicity of proposed biosimilar medicinal product, one Phase 3 study was submitted: A 26-week, randomised, open-label, parallel-group comparison of **Truvelog Mix 30** to NovoMix 30 in adult participants with diabetes mellitus using pre-mix insulin analogues (EFC15082).

Methods

Design of the study is outlined in the diagram below:

Figure 7: study design



Study Participants

The study included adult participants (males and non-pregnant females) with T1DM or T2DM diagnosed at least 12 months before screening, with HbA1c ≤ 10.0% (participants with HbA1c between 9.0% and 10.0% can be included if they are not candidates for an MDI regimen based on the discretion of the Investigator), body mass index (BMI) ≤ 35kg/m2 for participants with T1DM and ≤ 40 kg/m2 for participants with T2DM, treated with at least twice daily NovoMix 30, Humalog Mix 25 or Liprolog Mix 25 for at least 3 months prior to the screening visit.

Among exclusion criteria were any clinically significant abnormality identified either in medical history or during screening evaluation (e.g., physical examination, laboratory tests, electrocardiogram (ECG), vital signs), pancreatectomy and/or islet cell transplantation, severe renal disease, ALT or AST >3 times upper limit of the normal (ULN) or total bilirubin >1.5 times ULN, history of severe hypoglycaemia hospitalisation for recurrent diabetic ketoacidosis within 3 months prior to screening, retinopathy or maculopathy.

Treatments

Lifestyle and diet recommendations were to be given at screening and during the study in accordance with international or local guidelines for participants with T1DM or T2DM.

As a **test medicinal product**, Truvelog Mix 30 was used. It was supplied as a 100 U/ml suspension for injection supplied in 3 mL pre-filled disposable SoloStar pen. Each pen contains in total 300 units of Truvelog Mix 30 (i.e., protamine-crystallised insulin aspart/insulin aspart in the ratio 70/30). This pen allows dose setting in the range of 1 to 80 units with minimum of 1-unit increment.

As a **reference/comparator medicinal product**, NovoMix 30 (Novo Nordisk) was used. It was supplied as a 100 U/ml suspension for injection supplied in 3 mL pre-filled disposable FlexPen pen. Each pen contains in

total 300 units of NovoMix 30 (protamine-crystallised insulin aspart/insulin aspart in the ratio 70/30). This pen allows dose setting in the range of 1 to 60 units with minimum of 1-unit increment.

Both medicinal products were self-administered as subcutaneous injection, in the abdominal area, buttock, thighs, or upper arms, at least twice a day. The starting dose and frequency of both products was the same as the premixed insulin dose (conversion of NovoMix 30 or Humalog Mix 25 or Liprolog Mix 25 dose) on a unit to unit (1:1) basis and frequency used at the end of the screening period. The dose of either Truvelog Mix 30 or NovoMix 30 was to be adjusted approximately once per week or based on Investigator's clinical judgement, to achieve a target preprandial plasma glucose between 4.4 and 7.2 mmol/L (80 to 130 mg/dL) and a 2-hour postprandial plasma glucose of < 10.0 mmol/L (< 180 mg/dL) while avoiding hypoglycaemia.

Duration of treatment was per protocol up to 26 weeks.

No non-investigational medicinal products were planned to be used in this study.

Objectives

Primary objective of the study: To demonstrate non-inferiority of Truvelog Mix 30 in comparison to NovoMix 30 on HbA1c change from baseline to Week 26 in participants with Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM). A non-inferiority margin of 0.3% HbA1c was defined, in line with recommendations by regulatory agencies and based on historical precedent for comparative insulin studies in which a 0.3% non-inferiority margin is often used.

Secondary objective: To compare the effects of Truvelog Mix 30 with NovoMix 30 on immunogenicity parameters in participants with T1DM and T2DM and evaluate the safety of Truvelog Mix 30 and NovoMix 30.

Tertiary/exploratory objectives: To compare the effect of Truvelog Mix 30 and NovoMix 30 on glycaemic control and insulin dose, and to compare clinical effects of immunogenicity parameters on glycaemic control, insulin dose and safety.

Outcomes/endpoints

Efficacy endpoints:

- Primary endpoint was change from baseline to week 26 in HbA1c (In addition, if non-inferiority of Truvelog Mix 30 over NovoMix 30 was demonstrated, the inverse noninferiority of NovoMix 30 over Truvelog Mix 30 was also to be tested as a secondary analysis to further support similarity between Truvelog Mix 30 and NovoMix 30.)
- Tertiary/exploratory efficacy endpoints were number of participants with HbA1c < 7.0% at Week 26, change from baseline to Week 26 in FPG, change from baseline to Week 26 in mean 24-hour SMPG (7-point profile), change from baseline to Week 26 in plasma glucose excursions (2 hour PPG minus pre-prandial plasma glucose) at breakfast, lunch and dinner based on 7 point SMPG data, change from baseline to Week 26 in 7 point SMPG profile, change from baseline to Week 26 in daily insulin dose (Truvelog Mix 30 or NovoMix 30).

Safety endpoints were set as secondary endpoints, and were as follows: number of participants with at least one hypoglycaemic event, number of hypoglycaemic events per participant-year, number of participants with adverse events (AEs).

Immunogenicity secondary endpoint was number of participants with treatment-emergent AIA during the 26-week treatment period.

Randomisation and blinding (masking)

All participants were centrally assigned to randomised study treatment (Truvelog Mix 30 or NovoMix 30, in a 1:1 ratio) using an interactive response technology (IRT) system. Randomisation was stratified by type of diabetes (T1DM; T2DM), prior use of NovoMix 30 (Yes; No), geographical region (Indian; non-Indian) and HbA1c obtained at the screening visit (< 8.0%; ≥ 8.0%).

The study was open-label, as the SoloStar pen used for Truvelog Mix 30 and FlexPen used for NovoMix 30 are distinguishable. Although this was an open-label study, the Sponsor study team remained blinded to the treatment group until database lock. HbA1c, FPG, and AIAs were determined in central laboratories blinded to the treatment received. Selected AEs were adjudicated in a blinded fashion.

Statistical methods

The primary efficacy endpoint was analysed in the intent-to-treat (ITT) population (defined as all randomised participants, irrespective of compliance with the study protocol and procedures), using all post-baseline data available from randomisation up to Week 26 regardless of study treatment discontinuation (ITT estimand with treatment policy strategy). Participants were analysed in the treatment group to which they were randomised. The statistical test for non-inferiority assessment of Truvelog Mix 30 versus NovoMix 30 on the primary efficacy endpoint (change from baseline to Week 26 in HbA1c) was one-sided, with alpha level of 0.025 and using a non-inferiority margin of 0.3% HbA1c.

In order to account for missing data, multiple imputations were performed with a 'return to baseline' analysis (missing HbA1c values at Week 26 imputed as equal to the participant baseline plus an error). Imputed datasets were analysed using an analysis of covariance (ANCOVA) of the change from baseline to Week 26 in HbA1c, including the fixed categorical effects of treatment group (Truvelog Mix 30 , NovoMix 30) and randomisation strata of type of diabetes (T1DM, T2DM), geographical region (Indian, non-Indian), and prior use of NovoMix 30 (Yes, No), as well as the continuous fixed covariate of baseline HbA1c value. Results were combined using Rubin's formula.

In order to assess the impact of COVID-19 on the primary analysis results, a prespecified sensitivity analysis was performed with HbA1c values potentially impacted by COVID-19 treated as missing values, and all missing data due to COVID-19 imputed using a missing at random (MAR) approach.

A supportive analysis was conducted on the PP population to evaluate the robustness of the primary efficacy analysis after excluding participants that could significantly impact the analysis, including some participants with major or critical protocol deviations related to COVID-19.

Safety analysis and analysis of immunogenicity data were descriptive.

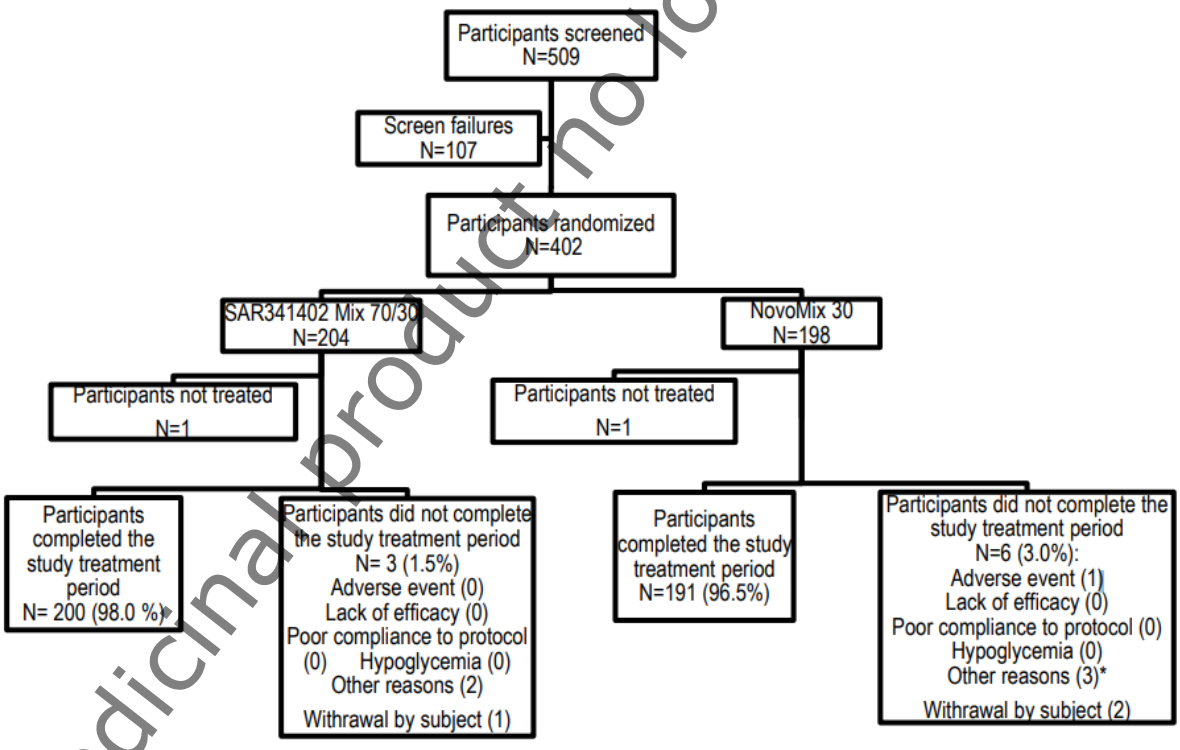
Results

Participant flow

A total of 402 adult participants (Truvelog Mix 30 : 204; NovoMix 30: 198) were randomised in the study, all of whom were included in the ITT population. Two participants, 1 in each group, were randomised but not treated.

Approximately 20% of participants (42 participants in each group) were excluded from the PP population. Reasons for excluding participants from the PP population were mostly related to the COVID-19 pandemic. Reasons not related to the COVID-19 pandemic were reported similarly in the 2 groups (10 participants in each group) and mostly corresponded to missing HbA1c value from central laboratory at Week 26 or premature IMP discontinuation. The vast majority of the participants completed the treatment period similarly in the 2 treatment groups.

Figure 8: Participant disposition



No critical protocol deviations were reported in this study. The proportion of participants with any major protocol deviation was balanced between treatment groups (130 [63.7%] participants in the Truvelog Mix 30 group and 119 [60.1%] in the NovoMix 30 group), with no apparent distribution pattern. Around 40% of major protocol deviations were not related to COVID-19 in both treatment groups. Overall, the most frequently reported major protocol deviations were related to assessments/procedures not performed, i.e., "planned sample (anti- Truvelog Mix 30 /NovoMix 30 antibodies) not performed" (Truvelog Mix 30 : 65

[31.9%] participants; and NovoMix 30: 51 [25.8%] participants), mainly due to haemolysed or lipaemic immunogenicity samples that could not be analysed at the laboratory; "planned sample (haematology or clinical chemistry) not performed" (Truvelog Mix 30 : 61 [29.9%] participants; and NovoMix 30: 50 [25.3%] participants); and "planned sample (HbA1c) not performed" (Truvelog Mix 30 : 40 [19.6%] participants; and NovoMix 30: 28 [14.1%] participants).

Baseline data

The majority of participants were Asian (from India – 52.2% and Philippines – 8.7%) and the rest of the participants were white (from Eastern Europe – 39.1%).

All demographics and baseline characteristics were well-balanced between the treatment groups.

Table 15: Demographics and participant characteristics at baseline – randomised population.

	SAR341402 Mix 70/30 (N=204)	NovoMix 30 (N=198)	All (N=402)
Age (years)			
Number	204	198	402
Mean (SD)	53.2 (14.9)	53.0 (15.5)	53.1 (15.2)
Median	56.0	56.5	56.0
Min ; Max	18 ; 83	18 ; 79	18 ; 83
Age group (years) [n (%)]			
Number	204	198	402
<65	157 (77.0)	143 (72.2)	300 (74.6)
≥65 to <75	40 (19.6)	51 (25.8)	91 (22.6)
≥75	7 (3.4)	4 (2.0)	11 (2.7)
Sex [n (%)]			
Number	204	198	402
Female	91 (44.6)	109 (55.1)	200 (49.8)
Male	113 (55.4)	89 (44.9)	202 (50.2)
Race [n (%)]			
Number	204	198	402
White	76 (37.3)	81 (40.9)	157 (39.1)
Asian	128 (62.7)	117 (59.1)	245 (60.9)
Ethnicity [n (%)]			
Number	204	198	402
Not Hispanic or Latino	204 (100)	198 (100)	402 (100)
Regions/ Countries [n (%)]			
Number	204	198	402
Eastern Europe	76 (37.3)	81 (40.9)	157 (39.1)
Poland	22 (10.8)	28 (14.1)	50 (12.4)
Russian Federation	14 (6.9)	18 (9.1)	32 (8.0)
Ukraine	40 (19.6)	35 (17.7)	75 (18.7)
Rest of the World	128 (62.7)	117 (59.1)	245 (60.9)
India	107 (52.5)	103 (52.0)	210 (52.2)
Philippines	21 (10.3)	14 (7.1)	35 (8.7)
Baseline Weight (kg)			
Number	204	198	402
Mean (SD)	72.0 (16.0)	71.0 (13.1)	71.5 (14.6)
Median	70.4	70.1	70.3
Min ; Max	40 ; 123	44 ; 114	40 ; 123
Baseline BMI (kg/m^2)			
Number	204	198	402
Mean (SD)	26.61 (4.73)	26.93 (4.70)	26.76 (4.71)
Median	26.22	26.44	26.35
Min ; Max	16.8 ; 39.8	17.8 ; 39.8	16.8 ; 39.8

	SAR341402 Mix 70/30 (N=204)	NovoMix 30 (N=198)	All (N=402)
Baseline BMI by category (kg/m^2) [n (%)]			
Number	204	198	402
<25	85 (41.7)	70 (35.4)	155 (38.6)
≥25 to <30	72 (35.3)	80 (40.4)	152 (37.8)
≥30	47 (23.0)	48 (24.2)	95 (23.6)
Baseline estimated GFR (mL/min/1.73 m^2)			
Number	204	198	402
Mean (SD)	86.82 (26.40)	85.49 (24.54)	86.17 (25.48)
Median	84.34	83.83	84.02
Min ; Max	31.3 ; 177.6	31.2 ; 198.5	31.2 ; 198.5
Baseline estimated GFR by category (mL/min/1.73 m^2) [n (%)]			
Number	204	198	402
≥90	82 (40.2)	85 (42.9)	167 (41.5)
≥60 to <90	94 (46.1)	88 (44.4)	182 (45.3)
≥30 to <60	28 (13.7)	25 (12.6)	53 (13.2)
Randomization strata of geographical region [n (%)]			
Number	204	198	402
Indian	107 (52.5)	103 (52.0)	210 (52.2)
Non-Indian	97 (47.5)	95 (48.0)	192 (47.8)
Randomization strata of type of diabetes [n (%)]			
Number	204	198	402
T1DM	54 (26.5)	51 (25.8)	105 (26.1)
T2DM	150 (73.5)	147 (74.2)	297 (73.9)
Randomization strata of HbA1c (%) at screening [n (%)]			
Number	204	198	402
<8.0	80 (39.2)	73 (36.9)	153 (38.1)
≥8.0	124 (60.8)	125 (63.1)	249 (61.9)
Randomization strata of prior use of NovoMix 30 [n (%)]			
Number	204	198	402
Yes	172 (84.3)	169 (85.4)	341 (84.8)
No	32 (15.7)	29 (14.6)	61 (15.2)

Note: Percentages are calculated using the number of patients randomized as denominator
BMI: Body mass index
GFR: glomerular filtration rate derived using MDRD formula
Source: 5.3.5.1 EFC15082, Appendix 16.2.4 Demographic data, data at baseline and medication details, 16.2.4.1

Numbers analysed

For numbers of patients analysed, see below:

Table 16: Analysis population.

n (%)	SAR341402 Mix 70/30	NovoMix 30	All
Randomized population	204 (100)	198 (100)	402 (100)
Efficacy populations			
Intent-to-Treat (ITT)	204 (100)	198 (100)	402 (100)
Per protocol (PP)	162 (79.4)	156 (78.8)	318 (79.1)
Safety population	203	197	400
Anti-insulin aspart antibody population	199	195	394

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

Outcomes and estimation

Primary efficacy endpoint

The primary efficacy endpoint was the change from baseline to Week 26 in HbA1c. A non-inferiority margin was set to 0.3% change in HbA1c.

The mean HbA1c at baseline was comparable in the 2 treatment groups. Similar decreases from baseline to Week 26 in HbA1c were seen in the 2 treatment groups with mean change (SE) of -0.55% (0.080) in the Truvelog Mix 30 group and -0.64% (0.080) in the NovoMix 30 group. However, the prespecified non-inferiority margin was not met (see table below).

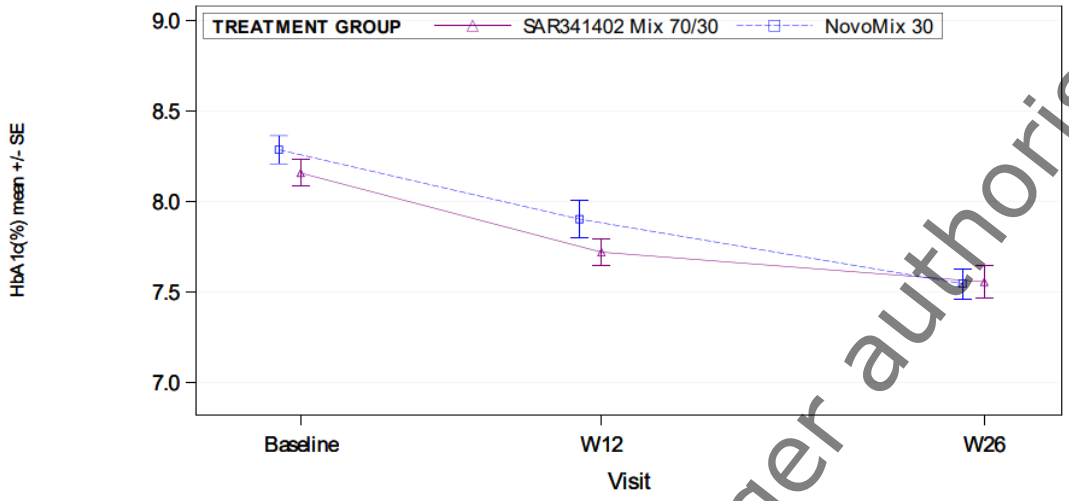
Table 17: Summary of change from baseline to Week 26 in HbA1c (%) using ANCOVA analysis (with return to baseline multiple imputation) - ITT population.

HbA1c (%)	SAR341402 Mix 70/30 (N=204)	NovoMix 30 (N=198)
Baseline		
Number	204	198
Mean (SD)	8.16 (1.05)	8.28 (1.09)
Median	8.20	8.30
Min ; Max	5.3 ; 10.5	5.7 ; 12.5
Change from baseline to Week 26		
Combined LS Mean (SE) [a]	-0.55 (0.080)	-0.64 (0.080)
95% CI	(-0.710 to -0.398)	(-0.793 to -0.480)
Combined LS Mean difference (SE) vs NovoMix 30 [a]	0.08 (0.113)	
95% CI	(-0.139 to 0.303)	

ANCOVA=Analysis of covariance

a Return-to-baseline multiple imputation of missing changes at Week 26 (10 000 imputations as patient's baseline plus an error) followed by ANCOVA with treatment group (SAR341402 Mix 70/30, NovoMix 30), the randomization strata of geographical region (Indian, non-Indian), type of diabetes (T1DM, T2DM), and prior use of NovoMix 30 (Yes, No) as fixed categorical effects, as well as the continuous fixed covariate of baseline HbA1c value. Results were combined using Rubin's formula

Figure 9: - HbA1c (%) - Mean (+/- SE) by visit during the randomisation period – ITT population



# Subjects			
SAR341402 Mix 70/30	204	161	179
NovoMix 30	198	172	178

A post-hoc sensitivity analysis was performed on the ITT population excluding one participant in the Truvelog Mix 30 group. This participant had an extreme outlying increase in HbA1c from baseline to Week 26 of 5.9%, which was almost twice the value of the next highest value (3.0%) observed in the Truvelog Mix 30 group; an HbA1c value of 7.1% at screening (defined as baseline since the HbA1c sample at baseline visit was drawn 5 minutes after the first IMP dose) and 13.0% at Week 26. Further investigation showed that that due to COVID-19 lockdown, applicant´s IMP expired and participant did not took the product according to the protocol, therefore the increase in HbA1c occurred at 26 weeks visit. With the exclusion of this participant with extreme outlying value from the ITT population, noninferiority of Truvelog Mix 30 compared to NovoMix 30 on change from baseline to Week 26 in HbA1c was achieved (see table below). Inverse non-inferiority of NovoMix 30 over Truvelog Mix 30 was also achieved.

Table 18: Summary of change from baseline to Week 26 in HbA1c (%) using ANCOVA analysis (with return to baseline multiple imputation) - ITT population excluding one participant.

HbA1c (%)	SAR341402 Mix 70/30 (N=203)	NovoMix 30 (N=198)
Baseline		
Number	203	198
Mean (SD)	8.16 (1.05)	8.28 (1.09)
Median	8.20	8.30
Min ; Max	5.3 ; 10.5	5.7 ; 12.5
Change from baseline to Week 26		
Combined LS Mean (SE) [a]	-0.58 (0.076)	-0.64 (0.076)
95% CI	(-0.734 to -0.435)	(-0.788 to -0.488)
Combined LS Mean difference (SE) vs NovoMix 30 [a]	0.05 (0.108)	
95% CI	(-0.158 to 0.266)	

ANCOVA=Analysis of covariance

a Return-to-baseline multiple imputation of missing changes at Week 26 (10 000 imputations as patient's baseline plus an error) followed by ANCOVA with treatment group (SAR341402 Mix 70/30, NovoMix 30), the randomization strata of geographical region (Indian, non-Indian), type of diabetes (T1DM, T2DM), and prior use of NovoMix 30 (Yes, No) as fixed categorical effects, as well as the continuous fixed covariate of baseline HbA1c value. Results were combined using Rubin's formula

Sensitivity analysis – impact of the COVID-19 pandemic

A sensitivity analysis was conducted on the ITT population to evaluate the COVID-19 impact on the primary efficacy analysis. HbA1c values potentially impacted by COVID-19 (as described above) were treated as missing values and all missing data due to COVID-19 were imputed using a MAR approach. This included the Week 26 value of the participant with extreme outlying value, which was treated as missing in this sensitivity analysis due to Visit 8 delay >8 weeks.

Non-inferiority of Truvelog Mix 30 compared to NovoMix 30 on change from baseline to Week 26 in HbA1c was achieved - the difference between Truvelog Mix 30 and NovoMix 30 was 0.05% (SE: 0.102; 95% CI = -0,149 to 0.253).

Supportive analysis

A supportive analysis was conducted on the PP population to evaluate the robustness of the conclusion of the primary efficacy analysis when excluding the participants that may have increased the chance of reaching the non-inferiority conclusion. In the PP population, non-inferiority of Truvelog Mix 30 compared to NovoMix 30 on change from baseline to Week 26 in HbA1c was achieved (LS Mean difference [SE] of Truvelog Mix 30 versus NovoMix 30: 0.07% [0.102]; and 95% CI: -0.131 to 0.269).

Tertiary/exploratory efficacy endpoints

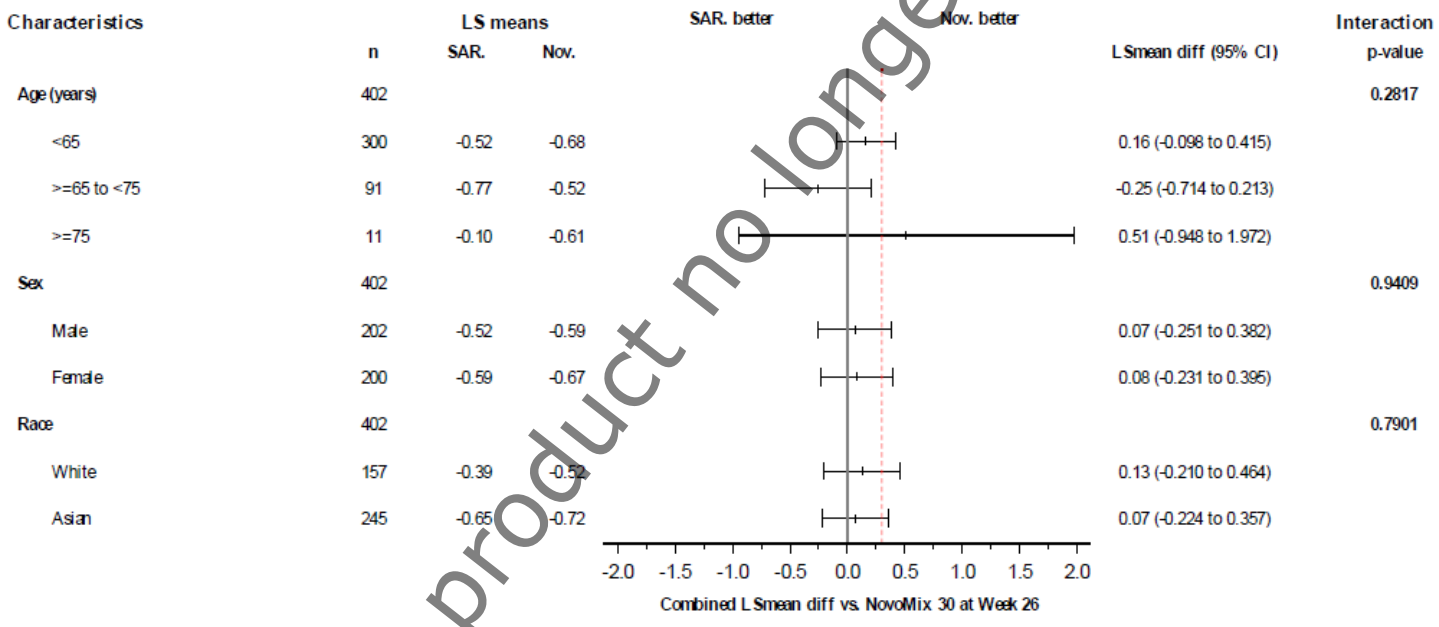
Tertiary/exploratory efficacy endpoints included the percentage of participants who reached the HbA1c target <7% at Week 26, change from baseline to Week 26 in FPG, change from baseline to Week 26 in mean 24-hour SMPG, seven-point SMPG profile, change in plasma glucose excursion. No clinically relevant differences were observed between the Truvelog Mix 30 and NovoMix 30.

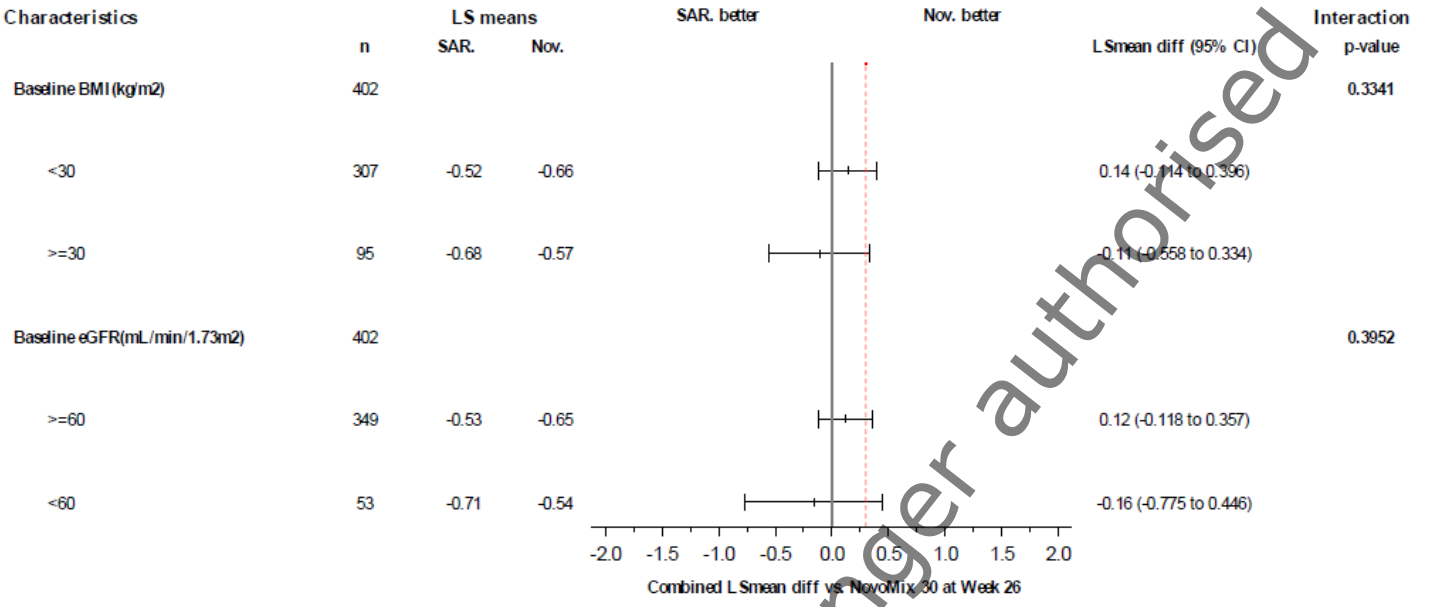
Ancillary analyses

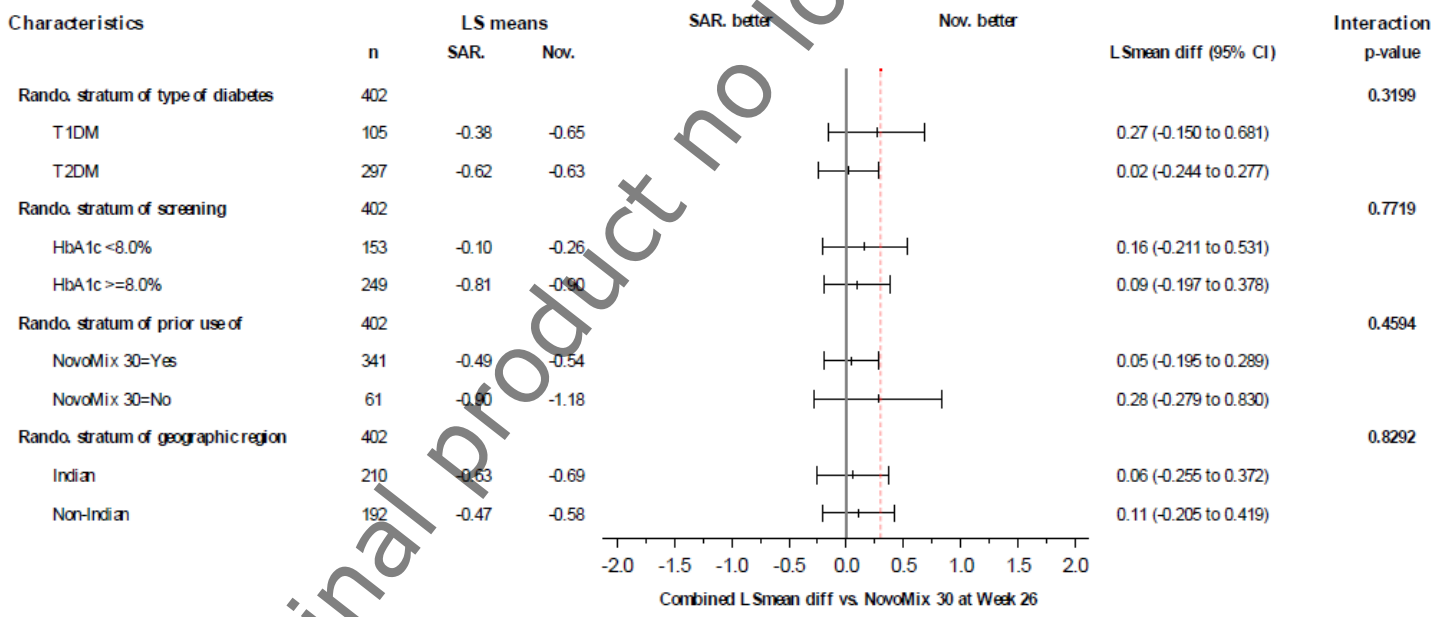
Subgroup analysis

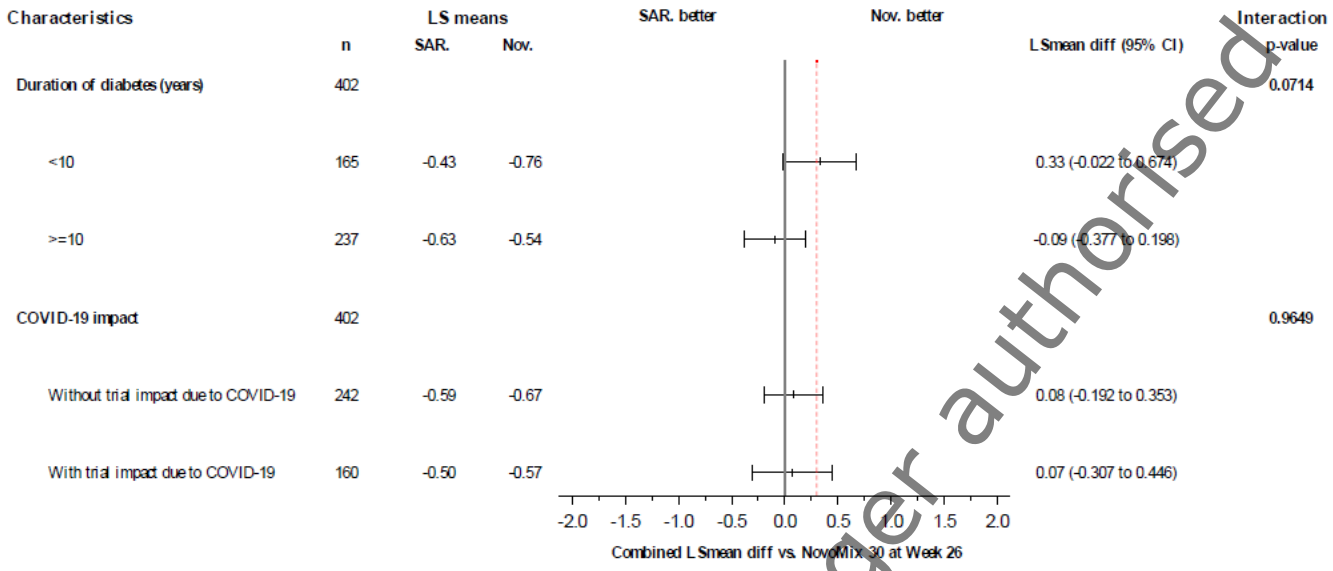
Subgroup analyses of the change from baseline to Week 26 in HbA1c were performed on the ITT population. The mean change from baseline to Week 26 in HbA1c for Truvelog Mix 30 versus NovoMix 30 was generally consistent across other subgroups defined by screening and baseline factors (race, age group, sex, baseline BMI, baseline eGFR, randomisation stratum of screening HbA1c, and duration of diabetes).

Figure 10: Forest plot of change from baseline to Week 26 in HbA1c (%) by subgroup using ANCOVA analysis (with return to baseline multiple imputation) - ITT population









ANCOVA=Analysis of covariance, SAR.=SAR341402 Mix 70/30, Nov.=NovoMix 30

P-values of subgroup-by-treatment interaction from an ANCOVA with treatment group (SAR341402 Mix 70/30, NovoMix 30), the stratum of geographical region (Indian, non-Indian) (except for race subgroup), type of diabetes (T1DM, T2DM), and prior use of NovoMix 30 (Yes, No) (except when used as subgroup), subgroup factor and subgroup factor-by-treatment interaction, as well as the continuous fixed covariate of baseline HbA1c value (except for screening HbA1c stratum subgroup)

Change in HbA1c by treatment-emergent anti-insulin aspart antibody

Change in HbA1c from baseline to Week 26 was similar between treatment groups in both subgroups of participants, those with treatment-emergent AIA and those without treatment-emergent AIAs. The treatment-by-treatment-emergent AIA interaction showed no evidence of heterogeneity of treatment effect across subgroups of AIA status (p=0.4516).

Table 19: Summary of change from baseline to Week 26 in HbA1c (%) by treatment-emergent AIA using ANCOVA analysis (with return to baseline multiple imputation) - AIA population.

HbA1c (%)	Treatment-emergent AIA: Yes[a]		Treatment-emergent AIA: No	
	SAR341402 Mix 70/30 (N=66)	NovoMix 30 (N=62)	SAR341402 Mix 70/30 (N=131)	NovoMix 30 (N=132)
p-value (treatment-by-subgroup interaction) = 0.4516				
Baseline				
Number	66	62	131	132
Mean (SD)	8.32 (1.07)	8.55 (1.16)	8.03 (1.02)	8.17 (1.06)
Median	8.45	8.40	8.00	8.20
Min ; Max	5.3 ; 10.5	5.9 ; 11.9	5.3 ; 10.3	5.7 ; 12.5
Week 12				
Number	48	53	113	117
Mean (SD)	7.88 (0.80)	8.17 (0.62)	7.65 (1.02)	7.77 (1.17)
Median	7.75	7.80	7.50	7.60
Min ; Max	6.5 ; 10.2	7.1 ; 13.7	5.4 ; 11.1	5.2 ; 11.5
Change from baseline				
Number	48	53	113	117
Mean (SD)	-0.31 (0.88)	-0.26 (1.16)	-0.38 (0.96)	-0.35 (0.94)
Median	-0.35	-0.30	-0.40	-0.30
Min ; Max	-2.3 ; 2.3	-2.8 ; 3.7	-2.8 ; 4.1	-3.0 ; 3.1
Week 26				
Number	59	59	116	117
Mean (SD)	7.73 (1.39)	7.65 (1.16)	7.43 (1.08)	7.47 (1.07)
Median	7.70	7.60	7.30	7.20
Min ; Max	5.0 ; 13.0	5.5 ; 11.2	5.1 ; 12.1	5.1 ; 10.5
Change from baseline				
Number	59	59	116	117
Mean (SD)	-0.68 (1.59)	-0.93 (1.05)	-0.59 (0.97)	-0.66 (1.08)
Median	-0.70	-0.70	-0.60	-0.50
Min ; Max	-3.4 ; 5.9	-4.0 ; 1.9	-2.9 ; 3.0	-3.6 ; 2.4
Combined LS Mean (SE) [b]	-0.55 (0.139)	-0.73 (0.139)	-0.60 (0.099)	-0.61 (0.098)
95% CI	(-0.818 to -0.274)	(-1.002 to -0.456)	(-0.798 to -0.411)	(-0.800 to -0.417)
Combined LS Mean difference (SE) vs NovoMix 30 [b]	0.18 (0.194)		0.00 (0.138)	
95% CI	(-0.198 to 0.564)		(-0.267 to 0.274)	

AIA: Anti-insulin aspart antibody, ANCOVA=Analysis of covariance

a Patients with pre-existing AIA that were boosted to a significant higher titer (at least 4-fold increase) compared to baseline, or patients without pre-existing AIA (or missing baseline) and with at least one positive AIA sample.

b Return-to-baseline multiple imputations of missing changes at Week 26 (using the 10 000 imputations performed for primary efficacy analysis) followed by ANCOVA with treatment group (SAR341402 Mix 70/30, NovoMix 30), the randomization strata of geographical region (Indian, non-Indian), type of diabetes (T1DM, T2DM), and prior use of NovoMix 30 (Yes, No), subgroup factor and subgroup factor-by-treatment interaction, as well as the continuous fixed covariate of baseline HbA1c value. Results were combined using Rubin's formula.

Assessment of the impact of the COVID-19 pandemic on the trial

Study EFC15082 was ongoing when the COVID-19 pandemic occurred; the main study was fully enrolled, but the majority of the participants were being treated in the study. The pandemic disruption resulted in the temporary closure of some sites (i.e., planned visits could not be performed), mainly in India and the

Philippines. Alternative methods in the conduct of the trial were implemented, such as over-the phone or at home visits, alternative methods of IMP dispensation, extension of the duration of the study in order to perform end-of-treatment visit.

The percentage of participants with trial impact (disruption) due to the COVID-19 pandemic (i.e., with major impact of the COVID-19 pandemic on study conduct) was similar between treatment groups (Truvelog Mix 30 : 42.6% [87/204]; NovoMix 30: 36.9% [73/198]).

Table 20: Participant disposition – Participants with or without trial impact due to COVID-19 – Randomised population.

n (%)	SAR341402 Mix 70/30 (N=204)	NovoMix 30 (N=198)
Patients without trial impact (disruption) due to COVID-19	117 (57.4)	125 (63.1)
Patients with trial impact (disruption) due to COVID-19	87 (42.6)	73 (36.9)
Premature EOT due to COVID-19	0	1 (0.5)
Premature EOS due to COVID-19	2 (1.0)	0
Critical or major protocol deviations due to COVID-19	87 (42.6)	73 (36.9)
Informed consent procedures	1 (0.5)	2 (1.0)
Randomization procedure	1 (0.5)	4 (2.0)
IMP Management	1 (0.5)	1 (0.5)
Concomitant Medications/ Therapy	5 (2.5)	4 (2.0)
Assessments/Procedures	85 (41.7)	71 (35.9)

EOT: End of Treatment, EOS: End of Study
n (%) = number and percentage of patients in each category
Note: Percentages are calculated using the number of patients randomized as denominator
A patient can be counted in several reason categories

No impact of the COVID-19 pandemic on baseline and Week 4 visits was reported. Impact of the COVID-19 pandemic was mainly observed on the Week 26 visit. This visit was impacted in almost half of the participants, similarly in the 2 groups (Truvelog Mix 30 : 45.5% [92/202]; NovoMix 30: 43.3% [84/194]). Most of these participants completed Week 26 but the visit was delayed.

Daily insulin doses were similar in the 2 treatment groups, regardless of trial impact (disruption) due to COVID-19. At Week 26, in the NovoMix 30 group, the increase from baseline in daily insulin doses was higher in participants for whom there was an impact of COVID-19 on the trial (0.313 U/kg) as compared to those for whom there was no impact (0.156 U/kg), but this difference was not observed in the Truvelog Mix 30 group and was not clinically relevant.

Summary of main efficacy results

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 biosimilarity assessment (see later sections).

Table 21: Summary of efficacy for trial EFC15082.

Title: A 26-week, randomized, open-label, parallel-group comparison of Truvelog Mix 30 to NovoMix 30 in adult participants with diabetes mellitus using pre-mix insulin analogues (EFC15082)			
Study identifier	EFC15082 (EudraCT: 2017-000092-84)		
Design	Phase 3, 6-month, multicentre, multinational, randomised, open-label, active-controlled, 2-arm parallel-group study to compare Truvelog Mix 30 to NovoMix 30 in adult patients T2DM or T1DM diagnosed for at least 12 months at the time of the screening, with HbA1c ≤10%, and who had been treated with at least twice daily NovoMix 30, Humalog Mix 25 or Liprolog Mix 25 for at least 3 months prior to the screening visit. Patients were randomised to receive Truvelog Mix 30 or NovoMix 30 (randomisation ratio 1:1). Randomisation was stratified by geographical region (Indian; non-Indian), type of diabetes (T1DM; T2DM), HbA1c obtained at the screening visit (<8.0%; ≥8.0%) and prior use of NovoMix 30 (Yes; No).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 weeks Up to 17 days N/A
Hypothesis	Non-inferiority (non-inferiority margin of 0.3% HbA1c)		
Treatments groups	Truvelog Mix 30		Truvelog Mix 30 (100 U/mL suspension for injection), SoloSTAR disposable prefilled pen. SC injection at least twice daily and according the locally-used product label for NovoMix 30. Selftitrated to achieve a target pre-prandial plasma glucose between 4.4 and 7.2 mmol/L (80 to 130 mg/dL) and a 2-hour postprandial plasma glucose of <10.0 mmol/L (<180 mg/dL), while avoiding hypoglycaemia.
	NovoMix 30		NovoMix 30 (100 U/mL suspension for injection), FlexPen disposable prefilled pen. SC injection at least twice daily and according the locally-used product label for NovoMix 30. Selftitrated to achieve a target pre-prandial plasma glucose between 4.4 and 7.2 mmol/L (80 to 130 mg/dL) and a 2-hour postprandial plasma glucose of <10.0 mmol/L (<180 mg/dL), while avoiding hypoglycaemia.
Endpoints and definitions	Primary endpoint	Change in HbA1c (%)	Change in HbA1c (%) from baseline to Week 26
	Tertiary/ exploratory efficacy endpoints	HbA1c <7%	Number (%) of patients with target HbA1c <7% at Week 26
		Change in FPG (mmol/L)	Change in FPG (fasting plasma glucose, mmol/L) from baseline to Week 26

		Change in 24-hour plasma glucose	Change in mean 24-hour plasma glucose (mmol/L) from baseline to Week 26 based on 7-point SMPG profile
		Change in PPG (mmol/L)	Change in postprandial plasma glucose (PPG) excursions (mmol/L) from baseline to Week 26 based on the 7-point SMPG profiles
		Change in 7-point SMPG profiles	Change in 7-point SMPG profiles per time-point from baseline to week 26
		Change in daily insulin does (U/kg)	Change in daily insulin dose (U/kg) from baseline to Week 26
Database lock	Information missing (LoQ)		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent-to-treat (ITT) population – change from baseline to Week 26 (primary analysis: ANCOVA with return to baseline multiple imputation 26 weeks		
Descriptive statistics and estimate variability	Treatment group	Truvelog Mix 30	NovoMix 30
	Number of subject	n=204	n=198
	Change in HbA1c (%) Combined LS Mean (SE) [95% CI]	-0.55 (0.080) [-0.710 to -0.398]	-0.64 (0.080) [-0.793 to -0.480]
	Combined LS Mean difference (SE) vs NovoMix 30 [95% CI]	0.08 (0.113) [-0.139 to 0.303]	
Analysis description	**Tertiary/Exploratory Analysis**		
	HbA1c <7% N (%)	58 (28.4)	62 (31.3)
	OR versus NovoMix 30 (95% CI)	0.824 [0.527 to 1.290]	

	Change in FPG (mmol/l) Combined LS Mean (SE) [95% CI]	-0.27 (0.294) [-0.842 to 0.311]	-1.01 (0.294) [-1.590 to -0.436]
	Combined LS Mean difference (SE) vs NovoMix 30 [95% CI]	0.75 (0.416) [-0.068 to 1.563]	
	Change in 24-hour plasma glucose (mmol/l) Combined LS Mean (SE) [95% CI]	-0.53 (0.171) [-0.866 to -0.196]	-0.83 (0.170) [-1.158 to -0.492]
	Combined LS Mean difference (SE) vs NovoMix 30 [95% CI]	0.29 (0.241) [-0.178 to 0.767)]	
	Change in PPG (mmol/L) Combined LS Mean (SE) [95% CI] **Breakfast** **Lunch** **Dinner**	 0.33 (0.208) [-0.082 to 0.734] 0.06 (0.244) [-0.422 to 0.534] 0.18 (0.236) [-0.283 to 0.642]	 -0.31 (0.205) [-0.713 to 0.090] -0.04 (0.243) [-0.521 to 0.431] 0.25 (0.232) [-0.204 to 0.707]
	Combined LS Mean difference (SE) vs NovoMix 30 [95% CI] **Breakfast** **Lunch** **Dinner**	 0.64 (0.293) [0.064 to 1.211] 0.10 (0.344) [-0.574 to 0.775] -0.07 (0.332) [-0.724 to 0.579]	

	Change in daily insulin does (U/kg) Mean (SD)	0.166 (0.298), n=199	0.213 (0.278), n=189
Analysis description	**Post-hoc sensitivity analysis: impact of outlier**		
Analysis population and time point description	Intent-to-treat (ITT) population excluding the outlying participant – change from baseline to Week 26 (using ANCOVA with return to baseline multiple imputation 26 weeks		
Descriptive statistics and estimate variability	Treatment group	Truvelog Mix 30	NovoMix 30
	Number of subject	n=203	n=198
	Change in HbA1c (%) Combined LS Mean (SE) [95% CI]	-0.58 (0.076) [-0.734 to -0.435]	-0.64 (0.076) [-0.788 to -0.488]
	Combined LS Mean difference (SE) vs NovoMix 30 [95% CI]	0.05 (0.108) [-0.158 to 0.266]	
Analysis description	**Prespecified sensitivity analysis: impact of COVID-19**		
Analysis population and time point description	Intent-to-treat (ITT) population – change from baseline to Week 26 (using ANCOVA with HbA1c values potentially impacted by COVID-19 treated as missing values		
Descriptive statistics and estimate variability	Treatment group	Truvelog Mix 30	NovoMix 30
	Number of subject	n=204	n=198
	Change in HbA1c (%) Combined LS Mean (SE) [95% CI]	-0.63 (0.072) [-0.772 to -0.489]	-0.68 (0.073) [-0.826 to -0.539]
	Combined LS Mean difference (SE) vs NovoMix 30 [95% CI]	0.05 (0.102) [-0.419 to 0.253]	
Analysis description	**Prespecified supportive analysis**		
Analysis population and time point description	Per protocol (PP) population - change from baseline to Week 26 (ANCOVA)		

Descriptive statistics and estimate variability	Treatment group	Truvelog Mix 30	NovoMix 30
	Number of subject	n=162	n=156
	Change in HbA1c (%) Combined LS Mean (SE) [95% CI]	-0.65 (0.071) [-0.791 to -0.511]	-0.72 (0.072) [-0.863 to -0.578]
	Combined LS Mean difference (SE) vs NovoMix 30 [95% CI]	0.07 (0.102) [-0.131 to 0.269]	

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

In the efficacy part of the dossier, applicant aims to prove the biosimilarity between test product Truvelog Mix 30 and reference product NovoMix 30. To do this, one phase 3 study was submitted (EFC15082). According to the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005_rev.1), in case of insulin biosimilar preparation, there is no need for specific efficacy studies since HbA1c endpoint is not considered sensitive enough to detect potentially clinically relevant differences between two insulins. Therefore, this study is considered as supportive only to the PK/PD study. However, since the secondary objective is to compare the effects of Truvelog Mix 30 with NovoMix 30 on immunogenicity parameters and compare safety between these products in participants with T1DM and T2DM, the results of this study are useful to prove the biosimilarity in terms of safety data.

Study EFC15082 was a 26-week, randomised, open-label, parallel-group comparison of Truvelog Mix 30 to NovoMix 30 in adult participants with diabetes mellitus using pre-mix insulin analogues. Study included adult participants (males and non-pregnant females) with T1DM or T2DM diagnosed at least 12 months before screening, with HbA1c ≤ 10.0%, treated with at least twice daily NovoMix 30, Humalog Mix 25 or Liprolog Mix 25 for at least 3 months prior to the screening visit. 25% of patients included were patients with Type 1 diabetes. As mixed insulins are most often used by T2DM patients, the majority of patients included had T2DM. In general, inclusion and exclusion criteria are acceptable.

The design of the study is appropriate to meet the objectives set in the study. The duration (26 weeks) of IMP administration is adequate and in line with the EMA guideline, as the anti-drug antibodies in insulin-treated patients are expected to develop early-on. The dosing was based on usual dosing of reference medicinal product. Open label design of the study is acceptable in this case, as the efficacy results with HbA1c endpoint are supportive only, and the major focus of this clinical trial is on immunogenicity, which can still be appropriately evaluated if the antibody determination is performed in a blinded manner. In this case,

HbA1c (for the primary efficacy endpoint analysis), FPG, and immunogenicity parameters were measured centrally, blinded to the treatment received.

The primary objective of the study was to demonstrate non-inferiority of Truvelog Mix 30 in comparison to NovoMix 30 on HbA1c change from baseline to Week 26 in participants with T1DM and T2DM. A non-inferiority margin of 0.3% HbA1c was defined, in line with recommendations of regulatory agencies and based on historical precedent for comparative insulin studies in which a 0.3% non-inferiority margin is often used. The secondary objective was to compare the safety and immunogenicity parameters between two mixed insulin products. Tertiary/exploratory objectives were to compare the effect of both insulins on glycaemic control and insulin dose, and to compare clinical effects of immunogenicity parameters on glycaemic control, insulin dose and safety.

The statistical test for the primary efficacy endpoint was one-sided, with alpha level of 0.025 and using a non-inferiority margin of 0.3% HbA1c. The primary endpoint was analysed in the ITT population. A multiple imputation approach for missing data was used with a 'return to baseline' analysis. Imputed datasets were analysed using an analysis of covariance (ANCOVA) of the change from baseline to Week 26 in HbA1c, including the fixed categorical effects of treatment group (Truvelog Mix 30 , NovoMix 30) and randomisation strata of geographical region (Indian, non-Indian), type of diabetes (T1DM, T2DM) and prior use of NovoMix 30 (Yes, No), as well as the continuous fixed covariate of baseline HbA1c value. Sensitivity analyses were defined to support the primary analysis. The methods are considered standard and acceptable.

Due to the COVID-19 pandemic during the treatment-on period of the study, a prespecified sensitivity analysis was performed. HbA1c values potentially impacted by COVID-19 were treated as missing values, and all missing data due to COVID-19 was imputed using a missing at random approach.

Efficacy data and additional analyses

The percentage of patients completing the treatment period were comparable in both treatment arms. Approximately 20% patients (42 participants in each group) were excluded from the PP population due to COVID-19 pandemic, sensitivity analysis assessing this issue was planned in the statistical analysis. Reasons for exclusion from PP due to other reasons than COVID-19 were reported similarly in both groups. Amount of patients discontinuing treatment were comparable (3 for test product vs. 6 for reference). No participants discontinued treatment due to lack of efficacy or hypoglycaemia.

No critical protocol deviations were reported in this study. The proportion of participants with any major protocol deviation was balanced between treatment groups (130 [63.7%] participants in the Truvelog Mix 30 group and 119 [60.1%] in the NovoMix 30 group), with no apparent distribution pattern. Around 40% of major protocol deviations were not related to COVID-19 in both treatment groups. In general, protocol deviations observed do not differ significantly between different treatment arms and were not considered critical.

The majority of participants were Asian (India – 52.2% and Philippines – 8.7%) and the rest of the participants were Caucasian (Eastern Europe – 39.1%). A minimum of 25 % of patients had T1DM, which is sufficiently representative. The distribution of men and women differed between treatment arms. In the Truvelog Mix 30 arm, 55% were men and 45 % were women, whereas in the Novomix 30 arm, 55% were women and 45% were men. Furthermore, a larger proportion had a BMI above 25 in the Novomix 30 arm compared to the Truvelog Mix 30 arm. There was a numerically higher increase in daily insulin dose in the NovoMix 30 arm (0.166 U/kg) than the Truvelog Mix 30 30 arm (0.278 U/kg), however the difference

between treatment arms was small and is not considered clinically relevant. Besides the above differences, demographic and disease characteristics are well-balanced in both treatment groups. Study population recruited reflects intended population.

The primary endpoint, change from baseline to Week 26 in HbA1c implementing the non-inferiority margin of 0.3 HbA1c, was not met for Truvelog Mix 30 compared to NovoMix 30 in the ITT population. The LS mean difference between Truvelog Mix 30 and NovoMix 30 was 0.08 (95% CI: 0.139 to 0.303).

According to the applicant, this result was primarily driven by 1 participant with T2DM in the Truvelog Mix 30 group. In a post-hoc sensitivity analysis performed on the ITT population excluding this Participant in the Truvelog Mix 30 group, the upper bound of the 2-sided 95% CI of the difference between Truvelog Mix 30 and NovoMix 30 was below the predefined non-inferiority margin of 0.3% (LS mean difference of -0.05% [95%CI: -0.158 to 0.266]). After exclusion of this patient, inverse non-inferiority of NovoMix 30 over Truvelog Mix 30 was also achieved. The excluded participant had an extreme outlying increase in HbA1c from baseline to Week 26 of 5.9%. The investigation revealed, that due to COVID-19 lockdown, applicant´s IMP expired and participant did not take the product according to the protocol, therefore the increase in HbA1c occurred at 26-week visit. Analysis of the complete ITT population is a golden standard in clinical trials. Post hoc analyses not predefined in the study protocol should not be acceptable. However, in this case HbA1c results are not a requirement for authorisation and therefore, the applicant´s justification can be accepted and this issue will not be pursued further. In a sensitivity analysis studying impact of COVID-19 on efficacy endpoint, non-inferiority of Truvelog Mix 30 compared to NovoMix 30 on change from baseline to Week 26 in HbA1c was achieved. The same results were observed in PP analysis.

In general, the presented primary efficacy endpoints need to be regarded as supportive only. According to the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005_rev.1), HbA1c is not considered sensitive enough to detect potentially clinically relevant differences between two insulins. Considering the quality major objection questioning analytical similarity and the observed PD differences, it is not possible to make any conclusions regarding biosimilarity. This uncertainty cannot be remedied by the efficacy results of the study EFC15082.

Tertiary endpoint, the percentage of participants who reached the HbA1c target <7% at Week 26, was similar in the 2 treatment groups – 28.4% in Truvelog Mix 30 group and 31.3% in NovoMix 30 group, with odds ratio 0.824 (95% CI = 0.527 to 1.290). From baseline to week 26, the decrease in FPG was -0.27 mmol/L in the Truvelog Mix 30 group and -1.01 mmol/L in the NovoMix 30 group (LS mean difference of 0.75 [95%CI:-0.068 to 1.563]). Even if there is a numerical difference between the groups, it can be accepted, as the 95% CI crosses one. Furthermore, the proposed endpoints are not sensitive enough to detect potentially clinically relevant difference in the efficacy study setting. Similar numerical difference was also present for the change from baseline to Week 26 in mean 24-hour SMPG and when change from baseline to Week 26 in plasma glucose excursion (mmol/L) at breakfast, lunch and dinner was assessed. Graphical presentation of the 7-point SMPG profiles showed similarity in the 2 treatment groups.

Subgroup analysis with regard to age, race, sex, baseline BMI, baseline eGFR, randomisation stratum of screening HbA1c and duration of diabetes showed in general consistent results in all the subgroups. No evidence of heterogeneity of treatment effect across subgroups was shown as indicated by the p-values above 0.10 for treatment-by-subgroup interactions except for the subgroup defined by duration of diabetes. Subgroup analysis presented by the applicant were sufficient.

When assessing the change in HbA1c by treatment-emergent anti-insulin aspart antibodies, the results suggest similar efficacy of Truvelog Mix 30 and NovoMix 30, regardless of the treatment-emergent AIA status.

Additionally, based on the submitted data, it is not probable that the results were affected by the COVID-19 pandemic.

2.5.7. Conclusions on the clinical efficacy

The primary endpoint of the phase 3 study (EFC15082) did not meet the pre-defined non-inferiority margin of HbA1c change in the ITT population when comparing Truvelog Mix 30 and NovoMix 30. However, non-inferiority was missed by a very small margin and after exclusion of 1 patient, primary endpoint was met. Although this can be attributed to an unforeseen event, i.e. the respective patient experienced a substantial increase in HbA1c due to running out of study medicinal product during the pandemic, post hoc analyses not predefined in the study protocol should not be acceptable. However, in this case HbA1c results are not a requirement for authorisation and therefore, the applicant´s justification can be accepted and this issue will not be pursued further. The submitted phase 3 study (EFC15082) provides only supportive evidence with respect to the biosimilarity of Truvelog Mix 30 and NovoMix 30. Nevertheless, immunogenicity and safety data from this study are pertinent to the safety comparison.

2.5.8. Clinical safety

As of the dossier cut-off date (06 November 2020), the clinical development programme of the Truvelog Mix 30 included 2 completed studies (PDY15084 and EFC15082). The two studies PDY15084 and EFC15082 were not pooled due to differences in study designs.

In the phase 3 study EFC15082, safety population consisted of 400 patients, compared to the PK/PD study PDY15084 where only 52 participants were enrolled. Therefore, the majority of the safety data comes from phase 3 study.

Patient exposure

The cumulative duration of treatment exposure was 108.35 participant-years in the Truvelog Mix 30 group and 104.96 participant-years in the NovoMix 30 group. The median duration of exposure was similar in both treatment groups (183 days for Truvelog Mix 30 and 184 days for NovoMix 30). The majority of participants in each treatment group were exposed to IMP for more than 25 weeks (Truvelog Mix 30 : 194 [95.6%]; and NovoMix 30: 189 [95.9%]).

Adverse events

Summary of adverse events

The percentage of participants experiencing TEAEs or serious TEAEs during the on-treatment period was similar in the Truvelog Mix 30 group and the NovoMix 30 group (see table below). There were no TEAEs leading to permanent treatment discontinuation reported in this study. During the on-treatment period, 1 participant in the NovoMix 30 group had a treatment-emergent SAE resulting in death.

Table 22: Overview of adverse event profile: Treatment-emergent adverse events by type of diabetes and overall during the on-treatment period - Safety population.

n (%)	T1DM		T2DM		All	
	SAR341402 Mix 70/30 (N=53)	NovoMix 30 (N=51)	SAR341402 Mix 70/30 (N=150)	NovoMix 30 (N=146)	SAR341402 Mix 70/30 (N=203)	NovoMix 30 (N=197)
Patients with any TEAE	9 (17.0)	9 (17.6)	27 (18.0)	32 (21.9)	36 (17.7)	41 (20.8)
Patients with any treatment-emergent SAE	1 (1.9)	1 (2.0)	1 (0.7)	2 (1.4)	2 (1.0)	3 (1.5)
Patients with any TEAE leading to death	0	0	0	1 (0.7)	0	1 (0.5)
Patients with any TEAE leading to permanent treatment discontinuation	0	0	0	0	0	0

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

Treatment emergent adverse events

The overall incidence of TEAEs was similar between treatment groups (Truvelog Mix 30 : 17.7%; NovoMix 30: 20.8%, see table below). The most frequently reported TEAEs in either treatment group by primary SOC were Infections and Infestations (Truvelog Mix 30 : 6.9% [14 participants]; NovoMix 30 group 11.7% [23 participants]). Treatment-emergent AEs in the other SOCs were reported in less than 3% of participants, regardless of the treatment group.

At the PT level, the most frequently reported TEAEs in either treatment group were nasopharyngitis (Truvelog Mix 30 : 1.5%; and NovoMix 30: 3.6%) and upper respiratory tract infection (Truvelog Mix 30 : 1.5%; and NovoMix 30: 2.0%). All other TEAEs were reported in less than 2.0% of participants regardless of treatment group.

No TEAEs in either treatment group were considered as related to IMP by the Investigator. Treatment-emergent AEs were mainly of mild to moderate intensity in both the treatment groups.

Table 23: Number (%) of participants with TEAE(s) by Primary SOC and PT during the on-treatment period - Safety population.

Primary System Organ Class Preferred Term n(%)	SAR341402 Mix 70/30 (N=203)	NovoMix 30 (N=197)
Any class	36 (17.7)	41 (20.8)
INFECTIONS AND INFESTATIONS	14 (6.9)	23 (11.7)
Nasopharyngitis	3 (1.5)	7 (3.6)
Upper respiratory tract infection	3 (1.5)	4 (2.0)
Bronchitis	2 (1.0)	2 (1.0)
Ear infection	2 (1.0)	0
Respiratory tract infection viral	2 (1.0)	1 (0.5)
Gangrene	1 (0.5)	0
Laryngitis	1 (0.5)	1 (0.5)
Respiratory tract infection	1 (0.5)	1 (0.5)
Gastroenteritis	0	2 (1.0)
Otitis media acute	0	1 (0.5)

Pharyngitis	0	3 (1.5)
Rhinitis	0	1 (0.5)
Tracheitis	0	1 (0.5)
Urinary tract infection	0	1 (0.5)
Viral upper respiratory tract infection	0	1 (0.5)
Vulvovaginitis	0	1 (0.5)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.5)	0
Polycythaemia vera	1 (0.5)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	2 (1.0)
Anaemia	0	1 (0.5)
Iron deficiency anaemia	0	1 (0.5)
METABOLISM AND NUTRITION DISORDERS	0	1 (0.5)
Hyperkalaemia	0	1 (0.5)
PSYCHIATRIC DISORDERS	2 (1.0)	0
Emotional distress	1 (0.5)	0
Insomnia	1 (0.5)	0
NERVOUS SYSTEM DISORDERS	1 (0.5)	2 (1.0)
Headache	1 (0.5)	1 (0.5)
Diabetic neuropathy	0	1 (0.5)
EYE DISORDERS	3 (1.5)	1 (0.5)
Cataract	2 (1.0)	0
Diabetic retinal oedema	1 (0.5)	0
Diabetic retinopathy	0	1 (0.5)
EAR AND LABYRINTH DISORDERS	0	1 (0.5)
Vertigo	0	1 (0.5)
CARDIAC DISORDERS	2 (1.0)	1 (0.5)
Arrhythmia	1 (0.5)	0
Tachycardia	1 (0.5)	0
Angina unstable	0	1 (0.5)
Cardiac failure	0	1 (0.5)
VASCULAR DISORDERS	2 (1.0)	0
Hypertension	1 (0.5)	0
Hypertensive crisis	1 (0.5)	0

Primary System Organ Class Preferred Term n(%)	SAR341402 Mix 70/30 (N=203)	NovoMix 30 (N=197)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	2 (1.0)
Cough	0	1 (0.5)
Rhinorrhoea	0	1 (0.5)
GASTROINTESTINAL DISORDERS	4 (2.0)	4 (2.0)
Abdominal pain	1 (0.5)	0
Abdominal pain upper	1 (0.5)	0
Diarrhoea	1 (0.5)	0
Food poisoning	1 (0.5)	0
Acid peptic disease	0	1 (0.5)
Dyspepsia	0	1 (0.5)
Gastritis	0	1 (0.5)
Vomiting	0	1 (0.5)
HEPATOBILIARY DISORDERS	1 (0.5)	1 (0.5)
Hyperbilirubinaemia	1 (0.5)	0
Hepatic pain	0	1 (0.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.5)	0
Pruritus	1 (0.5)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 (1.5)	4 (2.0)
Back pain	2 (1.0)	1 (0.5)
Myalgia	1 (0.5)	0
Arthralgia	0	3 (1.5)
RENAL AND URINARY DISORDERS	2 (1.0)	2 (1.0)
Dysuria	1 (0.5)	0
Urinary incontinence	1 (0.5)	0
Acute kidney injury	0	1 (0.5)
Diabetic nephropathy	0	1 (0.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (1.5)	5 (2.5)
Pyrexia	2 (1.0)	1 (0.5)
Pain	1 (0.5)	0
Fatigue	0	2 (1.0)
Peripheral swelling	0	1 (0.5)
Sudden cardiac death	0	1 (0.5)
INVESTIGATIONS	2 (1.0)	2 (1.0)
Alanine aminotransferase increased	1 (0.5)	0
Aspartate aminotransferase increased	1 (0.5)	0
Blood pressure increased	1 (0.5)	2 (1.0)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.5)	1 (0.5)
Tibia fracture	1 (0.5)	0
Limb injury	0	1 (0.5)

TEAE: Treatment-emergent adverse event, SOC: System organ class, PT: Preferred term
MedDRA dictionary: MedDRA 23.1
n (%) = number and percentage of patients with at least one TEAE
Note: Table sorted by SOC internationally agreed order and PT sorted by decreasing incidence in the SAR341202 Mix 70/30 group within SOC

Impact of COVID-19 pandemic

No TEAEs were reported as related to COVID-19 (i.e., no COVID-19 illness) in either treatment group. The incidence of TEAEs was similar in the 2 treatment groups, regardless of trial impact (disruption) due to COVID-19.

In participants with trial impact (disruption) due to COVID-19, the incidence of any TEAEs was numerically lower in the Truvelog Mix 30 group (12/87 [13.8%] participants) compared to the NovoMix 30 group (16/73 [21.9%] participants) but the difference was small (4 participants). The most frequently reported TEAE in either treatment group by primary SOC was Infections and Infestations (Truvelog Mix 30 group: 2 [2.3%] participants; NovoMix 30 group: 7 [9.6%] participants) and General Disorders and Administration Site Conditions (Truvelog Mix 30 : 2 [2.3%] participants; and NovoMix 30: 3 [4.1%] participants).

Adverse events of specific interest

Hypoglycaemia

During the on-treatment period, 62.1% participants in the Truvelog Mix 30 group and 70.1% participants in the NovoMix 30 group had at least one event of "any" hypoglycaemia.

Table 24: Number (%) of participants with at least one hypoglycaemia by type of diabetes and overall during the on-treatment period - Safety population.

Type of hypoglycemia n (%)	T1DM		T2DM		All	
	SAR341402 Mix 70/30 (N=53)	NovoMix 30 (N=51)	SAR341402 Mix 70/30 (N=150)	NovoMix 30 (N=146)	SAR341402 Mix 70/30 (N=203)	NovoMix 30 (N=197)
Any hypoglycemia	41 (77.4)	40 (78.4)	85 (56.7)	98 (67.1)	126 (62.1)	138 (70.1)
Severe hypoglycemia	0	0	0	0	0	0
Documented symptomatic hypoglycemia						
≤ 3.9 mmol/L (70 mg/dL)	29 (54.7)	24 (47.1)	51 (34.0)	65 (44.5)	80 (39.4)	89 (45.2)
< 3.0 mmol/L (54 mg/dL)	26 (49.1)	19 (37.3)	21 (14.0)	29 (19.9)	47 (23.2)	48 (24.4)
Asymptomatic hypoglycemia						
≤ 3.9 mmol/L (70 mg/dL)	33 (62.3)	35 (68.6)	55 (36.7)	69 (47.3)	88 (43.3)	104 (52.8)
< 3.0 mmol/L (54 mg/dL)	24 (45.3)	17 (33.3)	18 (12.0)	21 (14.4)	42 (20.7)	38 (19.3)
Probable symptomatic hypoglycemia	1 (1.9)	1 (2.0)	4 (2.7)	2 (1.4)	5 (2.5)	3 (1.5)
Relative hypoglycemia	1 (1.9)	0	5 (3.3)	5 (3.4)	6 (3.0)	5 (2.5)

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

The total number of hypoglycaemia events per participant-year was 1381 in the Truvelog Mix 30 group and 1424 in the NovoMix 30 group. The rate of "any" hypoglycaemia was similar in the 2 treatment groups (Truvelog Mix 30 : 12.62 events per participant-year of exposure; NovoMix 30: 13.43 events per participant-year of exposure). The rate ratio of Truvelog Mix 30 versus NovoMix 30 for 'any' hypoglycaemia was 0.91 (95% CI: 0.68 to 1.22).

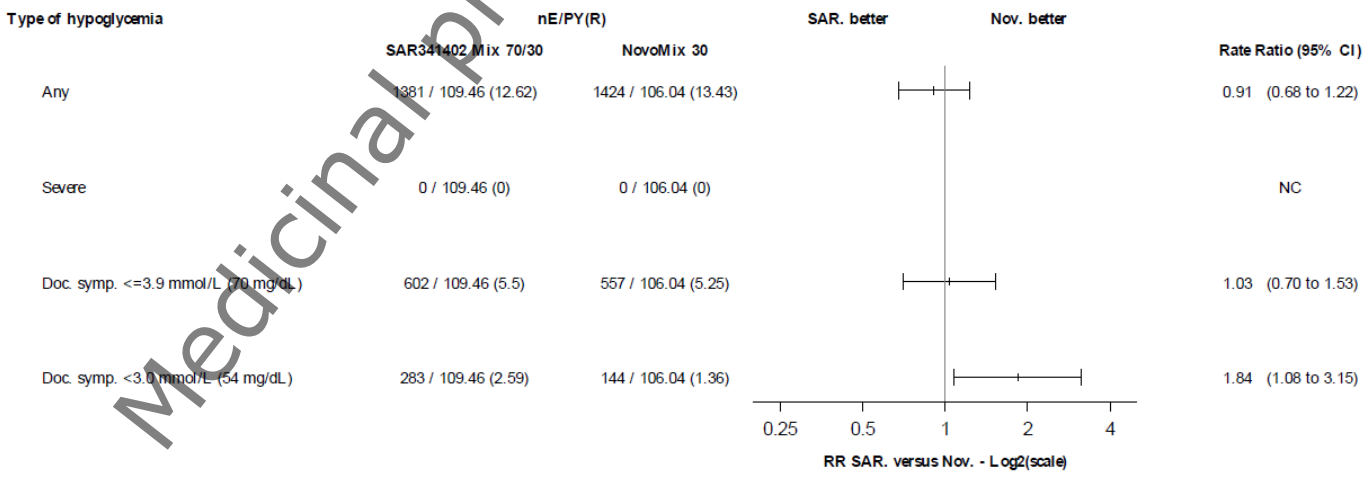
Table 25: Number of hypoglycaemia per participant-year of exposure by type of diabetes and overall during the on-treatment period – Safety population.

Type of hypoglycemia Number of events (rate per patient-years)	T1DM		T2DM		All	
	SAR341402 Mix 70/30 (N=53)	NovoMix 30 (N=51)	SAR341402 Mix 70/30 (N=150)	NovoMix 30 (N=146)	SAR341402 Mix 70/30 (N=203)	NovoMix 30 (N=197)
Total patient years	28.31	27.17	81.15	78.87	109.46	106.04
Any hypoglycemia	840 (29.67)	709 (26.10)	541 (6.67)	715 (9.07)	1381 (12.62)	1424 (13.43)
Severe hypoglycemia	0	0	0	0	0	0
Documented symptomatic hypoglycemia						
≤ 3.9 mmol/L (70 mg/dL)	358 (12.64)	274 (10.09)	244 (3.01)	283 (3.59)	602 (5.50)	557 (5.25)
< 3.0 mmol/L (54 mg/dL)	212 (7.49)	82 (3.02)	71 (0.87)	62 (0.79)	283 (2.59)	144 (1.36)
Asymptomatic hypoglycemia						
≤ 3.9 mmol/L (70 mg/dL)	476 (16.81)	431 (15.86)	280 (3.45)	422 (5.35)	756 (6.91)	853 (8.04)
< 3.0 mmol/L (54 mg/dL)	121 (4.27)	95 (3.50)	55 (0.68)	31 (0.39)	176 (1.61)	126 (1.19)
Probable symptomatic hypoglycemia	1 (0.04)	4 (0.15)	10 (0.12)	4 (0.05)	11 (0.10)	8 (0.08)
Relative hypoglycemia	5 (0.18)	0	7 (0.09)	6 (0.08)	12 (0.11)	6 (0.06)

In the overall safety population, the number of hypoglycaemia events and event rates per participant-year of exposure were similar between the 2 treatment groups for all categories, except for documented symptomatic hypoglycaemia (<3.0 mmol/L (54 mg/dL) with values numerically higher in the Truvelog Mix 30 group (283 [2.59]) compared to the NovoMix 30 group (144 [1.36]). This numerical difference between treatment groups was driven by 6 participants in the Truvelog Mix 30 group (5 with T1DM and 1 with T2DM, each reporting ≥20 events) who reported in total 155 out of 283 hypoglycaemia events in this category; while no participant reported more than 13 events in the NovoMix 30 group. In most of these participants, the daily insulin dose remained unchanged throughout the study, only one participant had insulin dose adjustment following repeated hypoglycaemia episodes. None of these hypoglycaemia events were accompanied by neuroglycopenic symptoms or met otherwise serious AE criteria. Out of the 155 documented symptomatic hypoglycaemia events (<3.0 mmol/L (54 mg/dL)) reported by the 5 participants with T1DM, 139 showed evidence of at least one precipitating factor i.e., missed, delayed or smaller meal and/or physical activity among those detailed above. No relationship between race, age group, sex, baseline BMI, baseline eGFR, screening HbA_{1c}, prior use of NovoMix 30, geographical region or duration of diabetes and the number of documented symptomatic hypoglycaemia events was found in the 5 participants with T1DM. These participants were counselled and had no insulin dose adjustment as planned per protocol. Post-hoc sensitivity analyses excluding these 6 participants showed similar results between treatment groups for number of events and event rates per participant-year of exposure across all hypoglycaemia categories, including documented symptomatic hypoglycaemia (<3.0 mmol/L [54 mg/dL]).

The rate ratio for Truvelog Mix 30 versus NovoMix 30 was close to 1 for all categories of hypoglycaemia, except for documented symptomatic hypoglycaemia <3.0 mmol/L (54 mg/dL; see figure below). After excluding the 6 participants in the Truvelog Mix 30 group who reported ≥20 hypoglycaemia events each, the rate ratio for Truvelog Mix 30 versus NovoMix 30 was close to 1 for all categories of hypoglycaemia, including documented symptomatic hypoglycaemia (<3.0 mmol/L [54 mg/dL]; rate ratio=0.92; 95% CI: 0.58 to 1.47).

Figure 11: Rate ratio for Truvelog Mix 30 versus NovoMix 30 of the number of hypoglycaemia per participant-year of exposure during the on-treatment period – Safety population



RR=Rate ratio, NC=model did not converge, SAR.=SAR341402 Mix 70/30, Nov.=NovoMix 30, Doc. Symp. = Documented symptomatic, nE = Number of events, PY = Total patient-years, R = Rate per patient-year

Distribution of hypoglycaemia events was comparable over the 24-hour day in both treatment groups.

In both treatment groups, the majority of documented symptomatic hypoglycaemia ≤3.9 mmol/L (70 mg/dL) occurred around noon and around dinner/bedtime and the time of the day with the lowest percentage of participants reporting at least one event was between 16:00 and 18:00.

Figure 12: Hourly rate of hypoglycaemia (any event) per patient-year during the on-treatment period – safety population

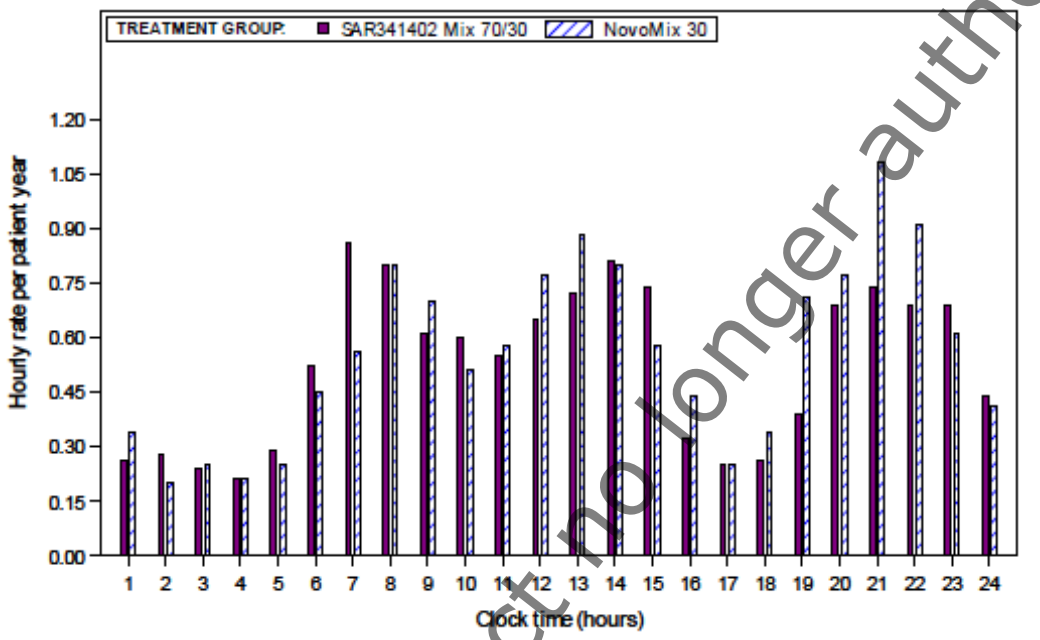


Figure 13: Hourly rate of documented symptomatic hypoglycaemia ≤3.9 mmol/L (70 mg/dl) per patient-year during the on-treatment period – safety population

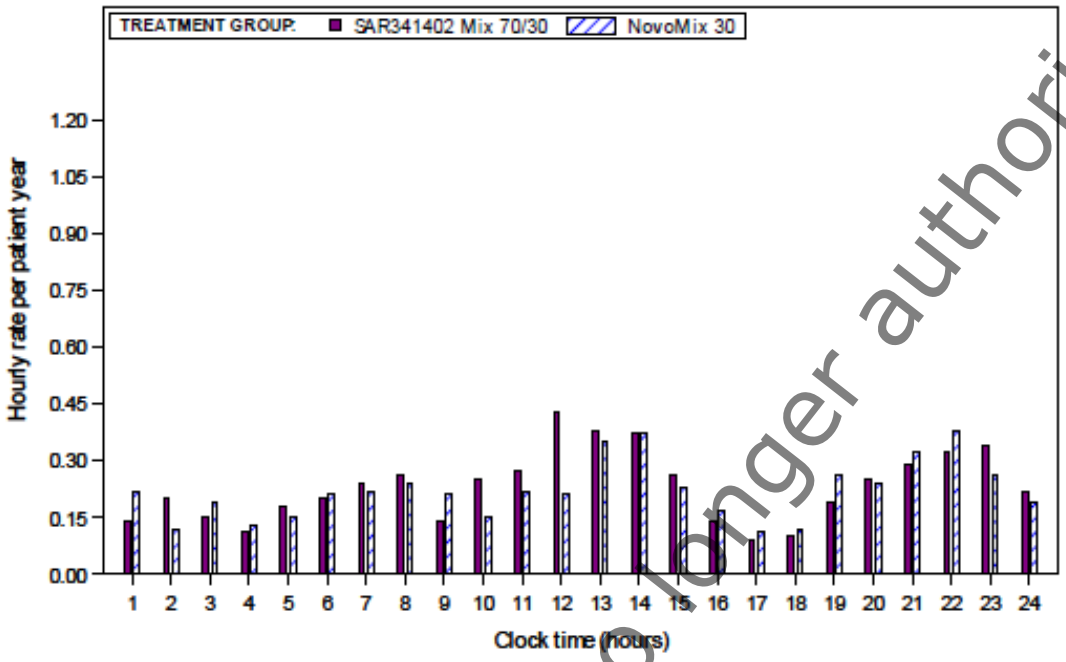


Figure 14: Hourly rate of documented symptomatic hypoglycaemia <3.0 mmol/l (54 mg/dl) per patient-year during the on-treatment period – safety population

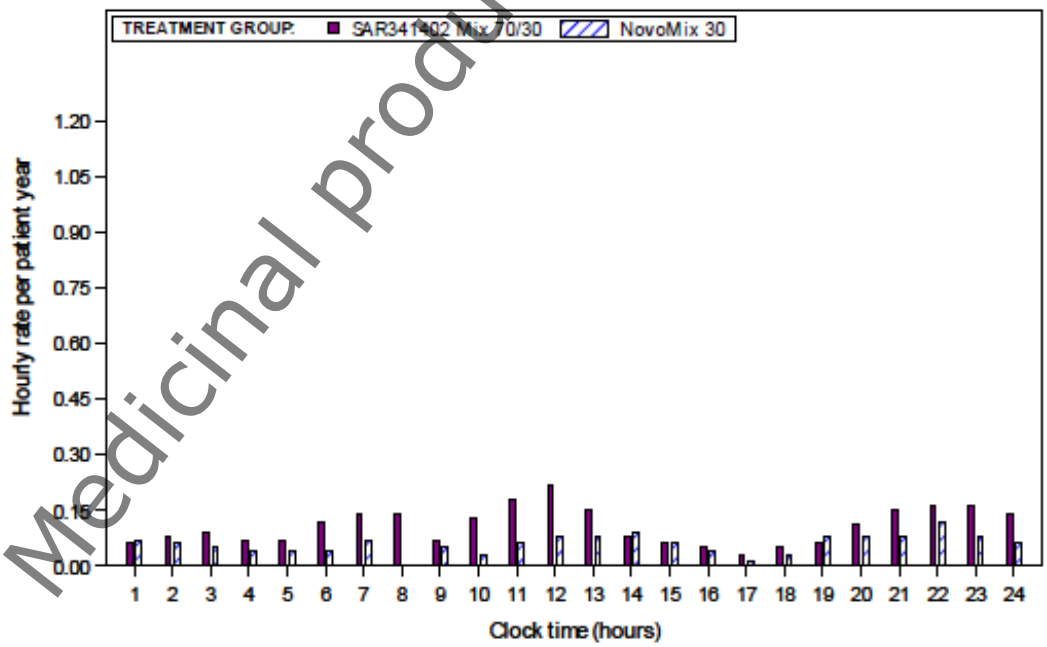


Figure 15: Cumulative mean number of documented symptomatic hypoglycaemia ≤3.9 mmol/L (70 mg/dl) per patient-year during the on-tretment period – safety population

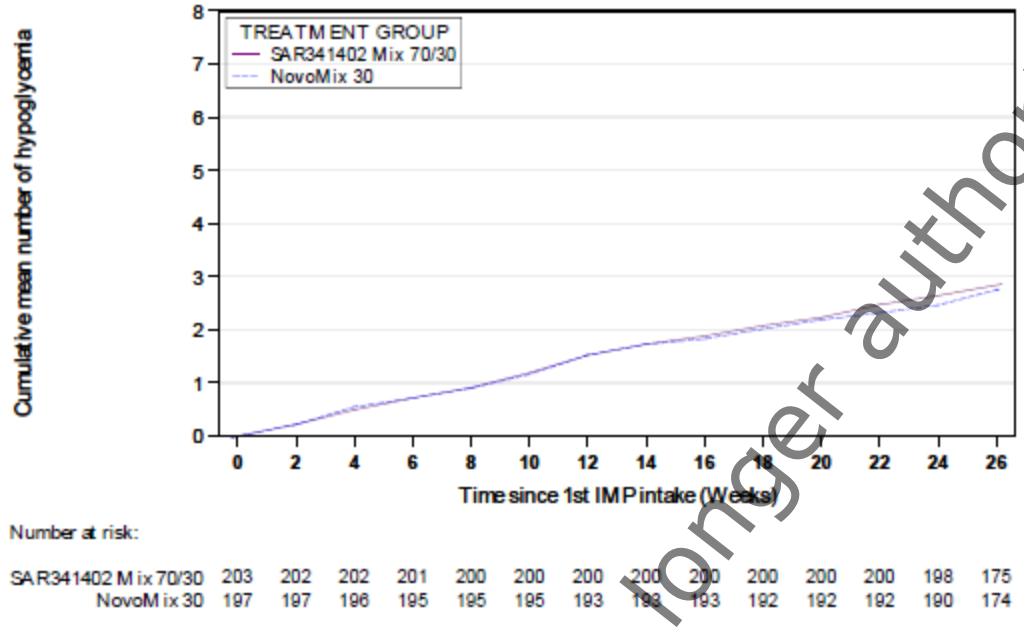
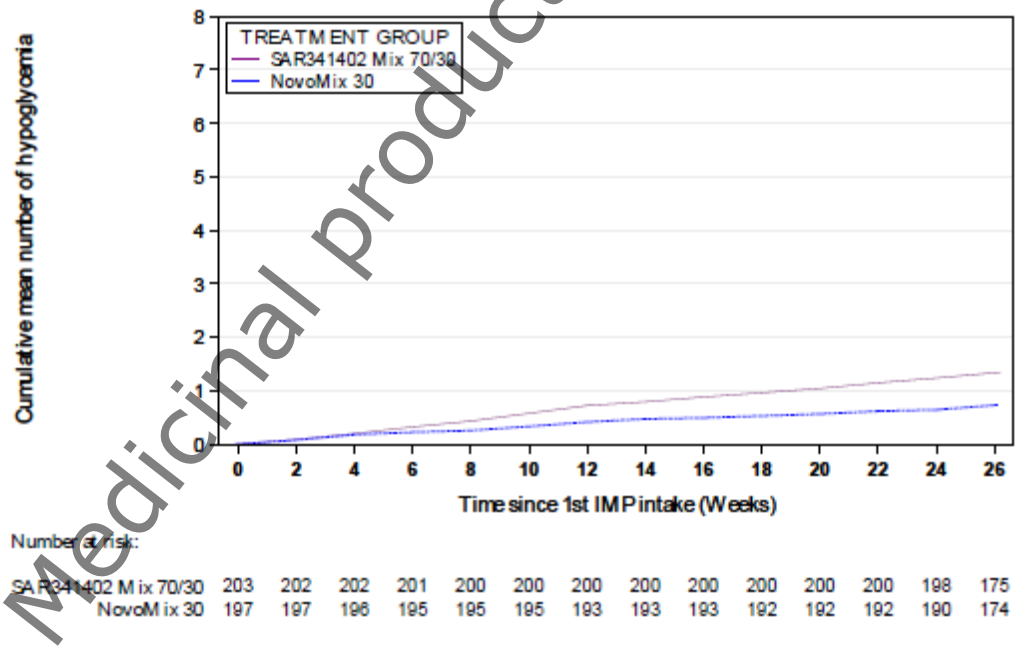


Figure 16: Cumulative mean number of documented symptomatic hypoglycaemia <3.0 mmol/l (54 mg/dl) per patient-year during the on-treatment period – safety population



Submitted subgroup analysis concerning hypoglycaemia by type of diabetes showed some numerical differences in the incidence of hypoglycaemia between the 2 treatment groups; however, no consistent trend was observed across hypoglycaemia categories in participants with T2DM or T1DM. The odds ratio of Truvelog

Mix 30 versus NovoMix 30 was 0.66 (95% CI: 0.36 to 1.23) for participants with T2DM and 1.65 (95% CI: 0.75 to 3.64) for participants with T1DM.

Subgroup analysis according to prior use of NovoMix 30 did not shown any clinically relevant difference between the two treatment groups.

The incidence of hypoglycaemia across the remaining subgroups by intrinsic and baseline factors (i.e., race, age group, sex, baseline BMI, baseline eGFR, screening HbA1c [<8.0%, ≥8.0%] and duration of diabetes) were generally consistent with the overall population for most categories of hypoglycaemia.

Subgroup analysis assessing the impact of COVID-19 pandemic of hypoglycaemia showed that the percentages of participants who reported at least one hypoglycaemia ("any" hypoglycaemia) was similar in the 2 treatment groups, regardless of COVID-19 impact. For all categories of hypoglycaemia, no noteworthy differences between treatment groups were observed and p-value of treatment-by-subgroup interaction showed no evidence of heterogeneity of treatment effect across subgroups. In general, the number of hypoglycaemia events and event rates per participant-year were lower in participants with trial impact compared to those without trial impact; for 'any' hypoglycaemia, the number of events and event rates were 343 (6.85) in the Truvelog Mix 30 group and 270 (6.37) in the NovoMix 30 group for those with trial impact, versus 1038 (17.47) and 1154 (18.14) for those participants without trial impact. Results of the hypoglycaemia analyses suggested that trial disruption due to COVID-19 resulted in underreporting of hypoglycaemia events similarly in both treatment groups, therefore, no impact is expected on the between-group comparison and the overall hypoglycaemia conclusions.

Injection site reaction

No injection site reactions were reported.

Hypersensitivity reactions

During the on-treatment period of study EFC15082, 1 participant with T2DM in the Truvelog Mix 30 group reported a TEAE of hypersensitivity reaction (PT: Pruritus). The event was mild in severity, non-serious, resolved without sequelae, and did not result in permanent treatment discontinuation. The Investigator considered the event as not related to IMP. No hypersensitivity reactions were reported in the NovoMix 30 group.

Alanine aminotransferase increase

In study EFC15082, one participant in the Truvelog Mix 30 group reported an ALT-related TEAE (PT: ALT increased). This non-serious event did not lead to permanent treatment discontinuation and was considered as not related to IMP by the Investigator.

Serious adverse events Serious adverse events and deaths

During the on-treatment period, serious TEAEs (regardless of relationship) were reported by a low and similar percentage of participants in the Truvelog Mix 30 group (2 [1.0%]) and the NovoMix 30 group (3 [1.5%]). At a PT level, no treatment-emergent SAEs occurred in more than 1 participant in either treatment group. No serious TEAEs of hypoglycaemia were reported in either treatment group during the on-treatment period. No serious TEAEs were considered as related to IMP by the Investigator in either treatment group.

Table 26: Number (%) of participants with treatment-emergent SAEs regardless of relationship and related to IMP by Primary SOC and PT during the on-treatment period - Safety population.

	SAR341402 Mix 70/30 (N=203)		NovoMix 30 (N=197)	
Primary System Organ Class Preferred Term n(%)	ALL	RELATED	ALL	RELATED
Any class	2 (1.0)	0	3 (1.5)	0
INFECTIONS AND INFESTATIONS	1 (0.5)	0	0	0
Gangrene	1 (0.5)	0	0	0
CARDIAC DISORDERS	0	0	1 (0.5)	0
Angina unstable	0	0	1 (0.5)	0
Cardiac failure	0	0	1 (0.5)	0
RENAL AND URINARY DISORDERS	0	0	1 (0.5)	0
Acute kidney injury	0	0	1 (0.5)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	1 (0.5)	0
Sudden cardiac death	0	0	1 (0.5)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.5)	0	0	0
Tibia fracture	1 (0.5)	0	0	0

IMP: Investigational medicinal product, SAE: Serious adverse event, SOC: System organ class, PT: Preferred term
MedDRA dictionary: MedDRA 23.1
n (%) = number and percentage of patients with at least one treatment-emergent SAE
Note: Table sorted by SOC internationally agreed order and PT sorted by decreasing frequency according to all TEAE summary within SOC.

Deaths

During the study, a total of 2 deaths were reported in the NovoMix 30 group: one occurred during on-treatment period (PT: sudden cardiac death) and the other occurred during post-treatment period (PT: Hanging). No death case was reported in the Truvelog Mix 30 group. None of the events leading to death were considered related to the IMP by the Investigator.

Laboratory findings

There were no relevant mean changes from baseline to Week 26 in either treatment group for any hematologic laboratory parameter (haemoglobin, haematocrits, erythrocytes, platelets, leukocytes, neutrophils, lymphocytes, eosinophils, basophils, and monocytes), any clinical laboratory parameters (lipid parameters, liver and renal parameters, and electrolytes), any serum lipid parameters (cholesterol and triglycerides), electrolytes (sodium and potassium), any of the renal function parameters (creatinine and eGFR [MDRD]), any of the hepatic function parameters (ALT, AST, alkaline phosphatase, and total bilirubin).

Safety in special populations

Type of DM

There was no differential treatment effect on the incidence and pattern of TEAEs across subgroups defined by type of diabetes. In T1DM, the incidence of TEAEs was 17.0% (9/53 participants) for Truvelog Mix 30 and 17.6% (9/51 participants) for NovoMix 30. In T2DM, the incidence of TEAEs was 18.0% (27/150 participants) for Truvelog Mix 30 and 21.9% (32/146 participants) for NovoMix 30. Consistent with the overall population, the most frequently reported TEAEs at the primary SOC level in participants with T1DM or T2DM were Infections and Infestations, similarly in both treatment groups.

No evidence of heterogeneity of treatment effect across subgroups was observed (as indicated by the p-value above 0.10 for treatment-by-subgroup interaction), except for documented symptomatic hypoglycaemia (<3.0 mmol/L [54 mg/dL]), with a p-value of 0.0750; the odds ratio of Truvelog Mix 30 versus NovoMix 30 was 0.66 (95% CI: 0.36 to 1.23) for participants with T2DM and 1.65 (95% CI: 0.75 to 3.64) for participants with T1DM.

Prior use of NovoMix 30

Subgroup analysis by randomisation stratum of prior use of NovoMix 30 showed that the incidence of TEAEs was similar in participants switching from commercial NovoMix 30 to Truvelog Mix 30 at randomisation compared with participants continuing with NovoMix 30 (Truvelog Mix 30 : 18.6% [32/172 participants]; and NovoMix 30 group: 22.0% [37/168 participants]); and also similar between those without prior use of NovoMix 30 (Truvelog Mix 30 : 12.9% [4/31 participants]; and NovoMix 30 group: 13.8% [4/29 participants]). Consistent with the overall population, the most frequently reported TEAEs at the primary SOC level in participants with or without prior use of NovoMix 30 were Infections and Infestations, similarly in both treatment groups.

Other subgroups

The frequency of TEAEs was overall similar between Truvelog Mix 30 and NovoMix 30 in the other subgroups defined by screening and baseline factors (including race, age group, sex, baseline BMI, baseline eGFR, duration of diabetes, and randomisation stratum of HbA1c at screening). There were limited number of participants in certain categories of subgroups (i.e., age groups ≥65 to <75 and ≥75 years, baseline BMI ≥30 kg/m², and baseline eGFR category <60 mL/min/1.73 m²).

Immunological events

<u>On-treatment anti-insulin aspart antibody response</u>

Among participants with available AIA sample at baseline, similar percentages of participants in the 2 treatment groups had detectable AIAs at baseline (Truvelog Mix 30 : 49.2% [91/185 participants]; NovoMix 30: 54.0% [95/176 participants]; see table below).

The percentage of participants with a treatment-emergent AIA response (i.e., treatment-boosted or treatment-induced AIAs) during the 26-week on-treatment period was similar between Truvelog Mix 30 (33.2% [66/199 participants]) and NovoMix 30 (31.8% [62/195 participants]). The risk difference between Truvelog Mix 30 and NovoMix 30 for the percentage of participants with treatment-emergent AIAs was 1.7% (90% CI: -5.90 to 9.22). Similar percentages of participants in the Truvelog Mix 30 group (70.4% [140/199])

and in the NovoMix 30 group (71.8% [140/195]) were positive for AIA at least at one time-point between baseline and Week 26.

The kinetics of the AIA response, in terms of duration of the AIA response (transient or persistent), were generally comparable in the 2 treatment groups. Among participants with treatment-boosted AIA, a persistent response was found in 17.6% of participants in the Truvelog Mix 30 group and 29.4% of participants in the NovoMix 30 group. Among participants with treatment-induced AIA, a persistent response was found in 20.4% of participants in the Truvelog Mix 30 group and 26.7% of participants in the NovoMix 30 group.

Table 27: Summary of AIA response during the on-treatment period - AIA population.

	SAR341402 Mix 70/30 (N=199)	NovoMix 30 (N=195)
Patients with AIA positive at baseline, n (%)	91/185 (49.2)	95/176 (54.0)
Median titer (1/dil)	16.0	16.0
Q1 ; Q3	8.0 ; 32.0	8.0 ; 32.0
Patients with treatment-boosted AIA, n (%)	17/91 (18.7)	17/95 (17.9)
Median peak titer [a] (1/dil)	64.0	32.0
Q1 ; Q3	32.0 ; 128.0	32.0 ; 64.0
Transient AIA response, n (%)	1/17 (5.9)	5/17 (29.4)
Persistent AIA response, n (%)	3/17 (17.6)	5/17 (29.4)
Indeterminate AIA response, n (%)	13/17 (76.5)	7/17 (41.2)
Patients with AIA negative or missing at baseline, n (%)	108/199 (54.3)	100/195 (51.3)
Patients with treatment-induced AIA, n (%)	49/108 (45.4)	45/100 (45.0)
Median peak titer [a] (1/dil)	8.0	8.0
Q1 ; Q3	8.0 ; 32.0	4.0 ; 16.0
Transient AIA response, n (%)	8/49 (16.3)	2/45 (4.4)
Persistent AIA response, n (%)	10/49 (20.4)	12/45 (26.7)
Indeterminate AIA response, n (%)	31/49 (63.3)	31/45 (68.9)
Patients with at least one positive AIA sample (prevalence) [b], n (%)	140/199 (70.4)	140/195 (71.8)
Patients with treatment-emergent AIA (incidence) [c], n (%)	66/199 (33.2)	62/195 (31.8)
Patients without treatment-emergent AIA, n (%)	131/199 (65.8)	132/195 (67.7)
Inconclusive patients, n (%)	2/199 (1.0)	1/195 (0.5)

AIA: Anti-insulin aspart 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)

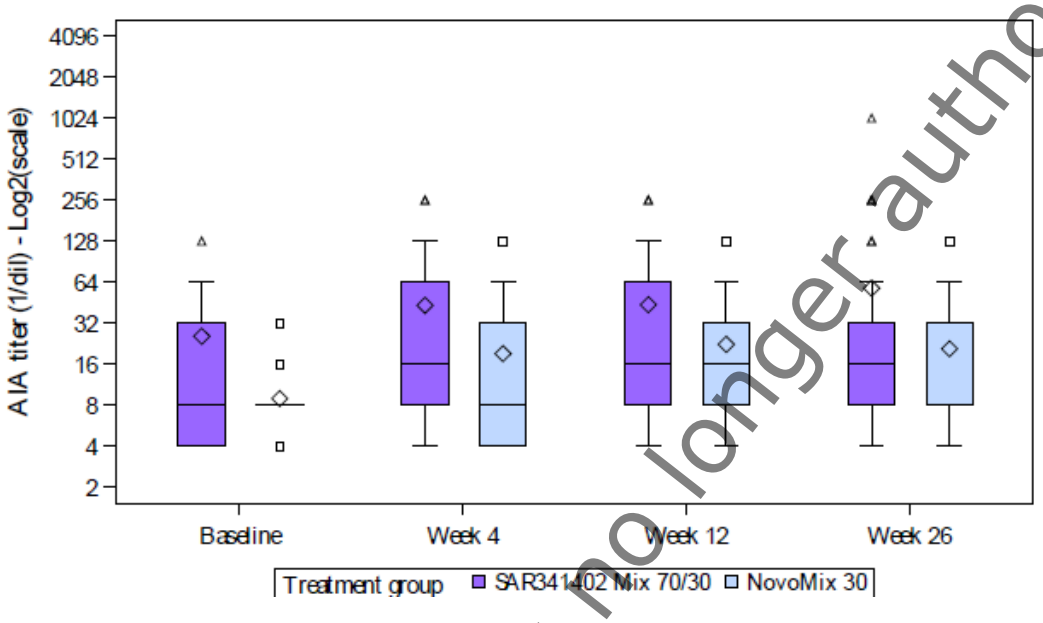
Note: Percentages are calculated using as denominator the number of patients: with positive or negative AIA sample at baseline (for patients with AIA positive at baseline), with AIA positive (resp. negative or missing) at baseline (for treatment-boosted [resp. treatment-induced] AIA), with treatment-boosted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

In the overall AIA population (i.e., including participants with missing AIA sample at baseline), the percentage of participants with positive AIA sample at baseline was similar in the 2 treatment groups (45.7% of participants in the Truvelog Mix 30 group and 48.7% of participants in the NovoMix 30 group) and increased slightly during the 26-week on-treatment period, similarly in the 2 groups. At Week 26, 62.9% of participants in the Truvelog Mix 30 group and 66.5% participants in the NovoMix 30 group were positive for AIA. In participants with positive AIA sample, AIA titers remained generally low. The median AIA titer was

16.0 (1/dil) in both treatment groups throughout the on-treatment period with a maximum interquartile range of 8.0 to 64.0 in the Truvelog Mix 30 group and 8.0 to 32.0 in the NovoMix 30 group.

Boxplots of AIA titers by visit are provided in 16.2.7.2.36 for participants with treatment-emergent AIAs.

Figure 17: Boxplot of AIA titers (1/dil) over time during the on-treatment period for patients with treatment-emergent AIA – AIA population



Among participants positive for AIA at baseline, cross-reactivity to human insulin was found in more than 85% of the participants at baseline. The percentage of participants with antibodies cross-reacting with human insulin was similar between both groups and ranged between 86.7% and 94.1% during the on-treatment period.

The results consistent with the overall population were observed when AIA positivity was analysed in subgroups according to the type of diabetes, prior use of NovoMix 30 and geographic region.

Influence of AIA on safety parameters

Hypoglycaemia

In the subgroup of participants with treatment-emergent AIAs, the percentage of participants with at least one hypoglycaemia was lower in the Truvelog Mix 30 group (60.6%) compared to the NovoMix 30 group (77.4%).

TEAEs and SAEs

The incidence of TEAEs was similar between treatment groups in participants with treatment-emergent AIAs (Truvelog Mix 30 : 9 [13.6%]; NovoMix 30: 10 [16.1%]) and those participants without treatment-emergent AIAs (Truvelog Mix 30 : 27 [20.6%]; NovoMix 30: 30 [22.7%]).

Injection site and hypersensitivity reactions

In participants with treatment-emergent AIAs, no injection site or hypersensitivity reactions were reported in either treatment group while one participant without treatment-emergent AIA in the Truvelog Mix 30 group had hypersensitivity reaction (PT: pruritus).

Neutralizing anti-insulin aspart antibody data

Similar percentages of participants had detectable NAbs at baseline in the 2 treatment groups (Truvelog Mix 30 : 3.8% [7/185 participants]; NovoMix 30 group: 5.7% [10/176 participants]). During the 26-week on-treatment period, the percentage of participants with a treatment-emergent NAb response (i.e., with treatment-induced or treatment-boosted NAb) was similar in the 2 treatment groups (Truvelog Mix 30 : 8.0% [16/199]; NovoMix 30: 8.2% [16/195]). The percentages of participants positive for NAb at least at one time-point between baseline and Week 26 were similar in the 2 treatment groups (Truvelog Mix 30 : 11.6% [23/199 participants]; NovoMix 30 group: 13.3% [26/195 participants]). Among participants with treatment-emergent NAbs, none of the participants had detectable NAbs at baseline in both treatment groups, i.e. all had treatment-induced NAb. The median peak NAb titer in both treatment groups was 20.0 (1/dil).

Impact of COVID-19 pandemic

The percentage of participants AIA positive at baseline or with detectable AIAs at least at one time point during the study (prevalence) was comparable between the participants with and without COVID-19 impact and between the treatment groups.

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to AES

During the on-treatment period, no TEAEs leading to permanent treatment discontinuation were reported in either treatment group in study EFC15082.

In study PDY15084, one participant had a fall (reported as a TEAE) which led to a TEAE of contusion (not considered related to study treatment) following administration of SAR341402 rapid-acting solution; these events led to discontinuation of the participant from the study, and thus, this participant only received IMP from the first treatment period (SAR341402 rapid-acting solution) during the study.

Post marketing experience

N/A

2.5.9. Discussion on clinical safety

In order to compare the safety of biosimilar medicinal product Truvelog Mix 30 with reference NovoMix 30, applicant submitted safety data from 2 studies – PK/PD study PDY15084 and phase 3 efficacy study EFC15082. As the phase 3 study had 400 patients enrolled for safety assessment compared to the PK/PD study with only 52 participant, the main safety assessment is based on phase 3 study. Safety results from the PK/PD study are considered to be supportive only. All the results mentioned below come from phase 3 study EFC15082.

With regard to the **patient exposure**, the safety data from phase 3 study were available for 203 patients in Truvelog Mix 30 group and 197 patients in NovoMix 30 group. The treatment lasted for more than 25 weeks for the majority of the participants and the duration of the exposure was similar in both groups. Around 48% of population had an exposure between 26 to 34 weeks. There is no safety information available on exposure >12 months. Hence the safety database is considered limited with regards to long term use which is foreseen for majority of the treated population. This is, however, acceptable for the evaluation of similarity and in line with the Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues EMEA/CHMP/BMWP/2005_Rev.1).

The percentage of participants experiencing **TEAEs** was similar in the Truvelog Mix 30 group and the NovoMix 30 group (17.7% vs. 20.8%). The most frequently reported TEAEs in either treatment group were Infections and Infestations (Truvelog Mix 30 : 6.9%; NovoMix 30 11.7%), at the PT level nasopharingitis and upper respiratory tract infection. No TEAEs were considered as treatment related by the investigator. As there was a COVID-19 pandemic during the study, applicant assessed its impact on the safety results. No TEAEs were reported as related to COVID-19 (i.e., no COVID-19 illness) in either treatment group. The incidence of TEAEs was similar in the 2 treatment groups, regardless of trial impact (disruption) due to COVID-19.

Serious TEAEs were reported by a low and similar percentage of participants in the Truvelog Mix 30 group (1.0%) and the NovoMix 30 group (1.5%). None of these SAEs was judged to be treatment related. Also, 2 **deaths** occurred in this study, both were in NovoMix 30 group and none was considered related to the IMP.

The incidence of any **hypoglycaemia** was similar between the two treatment groups (62.1% in the Truvelog Mix 30 group and 70.1% in the NovoMix 30 group). However, when divided into subgroups, patients with T1DM had higher incidence in documented symptomatic hypoglycaemia (54.7% in the Truvelog Mix 30 group vs. 47.1% in the NovoMix 30 group for ≤3.9 mmol/l and 49.1% in the Truvelog Mix 30 vs. 37.3% in the NovoMix 30 group for ≤3.0 mmol/l) and for asymptomatic hypoglycaemia (45.3% in the Truvelog Mix 30 group vs. 33.3% in the NovoMix 30 group for ≤3.0 mmol/l).

Similar results were observed for participant-year exposure - the rate of "any" hypoglycaemia was similar in the 2 treatment groups (Truvelog Mix 30 : 12.62 events per participant-year of exposure; NovoMix 30: 13.43 events per participant-year of exposure). However, for documented symptomatic hypoglycaemia (<3.0 mmol/L (54 mg/dL) there were values numerically higher in the Truvelog Mix 30 group (283 [2.59]) compared to the NovoMix 30 group (144 [1.36]). Numerically higher values were also observed for subgroup of T1DM patients in categories any hypoglycaemia, documented symptomatic hypoglycaemia and asymptomatic hypoglycaemia, and for subgroup T2DM in categories documented symptomatic hypoglycaemia (<3.0 mmol/L), asymptomatic hypoglycaemia (<3.0 mmol/L) and probable symptomatic hypoglycaemia. The rate ratio for documented symptomatic hypoglycaemia (<3.0 mmol/L (54 mg/dL) also favoured NovoMix30 (RR=1.84; 95% CI: 1.08 to 3.15). This is also obvious in the hourly rate of documented symptomatic

hypoglycaemia < 3.0 mmol/L (54 mg/dL) per patient-year during the on-treatment period and the cumulative mean number of events per participant during the on-treatment.

The applicant submitted justification that this numerical difference between treatment groups was driven by 6 participants in the Truvelog Mix 30 group (5 with T1DM and 1 with T2DM, each reporting ≥20 events) who reported in total 155 out of 283 hypoglycaemia events in this category; while no participant reported more than 13 events in the NovoMix 30 group. Out of the 155 documented symptomatic hypoglycaemia events (<3.0 mmol/L (54 mg/dL)) reported by the 5 participants with T1DM, 139 showed evidence of at least one precipitating factor i.e., missed, delayed or smaller meal and/or physical activity. No relationship between race, age group, sex, baseline BMI, baseline eGFR, screening HbA_{1c}, prior use of NovoMix 30, geographical region or duration of diabetes and the number of documented symptomatic hypoglycaemia events was found in the 5 participants with T1DM. These 5 participants reported a maximum of 1.34 events per patient-week for documented symptomatic hypoglycaemia (<3.0 mmol/L (54 mg/dL)), and a maximum of 2.26 events per patient-week for documented symptomatic hypoglycaemia (≤3.9 mmol/L (70 mg/dL)). The applicant claims that this is consistent with the data from the literature where an average of 2 episodes of symptomatic hypoglycaemia per week was reported in patients with type 1 diabetes (Cryer PE. Hypoglycaemia in type 1 diabetes mellitus. Endocrinol Metab Clin North Am. 2010 Sep;39(3):641-54). None of the hypoglycaemia events were severe (defined as an event requiring assistance), none met the definition of serious adverse event and none of these 5 participants permanently discontinued treatment due to hypoglycaemia events. It is also possible that the open label design of Study EFC15082 could have had an impact on hypoglycaemia events, that is, patients on IMP may have been more likely to measure blood glucose if experiencing feelings of hypoglycaemia. In addition, the study was not powered to show equivalence with regard to hypoglycaemia rate and treatment groups may not have been balanced with regard to hypoglycaemia risk.

Post-hoc sensitivity analyses excluding these 6 participants from Truvelog Mix 30 group showed similar results between treatment groups for number of events and event rates per participant-year of exposure across all hypoglycaemia categories, including documented symptomatic hypoglycaemia (<3.0 mmol/L). After the exclusion of 6 participants, the rate ratio for Truvelog Mix 30 versus NovoMix 30 was close to 1 for all categories of hypoglycaemia, including documented symptomatic hypoglycaemia (<3.0 mmol/L [54 mg/dL]; rate ratio=0.92; 95% CI: 0.58 to 1.47).

Considering other **adverse events of interest**, no injection site reaction, pregnancy or symptomatic overdose with IMP were observed. One TEAE of hypersensitivity reaction was observed in the Truvelog Mix 30 group in study EFC15082, however, it was not evaluated as allergic reaction. No clinically relevant differences were observed between patients receiving Truvelog Mix 30 or NovoMix 30 in **laboratory parameters**. Also, no treatment relevant **discontinuation** was observed.

In **immunogenicity** assessment, similar percentages of participants in the 2 treatment groups had detectable AIAs at baseline (Truvelog Mix 30 : 49.2%; NovoMix 30: 54.0%). The percentage of participants with a treatment-emergent AIA response during the 26-week on-treatment period was also similar between Truvelog Mix 30 (33.2%) and NovoMix 30 (31.8%), with risk difference 1.7% (90% CI: -5.90 to 9.22). No relevant differences in terms of duration of the AIA response (transient or persistent) could be observed between the two treatment groups. Also, no relevant differences in baseline antibodies or treatment-emergent antibodies were seen in different subgroups according to the type of diabetes, prior use of NovoMix 30 and geographic region. No influence of AIA on safety parameters (hypoglycaemia, TEAEs and SAEs, injection site and hypersensitivity reactions) was detected.

Percentages of participants with detectable NAbs at baseline was numerically higher in NovoMix 30 group (Truvelog Mix 30 : 3.8%; NovoMix 30 group: 5.7%). The percentage of participants with a treatment-emergent NAb response was similar in the 2 treatment groups.

Also, results showed that trial disruption due to COVID-19 had a limited impact on AIA response.

In general, the safety parameters of Truvelog Mix 30 and NovoMix 30 were comparable, with the exception of hypoglycaemic events and AIA titres mentioned above.

2.5.10. Conclusions on the clinical safety

The submitted data show the similarity of safety profiles between Truvelog Mix 30 and NovoMix 30.

2.6. Risk Management Plan

2.6.1. Safety concerns

Summary of safety concerns

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

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

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

None.

2.6.4. Conclusion

The CHMP considers that the risk management plan version 2.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. 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.

2.7.2. Periodic Safety Update Reports submission requirements

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

2.8. Product information

2.8.1. 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 NovoMix 30. The bridging report submitted by the applicant has been found acceptable.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

This procedure concerns a marketing authorisation application for Truvelog Mix 30 (soluble insulin aspart/protamine-crystallised insulin aspart in the ratio 30/70; 100 U/ml) according to the Article 10(4) of Directive 2001/83/EC. The reference medicinal product is NovoMix 30 suspension for injection, marketed by Novo Nordisk and authorised in the EU since 2000.

The proposed indication is the same as for the NovoMix 30:

Truvelog Mix 30 is indicated for treatment of diabetes mellitus in adults, adolescents and children aged 10 years and above.

Quality

A comprehensive analytical comparability study was performed to evaluate analytical similarity between Truvelog Mix 30 and the EU reference product NovoMix 30. The applicant's strategy to establish similarity of Truvelog Mix 30 with the EU reference product NovoMix 30 is endorsed. The attributes tested in the biosimilarity study cover all attributes relevant for the analytical comparison.

Non-clinical pharmacology

Several complementary functional assays were utilised to assess SAR341402 biological activity. The assays used included binding to human insulin receptor (IR-A and IR-B, respectively), including on-off kinetics and

receptor autophosphorylation, binding and activation of IGF-1 receptor, potency for induction of metabolic activities as well as mitogenic activity. *In vivo* pharmacological activity of SAR341402 was assessed as part of the two 1-month repeat-dose toxicity studies in rats and a local tolerability study in rabbits. Within the non-clinical programme, no investigation with Truvelog Mix 30 formulation in comparison with the reference medicinal product NovoMix was performed since aspart-protamine contains the same active substance as SAR341402, thus the same action on the pharmacological targets of insulin is expected. The applicant's justification for using Insulin Aspart SAR341402 drug substance in comparison to EU NovoRapid/US NovoLog in non-clinical comparability studies is considered acceptable. The applicant's strategy to establish similarity of SAR341402 with the references EU NovoRapid/US NovoLog is endorsed.

Clinical

Clinical development programme consisted of one PK/PD study (PDY15084) and one Phase 3 study (EFC15082) to compare efficacy, safety and immunogenicity of Truvelog Mix 30.

Study PDY15084

This study was a randomised, double-blind, 4-treatment, cross-over study to compare PK, PD and tolerability of Truvelog Mix 30 to NovoLog Mix 70/30 (US), NovoMix 30 (EU) and SAR341402 rapid-acting solution in participants with Type 1 diabetes mellitus (T1DM) using the euglycaemic clamp technique and was conducted in 2 cohorts. The performance of the euglycaemic clamp study in T1DM patients to demonstrate similarity is in accordance with the Guideline on the non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005_Rev 1).

Study EFC15082

This was a Phase 3, 26-week, randomised, open-label, parallel group study comparing Truvelog Mix 30 to NovoMix 30 in adult participants with type 1 or type 2 diabetes mellitus using pre-mix insulin analogues. According to the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005_rev.1), there is no need for specific efficacy studies since HbA1c is not considered sensitive enough to detect potentially clinically relevant differences between two insulins. Therefore, the efficacy study submitted is considered supportive only, while PK/PD study PDY15084 is pivotal to demonstrate comparable efficacy of the two insulin products. With regard to the safety assessment of biosimilarity, the focus should be on immunogenicity assessment. Due to the patient exposure and its duration, the study EFC15082 is appropriate to demonstrate the comparability between the two insulin products in terms of safety and immunogenicity assessment.

3.2. Results supporting biosimilarity

Quality

The analytical comparability study demonstrates analytical comparability between the test and the reference product with respect to insulin aspart protein structural features and its impurity profile as well as with regard to the drug product formulation.

Non-clinical pharmacology

The results demonstrate that the biological activity of the Insulin Aspart in SAR341402, NovoRapid and NovoLog are comparable in terms of IR-A and IR-B receptor binding and activation, the capability of receptor activated

inhibition of lipolysis in human adipocytes, suppression of gluconeogenesis in hepatic cells and glucose uptake into myocytes, which are the primary mechanisms of action, as well as IGF-1R receptor activation and induction of proliferation of human adenocarcinoma cells. Similarity in biological activity is considered to be demonstrated.

In the toxicological studies TSA1504 and TSA1518, similar exposure, in terms of Cmax and AUC0-8, was observed for equivalent doses of SAR341402, NovoRapid and NovoLog.

Clinical

PK/PD

Study **PDY15084** demonstrated similar PK profiles between Truvelog Mix 30 and NovoMix 30. The 90% confidence intervals of the treatment ratios for the primary PK parameters, INS-C_{max} and INS-AUC_{last} (0.85 to 1.00 and 0.91 to 1.07, respectively) were within the predefined acceptance range (0.8 to 1.25). These results were supported by the secondary PK endpoints.

All 90% CIs of INS-AUC, INS-$AUC_{0-24h,}$ INS-$AUC_{(0-4h)}$ and INS-AUC_{4-24h} included unity. The results for INS-AUC, INS-AUC_{0-24h} and post-hoc calculated INS-AUC_{0-12h} showed that the total exposure of Truvelog Mix 30 and the reference products can be deemed as similar.

Safety

The percentage of participants experiencing TEAEs was similar in the Truvelog Mix 30 group and the NovoMix 30 group. Serious TEAEs were reported by a low and similar percentage of participants in the Truvelog Mix 30 group and the NovoMix 30 group.

No increased immunogenicity of Truvelog Mix 30 compared to NovoMix 30 was observed. The percentage of participants with a treatment-emergent AIA response during the 26-week on-treatment period was similar between Truvelog Mix 30 and NovoMix 30. No clinically relevant differences in terms of duration of the AIA response (transient or persistent) could be observed between the two treatment groups.

3.3. Uncertainties and limitations about biosimilarity

Quality

Based on the results presented for analytical comparability, specifics of the test product and the reference product observed in particle size distribution and crystal length are considered negligible. There is no doubt on analytical similarity between test product and reference product with respect to insulin aspart protein structural features and its impurity profile as well as with respect to the formulated drug product. Analytical similarity between Truvelog Mix 30 and NovoMix 30 can be firmly concluded.

Clinical

PK/PD

The study **PDY15084** was primarily designed to demonstrate PK similarity of the biphasic preparation Truvelog Mix 30 with the reference products NovoLog Mix 70/30 and NovoMix 30.

Study was neither designed nor powered to formally demonstrate PD similarity between Truvelog Mix 30 and the reference products. PD endpoints were included as secondary objectives. For PD paramaters, 95% CIs for

GIR_{max} and $GIR\text{-}AUC_{0\text{-}24h}$ were calculated additionally to the 90% CIs for the PK endpoints to fulfil the EU guideline criteria and yielded the following results:

GIR_{max}, SAR Mix / NovoMix: 0.90 (0.75 to 1.07)

$GIR\text{-}AUC_{0\text{-}24h}$ SAR Mix / NovoMix: 0.93 (0.77 to 1.12).

Although evaluation of PD parameters is not a strict requirement for a new biosimilar insulin formulation containing an active ingredient that is already licensed as part of another biosimilar insulin formulation, PD data, if presented, are expected to "reasonably" support PK results (Guideline on nonclinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues. EMEA/CHMP/BMWP/32775/2005 Rev.1).

The available PD data suggested slight differences between Truvelog Mix 30 and the EU reference product NovoMix 30. The relevance of these clinical findings has been discussed by the applicant and justified by greater variability in PK and PD of insulin premixes in comparison to rapid acting insulin, by low dose of rapid acting insulin component which represent only a dose of 0.09 U/kg from the whole administered dose of 0.3 U/kg of the premix formulation. Moreover, the study was not powered to formally demonstrate equivalence of PD parameters. Since the evaluation of PD parameters is not a strict requirement for a new biosimilar insulin formulation containing an active ingredient that is already licensed as part of another biosimilar insulin formulation and since close similarity in physicochemical and functional characteristics and PK profiles has been shown, this issue is considered to be solved.

Efficacy

For the comparative study **EFC15082,** which is not a requirement for the proof of similar efficacy of the biosimilar insulin candidate, the primary objective was formally not met. The non-inferiority margin of 0.3 in HbA1c was not met for Truvelog Mix 30 compared to NovoMix 30 in the ITT population. The LS mean difference between Truvelog Mix 30 and NovoMix 30 was 0.08 (95% CI: 0.139 to 0.303). This was remedied by exclusion of one outlier, after which the primary endpoint was met. Although this can be attributed to an unforeseen event, i.e. the respective patients experienced a substantial increase in HbA1c due to running out of study medicinal product during the pandemic, post hoc analyses not predefined in the study protocol are generally not acceptable. However, in this case equivalence with regard to HbA1c results are not a requirement for authorisation and therefore, the exclusion of this outlier was accepted and the issue was not pursued further.

Safety

Although the overall hypoglycaemia rate was similar, patients with T1DM had higher incidence in documented symptomatic hypoglycaemia and asymptomatic hypoglycaemia in Truvelog Mix 30 compared to NovoMix group. According to the applicant, this was driven by 5 participants reporting more than 20 events of hypoglycaemia, each. No relationship between race, age group, sex, baseline BMI, baseline eGFR, screening HbA_{1c}, prior use of NovoMix 30, geographical region or duration of diabetes and the number of documented symptomatic hypoglycaemia events was found in these 5 participants. Evaluation showed that in all 5 participants most of the symptomatic hypoglycaemia events were related to standard confounding factors such as physical activity, missed, delayed or smaller meals, alcohol consumption and deviation from dosing instruction (mismatch in the timing or amount of insulin). Furthermore, the frequency of hypoglycaemia experienced by these 5 patients were not above the frequency of hypoglycaemia in T1DM patients reported in the literature. Therefore, this issue is considered related to precipitating factors and not product-related.

3.4. Discussion on biosimilarity

Based on the results of the analytical comparability study, analytical similarity between Truvelog Mix 30 and NovoMix 30 can be firmly concluded.

Based on the PK/PD euglycaemic clamp study, the applicant has demonstrated PK comparability for relevant PK parameters (INS-C_{max}, INS-$AUC_{last,}$ INS-AUC, INS-$AUC_{(0\text{-}24h),}$ INS-$AUC_{(0\text{-}4h)}$ and INS-$AUC_{(4\text{-}24h)}$) between Truvelog Mix 30 and NovoMix 30. The available PD data suggested slight differences between Truvelog Mix 30 and NovoMix 30. The applicant provided appropriate justification as to why the post-hoc defined lower equivalence margin was not met and why the small observed differences are not clinically relevant.

The results of the EFC15082 study cannot by itself prove biosimilarity between Truvelog Mix 30 and NovoMix 30, as the HbA1c parameter is not sensitive enough to detect potentially clinically relevant differences between two insulins.

The safety profiles of test and reference can generally be considered similar. The higher incidence of symptomatic hypoglycaemia and asymptomatic hypoglycaemia in Truvelog Mix 30 compared to NovoMix group in T1DM patients is considered to be related to precipitation factors and has been thus sufficiently justified.

Based on the totality of the evidence, including demonstration of close similarity in physicochemical and functional characteristics and in PK profiles, the notion that PD parameters are not a strict requirement for a new biosimilar insulin formulation containing an active ingredient that is already licensed as part of another biosimilar insulin formulation as well as the accepted justification that the small differences in PD parameters are not clinically relevant, biosimilarity between Truvelog Mix 30 and the reference insulin NovoMix 30 can be concluded.

3.5. Extrapolation of safety and efficacy

N/A

3.6. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Truvelog Mix 30 is considered biosimilar to NovoMix 30. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Truvelog Mix 30 is not similar to Amglidia within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Truvelog Mix 30 is favourable in the following indication:

Truvelog Mix 30 is indicated for treatment of diabetes mellitus in adults, adolescents and children aged 10 years and above.

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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.