BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	351(k)
Application Number	BLA 761325
Received Date	September 8, 2022
BsUFA Goal Date	September 8, 2023
Division/Office	Division of Diabetes, Lipid Disorders, and Obesity/ Office of Cardiology, Hematology, Endocrinology, and Nephrology
Review Completion Date	See DARRTS stamped date
Product Code Name	SAR341402
Proposed Nonproprietary Name[1]	Insulin aspart-szjj
Proposed Proprietary Name[1]	Merilog and Merilog SoloStar
Pharmacologic Class	Rapid acting human insulin analog
Applicant	Sanofi-aventis U.S. LLC
Applicant Proposed Indication(s)	To improve glycemic control in adults and pediatric patients with diabetes mellitus
Recommendation on Regulatory Action	Complete Response

[1]Section 7 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

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OBP = Office of Biotechnology Products
OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error and Prevention Analysis
DRISK = Division of Risk Management
DPMH = Division of Pediatric and Maternal Health

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
AE	Adverse Event
AIA	Anti-insulin aspart antibody
ARAC	Allergic Reaction Assessment Committee
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CAA	Clinical analytical assessment
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CSII	Continuous subcutaneous insulin infusion
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DIA	Division of Inspectional Assessment
DMC	Data Monitoring Committee
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
DP	Drug product
DS	Drug substance
eCTD	Electronic Common Technical Document
EPR	Essential Performance Requirements
E.U.-NovoRapid	European Union-approved NovoRapid
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFU	Instructions for use

IMP	Investigational medical product
IND	Investigational New Drug
IRB	Institutional review board
ITT	Intention to Treat
IV	Intravenous
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat
MOA	Mechanism of Action
NAb	Neutralizing Antibody
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
NIM	Non-inferiority margin
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PI	Prescribing information
PFP	Pre-filled pen
PK	Pharmacokinetics
PT	Preferred term
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SMPG	Self-monitored plasma glucose
SOC	System Organ Class
SOP	Standard Operating Procedures
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation
U.S.-Novolog	U.S.-licensed Novolog
USPI	U.S. Prescribing Information

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1. Executive Summary

1.1. Product Introduction

Sanofi-aventis U.S. LLC (hereafter referred to as Sanofi or "the Applicant") submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for SAR341402 as a proposed biosimilar to U.S.-licensed NovoLog (insulin aspart, BLA 020986). SAR341402 (proposed non-proprietary name insulin aspart-szjj; proposed proprietary name Merilog) is a rapid acting human insulin analog. The sequence of SAR341402 and U.S.-licensed NovoLog (U.S.-NovoLog) is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28. SAR341402 is produced by recombinant DNA technology using non-pathogenic laboratory strain of *Escherichia coli* as the production organism. SAR341402 is supplied at 100 units/mL (U-100) in a 3 mL single-patient use pre-filled pen for subcutaneous (SC) injection based on the Sponsor's SoloStar pen-injector platform. SAR341402 is also supplied at U-100 in a 10 mL multiple-dose vial for SC injection.

The Applicant is seeking licensure of SAR341402 for the following indication for which U.S.-NovoLog has been previously approved:

- to improve glycemic control in adults and pediatric patients with diabetes mellitus.

1.2. Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

Not applicable.

1.3. Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

The primary activity of insulin and its analogs, including U.S.-NovoLog, is the regulation of glucose metabolism through binding and activation of insulin receptors. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.

Comparative analytical testing including multiple orthogonal assays relevant to the mechanism of action of U.S.-NovoLog, plus comparative clinical pharmacodynamic (PD) data evaluating regulation of glucose metabolism, demonstrated that SAR341402 has the same mechanism of action as that of U.S.-NovoLog, to the extent known.

SAR341402 is proposed as below:

ROUTE OF ADMINISTRATION: subcutaneous injection (pen and vial)

DOSAGE FORM: injection

STRENGTH: 300 units per 3 mL single-patient use pre-filled pen and 1000 units per 10 mL multiple-dose vial; concentration 100 units/mL (U-100)

Each strength of SAR341402 in the pre-filled pen and the vial is the same as that of U.S.-NovoLog. SAR341402 also has the same dosage form and route of administration as that of U.S.-NovoLog.

Additionally, the condition(s) of use for which the Applicant is seeking licensure have been previously approved for U.S.-NovoLog.

1.4. Inspection of Manufacturing Facilities

All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. Based on the assessment of manufacturing site records using the Agency's authority under section 704(a)(4) of the FD&C Act, it was concluded that the Sanofi-Aventis Deutschland GmbH drug substance and drug product manufacturing facility was acceptable to support the approval of BLA 761325 and an on-site inspection was not necessary.

1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

Not applicable.

1.6. Biosimilarity Assessment

Table 1. Summary and Assessment of Biosimilarity

Comparative Analytical Studies[2]

[2]Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter therein for additional information regarding comparative analytical studies.

Summary of Evidence	○ SAR341402 is highly similar to U.S.-licensed Novolog, notwithstanding minor differences in clinically inactive components. SAR341042 has the same strengths, dosage form, and route of administration as those of U.S.-licensed Novolog. The Applicant used a comprehensive array of analytical methods that were suitable to evaluate critical quality attributes of SAR341402 and U.S.-licensed Novolog to support the demonstration that the products are highly similar. While differences were observed in a limited number of attributes, these do not preclude a demonstration that SAR341042 is highly similar to U.S.-licensed Novolog.
Assessment of Residual Uncertainties	○ There are no residual uncertainties from the product quality assessment.
Animal/Nonclinical Studies	
Summary of Evidence	○ In vitro studies evaluating the insulin receptor (IR) and insulin-like growth factor-1 (IGF-1) receptor binding, IR activation, metabolic activity, and mitogenic activity (IR- and IGF-1 receptor dependent) of SAR341402 and U.S.-Novolog demonstrated SAR341402 to be similar to U.S.-Novolog. ○ In vitro studies support the demonstration of biosimilarity.
Assessment of Residual Uncertainties	○ There are no residual uncertainties from the pharmacology/toxicology perspective.
Clinical Studies	
Clinical Pharmacology Studies	

Summary of Evidence	○ The pharmacokinetic (PK) and pharmacodynamic (PD) similarity between SAR341402 and US-licensed Novolog was demonstrated in adult patients with Type 1 Diabetes Mellitus (Study PDY12695) ○ PK and PD data from Study PDY12695 add to the totality of the evidence to support a demonstration of no clinically meaningful differences between SAR341402 and US-licensed Novolog
Assessment of Residual Uncertainties	○ There are no residual uncertainties from the clinical pharmacology perspective.
Additional Clinical Studies	
Summary of Evidence	○ FDA determined that, based on the information in the application, including the applicant's immunogenicity assessment, a comparative clinical study comparing SAR341402 and U.S.-NovoLog is not necessary in this 351(k) application. ○ The Applicant submitted immunogenicity, safety, and efficacy results comparing SAR341402 to U.S.- NovoLog (Study EFC15081). No clinical data comparing SAR341402 to U.S.-NovoLog, other than the PK/PD data from euglycemic clamp study PDY12695 were necessary to support a demonstration of biosimilarity of SAR341402 and U.S.-NovoLog. The additional data provided by the Applicant that were not necessary to evaluate biosimilarity of SAR341402 and U.S.-NovoLog did not preclude or conflict with conclusions based on other data or information.
Assessment of Residual Uncertainties	○ There are no residual uncertainties from the clinical perspective.
Extrapolation	

Summary of Evidence	○ The information submitted in the application, including the comparative analytical data and the PK/PD results (which together demonstrate that the mechanism of action (MOA) is the same in SAR341402 and U.S.-NovoLog, to the extent known) support a demonstration that SAR341402 and U.S.-NovoLog are highly similar, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences in terms of safety, purity, and potency. ○ An extrapolation of the finding of PK similarity of SAR341402 and U.S.-NovoLog in adult patients with T1D to adult and pediatric patients with diabetes mellitus (T1D and T2D) is justified because the same scientific factors that determine absorption, distribution, metabolism, and elimination in adult patients with T1D also determine absorption, distribution, metabolism, and elimination in adult and pediatric patients with diabetes mellitus. The extrapolation of the finding of PD similarity of SAR341402 and U.S.-NovoLog in adult patients with T1D to adult and pediatric patients with diabetes mellitus (T1D and T2D) is justified because the assessed PD endpoints evince the binding and activation of insulin receptors, which is the pertinent MOA for all conditions of use of U.S.-NovoLog (to the extent known). No comparison of any other scientific factors across the conditions of use were necessary to justify the extrapolation. The extrapolation does not require specific knowledge about the relationship between the PK and PD profiles observed in adults with T1D and the PK and PD profiles that would be observed in adult and pediatric patients with diabetes mellitus (T1D and T2D).

	○ The data and information in the application, including comparative PK and PD data demonstrating no meaningful differences in time-concentration profile and time-action profile over the duration of action of each product from Study PDY12695, support licensure for the conditions of use for which U.S.- NovoLog has been previously approved and for which the Applicant is seeking licensure. ○ The information submitted by the Applicant demonstrates that SAR341402 3 mL SoloStar pen is biosimilar to U.S.-NovoLog 3 mL Flexpen for the following indication (including all of the indicated patient populations) for which the Applicant is seeking licensure and for which U.S.-NovoLog 3 mL FlexPen has been previously approved: to improve glycemic control in adults and pediatric patients with diabetes mellitus. ○ The information submitted by the Applicant demonstrates that SAR341402 10 mL vial is biosimilar to U.S.-NovoLog 10 mL vial for the following indication (including all of the indicated patient populations) for which the Applicant is seeking licensure and for which U.S.-NovoLog 10 mL vial has been previously approved: to improve glycemic control in adults and pediatric patients with diabetes mellitus.
Assessment of Residual Uncertainties	○ There are no residual uncertainties from the clinical perspective.

1.7. Conclusions on Approvability

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that SAR341402 is highly similar to U.S.-NovoLog, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between SAR341402 and U.S.-NovoLog in terms of the safety, purity, and potency of the product. The information submitted by the Applicant, including adequate

justification for extrapolation of data and information, demonstrates that SAR341402 is biosimilar to U.S.-NovoLog for each of the following indications for which U.S.-NovoLog has been previously approved and for which the Applicant is seeking licensure of SAR341402: to improve glycemic control in adults and pediatric patients with diabetes mellitus.

However, data submitted in this application is not sufficient to support a conclusion that the manufacture of SAR341402 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. Therefore, the FDA review team recommends a Complete Response for this application, and the CDTL/ Division Signatory agree with that recommendation. The Complete Response Letter will outline the deficiencies and the information and data required to address the deficiencies.

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2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

Sanofi originally intended to submit a 505(b)(2) application for SAR341402 that would rely, in part, on FDA's finding of safety and effectiveness for U.S.- NovoLog. To that end, Sanofi had opened Pre-IND (PIND) (b) (4) for SAR341402 in December 2011 for which Written Responses were issued on May 25, 2012. A subsequent Type C meeting request resulted in Written Responses on December 5, 2012. Due to inactivity, the file for PIND (b) (4) was administratively withdrawn by the FDA on February 20, 2014.

On February 7, 2017, Sanofi notified the FDA that it was restarting the development of SAR341402 (as a drug) and requested a PIND meeting under PIND 133678. The meeting was granted, and Written Responses were issued on April 7, 2017. On May 31, 2017, Sanofi submitted a phase 3 clinical study protocol (Study EFC15081) to IND 133678, and the FDA issued a letter on August 8, 2017, containing non-hold comments for the protocol and clarifications on FDA's prior advice contained in the April 7, 2017, Written Responses. Study EFC15081 was titled, "Six-month, Randomized, Open-label, Parallel-group Comparison of SAR341402 to NovoLog/NovoRapid in Adult Patients with Diabetes Mellitus Also Using Insulin Glargine, with a 6-month Safety Extension Period."

On August 4, 2017, Sanofi submitted a Biosimilar Biological Product Development (BPD) Type 2 meeting request and meeting background package to PIND 136342 in order to obtain advice on the acceptability of its development program for SAR341402 to support a 351(k) Biologics License Application (BLA), in the event it would not obtain approval of its proposed 505(b)(2) application by the March 23, 2020, transition date

when insulin products previously approved as drugs would be deemed to be biologic products. Sanofi also sought advice on the design of a study intended to support a (b) (4) The following is a summary of the presubmssion regulatory history for SAR341402 under IND 136342:

November 7, 2017: BPD Type 2 meeting was held to discuss Sanofi's proposal for developing SAR341402 as (b) (4) biosimilar to U.S.-licensed NovoLog. Multidisciplinary advice was conveyed during this meeting (i.e., CMC, device, nonclinical, clinical pharmacology, clinical and statistical). Sanofi had already initiated Study EFC15081, based on prior advice received by the Agency under IND 133678.

- FDA advised Sanofi that to support 351(k) application, EFC15081 should be designed with the primary objective of addressing remaining residual uncertainty following conduct of the analytical and the PK/PD studies and support a demonstraton that there is no clinically meaningful differences between SAR341402 and U.S-NovoLog. The study should therefore be designed to allow an adequate evaluation of the following endpoints: immunogenicity, adverse reactions, measure of glycemia lowering, and other clinically meaningful measures.
- FDA recommend the following in terms of data collection: PK/PD endpoints, HbA1c, anti-insulin aspart antibodies (AIAs), neutralizing antibodies (nAbs) at baseline, 1 month, 3 months and 6 months. Sanofi was advised to accurately capture insulin dose by 'prandial,' 'basal,' and 'total' daily doses, using descriptive statistics, as insulin dose is also an important metric to assess the clinical significance of AIAs and nAbs.
- FDA also recommended that Sanofi enroll subjects from the T1D population because it is more sensitive than the T2D population to detect differences in immunogenicity.
- In their post meeting comments, FDA stated that it intends to consider the totality of the data collected during EFC1508 in its review of the comparative study; however, formal statistical testing for immunogenicity and HbA1c is reasonable. FDA also stated that a 500-patient study should be adequate in size to provide 80% power to test the difference between the proposed biosimilar and intended reference product for a range of anticipated event rates and corresponding similarity margins.
- FDA declined to discuss Sanofi's (b) (4) until agreement could be reached on Sanofi's approach to demonstrating biosimilarity.

November 14, 2018: Sanofi submitted an IND opening study protocol for switching study EFC15178 to support the development of SAR341402, as (b) (4) biosimilar to U.S.- NovoLog with plans to submit the BLA application under section 351(k) of the Public Health Service Act.

January 18, 2019: BPD Type 2 Written Responses were issued conveying advice regarding efficacy, safety, and immunogenicity information obtained from the main 6-month treatment period of study EFC15081 entitled, "Six-month, Randomized, Open-

label, Parallel-group Comparison of SAR341402 to NovoLog/NovoRapid in Adult Patients with Diabetes Mellitus Also Using Insulin Glargine, with a 6-month Safety Extension Period". (b) (4)

(b) (4)

(b) (4)

- [redacted]
- [redacted]
- [redacted]
- [redacted]

January 26, 2019: FDA issued non-hold comments for Sanofi submitted Protocol EFC15178 (b) (4) Sanofi was advised that additional information would be required for their SAR341402 NAb detection assay validation. FDA requested that Sanofi provide data to demonstrate that the NAb assay performs sufficiently with the intended T1D clinical study patient population.

July 1, 2019: BPD Type 2 meeting was held via teleconference during which Sanofi received the following multidisciplinary advice:

- (b) (4)

November 25, 2019: FDA Advice Letter was issued to the Applicant which referenced information within the newly published draft guidance for industry *Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products* (November 2019)[3] (hereafter referred to as the *'Insulin Immunogenicity Guidance'*). Consistent with this draft guidance, the FDA clarified that a comparative clinical immunogenicity study generally would be considered unnecessary to support a demonstration of biosimilarity for SAR341401 if the comprehensive comparative analytical assessment (CAA) adequately supports a demonstration of "highly similar" to U.S.-NovoLog as part of a demonstration of biosimilarity. FDA still expected the submission of a clinical comparative PK/P study (e.g., euglycemic clamp study). FDA noted that a comparative clinical immunogenicity study may still be necessary as a scientific matter to support licensure, for example, if there are differences in certain impurities or novel excipients that give rise to questions or residual uncertainty related to immunogenicity. FDA stated that, if Sanofi believed that data from a comparative clinical immunogenicity study may not be necessary, FDA recommends that the BLA submission include an immunogenicity assessment justifying why a comparative clinical study to assess immunogenicity is not necessary to support a demonstration of biosimilarity for SAR341402. In addition, FDA noted that its scientific thinking is that if Sanofi is able to demonstrate biosimilarity between SAR341402 and U.S.- Novolog without conducting a comparative clinical immunogenicity study, then generally such a study would not be needed as part of a demonstration that SAR341402 is (b) (4)

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-immunogenicity-considerations-biosimilar-and-interchangeable-insulin-products

December 11, 2019: BPD Type 2 CMC-only meeting was held to discuss data to support a future 351(k) BLA, including process validation, comparability, comparative analytical, and device topics. For Sanofi's pre-filled pen (PFP) injector device, which has a design identical to the currently marketed disposable SoloStar pen except for difference in the appearance (e.g. colors and labels), Sanofi was advised to clearly specify what components of the pen injector are changing from the approved SoloStar and to provide testing or a justification as to why the color changes would not impact the design verification testing.

April 8, 2020: The Agency communicated with Sanofi via email regarding Sanofi's (b) (4) Study Protocol Proposal submitted on February 4, 2020. The following recommendations were provided:

1) (b) (4)

2)

3)

May 4, 2021: BPD Type 2 CMC-only meeting was held to discuss additional information requested by FDA during the December 11, 2019 face-to-face meeting, as well as the Applicant's proposal regarding the threshold analysis for the device constituent part.

- Sanofi was advised that to evaluate the potential presence of unidentified impurities that could impact the safety and efficacy of the drug product, Sanofi should include all SAR341402 cartridge container closure systems manufactured by different suppliers and representative of raw material of all formulations in the evaluation of extractables and leachables.
- (b) (4)

(b) (4)

December 17, 2021: Sanofi submitted an Initial Pediatric Study Plan (iPSP) to the Agency. An Agreed iPSP No Agreement Letter was issued by the Agency on May 5, 2022. Sanofi submitted an iPSP-Other to the Agency on July 15, 2022.

January 24, 2022: BPD Type 4 meeting was held to discuss the planned 351(k) BLA submission for this product.

- Clinical data and immunogenicity assessment: FDA advised Sanofi that, consistent with the *Insulin Immunogenicity Guidance*, if Sanofi believes that data from a comparative clinical immunogenicity study may not be necessary, FDA recommends that the 351(k) BLA submission for SAR341402 include an immunogenicity assessment justifying why a comparative clinical study to assess immunogenicity is not needed to support demonstration of biosimilarity for SAR341402. Sanofi was advised that their submission should specify the proposed purpose of the data included to support their BLA.
- Pediatric extrapolation: FDA advised that in order to obtain an indication for improvement in glycemic control for the broad diabetic population for which U.S.-licensed NovoLog has been previously approved (i.e., adults and pediatric patients with diabetes mellitus), Sanofi must provide scientific justification for the extrapolation of the necessary clinical data relied upon to demonstrate biosimilarity to all indications in the adult and the pediatric populations for which they are seeking biosimilarity and interchangeability. Sanofi was advised that if the only clinical data relied upon to demonstrate biosimilarity of SAR341402 to U.S.-NovoLog is the finding of PK/PD similarity from Study PDY12695, an acceptable scientific justification is that the finding of PK similarity of the two products in adults may be extrapolated to children because the same scientific factors that determine absorption, distribution, metabolism, and elimination in adults determine absorption, distribution, metabolism, and elimination in children and that the finding of PD similarity of the two products in adults may be extrapolated to children because the assessed PD endpoints evince the binding and activation of insulin receptors, which is the pertinent MOA for all conditions of use of U.S.-licensed NovoLog (to the extent known). If the determination of biosimilarity and interchangeability of SAR341402 to U.S.-NovoLog in relies on clinical data beyond the PK and PD data from the euglycemic clamp study, the submission should include additional scientific justification for how those clinical data may be extrapolated to the pediatric population.
- Nonclinical data: Agency advised Sanofi to conduct an additional mitogenicity assay using a cell line that preferentially expresses the insulin receptor over the IGF-1 receptor as a part of a fully comprehensive in vitro comparison of mitogenic risk between SAR341402 and U.S.-NovoLog.
- Device, pen injector: FDA referred Sanofi to feedback provided during May

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April 27, 2022: Advice letter was issued to the Applicant stating that the Agency agreed that the Applicant may submit the additional requested mitogenicity study report (assay measuring cell proliferation of the specific cell line H4IIE) during the filing review period of the BLA.

August 11, 2022: The agency issued the Agreed iPSP Agreement Letter.

September 8, 2022: Applicant submitted 351(k) BLA 761325 for SAR341402 as a proposed biosimilar to U.S.-NovoLog.

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2.2. Studies Submitted by the Applicant

Refer to the Product Quality review, including the Comparative Analytical Assessment (CAA) Chapter for information regarding comparative analytical studies provided to support a demonstration of biosimilarity.

Table 2: Nonclinical Studies

Study Title	Study Number	Study Type	Test System	Test Article(s)
Pharmacology (Primary Pharmacodynamics)				
Comparability study of SAR341402: Binding affinity	DIVT0110	Insulin Receptor-A Binding Kinetics	Biochemical acellular purified protein	SAR341402, E.U.-NovoRapid®,

Study Title	Study Number	Study Type	Test System	Test Article(s)
to the human insulin receptor A				U.S.-NovoLog®
Further comparability study of SAR341402: Binding affinity to the human insulin receptor isoform A	DIVT0139	Insulin Receptor-A Binding Kinetics	Biochemical acellular purified protein	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Determination of binding affinity of SAR341402 to the insulin receptor B	DIVT0016	Insulin Receptor-B Binding Kinetics	Biochemical acellular purified protein	SAR341402, Human insulin, Insulin aspart (commercial formulation; Novo Rapid®)
Determination of binding affinity of SAR341402 to the insulin receptor B	DIVT0024	Insulin Receptor-B Binding Kinetics	Biochemical acellular purified protein	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog® Human insulin
Comparability study of SAR341402: Binding affinity to the human insulin receptor B (Amended Nonclinical Pharmacology Report)	DIVT0111	Insulin Receptor-B Binding Kinetics	Biochemical acellular purified protein	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Further comparability study of SAR341402: Binding affinity to the human insulin receptor isoform B	DIVT0140	Insulin Receptor-B Binding Kinetics	Biochemical acellular purified protein	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Determination of binding affinity of SAR341402 to the IGF-1 receptor	DIVT0017	Insulin Like Growth Factor 1 (IGF-1) Receptor Binding Kinetics	Biochemical acellular purified protein	SAR341402, Insulin, Insulin aspart (commercial formulation; Novo Rapid®)
Determination of binding affinity of SAR341402 to the IGF-1 receptor	DIVT0025	Insulin Like Growth Factor 1 (IGF-1) Receptor Binding Kinetics	Biochemical acellular purified protein	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®, Insulin
Comparability study of SAR341402: Binding kinetics to the human insulin receptor A (Amended Nonclinical Pharmacology Report)	DIVT0112	Insulin Receptor-A Binding Kinetics	Surface plasmon resonance biosensor-based interaction assay	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Further comparability study of SAR341402: Binding kinetics to the human insulin receptor isoform A	DIVT0141	Insulin Receptor-A Binding Kinetics	Surface plasmon resonance biosensor-based interaction assay	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Comparability study of SAR341402: Binding kinetics to the human insulin receptor B (Amended Nonclinical Pharmacology Report)	DIVT0113	Insulin Receptor-B Binding Kinetics	Surface plasmon resonance biosensor-based interaction assay	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Further comparability study of SAR341402: Binding kinetics to the human insulin receptor isoform B	DIVT0142	Insulin Receptor-B Binding Kinetics	Surface plasmon resonance biosensor-based interaction assay	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Comparability study of SAR341402: Binding kinetics to the human IGF-1 receptor (Amended Nonclinical Pharmacology Report)	DIVT0114	Insulin Like Growth Factor 1 (IGF-1) Receptor Binding Kinetics	Surface plasmon resonance biosensor-based interaction assay	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®

Study Title	Study Number	Study Type	Test System	Test Article(s)
Further comparability study of SAR341402: Binding kinetics to the human IGF1 receptor	DIVT0143	Insulin Like Growth Factor 1 (IGF-1) Receptor Binding Kinetics	Surface plasmon resonance biosensor-based interaction assay	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Comparability study of SAR341402: Autophosphorylation of the human insulin receptor A (Amended Nonclinical Pharmacology Report)	DIVT0115	Insulin Receptor-A Phosphorylation	Engineered Chinese Hamster Ovary cells overexpressing insulin receptor-A	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Further comparability study of SAR341402: Autophosphorylation of the human insulin receptor isoform A	DIVT0144	Insulin Receptor-A Phosphorylation	Engineered Chinese Hamster Ovary cells overexpressing insulin receptor-A	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Comparability study of SAR341402: Autophosphorylation of the human insulin receptor B (Amended Nonclinical Pharmacology Report)	DIVT0116	Insulin Receptor-B Phosphorylation	Engineered Chinese Hamster Ovary cells overexpressing insulin receptor-B	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Comparability study of SAR341402 and NovoRapid/NovoLog: Autophosphorylation of human insulin receptor B	DIVT0106	Insulin Receptor-B Phosphorylation	Engineered Chinese Hamster Ovary cells overexpressing insulin receptor-B	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Analysis of Insulin Receptor Autophosphorylation of SAR341402 using CHO-IR cells	DIVT0019	Insulin Receptor-B Phosphorylation	Engineered Chinese Hamster Ovary cells overexpressing insulin receptor-B	Insulin, SAR341402, Insulin aspart (Novo Rapid®, Novo Nordisk)
Comparison of Insulin Receptor Autophosphorylation of SAR341402 with NovoRapid® and NovoLog® using CHO-IR cells	DIVT0022	Insulin Receptor-B Phosphorylation	Engineered Chinese Hamster Ovary cells overexpressing insulin receptor-B	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Further comparability study of SAR341402: Autophosphorylation of the human insulin receptor isoform B	DIVT0145	Insulin Receptor-B Phosphorylation	Engineered Chinese Hamster Ovary cells overexpressing insulin receptor-B	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Comparability study of SAR341402: Autophosphorylation of the human IGF-1 receptor (Amended Nonclinical Pharmacology Report)	DIVT0117	IGF-1 receptor Phosphorylation	Mouse Embryonic Fibroblast cells overexpressing the human IGF1-R	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Comparability study of SAR341402 and NovoRapid/NovoLog: Autophosphorylation of human IGF-1 receptor	DIVT0103	IGF-1 receptor Phosphorylation	Mouse Embryonic Fibroblast cells overexpressing the human IGF1-R	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Analysis of IGF-1 receptor autophosphorylation of SAR341402 using MEF-IGF1R cells	DIVT0021	IGF-1 receptor Phosphorylation	Mouse Embryonic Fibroblast cells overexpressing the human IGF1-R	IGF-1, SAR341402, insulin aspart (Novo Rapid®, Novo Nordisk)

Study Title	Study Number	Study Type	Test System	Test Article(s)
Analysis of IGF-1 Receptor Autophosphorylation of SAR341402 using MEF-IGF1R cells	DIVT0026	IGF-1 receptor Phosphorylation	Mouse Embryonic Fibroblast cells overexpressing the human IGF1-R	IGF-1, SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Further comparability study of SAR341402: Autophosphorylation of the human IGF1 receptor	DIVT0146	IGF-1 receptor Phosphorylation	Mouse Embryonic Fibroblast cells overexpressing the human IGF1-R	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Comparability study of SAR341402: Lipolysis (glycerol release) in human in vitro differentiated adipocytes (Amended Nonclinical Pharmacology Report)	DIVT0118	Lipolysis Inhibition (release of glycerol and free fatty acids from adipocytes)	Human differentiated adipocytes	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Assessment of the metabolic activity of SAR341402 by measurement of glycerol release from human in vitro differentiated adipocytes	DIVT0032	Lipolysis Inhibition (inhibition of glycerol release)	Human differentiated adipocytes	Human insulin, E.U.-NovoRapid®, U.S.-NovoLog, SAR341402
Assessment of the metabolic potency of insulin and insulin analogues by measurement of glycerol release from human in vitro differentiated adipocytes	DIVT0020	Lipolysis Inhibition (inhibition of glycerol release)	Human differentiated adipocytes	Human insulin, Insulin aspart (NovoRapid, Novo Nordisk), SAR341402
Further comparability study of SAR341402: Lipolysis in human in vitro differentiated adipocytes	DIVT0147	Lipolysis Inhibition (release of glycerol and free fatty acids from adipocytes)	Human differentiated adipocytes	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Comparability study of SAR341402: Glucose uptake in rat L6 myocytes (Amended Nonclinical Pharmacology Report)	DIVT0119	Measurement of radioactive glucose uptake	Engineered rat skeletal muscle myoblast cells	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Comparability study of SAR341402 and NovoRapid/NovoLog: Glucose uptake in rat myocytes	DIVT0102	Measurement of radioactive glucose uptake	Engineered rat skeletal muscle myoblast cells	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Further comparability study of SAR341402: Glucose uptake in rat L6 myocytes	DIVT0148	Measurement of radioactive glucose uptake	Engineered rat skeletal muscle myoblast cells	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Comparability study of four batches of SAR341402: Glucose-6-phosphatase expression in human primary hepatocytes (Amended Nonclinical Pharmacology Report)	DIVT0120	Gluconeogenesis (Glucose-6-phosphatase gene expression using real-time quantitative polymerase chain reaction assay)	Genetically modified human primary hepatocyte cells	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Further comparability study of SAR341402: Glucose-6-phosphatase expression in human hepatocytes	DIVT0149	Gluconeogenesis (Glucose-6-phosphatase gene expression using real-time quantitative polymerase chain reaction assay)	Genetically modified human primary hepatocyte cells	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Assessment of the mitogenic potency of SAR341402 by measurement of 14C-thymidine incorporation in the	DIVT0014	IGF-1 Receptor-Dependent Mitogenicity Activity (stimulation of ^{14}C-thymidine uptake and	MCF-7 (human breast adenocarcinoma) cells	Human insulin, SAR341402,

Study Title	Study Number	Study Type	Test System	Test Article(s)
human breast adenocarcinoma cell line MCF-7		incorporation into cellular DNA)		insulin aspart (Novo Rapid®, Novo Nordisk)
Comparability study of SAR341402: 14C-thymidine incorporation in human breast adenocarcinoma cell line MCF-7 (Amended Nonclinical Pharmacology Report)	DIVT0121	IGF-1 Receptor-Dependent Mitogenicity Activity (stimulation of ^{14}C-thymidine uptake and incorporation into cellular DNA)	MCF-7 (human breast adenocarcinoma) cells	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Assessment of the mitogenic potency of SAR341402 by measurement of ^{14}C-thymidine incorporation in the human breast adenocarcinoma cell line MCF-7	DIVT0038	IGF-1 Receptor-Dependent Mitogenicity Activity (stimulation of ^{14}C-thymidine uptake and incorporation into cellular DNA)	MCF-7 (human breast adenocarcinoma) cells	Human insulin, SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Further comparability study of SAR341402: ^{14}C-Thymidine incorporation in human MCF-7 breast adenocarcinoma cells	DIVT0150	IGF-1 Receptor-Dependent Mitogenicity Activity (stimulation of ^{14}C-thymidine uptake and incorporation into cellular DNA)	MCF-7 (human breast adenocarcinoma) cells	SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Assessment of the mitogenic potency of SAR341402 by measurement of ^{14}C-thymidine incorporation in the human osteosarcoma cell line Saos-2	DIVT0015	IGF-1 Receptor-Dependent Mitogenicity Activity (stimulation of ^{14}C-thymidine uptake and incorporation into cellular DNA)	Saos-2 (human osteosarcoma cells)	Human insulin, SAR341402, Insulin aspart (Novo Rapid®, Novo Nordisk)
Assessment of the mitogenic potency of SAR341402 by measurement of ^{14}C-thymidine incorporation in the human osteosarcoma cell line Saos-2	DIVT0039	IGF-1 Receptor-Dependent Mitogenicity Activity (stimulation of ^{14}C-thymidine uptake and incorporation into cellular DNA)	Saos-2 (human osteosarcoma cells)	Human insulin, SAR341402, E.U.-NovoRapid®, U.S.-NovoLog®
Analysis of the insulin receptor autophosphorylation activity by the isolated product-related substance 28B-Succinimid-Ins-Aspart of SAR341402	DIVT0109	Insulin Receptor-B Phosphorylation	Engineered Chinese Hamster Ovary cells overexpressing insulin receptor-B	SAR341402, 28B-Succinimid-Ins-Aspart
Analysis of the IR autophosphorylation activity by the byproduct Ser9-acetyl-Insaspart of SAR341402	DIVT0122	Insulin Receptor-B Phosphorylation	Engineered Chinese Hamster Ovary cells overexpressing insulin receptor-B	SAR341402, Ser9-acetyl-Ins-aspart
Analysis of the IGFR autophosphorylation activity by the byproduct Ser9-Acetyl-Ins-Aspart of SAR341402	DIVT0124	IGF-1 receptor Phosphorylation	Mouse Embryonic Fibroblast cells overexpressing the human IGF1-R	SAR341402, Ser9-Acetyl-Ins-Aspart
Comparability study of SAR341402 on cell proliferation in rat hepatoma H4IIE cells	DIVT0151	IR-Dependent Mitogenicity Activity (stimulation of ^{14}C-thymidine uptake and incorporation into cellular DNA)	Rat hepatoma H4IIE cells	SAR341402, U.S.-NovoLog®
Toxicology				
SAR341402 - Local subcutaneous, intravenous, paravenous and	TOL1161	Local tolerance	Male rabbits; New Zealand White (NZW)	SAR341402,

Study Title	Study Number	Study Type	Test System	Test Article(s)
intramuscular tolerance study in male rabbits				Insulin Aspart (E.U.-NovoRapid®)

Table 3. Clinical Studies

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Study					
PDY12695	NCT 03202875	Comparative pharmacokinetics and pharmacodynamics of SAR341402, US-NovoLog, and EU-approved NovoRapid.	Randomized, double-blind, single dose, 3-treatment, 3-period, 6-sequence, cross-over, 12-hour euglycemic glucose clamp study	Patients with Type 1 Diabetes Mellitus	SAR341402: 30; US- NovoLog: 30; EU-approved NovoRapid: 30
Comparative Clinical Study(ies)					
EFC15081	NCT 03211858	To compare the safety, efficacy, immunogenicity, of SAR341402 with US-NovoLog	Multi-national, randomized, active-controlled, open-label, 2-arm parallel group study	Adults with T1D and T2D (US)	SAR341402: N=301 (T1D: 250, T2D: 51) US-NovoLog: N= 165 EU-NovoRapid: N= 131 (T1D: 247, T2D: 49)
PDY15083	NCT 03436498	To assess the safety of SAR341402 and US-NovoLog when used in external pumps in terms of the number of patients with infusion set occlusions	Randomized, active-controlled, open-label, 2-treatment, 2-period, 2-sequence crossover	Adults with T1D	SAR341402: N =43 US-NovoLog: N = 43

Study EFC15081 was submitted as supportive data, and was not necessary to the evaluation of biosimilarity; moreover, the data did not preclude or conflict with the conclusions based on other sources of data and information included in BLA 761325. Because Study EFC15081 was not necessary in this 351(k) application, it is discussed in **Section 13.3** (Clinical Appendices) rather than in the body of the Biosimilar Multidisciplinary Evaluation and Review (BMER).

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3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

The Office of Pharmaceutical Quality (OPQ), CDER, recommends that a complete response letter be issued to Sanofi-Aventis to outline the deficiencies and the information and data that will be required to support approval of BLA 761325 for SAR341402.

OPQ determined that the data submitted in the application, including the comparative analytical assessment between SAR341402, U.S.-licensed NovoLog, and E.U.-approved NovoRapid, are adequate to support the conclusion that:

- SAR341402 is highly similar to U.S.-licensed NovoLog, notwithstanding minor differences in clinically inactive components
- The analytical portion of the scientific bridge was established to support the relevance of the data generated from studies using E.U.-approved NovoRapid as the comparator for the assessment of biosimilarity. However, as data generated with EU-approved NovoRapid was not used to support a demonstration of biosimilarity, a scientific bridge to justify the relevance of data generated with a non-US-licensed comparator was not required.

However, OPQ has determined that the data submitted in this application are not sufficient to support a conclusion that the manufacture of the proposed product is well-controlled and leads to a product that is safe, pure, and potent.

The overall SAR341402 control strategy incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, and release and stability of the drug substance and drug product. However, the microbial control strategy is not adequate. The manufacturing processes and overall control strategies for SAR341402 in the license are not appropriately established to ensure consistency and quality of the final product; therefore, lot variability is a concern. The endotoxin control

strategy is inadequate because endotoxin removal steps were not identified or validated for the drug subtance process and the endotoxin specification for drug product is not adequately justified. It is unclear whether the level of endotoxin present at release meets the minimum USP requirement for insulin products. A fully validated endotoxin release test for drug product was not provided.

The assays used for immunogenicity assessment in the clinical study to support this BLA are adequately validated and suitable for their intended purpose. Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for Sanofi-Aventis Deutschland GmbH (FEI 3003195501), proposed for SAR341402 drug substance and drug product manufacture. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. Based on the assessment of manufacturing site records using the Agency's authority under section 704(a)(4) of the FD&C Act, it was concluded that the Sanofi-Aventis Deutschland GmbH drug substance and drug product manufacturing facility was acceptable to support the approval of BLA 761325 and an on-site inspection was not necessary.

SAR341402 drug product is manufactured to have the same strength, dosage form, and route of administration as the 100 Units/mL U.S.-licensed NovoLog in 10 mL vial and 3 mL prefilled pen. The 100 Units/mL SAR341402 in 10 mL vial and 3 mL prefilled pen have the same total content of drug substance in units in a container and the same concentration of drug substance in units per unit volume as the corresponding presentations of U.S.-licensed NovoLog. The strength of the SAR341402 vial and prefilled pens is the same as that of U.S.-licensed NovoLog.

3.2. Devices

3.2.1. Center for Devices and Radiological Health (CDRH)

Office of Health Technology 7 (CDRH/OHT7):

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Division of Drug Delivery, General Hospital and Human Factors (CDRH/DHT3C):

CDRH/DHT3C was consulted to review the device component of the Applicant's pre-filled pen (PFP). The insulin aspart solution pen injector is a multi-use, disposable device combined with a 3 mL cartridge that is used to dispense variable doses of insulin aspart solution for injection. The design of the insulin aspart solution pen injector is based on the already marketed SoloStar pen injector, which is combined with insulin glargine solution for injection 100 U/mL (Lantus, BLA 021081) and which has been modified for the application of the insulin aspart solution for injection.

CDRH/DHT3C's device review included an evaluation of the essential performance requirements (EPR) of the Applicant's PFP. The EPR (i.e., injection force and dose accuracy) were tested by the Applicant to verify and validate the performance of the device. The testing was performed on 200 pens, which CDRH/DHT3C considered to be an acceptable sample size. The specifications were validated and verified through testing of simulated aging and shipping. CDRH/DHT3C determined that the results are acceptable, and that the Applicant has adequately evaluated the performance of the combination product. The Applicant also provided adequate information to support the manufacturing control activities for the EPR of the combination product.

The Applicant performed risk analysis on the combination device, using Failure Mode and Effect Analyses (FMEA) approach, and identified the hazards associated with the combination product. CDRH/DHT3C considered the identified hazards as those expected for injection devices. CDRH/DHT3C determined that the hazards are sufficiently mitigated through the Applicant's risk mitigation activities and identified no additional concerns on the risks associated with the device.

In summary, CDRH/DHT3C determined that the device constituent of the combination product is approvable for the proposed indication.

3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the Applicant's use-related risk analysis (URRA) and comparative analyses submitted under IND 136342 for SAR341402 (insulin aspart-szjj) PFP, 300 units/3 mL (100 units per mL) (b) (4) to U.S.- NovoLog Flexpen and concluded that the Applicant does not need to submit the results of a comparative use human factors (CUHF) study to support a 351(k)(4) application seeking licensure as (b) (4) (b) (4) biosimilar to U.S.-NovoLog FlexPen (DMEPA review dated October 14, 2022).

The submission of BLA 761325 on September 8, 2022, included the Applicant's HF differentiation study results report, which evaluated adult patient, nurse, and pharmacist participants. On January 18, 2023, DMEPA issued an IR to the Applicant requesting HF differentiation study data for pediatric patients (10-17 years) with T1D and T2D. On May 22, 2023, the Applicant submitted the HF differentiation study results with pediatric patients.

The results of the HF differentiation study demonstrated one use error with a critical task. Based on review of the available participant's subjective feedback and the Applicant's root cause analysis from the HF differentiation study, DMEPA did not identify any risk controls to address the use error, and determined that the risks have been mitigated to an acceptable level and no further changes to the user interface are likely to further mitigate these risks. Refer to DMEPA review dated June 26, 2023, for more detailed information.

DMEPA also evaluated product specific label and labeling. The proposed prescribing information (PI) was determined to be acceptable. Comments to the Applicant were provided for the proposed instructions for use (IFU) and proposed carton and container labels. Refer DMEPA revew dated April 21, 2023, for details.

3.3. Office of Study Integrity and Surveillance (OSIS)

The bioanalytical method for quantification of plasma insulin levels was reviewed by FDA's Office of Study Integrity and Surveillance (OSIS) through a remote regulatory assessment (RRA). The OSIS reviewer Dr. Monica Javidnia observed no objectionable conditions*;* see Dr. Javidnia review in DARRTS on 02/22/2023 (Reference ID: 5130657). Refer to the clinical pharmacology section 5.3.1 below for additional details.

3.4. Office of Scientific Investigations (OSI)

No OSI audit was requested because Study EFC15081 was submitted as supportive data and was not necessary to the evaluation of biosimilarity.

Authors:

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Clinical Reviwer

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4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

Insulins and insulin analogs bind to and activate two isoforms of the insulin receptor formed by alternative splicing of the mRNA: insulin receptor A (IR-A) and insulin receptor B (IR-B). IR-B primarily exerts the metabolic actions of insulin, while IR-A activation serves a developmental function and, as evidenced by its expression in cancer cells, mediates mitogenic and proliferative actions. Mitogenicity of insulin and insulin analogs is also mediated through the insulin-like growth factor-1 (IGF-1) receptor. A battery of in vitro studies evaluating receptor binding, receptor activation, metabolic activity, and mitogenic activity were conducted to support a demonstration of biosimilarity between SAR341402 and US-Novolog.

The results of the in vitro studies support a demonstration of biosimilarity between SAR341402 and US-Novolog. Refer to the OBP/CMC section for detailed documentation (Section 3.1).

From a nonclinical perspective, because the toxicity of insulin products, barring differences in clinical PK parameters, is a direct function of their affinity and activity at insulin and IGF-1 receptors, the comprehensive battery of in vitro cell-free and cell-based studies are considered more sensitive than animal studies in detecting differences in toxicities, should they exist, between SAR341402 and US-Novolog. Similar characteristics in the battery of in vitro tests are thus considered adequate to support an assessment of biosimilarity. The battery of in vitro assays did not detect differences between SAR341402 and US-Novolog, and PK similarity was evaluated in a euglyemic clamp study in healthy subjects. In the absence of specific pharmacokinetic, physicochemical, or other identifiable concerns, in vivo assays are not anticipated provide additional meaningful information to inform the evaluation of toxicity.

Accordingly, animal studies comparing SAR341402 to US-Novolog were not required to support this 351(k) application.

4.1.1. Nonclinical Residual Uncertainties Assessment

There were no nonclinical residual uncertainties.

4.2. Product Information

Product Formulation

The SAR341402 is an insulin aspart product produced by recombinant DNA technology and is being developed as a biosimilar to US-NovoLog (100 U/mL).

Table 4: Composition of SAR341402 solution for injection in vials

Components [a]	Composition			Function	Reference to standards [b]
	Percentage [%]	Per mL [mg]	Per unit (10 mL vial) [mg]		
Insulin aspart *[equivalent to U (units) of insulin]*	0.35	3.50 *[100]*	35.0 *[1000]*	Drug substance	Ph. Eur., USP
Metacresol [c]	0.17	1.72	17.2	(b) (4)	Ph. Eur., USP
Phenol	0.15	1.50	15.0		Ph. Eur., USP
Sodium chloride	0.68	6.80	68.0		Ph. Eur., USP
Zinc chloride	< 0.01	0.04	0.4		Ph. Eur., USP
Polysorbate 20	< 0.01	0.02	0.2		Ph. Eur., NF
Sodium hydroxide	---	q.s. pH 7.4	q.s. pH 7.4		Ph. Eur., NF
Hydrochloric acid [d]	---	q.s. pH 7.4	q.s. pH 7.4		Ph. Eur., NF, in-house
Water for injection	q.s. 100	q.s. 1.0 mL	q.s. 10 mL		Ph. Eur., USP
(b) (4)				(b) (4)	Ph. Eur., NF

a Components are listed according to their pharmacopoeial names. If more than one monograph exists, other names are given in brackets, along with the compendial origin.
b Reference is made to the current edition of the Pharmacopoeia.
c For metacresol, the common chemical name "*m*-cresol" is also used within this document.
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(b) (4)

Source: BLA 761325, Module 3.2.P.1, Table 1

Comments on Excipients

Excipients are within the ranges that are found in the inactive ingredient database.

Table 5: Comparison between SAR341402 and U.S.-Novolog Formulations

Component	SAR341402	US-Novolog
Insulin aspart	100 Units	100 Units
Metacresol	1.72 mg	1.72 mg
Phenol	1.5 mg	1.5 mg
Sodium chloride	6.8	0.58 mg
Zinc chloride	40 mcg	19.6 mcg
Polysorbate 20	0.02	
Sodium hydroxide	q.s. pH 7.4	
Hydrochloric acid	q.s. pH 7.4	
Water for injection	q.s. 1.0 mL	USP
Disodium hydrogen phosphate dihydrate		1.25 mg

Glycerin		16.0 mg

Comments on Impurities of Concern

There were no impurities or degradants of toxicological concern.

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5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

The Applicant conducted study PDY12695 that compared the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of SAR341402 100 IU/mL with US-licensed NovoLog, 100 IU/mL, and EU-approved NovoRapid 100 IU/mL to support a demonstration of no clinically meaningful differences between SAR341402 and US-Novolog in terms of safety, purity and potency. Study PDY12695 was designed as a single-dose, randomized, 3-ways cross-over study in adult patients with Type 1 Diabetes Mellitus (T1D). While EU-approved NovoRapid 100 IU/mL was also included in the study, the Clinical Pharmacology review focused on the PK/PD similarity comparison between SAR341402 and US-licensed NovoLog in PDY12695. The study results provided an adequate time-concentration profile and time-action profile for each product based on reliable measures of systemic exposure (insulin concentrations) and glucose response (glucose infusion rate), using an euglycemic clamp procedure.

The scientific basis for relying on the comparative PK and PD data between SAR341402 and US-licensed NovoLog (in conjunction with the data and information from the comparative analytical analysis (CAA), including nonclinical in vitro assays), to support a demonstration of PK and PD biosimilarity to US-licensed NovoLog, is as follows:

- **Similarity in molar dose-** Demonstration that the molar dose ratio for SAR341402 (test insulin product) is similar to US-licensed NovoLog (reference product) as determined based on similarity in peak insulin concentration (C_{max}), total exposure or area under the insulin concentration curve between 0 to 12 hours ($AUC_{0\text{-}12h}$), the corresponding peak (GIR_{max}) and net glucose lowering effect (AUC-GIR (i.e., glucose infusion rate over time) from PD profiles in euglycemic clamp study) when given as the same unit/kg subcutanenous (SC) dose (i.e. same injection volume for a unit dose).

- **Similarity in response-** Demonstration of similarity in the time-action profile between SAR341402 and US-licensed NovoLog is on a unit-to-unit basis, i.e., SAR341402 has the same unit dose definition, time to peak action and duration, which supports that SAR341402 will be equally effective as US-licensed NovoLog. The similarity data from the single-dose, randomized, crossover design PK and PD similarity study conducted for SAR341402 and US-licensed NovoLog supports a conclusion that there are no clinically meaningful differences between the two treatment arms. In this submission, the demonstration of PK/PD similarity using the concept of average equivalence assessment for PK and PD parameters provides sufficient sensitivity for detecting clinically meaningful differences, should they exist, between SAR341402 and US-licensed NovoLog.

Table 6. Clinical Pharmacology Major Review Issues and Recommendations

Review issue	Recommendation and Comments
Pharmacokinetics	• PK similarity between SAR341402 and US-licensed NovoLog was demonstrated in adult patients with T1D (Study PDY12695). • The 90% confidence interval (CI) of the geometric mean ratio (GMR) for each product pairwise comparison for $AUC_{0\text{-}12h}$ and C_{max} were within the PK similarity acceptance criteria of 80-125% (Table 7). • The PK data supports a demonstration of no clinically meaningful differences between SAR341402 and US-licensed NovoLog.
Pharmacodynamics	• PD similarity between SAR341402 and US-licensed NovoLog was demonstrated in adult patients with T1D in this study (PDY12695). • The 90% confidence interval (CI) of the geometric least square mean ratio for each product pairwise comparison for AUC of glucose infusion rate ($AUC\text{-}GIR_{0\text{-}12h}$) and maximum GIR ($GIR_{max}$) were within the PD similarity acceptance criteria of 80-125% (Table 7). • The PD data supports a demonstration of no clinically meaningful differences between SAR341402 and US-licensed NovoLog.

Immunogenicity	• Not applicable. The single dose cross-over design of euglycemic clamp studies is appropriate for assessing PK/PD similarity, but not for evaluation of immunogenicity. As the PK/PD similarity is established, the likelihood of clinically relevant immunogenicity is minimal as the similarity in product quality attributes are also established. Based on the draft Guidance titled "Clinical Immuongenicity Considerations for Biosimilar and Interchangeable Insulin Products", a comparative clinical immunogenicity study is not needed to support a demonstration of biosimilarity.

Under this 351(k) BLA submission, SAR341402 is being proposed as a biosimilar biological product to US-licensed NovoLog. To demonstrate that SAR341402 is biosimilar to US-licensed NovoLog, the applicant submitted a single PK and PD similarity study, PDY12695. The Clinical Pharmacology review focused on the PK/PD similarity comparison between SAR341402 and US-licensed NovoLog in PDY12695.

Study PDY12695 was a randomized, double-blind, single-dose, 3-treatment, 3-period, 6-sequence, crossover, euglycemic glucose clamp study in adult patients with T1D designed to compare the PK and PD (i.e., glucose infusion rate [GIR]) profiles of SAR341402, US-licensed NovoLog, and EU-approved NovoRapid, following a single 0.3 Unit/kg bodyweight subcutaneous (SC) dose. The least-square geometric mean ratio (GMR) of the PK and PD parameters along with the 90% confidence intervals (CI) were within the prespecified margin of 80% to 125% (Table 7).

The results of the study established the PK and PD similarity between SAR341402 and US-licensed NovoLog, based on the primary PK endpoints of C_{max} and $AUC_{0\text{-}12h}$, and the primary PD endpoints of GIRmax and $AUC\text{-}GIR_{0\text{-}12h}$. Overall, the PK and PD results from Study PDY12695 support the demonstration of no clinically meaningful differences between SAR341402 and US-licensed NovoLog and add to the totality of the evidence to support a demonstration of biosimilarity between SAR341402 and US-licensed NovoLog.

Table 7. Summary of statistical analyses for assessment of PK and PD similarity for co-primary PK and PD endpoints (Study PDY12695)

	Parameter	Geometric Mean (%CV)			Geometric Mean Ratio (90% CI)		
		SAR341402 (n= 29)	US-NovoLog (n= 29)	EU-NovoRapid (n= 30)	SAR341402 vs US-NovoLog	SAR341402 vs EU-NovoRapid	US-NovoLog vs EU-NovoRapid
PK	INS-C_{max} (pg/mL)	5140 (28.4)	5510 (30.9)	5300 (26.6)	0.93 (0.87-1.01)	0.97 (0.9-1.05)	1.04 (0.96-1.12)
	INS-$AUC_{0\text{-}12}$ (pg*hr/mL)	13350.8 (34.7)	14342.5 (32.9)	14282.9 (30.6)	0.93 (0.88-0.97)	0.93 (0.89-0.97)	1.00 (0.96-1.05)

PD	**GIR-AUC$_{0-12}$ (mg/kg)**	1846.9 (27.3)	1871.1 (17.4)	1927.2 (20.5)	0.99 (0.91-1.07)	0.96 (0.89-1.04)	0.97 (0.90-1.05)
	GIR$_{max}$ (mg/kg/min)	9.1 (22.6)	8.8 (18.1)	8.8 (20.5)	1.03 (0.96-1.10)	1.02 (0.95-1.09)	0.99 (0.92-1.06)

Source: FDA analysis; Clinical Study PDY12695 body report and PD response data file

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

Study PDY12695 demonstrated PK and PD similarity between SAR341402 and US-licensed NovoLog. There are no residual uncertainties from the clinical pharmacology perspective.

5.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

Not applicable. The Applicant included EU-approved NovoRapid in the PK and PD similarity study (PDY12695); however, as data generated with EU-approved NovoRapid was not used to support a demonstration of biosimilarity, a scientific bridge to justify the relevance of data generated with a non-US-licensed comparator was not required, and the data was not considered necessary.

5.3. Human Pharmacokinetic and Pharmacodynamic Studies

To demonstrate that SAR341402 is biosimilar to US-licensed NovoLog, the Applicant submitted a single PK and PD similarity study, PDY12695. PDY12695 was designed to demonstrate similarity with regards to the primary pharmacokinetic and pharmacodynamic endpoints between SAR341402, US-licensed NovoLog, and EU-approved NovoRapid.

5.3.1. STUDY PDY12695

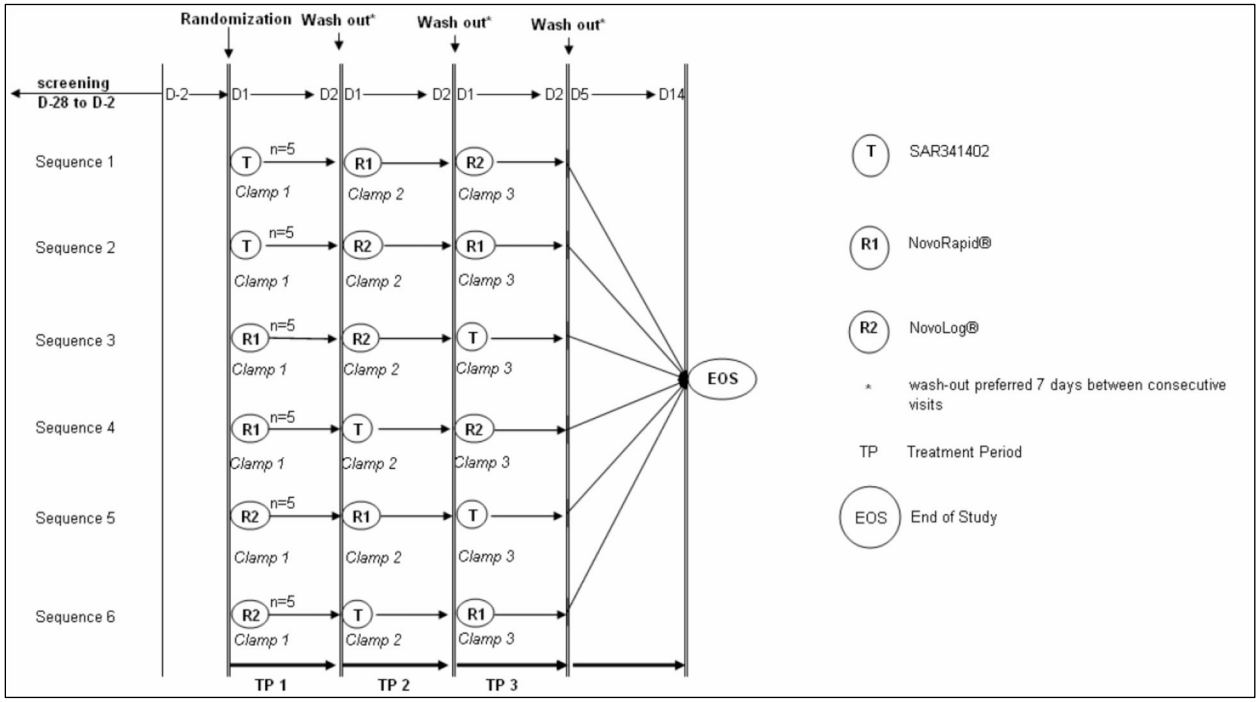
Clinical Pharmacology Study Design Features

PDY12695 was a randomized, double-blind, single dose, 3-treatment, 3-period, 6-sequence, cross-over, 12-hour euglycemic glucose clamp study in adult patients with T1D. The study was designed to demonstrate similarity with regards to the primary PK and PD endpoints between SAR341402 (100 IU/mL), US-licensed NovoLog (100 IU/mL), and EU-approved NovoRapid (100 IU/mL).

The study consisted of six visits: informed consent visit, screening visit, three treatment visits, and end-of-study (EoS) visit. The randomization of a subject occurred on the morning before treatment administration of the first treatment period. A single subcutaneous dose administration (0.3 U/kg body weight) of the test product (SAR341402) or the reference products (US NovoLog, EU NovoRapid) was administered follow by a wash out period of 5 to 18 days after dosing. Dosing was administered subcutaneously (SC) in the periumbilical area (using a standardized skin-fold technique).

Each Dosing Period included one 12-hour euglycemic glucose clamp and was identical in procedure with assessments for PK, PD, and safety endpoints. During the euglycemic clamp study, the blood glucose concentration, the glucose infusion rate (GIR) and the amount needed to keep a subject's blood glucose concentration at its target level was continuously measured and recorded using the Biostator device (continuous glucose monitoring system, Life Sciences Instruments, Elkhart, IN, USA). The amount of glucose required (GIR-AUC) is a measure of insulin mediated glucose uptake into tissues (glucose disposal or glucose lowering activity). The Biostator determines blood glucose levels in 1 min intervals and adjusts the glucose infusion rate in response to changes in blood glucose using a predefined algorithm. During the clamp, arterialized venous blood glucose concentration, which reflects the supply for total glucose utilization of all tissues, as well as glucose infusion rates was continuously monitored. Subjects were fasting for at least 9 hours prior to dosing and remained under fasting (apart from water) during the entire duration of glucose clamp. A meal was provided after the end of the clamp. Eligible subjects with T1D are not expected to have interfering levels of endogenous insulin as measured by C-peptide, hence C-peptide was not measured during the study and a fasting negative serum C-peptide (<0.3 nmol/L) was obtained at screening as an inclusion criterion. Therefore, the risk of potential interference from endogenous insulin on the PD measurements is highly unlikely.

Figure 1. Schematic of Study PDY12695 Design



Source: Clinical Study PDY12965 protocol

Clinical Pharmacology Study Endpoints

For Study PDY12695, the primary PK endpoints assessed by FDA were area under the insulin concentration curve from 0 to 12 hours ($AUC_{0\text{-}12h}$) and maximum observed insulin concentration (C_{max}).

The primary PD endpoints used by FDA were total area under the glucose infusion over the clamp duration from 0 to 12 hours ($AUC\text{-}GIR_{0\text{-}12h}$) and maximum glucose infusion rate (GIR_{max}).

To demonstrate similarity for PK and PD endpoints, the 90% CI of the geometric LS mean ratios for pairwise comparsions of the pre-specified PK and PD endpoints needs to fall within the pre-specified limits of 80-125%.

Bioanalytical PK Method and Performance

The quantitation of SAR341402 and US NovoLog in plasma samples was done using a validated method (DOH1275) that included automated immunoaffinity purification followed by Ultra-Performance Liquid Chromatography with Tandem Mass Spectrometry detection (LC-MS/MS). The calibration range for the analytes was 100 to 8000 pg/mL in human K2EDTA plasma and the method validation results met the pre-specified acceptance criterion in accordance with the "Bioanalytical Method Validation Guidance for Industry" from FDA. The validated method was found to achieve acceptable accuracy and precision when used for the study sample analysis.

The bioanalytical method for quantification of plasma insulin levels was reviewed by FDA's Office of Study Integrity and Surveillance (OSIS) through a remote regulatory assessment (RRA). The OSIS reviewer Dr. Monica Javidnia observed no objectionable conditions. See Dr. Javidnia review in DARRTS on 02/22/2023 (Reference ID: 5130657). In her review Dr. Dr.Javidnia also stated the following:

"During review of sample analysis data for Study PDY12695 (BLA 761325), I identified a discrepancy in the file named 'PC.xpt' in the submission data, with 36 samples having reportable concentration values >LLOQ in the 'PCORRES' column but reported as <LLOQ in the 'PCSTRESC' column. I confirmed the 'PCORRES' column data accuracy through source data from the analytical firm". Dr. Javidnia also noted *"I recommend the review division contact the sponsor to determine the reason for the sample values being reported as <LLOQ"*

The OCP review team sent an IR to the Applicant asking for clarification on this discrepancy. The Applicant sated the following:

"In study PDY12695, for subjects receiving IV rescue insulin (insulin glulisine) during the clamp (after dosing of IMP), concentration data for insulin aspart were only taken into account until the start time of administration of rescue insulin and were set to "missing" thereafter (section 8.7.2.4 of the clinical study report). Concentrations of 2 ng/mL

insulin glulisine interfere notably with the quantification of low concentrations of insulin aspart (assay validation report DOH1275, table 15.7). Therefore, measuring insulin aspart in presence of insulin glulisine can result in falsely high insulin aspart concentrations. The potential interference is supported by the erratic occurrence of concentrations of insulin aspart slightly above the LLOQ surrounded by concentrations below the LLOQ after start of insulin glulisine infusion. Therefore, to avoid determining falsely high concentrations of insulin aspart, concentration data after start of insulin glulisine infusion were excluded from the PK analysis." Adding *"In the pc.xpt file, the measured concentration data set is provided in column "PCORRES". The corrected concentration data set in which excluded concentrations above the LOQ were set to "<LLOQ" are provided in column "PCSTRESC". The concentration data set used for the PK analysis is provided in column "PCSTRESC" reflecting the rules that LLOQ values before Cmax are set to 0 and after Cmax to "missing" (no entry). The results provided in PK tables 23 to 26 reflect the outcome of the analysis considering only concentration data for insulin aspart until start of rescue insulin. Correspondingly, the ADaM data set reflects the PK parameters as used for the statistical analyses of PK parameters."*

The clinical pharmacology team reviewed the Applicant's response and the associated data and found the Applicant's reasoning for excluding samples with suspected interference from rescue insulin scientifically appropriate. Refer to the Appendix (**Section 13.2.1**) for information on the assay validation and performance parameters for insulin assays to measure insulin plasma concentrations.

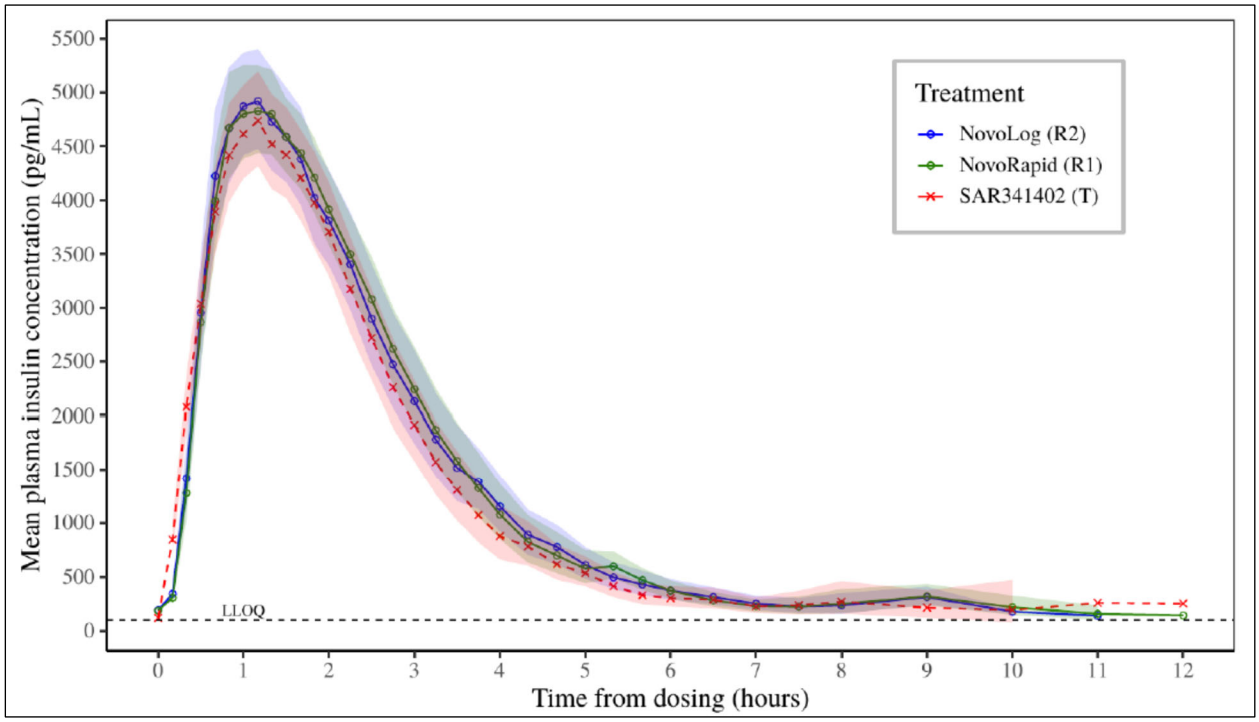
On July 10, 2023, OSIS reported a finding of minor discrepancies identified between premature end of euglycemic clamp times in the source records collected on site and the reported data listings. The timing discrepancy occurred in six subjects and lasted for few minutes. In response, the Clinical Pharmacology team sent an IR to the Applicant asking for clarification on this time discrepancy. The Applicant stated that the apparent discrepancy was related to subjects that had premature end of clamp. For all cases, rescue insulin was administered toward the end of the clamp duration and this timepoint was derived during the course of the biostatistical analysis as per pre-specifications in the protocol and SAP. For all cases listed, it is the last minute before the first administration of rescue insulin. Further, PD parameters were derived according to specifications in the protocol and the statistical analysis plan (SAP). During analysis, for all derived variables, for all timepoints after IV rescue insulin infusion, the glucose infusion rate (GIR) was put to 0. Finally, the timing discrepancy occurred toward the end of the clamp around 10 to 12 hours postdose of insulin aspart injection where the insulin concentration were nearing zero. Therefore, the time deviations between the time of disconnect from the Biostator and the derived time of premature end of clamp do not affect the analysis dataset used for PD analysis.

The Clinical Pharmacology team reviewed the Applicant's response and the associated data and found the Applicant's justification to be within those permitted by the clamp protocol and SAP and are scientifically appropriate.

PK Similarity Assessment

For the primary PK parameters ($AUC_{0\text{-}12h}$ and C_{max}) of the study drug products, the similarity criterion (90% CI of the geometric least-square mean ratio for test/reference within the limits of 80% and 125%) was met in all comparisons (Table 7). The mean plasma insulin concentration versus time profile show that the test and reference product are similar (Figure 2).

Figure 2. Mean (90% CI) plasma insulin concentration versus time profiles during the euglycemic clamp by treatment for Study PDY12695



LLOQ is 100 pg/mL.
Source: Figure 1 response to FDA Information request dated Feb 10, 2023

Bioanalytical PD Method and Performance

The euglycemic clamp technique was used to measure PD response. In this technique, glucose was administered intravenously to counter the glucose lowering effect of administered insulin products and to maintain plasma glucose. The temporal profile of glucose-infusion rate over time was the PD response measure in Study PDY12695.

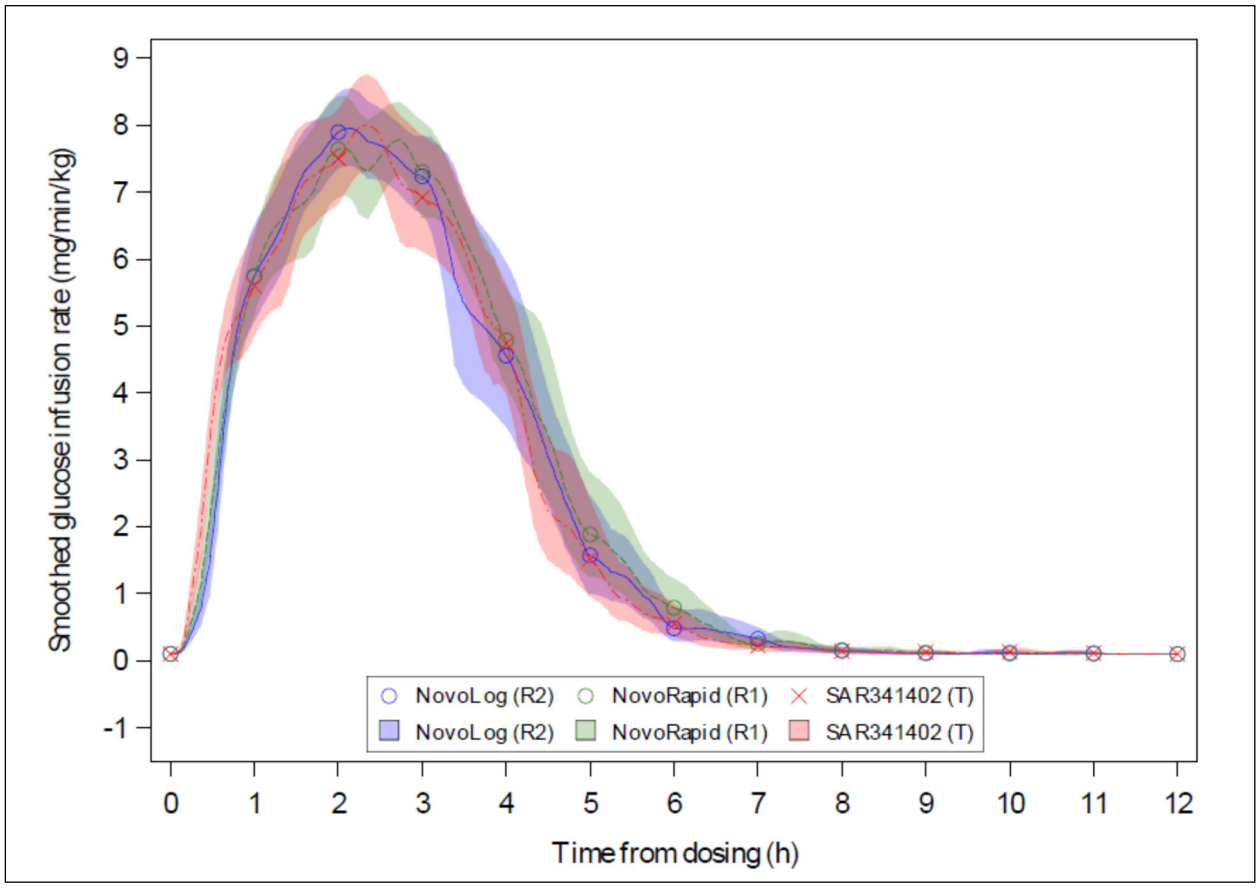
During the euglycemic clamp, the blood glucose concentration, the glucose infusion rate (GIR) and the amount needed to keep a subject's blood glucose concentration at its target level was continuously measured and recorded using the Biostator device (continuous glucose monitoring system, Life Sciences Instruments, Elkhart, IN, USA). The amount of glucose required (GIR-AUC) is a measure of insulin mediated glucose uptake into tissues (glucose disposal or glucose lowering activity). The Biostator determines blood glucose levels in 1 min intervals and adjusts the glucose infusion rate

in response to changes in blood glucose using a predefined algorithm. During the clamp, arterialized venous blood glucose concentration, which reflects the supply for total glucose utilization of all tissues, as well as glucose infusion rates was continuously monitored. Subjects were fasting for at least 9 hours prior to dosing and remained fasting (apart from water) during the entire duration of glucose clamp. A meal was provided after the end of the clamp. Eligible subjects with T1D are not expected to have interfering levels of endogenous insulin as measured by C-peptide, hence C-peptide was not measured during the study and a fasting negative serum C-peptide (<0.3 nmol/L) was obtained at screening as an inclusion criterion. Therefore, the risk of potential interference from endogenous insulin on the PD measurements is highly unlikely

PD Similarity Assessment

For the PD parameters, the similarity criterion (90% CI of the ratio test/reference within the limits 80.00% and 125.00%) was met in both pairwise comparisons for the primary PD parameters (AUC-$GIR_{0\text{-}12h}$ and GIR_{max}) (Table 7). Figure 3 shows the mean (90%CI) GIR versus time profile by treatment arms. On average, the PD response, as assessed by GIR over time, was consistent between the test and reference products.

Figure 3. Mean (90% CI) smoothed glucose infusion rate versus time profiles during the euglycemic clamp by treatment for Study PDY12695

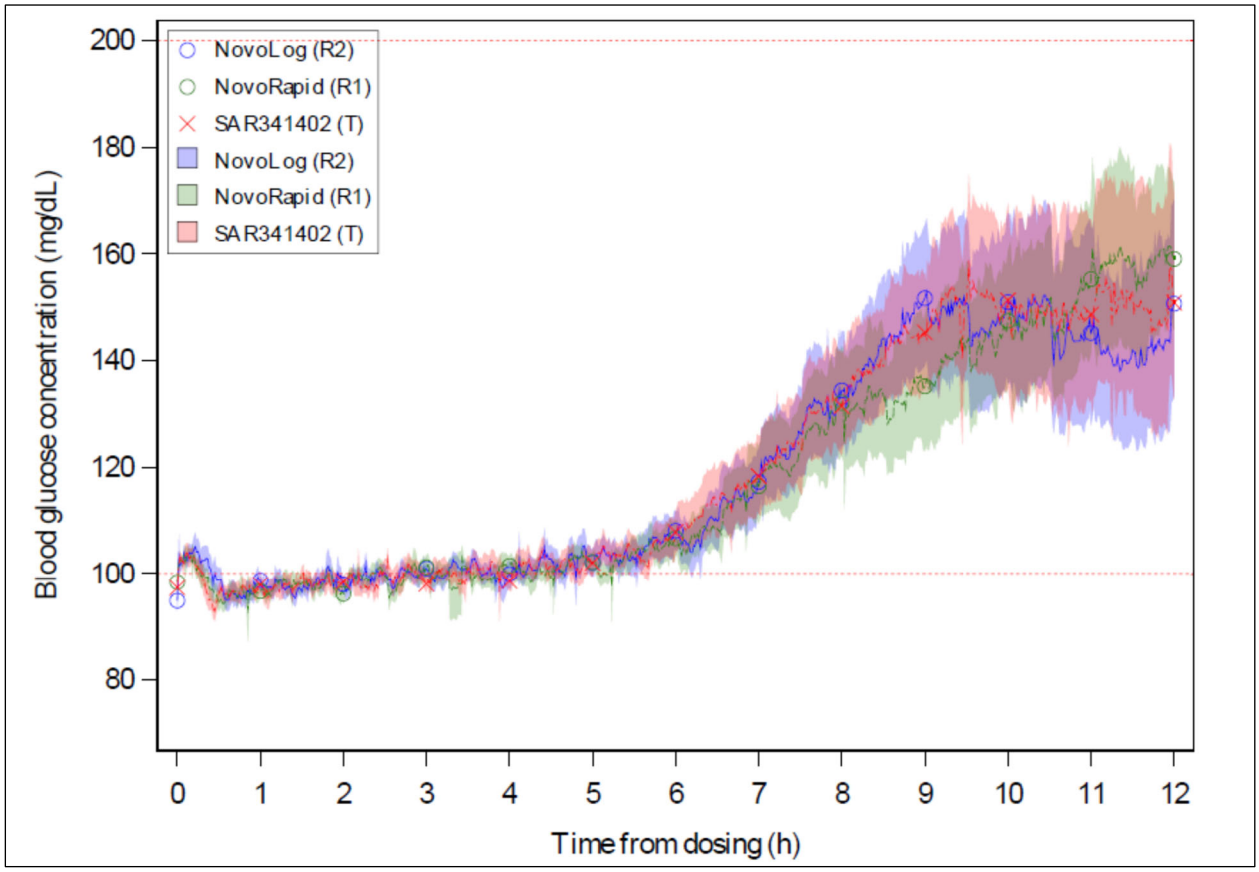


Source: Figure 2 response to FDA Information request dated Feb 10, 2023

The clamp quality was assessed by the CV% of blood glucose over the clamp duration (0 to end of euglycemia) and was reliably maintained within reasonable variability (median CV% values of 6.60%, 5.75%, and 6.40% for SAR341402, EU-approved NovoRapid and US-licensed NovoLog, respectively, indicative of successful performance of the euglycemic clamp technique.

Figure 4 shows the mean levels of blood glucose during the clamp duration which was found to be similarly maintained between the test and the reference products.

Figure 4. Mean (90% confidence limits) blood glucose concentration versus time profiles during the euglycemic clamp by treatment for Study PDY12695



lower level = 100 mg/dL, clamp target level. upper level = 200 mg/dL clamp stopping level.
Source: Figure 2 response to FDA Information request dated Feb 10, 2023

Authors:

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Clinical Pharmacology Reviewer

Edwin Chiu Yuen Chow PhD
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5.4. Clinical Immunogenicity Studies

A comparative clinical study, EFC15081, was conducted which included data describing the immunogenicity of SAR341402; however, this study was not adequately designed to support a rigorous assessment of immunogenicity. The *Insulin Immunogenicity Guidance* was issued after Study EFC15081 had been initiated. During the pre-BLA meeting, the Applicant was advised that a comparative clinical immunogenicity study generally would be considered unnecessary to support a demonstration of biosimilarity for SAR341402 if, among other things, the comprehensive and robust CAA adequately supports a demonstration of "highly similar" to U.S.-NovoLog as part of a demonstration of biosimilarity. FDA noted that the 351(k) BLA submission could instead include an immunogenicity assessment justifying why a comparative clinical study to assess immunogenicity is not necessary to support a demonstration of biosimilarity. FDA also stated that a comparative clinical immunogenicity study may still be necessary to support licensure if there is residual uncertainty regarding immunogenicity.

The Applicant included in its 351(k) BLA submission both an immunogenicity assessment as well as the data from EFC15081. The immunogenicity assessment and Study EFC15081 were reviewed by Dr. Dolly Misra as part of the clinical review (see **Section 6.4** and **Section 13.313.3**).

Authors:

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Clinical Reviwer

Patrick Archdeacon, MD
Clinical Team Lead/CDTL

6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

During the clinical development program for SAR341402, the Applicant conducted a comparative clinical study, EFC15081, to assess differences in efficacy between SAR341402 and U.S.-NovoLog. The primary objective of EFC15081 was to demonstrate that SAR341402 is noninferior to U.S.-NovoLog in glycemic control as assessed by HbA1c change from baseline to week 26. Immunogenicity data were collected and analyses were provided descriptively, without formal statistical testing.

FDA updated its scientific thinking regarding whether and when comparative clinical immunogenicity studies may be needed to support licensure of proposed biosimilar and interchangeable insulin products. FDA's updated thinking was outlined in the November 2019 *Insulin Immunogenicity Guidance*. This draft guidance states a comparative clinical immunogenicity study generally would be considered unnecessary to support a

demonstration of biosimilarity in a 351(k) BLA for a proposed insulin product seeking licensure as a biosimilar or interchangeable if the BLA contains a robust and comprehensive CAA demonstrating that the proposed insulin product is “highly similar” to its proposed reference product with very low residual uncertainty regarding immunogenicity and the application otherwise meets the standards for licensure under section 351(k) of the PHS Act. The guidance recommends that a 351(k) BLA for a biosimilar or interchangeable insulin product contain, among other things, an immunogenicity assessment justifying why a comparative clinical study to assess immunogenicity is not necessary to support a demonstration of biosimilarity.

Consistent with the *Insulin Immunogenicity Guidance*, the Applicant performed a comprehensive and robust CAA of SAR341402 and U.S.-NovoLog and submitted an immunogenicity assessment justifying why a comparative clinical study to assess immunogenicity was not necessary to support a demonstration of biosimilarity. The former adequately supported a demonstration that SAR341402 is highly similar to U.S.-NovoLog, notwithstanding minor differences in clinically inactive components. The results are summarized in **Section 3.1**. The latter adequately justified why a comparative clinical study to assess immunogenicity is not necessary to support a demonstration of biosimilarity. The immunogenicity assessment is discussed in **Section 6.4**. Based on the CAA findings and adequate immunogenicity assessment, FDA has determined that there is little or no residual uncertainty regarding immunogenicity for SAR341402; the data from EFC15081 are thus unnecessary, and FDA did not rely on EFC15081 in its evaluation of biosimilarity. Because EFC15081 was not necessary in this 351(k) application, it is discussed further in **Section 13.3** rather than in the body of the BMER.

Overall, the immunogenicity assessment submitted in this application contributes to the totality of evidence supporting a demonstration of no clinically meaningful differences between SAR341402 and U.S.-NovoLog in terms of safety, purity, and potency.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the clinical analyses that impact a demonstration of biosimilarity between SAR341402 and U.S.-NovoLog.

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

As noted above, the data from comparative clinical study EFC15081 are discussed in **Section 13.3** rather than in the body of the BMER because FDA considers the results supportive, but not necessary, of the evaluation of whether SAR341402 is biosimilar to U.S.-NovoLog.

6.3. Review of Safety Data

Studies PDY12695 and EFC15081 comprise the clinical data submitted for SAR341402 for BLA 761325.

Study PDY12695 was a euglycemic clamp study conducted to assess the PK/PD similarity of SAR341402 and U.S.-NovoLog. The design and clinical findings of Study PDY12695 are presented in **Section 5.3.1**. Euglycemic clamp studies provide time-concentration profiles and time-action profiles based on reliable measures of systemic exposure and glucose response. Study PDY12695 collected a limited amount of safety data during its conduct, but the safety data collected were not necessary to the evaluation of biosimilarity between SAR341402 and U.S.-NovoLog.

The comparative analytical data and the results of Study PDY12695 demonstrating PK and PD similarity between SAR341402 and U.S.-NovoLog support a demonstration of no clinically meaningful differences between SAR341402 and U.S.-NovoLog in terms of safety, purity, and potency, without reliance on safety data generated by Study PDY12695. Therefore, the limited safety data collected during the conduct of Study PDY12695 were inspected only to ensure that these data did not conflict with the conclusion of biosimilarity based on the analysis of the comparative analytical data and the finding of PK and PD similarity between SAR341402 and U.S.-NovoLog. Review of these limited safety data did not suggest any differences in the safety profiles of SAR341402 and U.S.- NovoLog.

As previously discussed, FDA considers the results of Study EFC15081 supportive, but not necessary, of the evaluation of whether SAR341402 is biosimilar to U.S.-NovoLog. Because the Applicant submitted the data from Study EFC15081, FDA reviewed the data to ensure that there are no unexpected safety findings which would preclude the licensure of the 351(k) application for SAR341402. Because Study EFC15081 was not necessary in this 351(k) application, the safety data are presented and discussed in **Section 13.3** rather than in this section of the BMER.

6.4. Clinical Conclusions on Immunogenicity

Consistent with the *Insulin Immunogenicity Guidance*, the Applicant submitted an immunogenicity assessment justifying why a comparative clinical study to assess immunogenicity is not necessary to support a demonstration of biosimilarity for SAR341402.

In the immunogenicity assessment, the Applicant referenced the results of the comprehensive clinical program for SAR341402. The immunogenicity findings of the comparative clinical study, Study EFC15081, were also included in the assessment.

The Agency does not agree with all of the arguments presented in the Applicant's immunogenicity assessment, including various assessments derived from data from Study EFC1508. Nevertheless, the Applicant does present information that comprises

an adequate justification for why a comparative clinical study to assess immunogenicity is not necessary to support a demonstration of biosimilarity.

The Applicant's CAA demonstrates that SAR341402 is highly similar to U.S.-NovoLog, notwithstanding minor differences in clinically inactive components. In addition, the FDA review of PK/PD similarity findings of Study PDY12695 concluded that the Applicant was able to demonstrate PK and PD similarity between SAR341402 and U.S.-NovoLog. In conjunction with the CAA, these results support a demonstration that there are no clinically meaningful differences between SAR341402 and U.S.-NovoLog. Finally, although the results from Study EFC15081 were unnecessary to demonstrate that there are no clinically meaningful differences between SAR341402 and U.S.-NovoLog, the findings from this study do not preclude or conflict with that conclusion. Therefore, there is no residual uncertainty regarding immunogenicity from a clinical perspective.

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6.5. Extrapolation

6.5.1. Division of Diabetes, Lipid Disorders, and Obesity

The information submitted in the application, including the comparative analytical data and the PK/PD results (which together demonstrate that the MOA is the same in SAR341402 and U.S.-NovoLog, to the extent known) supports a demonstration that SAR341402 and U.S.-NovoLog are highly similar, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences in terms of safety, purity, and potency.

An extrapolation of the finding of PK similarity of SAR341402 and U.S.-NovoLog in adults with T1D to adult and pediatric patients with diabetes mellitus (T1D and T2D) is justified because the same scientific factors that determine absorption, distribution, metabolism, and elimination in adults also determine absorption, distribution, metabolism, and elimination in pediatric patients with diabetes mellitus. The extrapolation of the finding of PD similarity of SAR341402 and U.S.-NovoLog in adults with T1D to adult and pediatric patients with diabetes mellitus (T1D and T2D) is justified because the assessed PD endpoints evince the binding and activation of insulin receptors, which is the pertinent MOA for all conditions of use of U.S.-NovoLog (to the extent known). No comparison of any other scientific factors across the conditions of use were necessary to justify the extrapolation. The extrapolation does not require specific knowledge about the relationship between the PK and PD profiles observed in adults with T1D and the PK and PD profiles that would be observed in other patients with diabetes mellitus. The data and information in the application, including comparative PK and PD data demonstrating no meaningful differences in time-concentration profile and time-action profile over the duration of action of each product

from Study PDY12695, support licensure for the conditions of use for which U.S.-NovoLog has been previously approved and for which the Applicant is seeking licensure.

The information submitted by the Applicant demonstrates that SAR341402 is biosimilar to U.S.-NovoLog for the following indication (including all of the indicated patient populations) for which the Applicant is seeking licensure and for which U.S. NovoLog has been previously approved: to improve glycemic control in adults and pediatric patients with diabetes mellitus.

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7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, insulin aspart-szjj, was found to be conditionally accepted by the Agency (DMEPA review dated May 5, 2023).

7.2. Proprietary Name

The Applicant's initial proposed proprietary name for SAR341402 of (b) (4) and (b) (4) SoloStar was determined to be unacceptable by DMEPA review because risk of potential medication errors due to name confusion with the currently marketed product, (b) (4) (DMEPA review dated April 14, 2023).

The proposed proprietary name for SAR341402 is conditionally approved as Merilog and Merilog SoloStar. This name has been reviewed by DMEPA, which concluded the name was acceptable (DMEPA review dated August 28, 2023).

7.3. Other Labeling Recommendations

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

The labeling for U.S.-NovoLog includes information related to continuous subcutaneous infusion (CSII) and intravenous administration (IV) in the DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS, and CLINICAL STUDIES sections of labeling.

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8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

A violation related to GCP non-compliance due to inappropriate source documentation and lack of Investigator oversight was found at site No. 840-0041 (Metairie, LA, US). A total of 4 patients were randomized in this site. The 4 patients from this site were excluded from the per-protocol population. The site was closed and the FDA was

notified in writing per 21CFR312.56(b). Given that these data comprised fewer than 1% of the study subjects, this violation did not affect the interpretation of safety or efficacy.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in **Section 13.1** and verifies that no compensation is linked to study outcome. The Principal Investigators did not disclose any proprietary interest to the sponsor.

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9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was held for this application, as it was determined that there were no issues where the Agency needed input from the Committee.

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Clinical Team Lead/CDTL

10. Pediatrics

Section 505B(I) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, an interchangeable product is not considered to have a "new active ingredient" for purposes of PREA.

As insulin SAR341402 has not been determined to be interchangeable with U.S.-NovoLog, it is considered to have a "new active ingredient" for purposes of PREA.

In the Applicant's iPSP (FDA agreement letter issued August 11, 2022), the Applicant noted that SAR341402 was being developed as a biosimilar "to treat the same licensed indication as U.S.-NovoLog." The Applicant stated that it intended to satisfy the pediatric assessment for pediatric patients for SAR341402 by submitting data and information that are sufficiently robust to demonstrate biosimilarity for the indication "to improve glycemic control in adults with diabetes mellitus" and support extending the demonstration of biosimilarity to include the pediatric condition for which U.S.-NovoLog has previously been licensed.

Based on the information above—including the fact that the Applicant is seeking licensure of SAR341402 for the same indication as U.S.-Novolog—there is no change to the Applicant's plan that no specific studies of SAR341402 in the pediatric population are needed. As described in **Section 6.5.1**, DDLO determined that the same conclusions made with respect to the adult population were also supported in the pediatric population.

The Pediatric Review Committee (PeRC) meeting was held on August 1, 2023, and the PeRC agreed with DDLO that the Applicant's findings of biosimilarity of SAR341402 to U.S.-NovoLog (based upon CAA and PK/PD similarity) and the Applicant's pediatric assessment support the extension of biosimilairity to include the pediatric condition for which U.S.-NovoLog has previously been licensed, without the need for specific studies with SAR341402 in the pediatric population.

Authors:

Dolly Misra, MD
Clinical Reviewer

Patrick Archdeacon, MDClinical
Clinical Team Lead/CDTL

11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None.

11.2. Recommendations for Postmarket Requirements and Commitments

None.

Authors:

Dolly Misra, MD
Clinical Reviewer

Patrick Archdeacon, MD
Clinical Team Lead/CDTL

12. Comments to Applicant

The data provided are inadequate to demonstrate that the Rabbit Pyrogen Test (RPT) is suitable to detect endotoxin in SAR341402 drug product as a release test. In response

to IR dated August 31st, 2023 you indicated that rabbit pyrogen test according to USP <151> is applied for Drug Product release testing to demonstrate the absence of endotoxins and other pyrogens. To circumvent the physiological responses in rabbits to the insulin, a glucose solution is injected in parallel to the application of the test solution. However, the data submitted to the BLA did not adequately demonstrate that insulin's mechanism of action does not result in physiological responses and temperature changes in the rabbits that are unrelated to endotoxin. Additionally, the data provided did not include endotoxin spiking studies to demonstrate that the RPT can adequately detect endotoxin present in SAR341402drug product. Provide an endotoxin test method for SAR341402drug product release that can reliably detect endotoxin over process-relevant time and temperature.

13. Appendices

13.1. Financial Disclosure

Covered Clinical Study: EFC15081, PDY15083

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 324		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 23		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 21 (see below) Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information

		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

A Financial Certification and Disclosure Form 3454 with information for both studies was completed and submitted. All clinical investigators certified to the absence of significant proprietary and/or equity interests, as required by 21CFR54.2(b). Twenty-three investigators from the U.S. (20 with EFC15081, 3 with PDY15083) reported receiving honoraria for various responsibilites associated with the studies (e.g., Advisory Board, Customer Interaction, General Consulting, Investigator Meeting, Marketing Advisory Board, Medical Advisory Board, Medical General Consulting, Meeting with Experts, Publication Support (Non Research), Speaker Program Participation, Host and Training). A bias minimization statement listing the actions implemented to protect studies from potential bias was provided. The steps to minimize bias appear to be appropriate. The proportion of investigators receiving honoraria comprised less than 10% of the total. Given that the data from PDY15083 were not reviewed for this submission and the data from EFC15081 were determined to be not necessary to the evaluation of of biosimilarity, these significant payments of other sorts to investigators of these studies do not raise any concerns for the review of this application.

13.2. Clinical Pharmacology Appendices

Author: Mohamad Kronfol PhD

13.2.1. Summary of Bioanalytical Method Validation and Performance

Pharmacokinetics

The assays for measuring plasma insulin concentrations levels were found adequate for the assessment of PK similarity.

The method validation entitled “validation of an ultra-performance liquid chromatographic method using tandem mass spectrometry detection and automated immunoaffinity purification for the determination of SAR341402 (100.00 to 8000.00 pg/ml) and cross-validation with two NovoLog products in human EDTA K2 plasma” and sample analysis for the study (PDY12695- BA1 - SAR341402) were performed at (b) (4).

More details on assay validation and performance of the assays in Study PDY12695 are listed below in Table 8.

Table 8. Summary of the bioanalytical method validation and in-study performance of the LC-MS/MS method used to measure plasma insulin concentrations in Study PDY12695

Bioanalytical method validation report name, amendments, and hyperlinks	DOH1275: Validation of an Ultra Performance Liquid Chromatographic Method Using Tandem Mass Spectrometry Detection and Automated Immunoaffinity Purification for the determination of SAR341402 (100.00 to 8000.00 pg/mL) in Human EDTA K2 Plasma	
Method description	UPLC method using tandem mass spectrometry detection and affinity purification	
Materials used for standard calibration curve and concentration	SAR341402, white powder, 4.90 mg/ampoule	
Validated assay range	100 pg/mL to 8000 pg/mL	
Material used for quality controls (QCs) and concentration	SAR341402, white powder, 4.90 mg/ampoule US-NovoLog, 3 mL cartridges, 100 units/mL (equivalent to 3.5 mg/mL) EU-NovoRapid, 3 mL cartridges, 100 units/mL (equivalent to 3.5 mg/mL)	
Minimum required dilutions (MRDs)	Not applicable	
Source and lot of reagents	Not applicable	
Regression model and weighting	Linear regression with $1/X^2$ weighting	
Validation parameters	**Method validation summary**	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8
	Cumulative accuracy (%bias) from LLOQ to ULOQ for SAR341402	-4.63-5.53 %
	Cumulative precision (%CV) from LLOQ to ULOQ for SAR341402	4.78-8.52 %
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QC levels for SAR341402 Cumulative accuracy (%bias) in 4 QC levels for US-NovoLog Cumulative accuracy (%bias) in 4 QC levels for EU-NovoRapid	-7.35-4.70 % -7.34-5.26% -9.33-4.04%
	Inter-batch %CV for SAR341402 Inter-batch %CV for US-NovoLog Inter-batch %CV for EU-NovoRapid	3.96-8.20 % 2.10-12.01% 3.09-5.07
	Total Error (TE)	Not calculated

Selectivity & matrix effect	Matrix Selectivity for Normal Donors: No significant interference observed in 10 out of 10 tested matrices for SAR341402 and its IS Matrix Selectivity for Other Donors (Including 5 Type 1 Diabetics): No significant interference observed in type 1 diabetic matrices for SAR341402 and its IS Selectivity at LLOQ Level for 10 Normal Donors: No effect on the quantitation of the analyte Selectivity at LLOQ Level for 5 Type 1 Diabetics: No effect on the quantitation of the analyte Matrix Effect (Including 10 Normal Donors): Mean IS-Normalized matrix factor: 0.9730376 and 1.0080743 Matrix Effect (Including 5 Type 1 Diabetics, 1 Type IV Hyperlipemic and 1 3% Hemolyzed): Mean IS-Normalized matrix factor: 0.9329843 and 0.9675614
Interference & specificity	No effect of commonly used drugs, concomitant medication (Human insulin, Insulin Lispro, Insulin Glargine, Insulin Glargine M1, Insulin Detemir, Insulin Glulisine) and anti-insulin antibodies
Hemolysis effect	No effect of 3 % hemolyzed samples on the quantitation of the analyte
Lipemic effect	Type IV hyperlipemic samples had no effect on the quantitation of the analyte
Dilution linearity & hook effect	A dilution quality control sample (DQC) at 80000 pg/mL of SAR341402, US-NovoLog and EU-NovoRapid was parallelly diluted twenty-fold six times in human EDTA K2 plasma prior to sample processing and analysis. The results met the pre-established acceptance criteria (50% DQCs must be within ± 20% of the nominal concentrations; mean % Bias within ± 20%; CV (%) ≤ 20%).
Bench-top/process stability	22h10min at room temperature and 22h17min at 4°C
Freeze-Thaw stability	4 cycles at -20°C and -80°C
Long-term storage	12, 106, 181, 399 and 565 days at -20ºC and -80°C
Parallelism	Not performed
Carry over	No significant carryover observed
Method performance in study PDY12695	
Assay passing rate	A total of 35 analytical runs were performed; of these 33 passed acceptance criteria, 2 runs were rejected for calibration acceptance criteria not met.
Standard curve performanc e	Inter-run %Bias: -2.00-3.00% Inter-run %CV: 3.3 -7.28%
QC performance	Inter-run %Bias: -5.33-1.00%

	Inter-run %CV: 3.96 -6.02%
Method reproducibility	A total of 213 samples were reanalyzed (ISR) to demonstrate that results obtained from study sample analysis are reproducible. A total of 99.06% of the reanalyzed samples meet the criteria of assay reproducibility (no more than 33.3% of the ISR samples should have a concentration greater than ± 20% of the average of the original and repeat values)
Study sample analysis/ stability	Samples (first collection date November 20, 2012) were analyzed within the documented stability period of 565 days at approximately -20°C and -80°C

Pharmacodynamics

Blood glucose concentration at its target level was measured and recorded using the Biostator device (continuous glucose monitoring system, Life Sciences Instruments, Elkhart, IN, USA). Briefly, 20% glucose solution will be infused with the Biostator to keep subjects individual blood glucose at the determined target level. A second infusion pump (part of the Biostator) will deliver 0.9% sodium chloride solution to keep the line patent. The Biostator determines blood glucose levels in 1 min intervals and adjusts the glucose infusion rate in response to changes in blood glucose using a predefined algorithm.

13.3. Clinical Appendices

Author: Dolly Misra, MD

As previously discussed, the Applicant submitted Study EFC15081 in support of this 351(k) application. FDA determined that the data from Study EFC15081 were not necessary to the evaluation of biosimilarity of SAR341402 to U.S.-NovoLog. Because the Applicant submitted Study EFC15081, it was reviewed to confirm that its results did not preclude or conflict with conclusions based on other data and information; thus, the review of these data was conducted solely by the clinical reviewer without a separate statistical review. Review of the immunogenicity and safety data from Study EFC15081 did not reveal any observed differences between SAR341402 and U.S.-NovoLog that precluded or conflicted with the conclusions based on other data and information submitted to BLA 761325.

The minimal safety data collected during the conduct of Study PDY12695 were also reviewed by the clinical reviewer. Although only the PK and PD data from Study PDY12695 were necessary to support the conclusions of the review of BLA 761325, the safety data were reviewed to confirm that they did not preclude or conflict with conclusions based on other data and information. Review of the safety data from Study PDY12695 did not reveal any differences observed between SAR341402 and U.S.-

NovoLog that precluded or conflicted with the conclusions based on other data and information submitted to BLA 761325.

Section 13.3.1 reviews the efficacy findings of Study EFC15081 and includes a summary of the study design, objectives and endpoints; statistical methodolologies; overview of subject disposition; summary of subject demographic and baseline characteristics; presentation of primary efficacy analyses, other outcomes of interest, and subgroup analyses. The details of the design and primary outcomes of Study PDY12695 are presented by Dr. Mohamad Kronfol in **Section 5.3.1**.

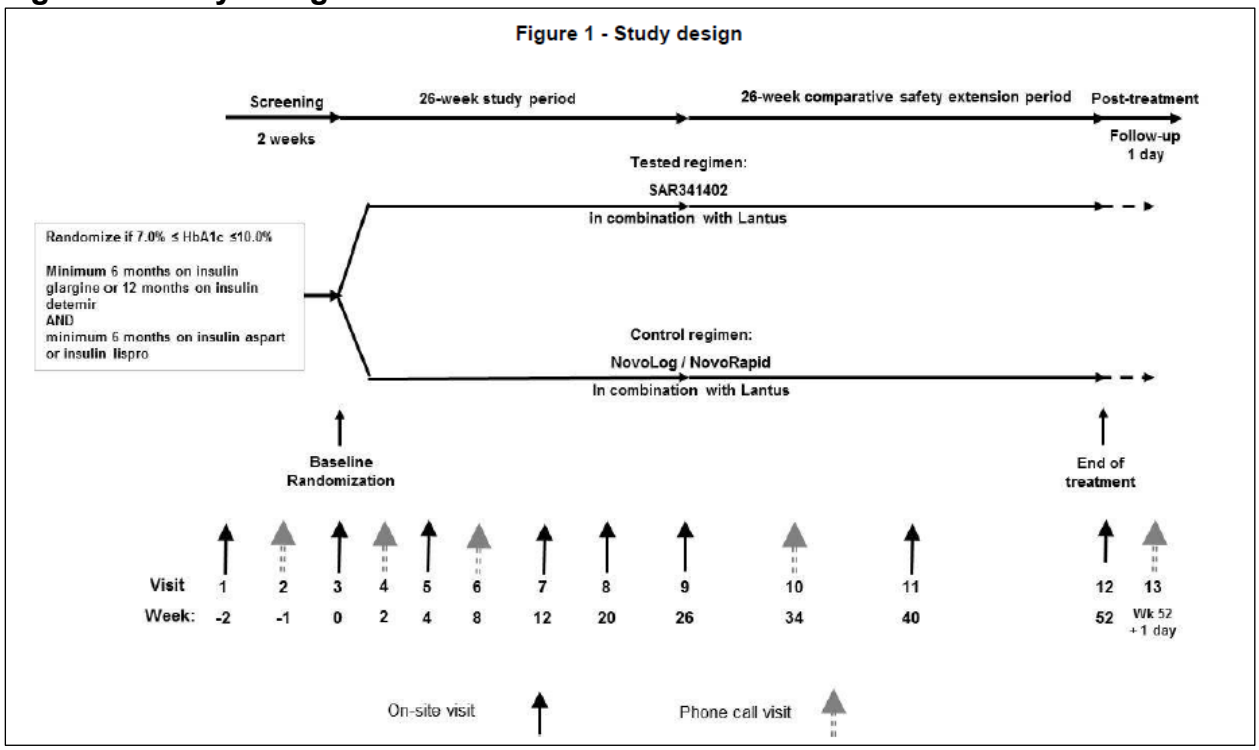
Sections 13.3.2, 13.3.3, and **13.3.4** include a discussions concerning the safety data from EFC15081 and a separate summary of the findings from PDY12695. The review is focused on the safety outcomes of interest for insulin products. The safety data from both 6- and 12- month studies were reviewed. The immunogenicity data were accumulated over 12-months. The 6-month safety data are presented and discussed in the review. The 12- month findings are summarized and detailed when the findings and conclusions differ from the 6-month data.

13.3.1. Efficacy Overview and Clinical Outcomes

Study Design, Objectives and Endpoints

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

Figure 5. Study Design



Source: Study EFC15081 CSR page 24, (Figure 1)

EFC15081 was a multinational study conducted in 82 centers across 7 countries (Finland, Germany, Hungary, Japan, Poland, Russian Federation, and United States). This was a randomized, active-controlled, open-label, parallel group study. The aim of this study was to compare the efficacy and safety, including immunogenicity, of the investigational medical products (IMPs), SAR341402 solution and U.S.-NovoLog, in a broad population of adults with T2D.

EFC15081 enrolled 497 adults with T1D (globally) and an additional 100 patients with T2D (solely from the U.S.) who were receiving multiple daily injection (MDI) therapy with lispro or aspart as prandial insulin and glargine or detemir as basal insulin for the preceeding six months. Any glucose-lowering agents including injectable non-insulin peptides (e.g., Symlin, glucagon-like peptide-1 receptor agonists) other than insulins listed were prohibited during the study. Use of oral anti-diabetes therapy in subjects with T2D prior to the study were permitted to continue at a stable dose except sulfonylureas, which were discontinued at baseline.

EFC15081 included a 2-week screening perioid, a 26-week (6-month) main treatment period, a 26-week (6-month) comparative safety extension period, and a one-day post-treatment follow-up, as depicted in **Figure 5**. Details of timing of visits and scheduled assessments are provided in **Table 21**.

Following a 2-week screening period, eligible subjects were randomized in 1:1 ratio to receive either SAR341402 or comparator. Treatment assignment was stratified by geographical region (Europe, U.S., Japan), type of diabetes mellitus (T1D, T2D), HbA1c value at screening (<8.0%, ≥8.0%), and prior use of insulin aspart (Yes, No). The comparator was U.S.-NovoLog in the U.S. and E.U.-NovoRapid in Europe and Asia. To support the use of both U.S.-NovoLog and E.U.-NovoRapid as comparators to SAR341402, the comparative analytical assessment included all three products and the euglycemic clamp study, PDY12695, was designed as a 3-treatment, 3-period crossover study to compare the the exposure and activity of all three products. Insulin glargine 100 U/mL was used as the mandatory background basal insulin therapy during the study.

SAR341402 was self-administered by SC injection using disposable SoloStar PFP and comparator using disposable FlexPen. Pranidal insulin injections were given before the start of a meal as part of MDI regimen. Treatment was initiated with a unit to unit conversion from the prandial insulin dose used prior to the study.

During the study, IMPs were to be adjusted to achieve a 2-hour postprandial plasma glucose < 180 mg/dL, while avoiding hypoglycemia. For the purpose of the protocol, 2 hours postprandial is defined as 2 hours after the start of the meal. If pre-prandial glucose tests were used, the recommended target range for fasting, pre-prandial plasma glucose was 80 to 130 mg/dL, while avoiding hypoglycemia. Best efforts were to be made to reach the prespecified glycemic target ranges in the first 12 weeks of the study so that steady state conditions with IMPs could be attained for the latter half of the 26-week main treatment period. An internal team, blinded to the treatment groups, reviewed compliance with the treat-to-target goals of the trial.

Key Eligibility Criteria:
Inclusion:

- Adult subjects with T1D or T2D diagnosed for at least 12 months
- Receiving MDI regimen with
    - prandial insulin of U.S.-NovoLog/E.U.-NovoRapid or insulin lispro (100 U/mL) in the last 6 months prior to screening
    - basal insulin of insulin glargine (100 U/mL) in the last 6 months prior to screening or insulin detemir (Levemir) in the last 12 months prior to screening
- Signed written informed consent
- Appropriate contraception in women of child-bearing potential

Exclusion:

- HbA1c <7% or >10% at screening
- Less than 1 year on continuous insulin treatment
- Use of insulin pump in the last 3 months before screening
- Patients with T1D: use of glucose-lowering agents other than insulin including use of non-insulin injectable peptides in the last 3 months prior to screening
- Patients with T2D: use of glucagon-like peptide-1 (GLP-1) receptor agonists in the last 3 months before screening

- Use of oral antidiabetic drugs not on stable dose in the last 3 months before screening visit (sulfonylureas discontinued at baseline).
- Body mass index (BMI) ≥35 kg/m^2 with T1D and ≥40 kg/m^2 in with T2D
- Pregnant or lactating women
- Estimated glomerular filtration rate <30 mL/min/1.73/m^2
- Liver transaminase levels >3 upper limit of the normal laboratory range (ULN), or total bilirubin >1.5 ULN (except in case of Gilbert's syndrome)
- Uncontrolled hypertension
- Other significant unstable hepatic, gastrointestinal, cardiovascular, respiratory or other major systemic conditions that might interfere with evaluation of IMP per Investiagator's judgement.

Study Objectives:
Primary objective: to demonstrate non-inferiority (NIM = 0.3) of SAR341402 to U.S.-NovoLog in HbA1c change from baseline to Week 26 in patients with T1D or T2D also using Lantus.

Key secondary objectives:
- to assess safety of SAR341402 and U.S-NovoLog
- to assess the immunogenicity of SAR341402 and U.S-NovoLog;
- to assess the relationship of AIA with efficacy and safety;

Study Endpoints:
Primary efficacy endpoint: change in HbA1c from baseline to Week 26.

Safety outcomes: hypoglycemia, adverse events (AE), serious adverse events (SAEs), injection site reactions, hypersensitivity reactions, vital signs, lab data and body weight.

Immunogenicity endpoints: AIA positive or negative status, AIA titer, cross-reactivity to human insulin (positive/negative status), and treatment-induced, treatment-boosted and treatment-emergent AIAs during the entire 12-month on-treatment period.

Other outcomes of interest: change in daily basal, mealtime, and total insulin dose from baseline to Week 26 (U/kg body weight).

***Reviewer comment**: HbA1c has been accepted by FDA as an established surrogate outcome measure of efficacy of anti-hyperglycemic agents. Subjects with T1D enrolled in EFC15081 are a sensitive population for assessing differences in immunogenicity related to treatment. The treatment duration of 26-weeks and 26-week safety extension are considered an adequate period of exposure to detect differences in immunogenicity, HbA1c as well as safety parameters between the treatment arms.*

Statistical Methods

Sample size determination:

A sample size of 580 patients (290 patients per arm; approximately 480 patients with T1D and 100 patients with T2D) was considered sufficient to ensure that the upper bound of the 2-sided 95% confidence interval (CI) for the adjusted mean difference between SAR341402 and U.S.-NovoLog/ E.U.-NovoRapid would not exceed a NIM of 0.3% HbA1c with at least 95% power. This sample size was also considered sufficient to ensure that the lower bound of this 2-sided 95% CI would not be below -0.3% HbA1c with at least 95% power, thus providing at least 90% power to show both non-inferiority of SAR341402 over U.S.-NovoLog/ E.U.-NovoRapid (primary analysis) and inverse non-inferiority of U.S.-NovoLog/ E.U.-NovoRapid over SAR341402 (secondary analysis). These calculations assume a common standard deviation (SD) of 1.0% and a true difference in HbA1c between the treatment groups of zero. The NIM of 0.3% HbA1c for the adjusted mean difference between SAR341402 and U.S.-NovoLog/ E.U.-NovoRapid was chosen as it is in line with recommendations by regulatory agencies, including FDA, and based on historical precedent for comparative insulin studies in which a NIM of 0.3% is often used.

Primary efficacy analysis:
The statistical test for the primary efficacy endpoint (change in HbA1c from baseline to Week 26) was one-sided, with alpha level of 0.025 and using a NIM of 0.3%. The primary endpoint was analyzed in the *intent-to-treat (ITT) population* (defined as all randomized patients, irrespective of compliance with the study protocol and procedures) using all post-baseline data available during the main 6-month randomized period (ITT estimand).

A multiple imputation approach in two parts was used with missing data imputed separately for patients who prematurely discontinued IMP during the main 6-month randomized period and patients who completed the main 6-month treatment period.

Data obtained after the imputations were analyzed using an analysis of covariance (ANCOVA) of the change in HbA1c from baseline to Week 26, including the fixed categorical effects of treatment group (SAR341402, U.S.-NovoLog/ E.U.-NovoRapid), randomization strata of geographical region and type of diabetes (Europe T1D, U.S. T1D, U.S. T2D, Japan T1D), screening HbA1c (<8.0%, ≥8.0%), and prior use of U.S.-NovoLog/E.U.-NovoRapid (Yes, No), and the continuous fixed covariate of baseline value. The adjusted least squares mean (LS mean) of the change in HbA1c from baseline to Week 26 for each treatment group was estimated, as well as the between-group LS mean difference of SAR341402 versus U.S.-NovoLog/E.U.-NovoRapid, with the corresponding standard errors (SE) and 2-sided 95% CIs.

Non-inferiority was demonstrated if the upper bound of the 2-sided 95% CI of the difference between SAR341402 and U.S.-NovoLog/E.U.-NovoRapid on ITT population was <0.3%. If non-inferiority of SAR341402 over U.S.-NovoLog/E.U.-NovoRapid was demonstrated, using a hierarchical step-down testing procedure, the inverse non-inferiority (of U.S.-NovoLog/E.U.-NovoRapid over SAR341402) was tested looking at the lower bound of the 2-sided 95% CI of the difference between SAR341402 and U.S.-NovoLog/ E.U.-NovoRapid in the ITT population. Non-inferiority of U.S.-NovoLog/ E.U.-

NovoRapid over SAR341402 was demonstrated if the lower bound was >-0.3%. If SAR341402 was shown to be non-inferior to U.S.-NovoLog/E.U.-NovoRapid and U.S.-NovoLog/E.U.-NovoRapid non-inferior to SAR341402, similar efficacy (statistical equivalence) of SAR341402 and U.S.-NovoLog/E.U.-NovoRapid was assumed.

Analysis of safety endpoints:
Safety analyses during the main 6-month treatment period were descriptive, based on the *safety population* (defined as all randomized patients who receive at least one dose of IMP).

Analysis of anti-insulin aspart antibody (AIA) response:
Immunogenicity analyses during the 12-month on-treatment period were descriptive (no formal statistical testing), based on the *AIA population* (defined as all patients from the safety population with at least one AIA sample available for analysis during the 12-month on-treatment period). The analysis focused on the change in AIA response observed following the IMP administration:

- Patients with *treatment-induced* AIAs were defined as patients with AIAs that developed de novo (seroconversion) following the IMP administration.
- Patients with *treatment-boosted* AIAs were defined as patients with pre-existing AIAs with at least 4-fold increase in titer values following the IMP administration
- Patients with *treatment-emergent* AIAs (AIA incidence) were defined as patients with treatment-induced or treatment-boosted AIAs.

Analysis of neutralizing antibody response:
The analyses of NAb data were based on the AIA population. The analysis focused on the change in NAb response observed following the IMP administration. Patients with *treatment-emergent NAb (NAb incidence)* were defined, for the 12-month analyses, as patients with treatment-emergent AIA and with at least one positive NAb sample during the 12-month on-treatment period.

Reviewer comment: *Of note, EFC15081 was initiated while SAR341402 was being developed as a drug under the 505(b)(2) regulatory pathway (under IND 133678). The study sample size of ~580 subjects was powered to demonstrate noninferiority and inverse noninferiority of SAR341402 and U.S.-NovoLog. The International Council for Harmonization (ICH) E10 states that the NIM cannot be greater than the smallest effect size that the active drug would be reliably expected to have, compared with placebo, in the setting of a planned trial. For diabetes studies, an NIM of 0.3-0.4% has historically been accepted by FDA for investigations of insulin products. During a BPD Type 2 meeting (under IND 136342) for development of SAR341402 as a biosimilar to U.S.-NovoLog (see additional details provided in presubmission history* ***Section 2.1****), FDA advised the Applicant that in order to support a 351(k) application, EFC15081 should be designed with the primary objective of addressing any residual uncertainty of immunogenicity (following the conduct of the analytical and the PK/PD studies), and should support a demonstraton that there is no clinically meaningful difference between SAR341402 and U.S.-NovoLog. Accordingly, FDA recommended study endpoints include immunogenicity in addition to measures of glycemia lowering and safety. FDA*

also suggested that, although it intends to consider the totality of the data collected during EFC1508 in its review of the comparative study, formal statistical testing for immunogenicity and HbA1c is reasonable. The Applicant modified study EFC15081 following this BPD Type 2 meeting an added immunogenicity assessments to EFC15081; however, these secondary endpoints were analyzed descriptively, with no formal statistical testing. Nevertheless, as per the Insulin Immunogenicity Guidance, FDA determined that based on the review of the CAA and Study PDY12695 and the Applicant's immunogenicity assessment, a comparative clinical study for immunogenicity is not necessary; therefore, the data from EFC15081 were considered supportive, but not necessary, of the evaluation of whether SAR341402 is biosimilar to U.S.-NovoLog. The data from EFC15081 were therefore reviewed only to ensure that the findings did not preclude or confilct with the conclusions based on other data and information submitted to BLA 761325.

Disposition of Subjects

A total of 846 subjects were screened for EFC15081, of whom 249 (29.4%) were screen failures (**Figure 6**). The most common reason for screen failure was HbA1c outside of eligibility range at the screening visit. A total of 597 subjects were randomized and treated, 301 in the SAR341402 group and 296 in the U.S.-NovoLog/E.U.-NovoRapid group. The majority of subjects completed the main 6-month treatment period for both treatment groups (92.7% of SAR341402; 92.6% of U.S-NovoLog/ E.U.-NovoRapid).

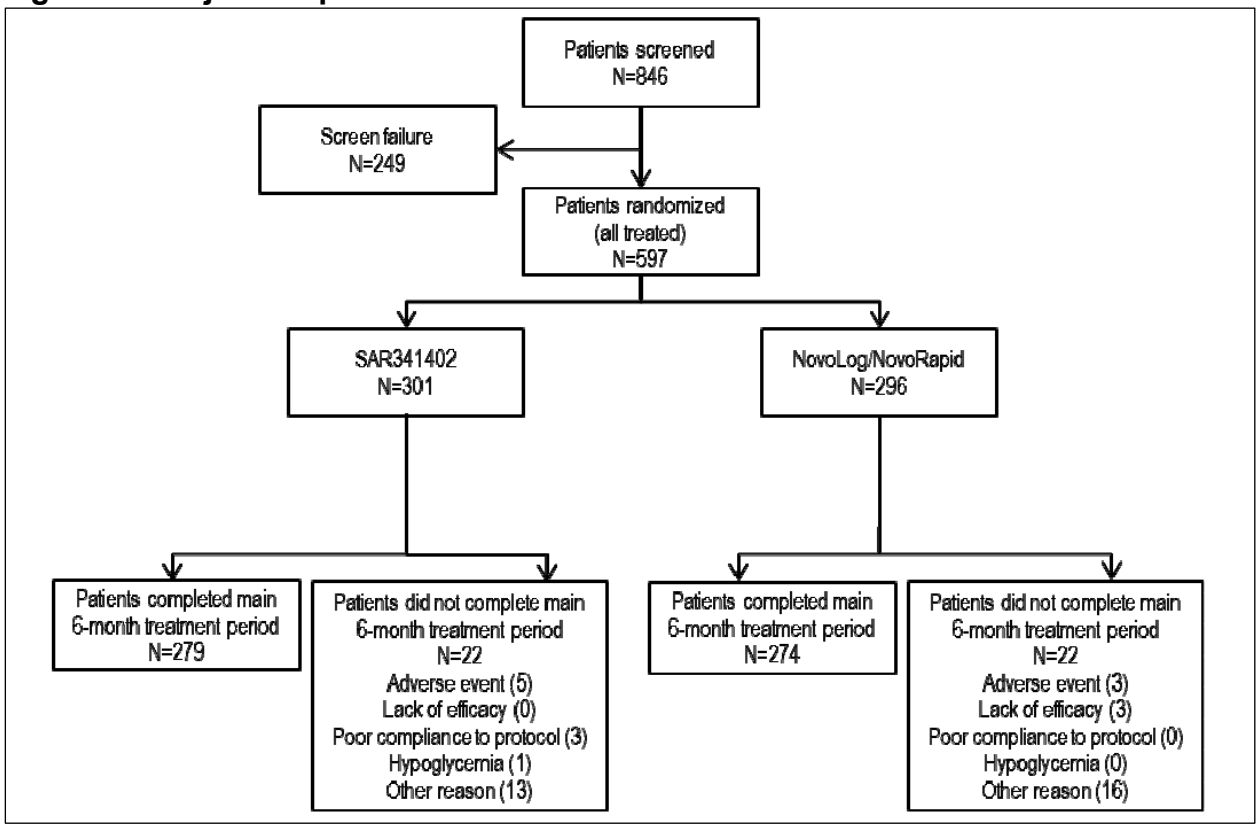
U.S. Site No. 840-0041was closed during the study due to GCP non-compliance (see **Section 8** for details). In total, 4 subjects (2 SAR341402; 2 U.S.- NovoLog) from the site were discontinued from treatment during the main 6-month period. All 4 subjects were included in the ITT, safety and AIA populations.

Among the 296 patients randomized to comparator, 165 (55.7%) were randomized to U.S.- NovoLog (in the U.S.) and 131 (44.3%) were to E.U-NovoRapid.

During the main 6-month treatment period, the percentage of patients who discontinued IMP was low and similar in the 2 treatment groups (7.3% SAR341402; 7.4% U.S.-NovoLog/ E.U.-NovoRapid). As per protocol, patients who prematurely discontinued the treatment were supposed to remain in the study; however, 10 patients (3.3%) in the SAR341402 group and 14 patients (4.7%) in the U.S.-NovoLog/E.U.-NovoRapid group withdrew from the study before Week 26.

In both groups, the most common reason for treatment discontinuation occurred in the category "Other" (13 SAR341402; 16 U.S.-NovoLog/ E.U.-NovoRapid). The most frequently reported reasons in this category "Other" were patient decision or consent withdrawal, and included site closure, and patients lost to follow-up for whom no further information was available (4 SAR341402; 2 U.S.-NovoLog/ E.U.-NovoRapid).

Figure 6. Subject Disposition



Source: Study EFC15081 CSR page 69 (Figure 2)

Protocol Deviations

During the course of EFC15081, major protocol deviations related to defective test strips occurred which affected ~70% of study participants for a portion of the 12-month on-treatment period. In brief, all study subjects were provided with a wireless glucometer (Entra BLE Smart Glucometer), together with test strips (BLE Smart Test strips) to be used during EFE15081 for collecting self-monitored plama glucose (SMPG) measurements. Seven months after study start, the company managing the Applicant-provided e-diaries linked with the glucometers informed the Applicant that 4 out of 6 lots of the test strips provided for the study did not meet the specifications for blood glucose accuracy standards. Consequently, the average blood glucose readings with the defective test strips were between 0.1% and 14.8% *higher* than the average values obtained with non-defective test strips.

In total, defective test strips were used for various durations by potentially 423 out of 597 (~70%) randomized subjects as follows:

- Europe: 197/197 (100%) subjects are expected to have been exposed to defective test strips from September 22, 2017 until April 5, 2018.
- U.S.: 226/335 (67%) subjects are expected to have been exposed to defective test strips from January 16, 2018 until April 9, 2018. The remaining 109/335 (33%) subjects did not use defective test strips.
- Japan: no subjects used defective strips.

Investigational sites were contacted and study participants were informed to stop using the study glucometer with the affected test strip lots to avoid falsely high blood glucose readings. Health Authorities for all the participating countries were also informed in accordance with local laws and regulations pertaining to the reporting of safety information.

The Applicant reports that the defective test strips should have been distributed equally between treatment groups. Accordingly, the Applicant estimates that the extent of usage of defective test strips would not be expected to be substantially different between the treatment groups, and the potential impact would be similar between groups and thus would not affect the between-group comparison. However, the Applicant performed a variety of analyses to assess the potential impact of the usage of defective test strips on the study results.

The Applicant calculated the cumulative duration of the period when defective test strips were used as approximately 55 patient-years (SAR341402: 55.18; U.S.-NovoLog/ E.U.-NovoRapid: 55.71) as compared to approximately 90 patient-years for the period when non-defective test strips were used (SAR341402: 90.74; NovoLog/NovoRapid: 87.37). The cumulative duration of use of defective test strips was similar in the 2 treatment groups as was the cumulative duration of use of non-defective test strips.

After comparing the data between groups for various glycemia related outcomes while using defective and non-defective strips, the Applicant concluded that there was no

evidence of impact observed on the insulin doses and efficacy endpoint. Similarly, the Applicant determined that the transient use of defective test strips did not lead to an increased incidence of SAEs related to hypoglycemia or medication errors. The Applicant's post-hoc analyses revealed that the rate of severe hypoglycemia did not increase with the use of defective test strips. The rate of hypoglyceima was higher in patients who used defective test strips than in those who did not use defective test strips; however, the rates of hypoglycemia were similar between the two treatment arms when patients used non-defective test strips.

Reviwer comment:

- *The clinical impact of defective test strips can affect both efficacy and safety data. Overadjustment of insulin doses based upon falsely elevated glucose values may result in greater mean HbA1c reduction. Elevated values also increase risk of hypoglycemia due to excess insulin dosing or, alternatively, delaying appropriate treatment of hypoglycemia sypmptoms because of falsely reassuring readings.*
- *The Applicant's additional analyses calulated "cumulative duration of the period when defective test strips were used" and suggested that this was comparable between the treatment groups. These calculations also suggested similar cumulative duration for the non-defective strips. While I agree that, in theory, the defective strips would likely have been distributed evenly between groups, I'm less certain that estimated exposure to the defective test strips can be as reliably assumed given that it is possible that some subjects, in either group, may have been monitoring more or less often than the protocol required, and thus duration of effect of defective test strips may have differed from the Applicant's estimation.*
- *Nevertheless, the Applicant's additional analyses, comparing the primary endpoint for regions affected by defective test strip distribution (Europe and U.S.) vs the unaffected region (Japan) suggest no significant differences. Additionally, rates of severe hypoglycemia and medication errors, regardless of treatment group, were similar during the period when defective test strips were used and in the perioid when non-defective test strips were used. The findings of these post-hoc analyses provide reassurance that the conclusions of efficacy and safety of this supportive study were not confounded by this major protocol deviation.*

Demographics and Baseline Characteristics

A total of 597 subjects were randomized and treated, 301 in the SAR341402 group and 296 in the U.S.-NovoLog/ E.U.-NovoRapid group. All randomized patients were included in the ITT population (efficacy population) and all patients received the IMP (safety population).

There were no differences between treatment groups in the proportion of patients completing the main 6-month treatment period. Overall, 553 subjects (92.6 %) in the randomized population completed the main 6-month treatment period. A similar proportion of subjects in each treatment group discontinued the study treatment prematurely (SAR341402: 22/301 [7.3%]; U.S.-NovoLog/ E.U.-NovoRapid: 22/296 [7.4%]).

Demography and baseline characteristics were well-balanced between the 2 treatment groups (**Table 9**). The median age of the randomized population was 49 years (T1D: 45 years; T2D: 64 years) and 16.6% of the subjects were ≥65 years. Male subjects comprised 59.6% of the subjects. Whites made up the majority of the study population (82.6%), followed by Asians (12.5%) and Black or African American (3.2%). U.S. subjects comprised the majority of the study (56.1%) followed by Europe (33%) and Japan (10.9%).

Approximately 64% of subjects had previously been treated with U.S-NovoLog/E.U.-NovoRapid.The mean duration of diabetes prior to study start was 19.5 years (T1D: 19.6 years; T2D:18.9 years). Baseline metabolic control was similar, with mean HbA1c of ~8.0% for both treatment groups. Baseline insulin doses for basal and mealtime insulin (U/kg) were also similar in the the treatment arms.

***Reviewer comment**: Black/ African Americans are under-represented in the study population; however, for an insulin product, I do not believe that this imbalance precludes the generalizability of the study findings.*

Table 9. Summary of participant demographics and baseline characteristics (Randomized population)

Number of patients randomized	SAR341402 (N=301)	NovoLog/NovoRapid (N=296)	All (N=597)
Age (years) (median)	49.0	49.5	49.0
≥65 years [n (%)]	47 (15.6)	52 (17.6)	99 (16.6)
Male [n (%)]	179 (59.5)	177 (59.8)	356 (59.6)
Weight (kg) [mean (SD)]	81.7 (17.6)	81.6 (17.8)	81.6 (17.7)
BMI (kg/m²) [mean (SD)]	27.45 (4.58)	27.46 (4.99)	27.45 (4.78)
≥30 kg/m² [n (%)]	94 (31.2)	87 (29.4)	181 (30.3)
GFR (MDRD) <60 mL/min/1.73m² [n (%)]	28 (9.3)	28 (9.5)	56 (9.4)
Race [n (%)]			
White	248 (82.7)	242 (82.6)	490 (82.6)
Black or African American	11 (3.7)	8 (2.7)	19 (3.2)
Asian	37 (12.3)	37 (12.6)	74 (12.5)
Ethnicity [n (%)] Hispanic or Latino	27 (9.0)	19 (6.4)	46 (7.7)
Randomization strata of type of diabetes [n (%)] T1D	250 (83.1)	247 (83.4)	497 (83.2)
T2D	51 (16.9)	49 (16.6)	100 (16.8)
Type of comparator [n (%)] NovoLog	170 (56.5)	165 (55.7)	335 (56.1)
NovoRapid	131 (43.5)	131 (44.3)	262 (43.9)
Randomization strata of prior use of NovoLog/NovoRapid [n (%)]			
No	109 (36.2)	108 (36.5)	217 (36.3)
Yes	192 (63.8)	188 (63.5)	380 (63.7)
Randomization strata of geographical region [n (%)]			
Europe	98 (32.6)	99 (33.4)	197 (33.0)
Japan	33 (11.0)	32 (10.8)	65 (10.9)
US	170 (56.5)	165 (55.7)	335 (56.1)
Randomization strata of screening HbA1c categories [n (%)]			
HbA1c < 8.0%	143 (47.5)	138 (46.6)	281 (47.1)
HbA1c ≥ 8.0%	158 (52.5)	158 (53.4)	316 (52.9)
Duration of diabetes (years) (median)	16.9	17.3	17.2
≥10 years [n (%)]	235 (78.1)	229 (77.4)	464 (77.7)
Diabetic late complications [n (%)]	142 (47.2)	137 (46.3)	279 (46.7)
Diabetic retinopathy	90 (29.9)	85 (28.7)	175 (29.3)
Diabetic neuropathy	86 (28.6)	82 (27.7)	168 (28.1)
Use of insulin glargine in the 6 months prior to the study [n (%)]	238 (79.1)	237 (80.1)	475 (79.6)
Use of insulin aspart in the 6 months prior to the study [n (%)]	169 (56.5)	161 (54.4)	330 (55.5)
Insulin dose at baseline*a* (U/kg) [mean (SD)]			
Basal insulin	0.390 (0.191)	0.386 (0.231)	0.388 (0.212)
Mealtime insulin	0.398 (0.229)	0.394 (0.247)	0.396 (0.238)
Total insulin	0.789 (0.340)	0.777 (0.404)	0.783 (0.373)
HbA1c (%) [mean (SD)]	8.00 (0.77)	7.94 (0.70)	7.97 (0.74)

SD: standard deviation; N: number; BMI: body mass index; GFR: glomerular filtration rate; MDRD: modification of diet in renal disease (MDRD) formula; T1D: type 1 diabetes mellitus; T2D: type 2 diabetes mellitus; HbA1c: glycated hemoglobin; US: United States.
a Insulin dose at baseline is defined as the median of daily doses available in the week prior to the first injection of IMP

Source: Study EFC15081 Clinical Overview page 33 (Table 6)

Review of Clinical Outcomes Primary Endpoint

Table 10. Summary of change in HbA1c (%) from baseline to Week 26 using ANCOVA analysis with retrieved dropout multiple imputation (ITT population)

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

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

Source: Study EFC15081 CSR page 101 (Table 14)

Table 10 summarizes the primary efficacy outcome from EFC15081. The LS mean changes in HbA1c from baseline to Week 26 in the SAR341402 group (-0.38%) and the U.S.-NovoLog/ E.U.-NovoRapid group (-0.30%) were similar, with a difference of -0.08% (95% CI: -0.192 to 0.039). Non-inferiority of SAR341402 versus U.S.-NovoLog/ E.U.-NovoRapid was demonstrated as the upper bound of the 2-sided 95% CI of the difference between SAR341402 and U.S.-NovoLog/ E.U.-NovoRapid was below the pre-specified NIM of 0.3%.

The inverse non-inferiority of U.S.-NovoLog/ E.U.-NovoRapid versus SAR341402 was tested as a second step analysis: the inverse non-inferiority was also demonstrated as the lower bound of the 2-sided 95% CI of the difference between SAR341402 and U.S.-NovoLog/ E.U.-NovoRapid was above -0.3%. The efficacy of SAR341402 on change in HbA1c from baseline to Week 26 is not clinically different to that of U.S.-NovoLog/ E.U.-NovoRapid.

Sensitivity analyses to assess the impact of the missing HbA1c data at Week 26 (SAR341402: 18/301 patients [6.0%]; U.S.-NovoLog/ E.U.-NovoRapid: 18/296 patients [6.1%]) on the primary analysis demonstrated results that were consistent with the primary analysis. Analysis using the multiple imputation method modeling a “return-to-baseline” for patients having missing data at Week 26 supported the primary analysis

results: LS mean difference in HbA1c change from baseline to Week 26 between SAR341402 and U.S.-NovoLog/ E.U.-NovoRapid of -0.07% (95% CI: -0.178 to 0.036).

A supportive analysis was conducted on the per-protocol population to evaluate the robustness of the conclusion of the primary efficacy analysis when excluding the subjects that might have increased the chance of reaching non-inferiority conclusion. Results of this analysis also supported the primary analysis results with a LS mean difference in HbA1c change from baseline to Week 26 between SAR341402 and U.S.-NovoLog/ E.U.-NovoRapid of -0.07% [95% CI: -0.174 to 0.032].

The HbA1c levels remained fairly stable during the 6-month safety extension period. At Week 52, the LS mean change in HbA1c from baseline was similar to that of Week 26 findings: SAR341402 (-0.25%) vs U.S.-NovoLog/ E.U.-NovoRapid (-0.26%), with the LS mean difference between the SAR341402 and the U.S.-NovoLog/ E.U.-NovoRapid group of 0.01% (95% CI: -0.146 to 0.173%).

Subgroup Analyses

No relevant differences between SAR341402 and U.S.-NovoLog/ E.U.-NovoRapid were seen in subgroup analyses defined by type of diabetes, type of comparator, prior use of U.S.-NovoLog/ E.U.-NovoRapid, regions, race, ethnicity, age group, sex, BMI, eGFR, randomization stratum of screening HbA1c, and duration of diabetes diagnosis. No evidence of heterogeneity of treatment effect was observed across any of the subgroups.

The mean decrease in HbA1c from baseline to Week 26 was similar between SAR341402 and U.S.-NovoLog, as well as between SAR341402 and E.U.-NovoRapid. Efficacy assessment in the subgroup of patients with T1D, comprising the vast majority of the study population, also showed similar results with SAR341402 and U.S.-NovoLog/ E.U.-NovoRapid and were generally consistent with those for the overall population.

***Reviewer comment**: Study EFC15081 demonstrated noninferiority and reverse noninferiority of SAR341402 and U.S.-NovoLog/ E.U.-NovoRapid in HbA1c reduction at 26 Weeks and the results were robust to sensitivity analyses using alternative missing data assumptions. These efficacy findings provide supportive, but not necessary, data for the demonstration of no clinically meaningful differences between SAR341402 and U.S.-NovoLog.*

Other Criteria of Interest: Insulin Doses

Table 11. Summary of daily insulin dose (U/kg) observed and change from baseline values during the main 6-month and 12-month on-treatment periods (Safety population)

Daily insulin dose (U/kg)	SAR341402 (N=301)	NovoLog/NovoRapid (N=296)
Basal insulin		
Baseline		
Number	297	294
Mean (SD)	0.390 (0.191)	0.386 (0.231)
Week 26		
Number	273	272
Mean (SD)	0.396 (0.178)	0.388 (0.210)
Change from baseline to Week 26		
Number	271	270
Mean (SD)	0.005 (0.081)	0.003 (0.088)
Week 52		
Number	256	255
Mean (SD)	0.395 (0.185)	0.383 (0.215)
Change from baseline to Week 52		
Number	253	253
Mean (SD)	0.006 (0.085)	0.005 (0.095)
Mealtime insulin		
Baseline		
Number	299	293
Mean (SD)	0.398 (0.229)	0.394 (0.247)
Week 26		
Number	270	266
Mean (SD)	0.391 (0.228)	0.413 (0.233)
Change from baseline to Week 26		
Number	268	265
Mean (SD)	-0.011 (0.133)	0.011 (0.116)
Week 52		
Number	253	256
Mean (SD)	0.404 (0.251)	0.416 (0.250)
Change from baseline to Week 52		
Number	251	255
Mean (SD)	-0.001 (0.152)	0.009 (0.123)
Total insulin		
Baseline		
Number	295	291
Mean (SD)	0.789 (0.340)	0.777 (0.404)
Week 26		
Number	267	265
Mean (SD)	0.790 (0.341)	0.803 (0.372)
Change from baseline to Week 26		
Number	263	262
Mean (SD)	-0.007 (0.167)	0.015 (0.170)
Week 52		
Number	253	254
Mean (SD)	0.798 (0.368)	0.800 (0.400)
Change from baseline to Week 52		
Number	248	251
Mean (SD)	0.005 (0.175)	0.013 (0.165)

SD: standard deviation.

Source: Study EFC15081 Clinical Overview, pages 34-35 (Table 7)

Because efficacy outcomes are dependent upon optimal insulin dose titration, the summaries and analyses of basal, mealtime, and total daily insulin dose (U/kg) at baseline and weeks 26 and 52 were inspected. As noted in **Table 11**, daily basal and mealtime insulin doses were comparable in the SAR341402 and U.S.-NovoLog/ E.U.-NovoRapid groups at baseline. Small changes in mean insulin doses from baseline were observed over the main 6-month treatment period and the 6-month safety extension period, with no clinically significant difference between groups. Mean basal and mealtime insulin doses remained almost unchanged during the main 6-month and 12-month on-treatment periods in the 2 treatment groups.

Reviewer comment*: In Study EFC1508, there were no clinically significant observed treatment differences in change from baseline to Week 26 and Week 52 for insulin doses for both treatment groups. These findings provide supportive, but not necessary, data for the demonstration of no clinically meaningful differences between SAR341402 and U.S.-NovoLog/ E.U.-NovoRapid.*

13.3.2. Safety Database and Safety Overview

Clinical Studies Used to Evaluate Safety.

PDY12695 was a randomized, double-blind, single dose, 3-treatment, 3-period, 6-sequence, cross-over, 12-hour euglycemic glucose clamp study in adult patients with T1D. In total, 89 subjects received a single SC dose administration of SAR341402 (0.3 U/kg body weight). The minimal safety data collected during the conduct of Study PDY12695 were reviewed to confirm that they did not preclude or conflict with the conclusion of biosimilarity based on the analysis of the comparative analytical data and the finding of PK and PD similarity between SAR341402 and U.S.-NovoLog.

EFC15081 was a 26 week study, with a 6-month safety extension period, which enrolled 597 subjects: 497 with T1D and 100 with T2D. A total 301 subjects received SAR341402 and 296 received U.S.-NovoLog/ E.U.-NovoRapid, with all doses of insulin self-administered. As previously discussed, FDA considers the results of EFC15081 supportive, but not necessary, of the evaluation of SAR341402 as biosimilar to U.S.-NovoLog. These data were reviewed to ensure that there are no unexpected safety findings which would preclude the licensure of the 351(k) application for SAR341402.

Given the differences in study populations, durations, dosing, and designs, the results of PDY12695 and EFC15081 were not integrated in the safety assessment.

PDY12695 Safety Summary

The safety review of PDY12695 did not reveal any concerning safety signals.

Generally, study treatments were well tolerated. No subject experienced a TEAE leading to study discontinuation. One subject experienced a SAE of joint dislocation,

which occurred while playing soccer 1 day after administration of E.U.-NovoRapid, which is unlikely related to the single dose of IMP administered 24 hours prior to the event.

The most frequently reported TEAE was vomiting (4 TEAEs reported by 3 subjects), followed by headache (3 TEAEs reported by 2 subjects) and nasopharyngitis (2 TEAEs reported by 2 subjects). Of the 4 TEAEs of vomiting, 2 followed administration of E.U.-NovoRapid, 1 followed administration of SAR341402, and 1 followed administration of U.S.-NovoLog. Two of the 3 TEAEs of headache followed administration of E.U.-NovoRapid, with the other following SAR341402. One TEAE of nasopharyrngitis followed SAR341402 and one followed E.U.-NovoRapid. No clinically significant abnormalities were recorded for laboratory parameters during the study period. The incidence of potentially clinically significant abnormalities in vital signs and electrocardiograms was low with no trend observed for the 3 different insulin aspart products.

One injection site reaction (erythema at injection site) following administration of SAR341402 was reported as a TEAE and was rated as mild in intensity. Overall, there were no trends observed for visual analog scale pain levels at the injection site for the 3 different insulin aspart products.

Anti-insulin antibodies were assessed at baseline to exclude anti-insulin antibody positive participants from the study. No further immunogenicity assessments were performed during PDY12695.

Reviewer comment*: Review of these limited safety data collected during PDY12695 do not suggest any differences in the safety profiles of SAR341402 and U.S.- NovoLog that would preclude or conflict with conclusions based on other data and information.*

EFC15081 Safety Summary

Study exposure

The safety analysis set for for EFC15081 includes all subjects who took at least one dose of the study medication after randomization. For safety analyses, subjects were categorized according to the treatment that they actually received.

The cumulative duration of treatment exposure during the main 6-month treatment period and 6-month safety extension was comparable between treatment arms:

- 279.95 patient-years in the SAR341402 group and
- 274.91 patient-years in the U.S.-NovoLog/ E.U.-NovoRapid group.

The median duration of exposure was 364 days for both treatment groups. The vast majority of subjects in the both treatment groups were exposed to IMP for more than 51 weeks (SAR341402: 254 subjects [84.4%]; NovoLog/NovoRapid: 254 subjects [85.8%]).

Categorization of adverse events

An AE was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that did not necessarily have a causal relationship with the product. A TEAE was defined as an AE occurring after the first administration of SAR341402 or U.S.-NovoLog after randomization.

SAEs were those AEs that occurred at any dose that result in death, life-threatening experience, inpatient hospitalization or prolongation of hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or important medical events based on medical judgement.

Laboratory AEs included an abnormality which is clinically significant: an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management.

Safety assessments in Study EFC15081 included AEs, SAEs, vital signs and weight, laboratory measures, hypoglycemia, injection site reactions, hypersensitivity reactions, and antibody assessments. Timing of safety assessments are summarized in **Table 21**.

All hypoglycemia events were reported on a dedicated hypoglycemia page in the e-CRF and were not considered as AEs. Only hypoglycemia events meeting the criteria of an SAE were to be reported on both the dedicated hypoglycemia form and the SAE form in the e-CRF. All events of severe hypoglycemia including symptoms of seizure, unconsciousness or coma were to be reported as SAEs. Biochemical confirmation of hypoglycemia was done by SMPG using a blood glucose device provided by the Sponsor.

SMPG value related to hypoglycemia was transferred from the plasma glucose meter to the participant e-diary via Bluetooth. All hypoglycemia episodes were to be documented by the participant on the hypoglycemic episode page of the e-diary, and were secondarily transferred to the dedicated hypoglycemia page in the e-CRF.

Hypoglycemia events were categorized according to the following ADA definitions:

- Severe hypoglycemia, defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
    - These episodes may have been associated with sufficient neuroglycopenia to induce seizure, unconsciousness or coma. Plasma glucose measurements may not have been available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal was considered sufficient evidence that the event was induced by a low plasma glucose concentration.
    - The definition of severe hypoglycemia included all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place participants at risk for injury to themselves or others. This means that the participant required assistance

of another person to administer carbohydrates or to provide other resuscitative actions. Assisting a participant only out of kindness was not considered a “requires assistance” incident.
    - Severe hypoglycemia will be qualified as SAE only if it fulfills SAE criteria. All events of seizures, unconsciousness or coma are reported as SAEs.
- Documented symptomatic hypoglycemia, defined as an event with symptoms of hypoglycemia and with a measured plasma glucose concentration less than or equal to 70 mg/dL.
- Asymptomatic hypoglycemia, defined as an event without symptoms of hypoglycemia but with a measured plasma glucose concentration less than or equal to 70 mg/dL.
- Probable symptomatic hypoglycemia, defined as an event with symptoms of hypoglycemia and missing plasma glucose concentration.
- Relative hypoglycemia (also termed “pseudohypoglycemia”), defined as an event with symptoms of hypoglycemia but with a measured plasma glucose concentration greater than 70 mg/dL.

Injection site reactions and hypersensitivity reactions are to be recorded in the e-CRF and assessed at the study site. Hypersensitivity events are to be reviewed by the Allergic Reaction Assessment Committee (ARAC) to adjudicate and determine the nature fo each event.

13.3.3. Major Safety Results

Overview of Adverse Events

Table 12 provides an overview of the various TEAEs occurring between treatment groups over the main 6-month treatment period and the 6-month safety extension period of study EFC15081. The percentage of subjects experiencing TEAEs, SAEs, and TEAEs leading to treatment discontinuation was generally similar in the SAR341402 group and the U.S.-NovoLog/ E.U.-NovoRapid group. A total of 6 deaths were reported in study EFC15081: 2 during the main 6-month period and 4 during the 6-month safety extension period. One participant (0.3%) died in the SAR341402 group and 5 participants (1.7%) died in the U.S.-NovoLog/ E.U.-NovoRapid group. Additional details about these AEs are provided in the following sections.

Table 12. Overview of treatment-emergent adverse events during the main 6-month and 12-month on-treatment periods - Safety population

	Main 6-month on-treatment period		12-month on-treatment period	
n (%)	**SAR341402 (N=301)**	**NovoLog/ NovoRapid (N=296)**	**SAR341402 (N=301)**	**NovoLog/ NovoRapid (N=296)**
Patients with any TEAE	156 (51.8)	146 (49.3)	184 (61.1)	168 (56.8)
Patients with any treatment-emergent SAE	25 (8.3)	18 (6.1)	36 (12.0)	29 (9.8)

Patients with any TEAE leading to death	0	2 (0.7)	1 (0.3)	3 (1.0)
Patients with any TEAE leading to permanent treatment discontinuation	5 (1.7)	3 (1.0)	6 (2.0)	4 (1.4)

TEAE: Treatment-emergent adverse event, SAE: Serious adverse event
n (%) = number and percentage of patients with at least one TEAE
Source: Study EFC15081 Clinical Overview (Table 18)

Deaths

Table 13 provides a list of deaths occurring during study EFC15081, all of which were assessed as not related to IMP by the Applicant. Additional details of the deaths are provided below.

Table 13. Summary of deaths reported during the main 6-month and 12-month on-treatment periods - Safety population

Deaths occurring during the main 6-month period	(b) (6) NovoLog/NovoRapid	Death on-treatment resulting from TEAE	Sudden death with multiorgan failure in a 73-year-old female participant with T2D
	(b) (6) NovoLog/NovoRapid	Death post-treatment resulting from post-treatment AE	Hypovolemic shock in a 68-year-old male participant with T2D hospitalized for myocardial infarction
Deaths occurring during the 6-month safety extension period	(b) (6) SAR341402	Death on-treatment resulting from a TEAE that started after the main 6-month period	71-year-old male participant with T1D found dead at home with diabetic ketoacidosis
	(b) (6) NovoLog/NovoRapid	Death on-treatment resulting from a TEAE that started after the main 6-month period	Cardiac arrest and sepsis in a 67-year-old male participant with T1D
	(b) (6) NovoLog/NovoRapid	Death post-treatment resulting from TEAE that started during the main 6-month period	Prolymphocytic leukemia in a 67-year-old male participant with T2D
	(b) (6) NovoLog/NovoRapid	Death post-treatment resulting from a post-treatment AE that started after the main 6-month period	Sepsis in a 68-year-old male participant with T1D

Source: Study EFC15081 Clinical Overview Page 54 (Table 20)

- Subject (b) (6) on U.S.-NovoLog/E.U.-NovoRapid died on-treatment day (b) (6) from a TEAE of sudden death with multiorgan failure. Subject had comorbidities of retinopathy, nephropathy, and neuropathy and presented with cellulitis 2 months prior to death. Subject underwent angioplasty for peripheral artery disease of tibial and superficial femoral arteries 2 weeks prior to death which occurred at her home.
- Subject (b) (6) he subject was hospitalized on day (b) (6) or TEAE of myocardial infarction and peptic ulcer hemorrhage. Treatment with U.S.-NovoLog/E.U.-NovoRapid was discontinued. Subject died of hypovolemic shock (b) (6) weeks later.
- Subject (b) (6) died on treatment with SAR341408. The subject was found dead at home on day (b) (6) and was diagnosed with diabetic ketoacidocis. He had

history of T1D for over 40 years and concomitant history of depression, mild dementia and medical noncompliance.

- Subject (b) (6) was diagnosed with prolymphocytic leukemia, leading to discontinuation of treatment with U.S.-NovoLog/E.U.-NovoRapid on day 179. The subject died approximately (b) (6) months after IMP discontinuation with progression of leukemia.
- Subject (b) (6) discontinued U.S.-NovoLog/E.U.-NovoRapid on day 250 due to generalized weakness. The patient had complicated history of recurrent, persistent AEs of diabetic foot infection, cellulitis, and osteomyelitis. On day (b) (6) the subject was hospitalized with sepsis, lethargy, malnutrition due to inability to tolerate tube feeds. Subject died on day (b) (6) of sepsis.
- Subject (b) (6) died on treatment with U.S.-NovoLog/E.U.-NovoRapid. On Day (b) (6) of the study, the patient experienced SAEs of sepsis with acute respiratory failure and cardiac arrest.

Reviewer comment*: It is notable that 5 of the 6 deaths that occurred during ECF15081 were in subjects from the U.S.-NovoLog/E.U-NovoRapid group; however, the study population was at high risk for cardiovascular disease with mean age of 49 years and mean duration of diabetes mellitus of 17 years. Upon reviewing the details in the narratives of the cases, I agree with the Applicant that these 6 deaths were unlikely related to the IMP. It is most likely that the unfavorable imbalance for U.S.-NovoLog/E.U-NovoRapid group is due to chance.*

Dropouts and/or Discontinuations

The incidence of TEAEs leading to permanent treatment discontinuation was low and similar in the 2 treatment groups (SAR341402: 1.7% [5 patients] vs U.S.-NovoLog/E.U.-NovoRapid: 1.0% [3 patients]). As listed in **Table 14**, no AE preferred term (PT) was listed more than once as the cause for treatment discontinuation.

In the 6-month safety extension period, only 1 additional discontinuation due to TEAE was reported from each treatment group. In addition, 1 discontinuation occurred due to pregnancy in the SAR341402 group on day 315 of treatment. The outcome of the pregnancy was unknown.

Table 14. Summary of TEAEs Leading to Discontinuation during the main 6-month treatment period – Safety population

System Organ Class - Preferred Term	NovoLog/NovoRapid (N=296) n (%)	SAR341402 (N=301) n (%)	Risk Difference RD (95% CI)	Forest Plot
Blood and lymphatic system disorders	**0 (0.0)**	**1 (0.3)**	-0.33 (-0.98, 0.32)	
Neutropenia	0 (0.0)	1 (0.3)	-0.33 (-0.98, 0.32)	

System Organ Class - Preferred Term	NovoLog/NovoRapid (N=296) n (%)	SAR341402 (N=301) n (%)	Risk Difference RD (95% CI)	Forest Plot
Cardiac disorders	**1 (0.3)**	**0 (0.0)**	0.34 (-0.32, 1.00)	
Myocardial infarction	1 (0.3)	0 (0.0)	0.34 (-0.32, 1.00)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.3)**	**0 (0.0)**	0.34 (-0.32, 1.00)	
Prolymphocytic leukaemia	1 (0.3)	0 (0.0)	0.34 (-0.32, 1.00)	
Nervous system disorders	**0 (0.0)**	**1 (0.3)**	-0.33 (-0.98, 0.32)	
Headache	0 (0.0)	1 (0.3)	-0.33 (-0.98, 0.32)	
Renal and urinary disorders	**0 (0.0)**	**1 (0.3)**	-0.33 (-0.98, 0.32)	
Renal pain	0 (0.0)	1 (0.3)	-0.33 (-0.98, 0.32)	
Skin and subcutaneous tissue disorders	**1 (0.3)**	**2 (0.7)**	-0.33 (-1.46, 0.80)	
Dermatitis allergic	0 (0.0)	1 (0.3)	-0.33 (-0.98, 0.32)	
Urticaria	1 (0.3)	1 (0.3)	0.01 (-0.92, 0.93)	

Source: Reviewer generated using OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "NovoLog/NovoRapid" and SAFFL = "Y" (NovoLog/NovoRapid); TRT01A = "SAR341402" and SAFFL = "Y" (SAR341402); TRTEMFL = "Y" and PSOCFL = "Y" and AEACN1 = "DRUG WITHDRAWN" (Adverse Events).
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Serious Adverse Events:

SAEs were reportedby a comparable number of subjects in each treatment group: 25 (8.3%) in the SAR341402 group vs 18 (6.1%) in the U.S.-NovoLog/E.U.-NovoRapid group.

SAEs were distributed over a variety of System Organ Classes (SOC) without any clustering by PT. In the treatment groups, the most frequently reported SAEs by SOC were Nervous system disorders (SAR341402: 3.0% [9 subjects]; U.S.-NovoLog/ E.U-NovoRapid: 2.4% [7 subjects]). The most frequently reported SAE at the PT level was hypoglycemic unconsciousness: SAR341402: 2.0% (6 subjects with a total of 9 events) vs U.S.-NovoLog/ E.U-NovoRapid: 1.0% (3 subjects with a total of 4 events). It is notable that the Applicant chose to categorize severe hypoglycemia events as SAEs only if they fulfilled SAE criteria.

During the 12-month on-treatment period, the number of SAEs was similar in both treatment groups and comparable with the pattern seen in the main 6-month period.

Table 15. Summary of Serious Adverse Reactions during the main 6-month treatment period – Safety population

Summary of Serious TEAEs		
Preferred Term	**NovoLog/NovoRapid (N=296) n (%)**	**SAR341402 (N=301) n (%)**
Hypoglycaemic unconsciousness	3 (1.0)	6 (2.0)
Accidental overdose	2 (0.7)	3 (1.0)
Hypoglycaemia	1 (0.3)	3 (1.0)
Device use error	0 (0.0)	2 (0.7)
Diabetic foot	0 (0.0)	2 (0.7)
Diabetic ketoacidosis	0 (0.0)	2 (0.7)
Rotator cuff syndrome	0 (0.0)	2 (0.7)
Acute myocardial infarction	0 (0.0)	1 (0.3)
Atelectasis	0 (0.0)	1 (0.3)
Bronchitis bacterial	0 (0.0)	1 (0.3)
Carpal tunnel syndrome	0 (0.0)	1 (0.3)
Chest pain	0 (0.0)	1 (0.3)
Clostridium difficile colitis	0 (0.0)	1 (0.3)
Gastric ulcer	0 (0.0)	1 (0.3)
Herpes zoster	0 (0.0)	1 (0.3)
Intervertebral disc protrusion	0 (0.0)	1 (0.3)
Pyelonephritis acute	0 (0.0)	1 (0.3)
Small intestinal haemorrhage	0 (0.0)	1 (0.3)
Syncope	0 (0.0)	1 (0.3)
Transient ischaemic attack	0 (0.0)	1 (0.3)
Ulna fracture	0 (0.0)	1 (0.3)
Angina pectoris	1 (0.3)	0 (0.0)
Cellulitis	2 (0.7)	0 (0.0)
Colon adenoma	1 (0.3)	0 (0.0)
Diabetic foot infection	1 (0.3)	0 (0.0)
Hepatic cancer	1 (0.3)	0 (0.0)
Hypoglycaemic coma	1 (0.3)	0 (0.0)
Hypoglycaemic seizure	2 (0.7)	0 (0.0)
Intercapillary glomerulosclerosis	1 (0.3)	0 (0.0)
Loss of consciousness	1 (0.3)	0 (0.0)
Myocardial infarction	1 (0.3)	0 (0.0)
Osteomyelitis chronic	1 (0.3)	0 (0.0)
Pancreatic carcinoma	1 (0.3)	0 (0.0)
Peptic ulcer haemorrhage	1 (0.3)	0 (0.0)
Pneumonia	1 (0.3)	0 (0.0)
Polyneuropathy	1 (0.3)	0 (0.0)
Procedural pain	1 (0.3)	0 (0.0)
Prolymphocytic leukaemia	1 (0.3)	0 (0.0)
Road traffic accident	1 (0.3)	0 (0.0)
Sudden death	1 (0.3)	0 (0.0)
Wound infection	1 (0.3)	0 (0.0)

Summary of Serious TEAEs		
Preferred Term	NovoLog/NovoRapid (N=296) n (%)	SAR341402 (N=301) n (%)

Source: Reviewer generated using OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "NovoLog/NovoRapid" and SAFFL = "Y" (NovoLog/NovoRapid); TRT01A = "SAR341402" and SAFFL = "Y" (SAR341402); TRTEMFL = "Y" and AESER = "Y" (Adverse Events).
Percent Threshold: Any Column > 0%.

Common Treatment Emergent Adverse Events

The safety profiles in terms of type of TEAEs and frequency of occurrence were generally similar between the SAR341402 and the U.S.-NovoLog/E.U.-NovoRapid groups. A total of 156/301 (51.8%) patients in the SAR341402 group and 146/296 (49.3%) in the U.S.-NovoLog/E.U.-NovoRapid group reported TEAEs during the main 6-month treatment period (**Table 16**).

The most frequently reported TEAEs at the PT level were nasopharyngitis (SAR341402: 8.3% vs U.S.-NovoLog/NovoRapid: 8.4%), upper respiratory tract infections (SAR341402: 5.3% vs U.S.-NovoLog/E.U.-NovoRapid: 8.8%) and influenza (SAR341402: 5.0% vs U.S.-NovoLog/E.U.-NovoRapid: 3.0%). All other TEAEs were reported in fewer than 3% of participants regardless of treatment group.

At the SOC level, reported TEAEs were comparable between treatment groups with the exception of nervous system disorders (SAR341402: 35 [11.6%] vs U.S.-NovoLog/E.U.-NovoRapid: 19 [6.4%]). The higher proportion of reports for the SAR341402 group was driven mostly due to headaches (SAR341402: 6 [2.0%] vs U.S.-NovoLog/E.U.-NovoRapid: 1 [0.3%]).

During the 6-month safety extension period, the pattern of TEAEs was similar in the 2 treatment groups. The most frequently reported TEAEs at the PT level were the same as in the main 6-month treatment period. Also during both the main treatment period and the safety extension period, the majority of TEAEs were mild to moderate in severity.

Table 16. Summary of Treatment Emergent Adverse Events occurring in greater than 1% of subjects during the main 6-month treatment period – Safety population

Summary of TEAEs		
System Organ Class - Preferred Term	NovoLog/NovoRapid (N=296) n (%)	SAR341402 (N=301) n (%)
Infections and infestations	**84 (28.4)**	**88 (29.2)**
Nasopharyngitis	25 (8.4)	25 (8.3)
Upper respiratory tract infection	26 (8.8)	16 (5.3)
Influenza	9 (3.0)	15 (5.0)

Summary of TEAEs		
System Organ Class - Preferred Term	NovoLog/NovoRapid (N=296) n (%)	SAR341402 (N=301) n (%)
Sinusitis	6 (2.0)	5 (1.7)
Bronchitis	0 (0.0)	4 (1.3)
Bronchitis bacterial	1 (0.3)	3 (1.0)
Cystitis	3 (1.0)	1 (0.3)
Viral upper respiratory tract infection	3 (1.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**82 (27.7)**	**86 (28.6)**
Cough	2 (0.7)	7 (2.3)
Gastrointestinal disorders	**35 (11.8)**	**43 (14.3)**
Gastroenteritis	4 (1.4)	8 (2.7)
Vomiting	2 (0.7)	5 (1.7)
Diarrhoea	6 (2.0)	4 (1.3)
Pharyngitis	2 (0.7)	4 (1.3)
Musculoskeletal and connective tissue disorders	**35 (11.8)**	**38 (12.6)**
Back pain	3 (1.0)	4 (1.3)
Pain in extremity	3 (1.0)	4 (1.3)
Musculoskeletal pain	4 (1.4)	3 (1.0)
Arthralgia	6 (2.0)	2 (0.7)
Osteoarthritis	3 (1.0)	0 (0.0)
Nervous system disorders	**19 (6.4)**	**35 (11.6)**
Headache	1 (0.3)	6 (2.0)
Carpal tunnel syndrome	0 (0.0)	3 (1.0)
Injury, poisoning and procedural complications	**26 (8.8)**	**30 (10.0)**
Rotator cuff syndrome	0 (0.0)	6 (2.0)
Accidental overdose	3 (1.0)	5 (1.7)
Fall	0 (0.0)	4 (1.3)
Laceration	1 (0.3)	4 (1.3)
Device use error	1 (0.3)	3 (1.0)
Contusion	3 (1.0)	1 (0.3)
Metabolism and nutrition disorders	**21 (7.1)**	**27 (9.0)**
Skin and subcutaneous tissue disorders	**23 (7.8)**	**26 (8.6)**
Vascular disorders	**23 (7.8)**	**23 (7.6)**
Hypertension	8 (2.7)	5 (1.7)
Endocrine disorders	**12 (4.1)**	**19 (6.3)**
Hypoglycaemic unconsciousness	3 (1.0)	6 (2.0)
Diabetic neuropathy	1 (0.3)	3 (1.0)
Hypoglycaemia	1 (0.3)	3 (1.0)
General disorders and administration site conditions	**17 (5.7)**	**13 (4.3)**
Pyrexia	2 (0.7)	4 (1.3)
Injection site bruising	3 (1.0)	1 (0.3)
Cardiac disorders	**9 (3.0)**	**9 (3.0)**
Oedema peripheral	4 (1.4)	3 (1.0)
Eye disorders	**4 (1.4)**	**9 (3.0)**
Immune system disorders	**10 (3.4)**	**9 (3.0)**
Urticaria	4 (1.4)	1 (0.3)

Summary of TEAEs		
System Organ Class - Preferred Term	NovoLog/NovoRapid (N=296) n (%)	SAR341402 (N=301) n (%)
Renal and urinary disorders	9 (3.0)	8 (2.7)
Investigations	3 (1.0)	6 (2.0)
Blood and lymphatic system disorders	5 (1.7)	3 (1.0)
Hepatobiliary disorders	1 (0.3)	3 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.4)	3 (1.0)
Reproductive system and breast disorders	1 (0.3)	3 (1.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "NovoLog/NovoRapid" and SAFFL = "Y" (NovoLog/NovoRapid); TRT01A = "SAR341402" and SAFFL = "Y" (SAR341402); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Any Column ≥ 1%.

Reviewer comment*: In terms of overall TEAEs, TEAEs leading to treatment discontinuations and SAEs, the proportion of subjects reporting events are comparable between treatment groups. The imbalance in deaths not favoring U.S.-NovoLog/E.U.-NovoRapid in EFC15081 is most likely due to chance, given the high risk population enrolled in the study. Similarly, the numerical imbalance in SOC of nervous system disorders not favoring SAR431402 is also likely due to chance given that there is no known causal mechanism for insulin products to result in nervous system symptoms. In my opinion, the minor imbalances noted between treatment groups do not appear to be significant or raise a clinical concern.*

Other Product-Specific Safety Concerns

Local allergic reactions:
TEAEs of injection site reaction were reported in few subjects during study EFC15081 with similar frequency in both treatment groups (SAR341402: 0.7% [2] vs U.S.-NovoLog/E.U.-NovoRapid: 1.4% [4]). No additional injection site reactions were reported during the 6-month safety extension period.

Systemic hypersensitivity and immune mediated adverse events:
Hypersensitivity reactions were rare during study EFC15801 and were reported by similar percentages of subjects (3.7%) in both treatment groups. The most frequently reported events were conjunctivitis and dermatitis allergic (reported in 2 subjects [0.7%] each) in the SAR341402 group and urticaria (reported in 4 subjects [1.4%]) in the U.S.-NovoLog/E.U.-NovoRapid group. None of the other events were reported in more than 1 participant in either group. No events were categorized as serious. The events were considered as related to the IMP in 2 (0.7%) subjects in the SAR341402 group and in 1 (0.3%) subject in the U.S.-NovoLog/E.U.-NovoRapid group.

TEAEs of hypersensitivity reaction resulted in permanent IMP discontinuation in 2 subjects in the SAR341402 group and in 1 subject in the U.S.-NovoLog/E.U.-NovoRapid

group. Fourteen (14) events of hypersensitivity reactions were adjudicated as allergic reactions by the ARAC (6 events reported in 5 patients in the SAR341402 group; 8 events reported in 8 patients in the U.S.-NovoLog/E.U.-NovoRapid group). Only 2/14 events were considered by the ARAC as related to IMP (one event of urticaria in each treatment group). Both of those events led to permanent IMP discontinuation.

A low and similar percentage of subjects in the 2 groups had TEAEs of hypersensitivity reaction during the 6-month safety extension period: 5.6% of subjects in the SAR341402 group (17 participants, with a total of 20 events) and 7.1% of subjects in the U.S.-NovoLog/E.U.-NovoRapid group (21 participants, with a total of 22 events). In the 6-month safety extension period, hypersensitivity reactions were reported by an additional 16 subjects (6 in the SAR341402 group with a total of 8 events and 10 in the U.S.-NovoLog/E.U.-NovoRapid group with a total of 10 events). Two of these events (pneumonitis and acute respiratory failure), one in each treatment group, were considered as serious but not related to IMP by the Investigator.

Device-related safety events:
The AE of *device use error* was reported by 2 subjects in the SAR341402 treatment group. Details from the narratives are provided below.

- Subject (b) (6) 57 year old white, Hispanic man with T2D experienced SAE of accidental overdose with SAR341402 due to device use error resulting in hypoglycemia. He accidentally injected 102 units of SAR341402 instead of basal insulin at bedtime and experienced a blood glucose of 63 mg/dL with symptoms of shaky trembling, heart pounding, sweating, drowsiness, dizziness, confusion. The subject was able to self-administer orange juice with correction of his glucose levels.
- Subject (b) (6) 64 year old white woman with T1D experienced SAE of accidental overdose with SAR341402 resulting in *hypoglycaemic unconsciousness*. She accidentally grabbed the wrong insulin pen device and injected 40 units of SAR341402 instead of basal insulin which resulted in glucose of 49 mg/dL which she was able to self-treat with carbohydrate intake. Two hours later the patient lost consciousness due to severe hypoglycemia and took juice to increase the sugar level. The patient also experienced confusion, drowsiness or dizziness, and shaky trembling. The patient was not capable of treating self and required assistance. The patient regained consciousness and had glucose of 151 mg/dL.

Reviewer comment*: The review of narrative reports of 'device use error' actually indicate a human error in administering the incorrect type of insulin. There are no clinical concerns related to a faulty device for SAR341402 .*

Hypoglycemic adverse events:
During the main 6-month treatment period, the majority of subjects had at least one event of hypoglycemia regardless of the category: SAR341402 96.7% (291/301) vs U.S.-NovoLog/E.U.-NovoRapid 96.3% (285/296).

As summarized in **Table 17**, during the main 6-month treatment period, hypoglycemia was reported by a similar proportion of subjects in the SAR341402 and U.S.-NovoLog/E.U.-NovoRapid groups for all categories of hypoglycemia (any, severe, documented symptomatic and asymptomatic). Similarly, there were no significant differences in the event rates per patient-year of exposure.

Severe hypoglycemia was reported by 4.0% of patients in the SAR341402 group and 3.4% of patients in the U.S.-NovoLog/E.U.-NovoRapid group. Similarly, the he event rate of severe hypoglycemia per participant-year of exposure was low and comparable between both treatment groups: 0.14 in the SAR341402 group and 0.10 in the U.S.-NovoLog/E.U.-NovoRapid group.

Severe hypoglycemia was mainly reported in subjects with T1D, with only 1 subject with T2D (U.S.-NovoLog/E.U.-NovoRapid group) having had a severe hypoglycemia event. The majority of subjects with severe hypoglycemia had a prompt recovery after corrective treatment (i.e., oral carbohydrate, glucagon, or intravenous glucose). The most common symptoms reported in association with severe hypoglycemia were:

- coma loss of consciousness (SAR341402: 6/301 U.S.-NovoLog/E.U.-NovoRapid: 5/296).
- confusion (SAR341402: 6/301 vs U.S.-NovoLog/E.U.-NovoRapid: 7/296).
- drowsy or dizzy (SAR341402: 5/301 vs U.S.-NovoLog/E.U.-NovoRapid: 5/296).

Table 17. Incidence (%) and rate (events per patient year of exposure) of hypoglycemia during the main 6-month treatment period -Safety population

	Number (%) of participants with at least one hypoglycemia		Number of hypoglycemia (rate per participant- year of exposure)	
Type of hypoglycemia	**SAR341402 (N=301)**	**NovoLog/NovoRapid (N=296)**	**SAR341402 (N=301)**	**NovoLog/NovoRapid (N=296)**
Total patient years	-	-	145.92	143.09
Any hypoglycemia	291 (96.7)	285 (96.3)	10646 (72.96)	9917 (69.31)
Severe hypoglycemia	12 (4.0)	10 (3.4)	20 (0.14)	14 (0.10)
Documented symptomatic hypoglycemia				
< 3.0 mmol/L (54 mg/dL)	206 (68.4)	193 (65.2)	1619 (11.10)	1400 (9.78)
Asymptomatic hypoglycemia				
< 3.0 mmol/L (54 mg/dL)	125 (41.5)	117 (39.5)	592 (4.06)	655 (4.58)

Source: Study EFC15081 Clinical Overview page 48-49 (Table 15 modified))

During the 6-month safety extension period, as summarized in **Table 18**, severe hypoglycemia was reported by similar percentages of subjects in the treatment groups (SAR341402: 6.0% [18/301] vs U.S.-NovoLog/E.U.-NovoRapid: 4.7% [14/296]). As compared to the main 6-month treatment period, the 6-month safety extension period included an additional 10 subjects (6 in the SAR341402 and 4 in the U.S.-NovoLog/E.U.-NovoRapid) with severe hypoglycemia reports. The rate of severe hypoglycemia events per participant-year of exposure remained low and similar in the treatment groups: 0.12 in the SAR341402 and 0.08 in the U.S.-NovoLog/E.U.-NovoRapid.

Table 18. Incidence (%) and rate (events per patient year of exposure) of hypoglycemia during the 12-month on-treatment period -Safety population

	Number (%) of participants with at least one hypoglycemia		Number of hypoglycemia (rate per participant-year of exposure)	
Type of hypoglycemia	**SAR341402 (N=301)**	**NovoLog/NovoRapid (N=296)**	**SAR341402 (N=301)**	**NovoLog/NovoRapid (N=296)**
Total patient years	-	-	280.78	275.72
Any hypoglycemia	295 (98.0)	290 (98.0)	18530 (66.00)	17773 (64.46)
Severe hypoglycemia	18 (6.0)	14 (4.7)	33 (0.12)	22 (0.08)
Documented symptomatic hypoglycemia				
< 3.0 mmol/L (54 mg/dL)	233 (74.1)	220 (74.3)	2631 (9.37)	2458 (8.91)
Asymptomatic hypoglycemia				
< 3.0 mmol/L (54 mg/dL)	152 (50.5)	139 (47.0)	1102 (3.92)	1195 (4.33)

Source: Study EFC15081 Clinical Overview page 50 (Table 17 modified)

Reviewer comment*: The incidence and rates of all categories of hypoglycemia did not differ between treatment groups, including severe hypoglycemic events. The safety profile of SAR341402 appears comparable to U.S.-NovoLog and reflects the known AEs common to all insulin products. Results of Study ECF15081 do not suggest any clinically meaningful differences between SAR341402 and U.S.-NovoLog.*

13.3.4. Additional Safety Evaluations: Immunogenicity

Analysis populations and immunogenicity assessments

Immunogenicity assessments occurred from baseline and through the main 26-week treatment period and the 26-week safety extension perioid. Samples were collected at day 1 and weeks 4, 12, 26, 40, 52 and/or at end of treatment (EOT) in case of premature IMP discontinuation. Samples drawn at least 8 hours after the last administration of mealtime insulin.

The analyses for AIA and NAb were based on the AIA population, defined as all randomized participants who received at least one dose of IMP and with at least one AIA sample available for analysis during the 12-month on-treatment period. The samples were analyzed according to the treatment received, and separate analyses were performed for subjects with T1D and T2D.

Immunogenicity Endpoints

The following definitions were used to identify participants with a change in AIA response during the 12-month on-treatment period:

- treatment-induced: participants with AIAs that developed de novo (seroconversion) following the IMP administration (i.e., participants without pre-existing AIA or with missing sample at baseline with at least one positive AIA sample at any time during the 12-month on-treatment period).
- treatment-boosted: participants AIA positive at baseline with at least one AIA sample with at least a 4-fold increase in titers compared to baseline value.

Participants with treatment-emergent AIA (Yes, No, Inconclusive) were derived as follows:

- treatment-emergent AIAs (AIA incidence): participants with treatment-induced or treatment-boosted AIAs.
- without treatment-emergent AIAs: participants without treatment-induced or treatment-boosted AIAs.
- inconclusive: participants who could not irrefutably be classified as participants without treatment-emergent AIAs; these participants were not included in the above categories and were listed separately.

Analyses of NAbs were performed retrospectively using saved blood samples for AIA determination collected during main 6-month treatment period and 6-month safety extension period. The NAb status (positive or negative) was assessed on confirmed AIA positive samples. Participants with treatment-emergent NAb (Yes, No, Inconclusive) were derived taking into account the AIA emergence status:

- treatment-emergent NAbs (NAb incidence): participants with treatment-emergent AIAs and with at least one positive NAb sample during the 12-month on-treatment period
- without treatment-emergent Nabs: participants without treatment-emergent AIAs or with only negative NAb sample during the 12-month on-treatment period
- inconclusive: participants who could not irrefutably be classified as participants without treatment-emergent Nabs; these participants were not included in the above categories and were listed separately.

Summary of AIA Response

AIA

For the 12-month analyses, the AIA population included 590 participants (SAR341402: 298; U.S.-NovoLog/E.U.-NovoRapid: 292). Overall, a similar AIA response was noted between the treatment groups, as summarized in **Table 19.**

At baseline, the percentage of subjects who had positive AIA titers was comparable between the two groups (SAR341402: 35.3%; U.S.-NovoLog/ E.U.-NovoRapid: 36.7%).

Treatment-emergent AIA response during the 12-month on-treatment period was similar between the treatment groups (SAR341402: 25.5%; U.S.-NovoLog/ E.U.-NovoRapid: 29.1%).

- Treatment-boosted AIAs were similar between groups: SAR341402 9.4% vs U.S.-NovoLog/ E.U.-NovoRapid 13.3%.
- Treatment-induced AIAs were also observed in similar percentages of subjects in the treatment groups: SAR341402 33.2% vs U.S.-NovoLog/ E.U.-NovoRapid 37.1%.

The risk difference between SAR341402 and U.S.-NovoLog/ E.U.-NovoRapid on the percentage of participants with treatment-emergent AIAs was -2.9% (90% CI: -8.58% to 2.84%).

Among participants positive for AIA, cross-reactivity to human insulin was observed in more than 90% of the participants at baseline and was generally similar between both groups, ranging between 87.5% and 96.9% during the 12 month on-treatment period.

Table 19. Summary of anti-insulin aspart antibody response during the 12-month on-treatment period AIA population

	SAR341402 (N=298)	NovoLog/NovoRapid (N=292)
Patients with AIA positive at baseline, n (%)	96/272 (35.3)	98/267 (36.7)
Patients with treatment-boosted AIA, n (%)	9/96 (9.4)	13/98 (13.3)
Patients with AIA negative or missing at baseline, n (%)	202/298 (67.8)	194/292 (66.4)
Patients with treatment-induced AIA, n (%)	67/202 (33.2)	72/194 (37.1)
Patients with treatment-emergent AIA (incidence), n (%)	76/298 (25.5)	85/292 (29.1)
Patients with at least one positive AIA sample (prevalence), n (%)	163/298 (54.7)	170/292 (58.2)

Participants without treatment-emergent AIA, n (%)	218/298 (73.2)	207/292 (70.9)
Inconclusive participants, n (%)	4/298 (1.3)	0/292

AIA: Anti-insulin antibody
Prevalence: patients AIA positive at baseline or with treatment induced AIAs
Incidence: patients with treatment-boosted or treatment-induced AIAs (i.e., 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

Source: Study EFC15081 Integrated Summary of Immunogenicity (Table 9, modified)

Clinical Impact of Immunogenicity

Because AIA formation may change the PK and PD of the insulin by binding or neutralizing the insulin, the effects of AIA on glycemic control (both hyperglycemia and hypoglycemia), AEs, and insulin doses were inspected. This section summarizes the effect of AIA on efficacy and safety parameters.

Efficacy and Insulin Doses:
Overall, no clinical impact of AIAs on efficacy or insulin doses was observed in study EFC15081 (**Table 20**).

Change in HbA1c from baseline to Week 52 was similar between treatment groups in the subgroup of subjects with treatment-emergent AIAs and the subgroup without treatment-emergent AIAs. The treatment-by-treatment-emergent AIA interaction also showed no evidence of heterogeneity of treatment effect across subgroups of AIA status (p=0.497). These results suggest similar efficacy of SAR341402 and U.S.-NovoLog/ E.U.-NovoRapid, regardless of the treatment-emergent AIA status.

The mean changes in doses of daily basal insulin, mealtime insulin, and total insulin from baseline to Week 52 do not suggest the need of increasing insulin doses in the subgroup of subjects with treatment-emergent AIAs compared to the subgroup of participants without treatment-emergent AIAs.

Reviewer comment*: In summary, treatment-emergent AIAs had no impact on clinical efficacy in terms of differences in HbA1c or insulin doses in subjects receiving SAR341402 vs U.S.-NovoLog/ E.U.-NovoRapid. These findings provide supportive, but not necessary, data for the demonstration of no clinically meaningful differences between SAR341402 and U.S.-NovoLog/ E.U.-NovoRapid.*

Table 20. Summary of effects of treatment-emergent anti-insulin aspart antibodies on efficacy and safety parameters during the 12-month on-treatment period – AIA population

	Treatment-emergent AIA			
	Yes[a]		No	
	SAR341402 (N=76)	NovoLog/ NovoRapid (N=85)	SAR341402 (N=218)	NovoLog/ NovoRapid (N=207)
HbA1c (%)				
Baseline (mean; SD)	7.99 (0.78)	7.86 (0.72)	8.00 (0.76)	7.96 (0.69)
Week 52 (mean; [SD])	7.62 (1.03)	7.58 (0.90)	7.71 (0.93)	7.64 (0.82)
Change from BL to W52 (LS mean; [SE[b]])	-0.32 (0.092)	-0.26 (0.090)	-0.23 (0.068)	-0.27 (0.067)
Daily mealtime insulin dose (U/kg)				
Baseline (mean; [SD])	0.411 (0.193)	0.398 (0.275)	0.397 (0.243)	0.397 (0.234)
Week 52 (mean; [SD])	0.412 (0.211)	0.407 (0.284)	0.402 (0.268)	0.420 (0.235)
Change from BL to W52 (mean; [SD])	0.007 (0.167)	0.014 (0.095)	-0.004 (0.148)	0.007 (0.134)
Total insulin dose (U/kg)				
Baseline (mean; SD)	0.821 (0.342)	0.808 (0.512)	0.778 (0.340)	0.771 (0.350)
Week 52 (mean; [SD])	0.824 (0.328)	0.809 (0.473)	0.791 (0.385)	0.795 (0.366)
Change from BL to W52 (mean; SD)	0.013 (0.167)	0.010 (0.154)	0.002 (0.179)	0.014 (0.170)
Any hypoglycemia (n; %)	76 (100.0 %)	85 (100.0 %)	214 (98.2 %)	203 (98.1 %)
Severe hypoglycemia (n; %)	4 (5.3 %)	6 (7.1 %)	14 (6.4 %)	8 (3.9 %)
Documented symptomatic hypoglycemia				
≤3.9 mmol/L (70 mg/dL)	71 (93.4)	82 (96.5)	198 (90.8)	183 (88.4)
<3.0 mmol/L (54 mg/dL)	62 (81.6)	73 (85.9)	157 (72.0)	145 (70.0)
Common TEAEs[c] (n; %)	46 (60.5)	48 (56.5)	135 (61.9)	119 (57.5)
Serious TEAEs (n; %)	11 (14.5)	4 (4.7)	25 (11.5)	25 (12.1)
Injection site reactions (n; %)	1 (1.3)	0	1 (0.5)	4 (1.9)
Hypersensitivity reactions (n; %)	6 (7.9)	6 (7.1)	10 (4.6)	14 (6.8)

BL: baseline; AIA: anti-insulin antibody; SD: standard deviation; SE: standard error; TEAE: treatment-emergent adverse event.

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

b ANCOVA analysis (with retrieved dropout multiple imputation)

c Common TEAEs defined as HLTs ≥2% in any treatment group

Source: 5.3.5.1 EFC15081-12 months, Appendix 16.2.7 Other safety observations, 16.2.7.3.1.1, 16.2.7.4.6.1, 16.2.7.4.10.1, 16.2.7.5.1.1, 16.2.7.6.1.1, 16.2.7.6.3.1, 16.2.7.6.5.1, 16.2.7.6.9.1.

Source: Integrated Summary of Immunogenicity page 23 (Table 9)

Safety and Hypoglycemia

Overall, the proportion of subjects with at least one hypoglycemia event were similar in both treatment groups for any of the category of hypoglycemia evaluated across subgroups by treatment-emergent AIA (**Table 20**).

In the subgroup of participants *with* treatment-emergent AIAs, severe hypoglycemia was reported by 5.3% (4/76) participants in the SAR341402 group and 7.1% (6/85) in the U.S.-NovoLog/ E.U.-NovoRapid group. In the subgroup of participants *without* treatment-emergent AIAs, severe hypoglycemia was reported by 6.4% (14/218) participants in the SAR341402 group and 3.9% (8/207) in the U.S.-NovoLog/ E.U.-NovoRapid group.

Safety and TEAEs

As summarized in **Table 20**, the incidence of common TEAEs in participants with treatment-emergent AIAs was similar between the treatment groups: SAR341402: 60.5% [46/76] vs U.S.-NovoLog/ E.U.-NovoRapid: 56.5% [48/85].

In participants *with* treatment-emergent AIAs, the proportion of subjects with SAEs was higher in the SAR341402 group than in the U.S.-NovoLog/ E.U.-NovoRapid group (SAR341402: 14.5% [11/76] vs U.S.-NovoLog/ E.U.-NovoRapid: 4.7% [4/85]). This difference was mostly driven by TEAEs in the system organ class (SOC) nervous system disorders (SAR341402: 6/76; U.S.-NovoLog/ E.U.-NovoRapid: 2/85).

Of note, in the nervous system disorders SOC, serious TEAEs related to hypoglycemia were reported by a similar number of participants in the 2 groups:

- SAR341402: 3 subjects experienced hypoglycemia unconsciousness;
- U.S.-NovoLog/ E.U.-NovoRapid group: 1 subject had hypoglycemia seizure and 1 participant experienced hypoglycemia unconsciousness

The Applicant states that the small denominator in the subgroup of participants with treatment-emergent AIAs can exaggerate the numerical differences in proportions.

In participants *without* treatment emergent AIAs, the percentage of subjects with SAEs was similar in the 2 groups (SAR341402: 11.5% participants; U.S.-NovoLog/ E.U.-NovoRapid: 12.1% participants).

Reviewer comment*: In summary, a numerical imbalance in SAEs was noted in subjects with treatment-emergent AIAs not favoring SAR341402 group, which was driven by nervous system disorders SOC. The Applicant highlights the fact that treatment-emergent AIAs had no impact on clinical safety in terms of hypoglycemia in subjects receiving SAR341402 vs U.S.-NovoLog/ E.U.-NovoRapid and attributes the noted imbalance likely to chance and the exaggeration of proportional differences because of the small number of patients in this subset with treatment-emergent AIAs. Given that there does not appear to be a plausible mechanism to explain an impact of insulin or AIA on the nervous system, I agree with the Applicant that this isolated imbalance is likely due to chance. These findings provide supportive, but not necessary, data for the demonstration of no clinically meaningful differences between SAR341402 and U.S.-NovoLog/ E.U.-NovoRapid.*

Summary of NAb Response and Clinical Impact

The percentages of subjects with treatment-emergent NAbs during the 12-month on-treatment period were low in the treatment groups (SAR341402 [7/298] 2.3% vs U.S.-NovoLog/ E.U.-NovoRapid [17/292] 5.8%). With these low numbers, no appreciable clinical impacts of Nab were observed.

Assessment of the change in HbA1c and insulin doses by treatment-emergent NAbs status indicated no potential effects of NAbs on glycemic control. The treatment-by-

treatment-emergent NAb interaction also revealed no evidence of heterogeneity of treatment effect on HbA1c across subgroups of NAb status, suggesting similar efficacy in the 2 treatment groups, regardless of the treatment-emergent NAb status.

Similarly, no relevant difference between the 2 treatment groups in the change in HbA1c from baseline to Week 52 in participants with or without detectable NAbs at baseline was found. The mean changes from baseline to Week 52 in insulin doses do not suggest the need for higher insulin doses in the subgroup of participants with treatment-emergent NAbs compared to the subgroup of participants without treatment-emergent Nabs. Of note, the small number of participants with treatment-emergent NAbs limit the ability to interpret the data conclusively.

***Reviewer comment**: In sum, the data from EFC15081 reveal a similar immunogenic profile for SAR341402 and U.S.-NovoLog. No differences in HbA1c or insulin doses are noted between AIA positive vs AIA negative subjects. Importantly, the observed difference in proportion of AIA positive subjects experiencing SAE with SAR341402 vs U.S.-NovoLog was not driven by differences in severe hypoglycemia events. Given that there does not appear to be a plausible mechanism to explain an impact of insulin or AIA on the nervous system, I agree that this isolated imbalance appears likely to be due to chance. Overall, the immunogenic findings do not suggest any differences in the safety profiles of SAR341402 and U.S.- NovoLog that would preclude or conflict with conclusions based on other data and information.*

Table 21. EFC15081 Schedule of Activities

Table 1 – Study flowchart (as per amendment 2)

Period	Screening		Treatment period (26 weeks)							Comparative Safety Extension period (26 weeks)			Post treatment/Follow-up
Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13
Week:	Wk-2	Wk-1 ☎[a]	Wk 0 (Baseline)	Wk2 ☎[a]	Wk4	Wk8 ☎[a]	Wk12	Wk20	Wk26[b] (Endpoint)	Wk34 ☎[a]	Wk40	Wk52[b] (End of treatment)	+1 day[c] ☎[a]
Day (window [days])	-14	-7 (±3)	1 (±3)	14 (±3)	28 (±3)	56 (±3)	84 (±3)	140 (±3)	182 (±3)	238 (±5)	280 (±5)	364 (±5)	
Informed consent	X												
Inclusion/Exclusion criteria	X		X										
Demography, medical history, diabetes history	X												
Physical examination	X								X			X	
Vital signs[d]	X		X		X		X	X	X		X	X	
Body weight, height[e]	X		X						X			X	
12-lead ECG	X												
Dispensation of study glucometer and e-diary	X												
Training (glucometer, SMPG profiles, hypoglycemia reporting e-diary)	X		X										
Training or refresher instructions on glucose meter use and routine review of diet and lifestyle counseling along with instructions on dosage self-adjustment including carbohydrate intake[f]	X	X	X	X	X	X	X	X	X	X	X	X	
Dispensation of study medication[g]			X		X		X	X	X		X		
• IMP (SAR341402 or NovoLog/NovoRapid)			X		X		X	X	X		X		
• NIMP (Lantus)			X		X		X	X	X		X		
Counting / collecting used, unused and in use pens					X		X	X	X		X	X	

Period	Screening		Treatment period (26 weeks)							Comparative Safety Extension period (26 weeks)			Post treatment/Follow-up
Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13
Week:	Wk-2	Wk-1 ☎[a]	Wk 0 (Baseline)	Wk2 ☎[a]	Wk4	Wk8 ☎[a]	Wk12	Wk20	Wk26[b] (Endpoint)	Wk34 ☎[a]	Wk40	Wk52[b] (End of treatment)	+1 day[c] ☎[a]
Day (window [days])	-14	-7 (±3)	1 (±3)	14 (±3)	28 (±3)	56 (±3)	84 (±3)	140 (±3)	182 (±3)	238 (±5)	280 (±5)	364 (±5)	
Compliance check (Review of diary, returned IMP)					X		X	X	X		X	X	
IRT call	X		X		X		X	X	X		X	X	X
Visit date confirmation in e-diary web portal		X	X	X	X	X	X	X	X	X	X	X	
Randomization[h]			X										
Patient to come fasting to study site	X		X				X		X		X	X	
Insulin dose collected[i]			X		X		X		X		X	X	
7-point SMPG[j]			X				X		X			X	
SMPG to support insulin dose titration[k]		X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Central laboratory													
HbA1c	X		X				X		X		X	X	
Fasting plasma glucose			X				X		X		X	X	
C-peptide (fasting)			X										
Anti-insulin antibody[l]			X		X		X		X		X	X	
Safety laboratory													
Hematology[m], Clinical chemistry[n]	X								X			X	
Lipids (fasting)[o]	X								X			X	
Hepatitis serology	X												
Pregnancy test (WOCBP only)[p]	X		X				X		X		X	X	
Serum FSH and estradiol (menopausal women only)	X												
AE / SAE	To be assessed and reported (if any) throughout the study (report SAE to the sponsor within 24 hours)												X
Injection site reactions	To be assessed and reported (if any) throughout the study												X
Hypersensitivity reactions	To be assessed and reported (if any) throughout the study												X

Period	Screening		Treatment period (26 weeks)							Comparative Safety Extension period (26 weeks)			Post treatment/Follow-up
Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13
Week:	Wk-2	Wk-1 ☎[a]	Wk 0 (Baseline)	Wk2 ☎[a]	Wk4	Wk8 ☎[a]	Wk12	Wk20	Wk26[b] (Endpoint)	Wk34 ☎[a]	Wk40	Wk52[b] (End of treatment)	+1 day[c] ☎[a]
Day (window [days])	-14	-7 (±3)	1 (±3)	14 (±3)	28 (±3)	56 (±3)	84 (±3)	140 (±3)	182 (±3)	238 (±5)	280 (±5)	364 (±5)	
Hypoglycemia recording	To be assessed and reported (if any) throughout the study SMPG to be performed and documented in e-diary / e-CRF in case of symptoms suggesting hypoglycemia												X

ALP: alkaline phosphatase, ALT: alanine transaminase, AST: aspartate transaminase, eGFR: estimated glomerular filtration rate, FSH: follicle stimulating hormone, IMP: investigational medicinal product, IRT: interactive response technology, NIMP: noninvestigational medicinal product, SMPG: self-measured plasma glucose, Wk: week

a Mandatory telephone visit or optional clinical visit.

b Or early termination visit. When early termination, refer to the e-CRF completion guidelines.

c Or 2 to 3 days in the event this visit fell on a weekend or holiday.

d Heart rate, blood pressure (BP). At screening visit only: determination of reference arm for BP.

e Height only at Visit 1.

f Site was to provide training at screening visit and baseline visit on the correct handling including regular calibration of the glucose meter provided by the Sponsor; regular refresher instructions was to be provided at each on-site visit throughout the study.

g Patients were to be trained on the use of IMP and NIMP pens and needles by the study staff and provided with instruction leaflets during the randomization visit.

h Randomization was to be performed only after all baseline evaluations had been done.

i Mealtime and basal insulin doses were to be documented in the 7 days prior to Baseline (Visit 3) and during the first 7 days after start of IMP, and on 2 days in the weeks prior to Visit 5 (Week 4), Visit 7 (Week 12), Visit 9 (Week 26), Visit 11 (Week 40) and Visit 12 (Week 52).

j 7-point SMPGs (fasting pre-breakfast, 2 hours post-breakfast, pre- and 2 hours after lunch, pre- and 2 hours after dinner, and at bedtime) were to be requested on at least 2 days in the week before Visit 3 (Baseline), Visit 7 (Week 12), Visit 9 (Week 26 [Endpoint]), and Visit 12 (Week 52; End of treatment), measured in a single, 24-hour period; they had to be recorded into the e-diary before the visit.

k SMPG for titration oversight and supporting insulin dosing and carbohydrate intake documentation were recommended daily during the first weeks of study treatment until reaching target ranges for SMPG, and thereafter on at least 3 days each week or more frequently as requested by the Investigator (as specified in titration manual):

- ➔ To assist titration of the basal insulin (Lantus): fasting (pre-breakfast) SMPG.
- ➔ To assist titration of SAR341402 or NovoLog/NovoRapid: either postprandial or next-meal preprandial (in the case of dinner, bedtime) SMPG was to be used, depending on the preference of the Investigator and patient and consistent with standard of care.

These SMPGs, supporting optimization of the basal and mealtime insulin dose were recommended to be recorded in the e-diary at least weekly; they were to be uploaded in the web portal for review by the site or the Sponsor (titration oversight working group). See titration oversight manual. The results were to be discussed between Investigator and patient during on-site and scheduled or unscheduled telephone visits at the discretion of the Investigator. 7-point SMPG could also be used for titration oversight.
For SMPG ≤3.9 mmol/L (≤70 mg/dL) the hypoglycemia form had to be completed.

l Eight-hour delay had to be respected between the last mealtime insulin dose and antibody sampling.

m Hematology: erythrocytes, hemoglobin, hematocrit, leukocytes, differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets.

n Clinical chemistry: sodium, potassium, creatinine, eGFR (MDRD), ALT, AST, ALP and total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin).

o Serum lipids: total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides (in fasting conditions).

p For women of childbearing potential (WOCBP): Serum pregnancy test for screening; urine pregnancy test for subsequent monitoring.

Source: Study EFC15801 CSR page 38-40 (Table 1)

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/s/

PATRICK ARCHDEACON
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