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APPLICATION NUMBER:

209196Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2) NDA
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Division / Office	Division of Metabolism and Endocrinology Products/OND
Reviewer Name(s)	Sonia Doi, MD, PhD
Review Completion Date	7/30/2017
Established Name	Insulin lispro injection
(Proposed) Trade Name	Admelog/Admelog Solostar
Therapeutic Class	Insulin
Applicant	Sanofi-Aventis
Formulation(s)	Solution for subcutaneous injection
Dosing Regimen	Individualized
Indication(s)	Treatment of diabetes mellitus
Intended Population(s)	Adults and children with type 1 and adults with type 2 diabetes mellitus

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Abbreviations

21-CFR	Code of Federal Regulations Title 21
ACLS	Advance cardiovascular life support
ADA	American Diabetes Association
AE	Adverse event
AIA	Anti-insulin antibody
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARAC	Allergic Reaction Assessment Committee
AST	Aspartate aminotransaminase
AUC	Area under the curve
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CDRH	Center for Devices and Radiological Health
CFU	Colony forming units
CI	Confidence interval
CPR	Cardiopulmonary resuscitation
CSII	Continuous subcutaneous insulin infusion
CSR	Clinical study report
DCCT	Diabetes Control and Complication Trial
DKA	Diabetic ketoacidosis
DND BE	Division of New Drug Bioequivalence Evaluation
DPP-4	Dipeptidyl peptidase-4
ECG	Electrocardiogram
e-CRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOP2	End-of-phase 2
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GCP	Good clinical practices
GHDB	General Hospital Devices Branch
GIR	Glucose infusion rate
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c
HLGT	High level group term
HLT	High level term
IGF-1R	Insulin growth factor-1 receptor
IMP	Investigational medicinal product
IND	Investigational New Drug
IR-A	Insulin receptor A
IR-B	Insulin receptor B
ITT	Intent-to-treat

IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
LLT	Low level term
MCF-7	Human breast cancer cell line
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measurements
NaCl	Sodium chloride
NAI	No action indicated
NDA	New Drug Application
NIMP	Non-investigational medicinal product
NOAEL	No observed adverse event level
ODE	Office of Device Evaluation
OIR	Office of In Vitro Diagnostics and Radiological Health
OPQ	Office of Product Quality
OSIS	Office of Study Integrity and Surveillance
PCSA	Potentially clinically significant abnormality
PD	Pharmacodynamic
PhEur	European Pharmacopeia
PK	Pharmacokinetic
PMA	Premarket approval
PT	Preferred term
PV	Paravenous
rDNA	Recombinant deoxyribonucleotide acid
REMS	Risk evaluation and mitigation strategies
SAE	Serious adverse event
SAOS-2	Human osteosarcoma cell line
SC	Subcutaneous
SD	Standard deviation
SGLT-2	Sodium-glucose cotransporter-2
SMPG	Self-measured plasma glucose
SMQ	Standardized MedDRA query
SOC	System organ class
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TAMC	Total aerobic microbial count
TEAE	Treatment-emergent adverse event
UKPDS	United Kingdom Prospective Diabetes Study
ULN	Upper limit of normal
USP	United States Pharmacopeia

1 Recommendations/Risk Benefit Assessment

The current application is for approval of SAR342434 (hereafter also referred to as Admelog), an insulin lispro product. The Applicant has submitted a 505(b)(2) application that relies, in part, on the Food and Drug Administration's (FDA's) finding of safety and effectiveness for the listed drug Humalog (insulin lispro) injection for approval.

1.1 Recommendation on Regulatory Action

I recommend approval for NDA 209196 (insulin lispro) for use as an adjunct to diet and exercise to improve glycemic control in adults and children with diabetes mellitus pending resolution of the outstanding regulatory issues.

The data submitted by the applicant are sufficient to conclude a favorable risk-benefit profile and adequately justify reliance upon FDA's prior findings of safety and effectiveness for insulin lispro.

1.2 Risk Benefit Assessment

Insulin lispro is a rapid-acting insulin for use as mealtime bolus injection in diabetic patients. Insulin lispro is generally added to therapy with basal insulin or oral anti-diabetic agents. The benefit of insulin lispro comes from its effect on reducing post-prandial blood glucose, thus resulting in improvement of the hemoglobin A1c (HbA1c) level. The benefit of SAR342434 in improving HbA1c level was determined to be not different from that of the US-approved insulin lispro product.

The major risk with the use of insulin lispro is the occurrence of hypoglycemia, and in particular severe hypoglycemia as it may result in death. Other risks include local injection site reactions and the potential for allergic/hypersensitivity reactions. Overall, my review of the safety parameters analyzed for SAR342434 in the T1DM and T2DM populations, including the occurrence of death, serious adverse events and assessment of immunogenicity showed that the risk of adverse events is generally comparable to that reported for the approved-insulin lispro product in both the T1DM and T2DM populations.

Based on my review of the data submitted for SAR342434 in this NDA, I consider that the benefits outweighs the risks of using this product (b) (4) to improve glycemic control in adults and children with diabetes mellitus.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I do not recommend a Risk Evaluation and Mitigation Strategy (REMS) for this NDA.

1.4 Recommendations for Postmarket Requirements and Commitments

I do not recommend any postmarketing requirements or commitments for this NDA.

2 Introduction and Regulatory Background

Diabetes mellitus has become an epidemic in the United States and a 2016 CDC Report estimates that more than 29 million Americans are currently living with diabetes⁽¹⁾. Both type 1 diabetes (T1DM) and type 2 diabetes (T2DM) are serious chronic disorders characterized by hyperglycemia.

Approximately 5% of the people with diabetes have T1DM⁽²⁾. This form of diabetes is usually diagnosed in children and young adults and is generally caused by autoimmune destruction of pancreatic β -cells resulting in deficiency of insulin secretion. Patients with T1DM depend on insulin replacement for survival.

The majority of patients with diabetes have T2DM. The etiology of T2DM is multifactorial, but the underlying pathophysiology is believed to be insulin resistance and a relative insulin deficiency resulting in hyperglycemia. Management of glucose control in T2DM patients includes diet, weight control, and anti-diabetic drugs (both oral and injectable). Insulin may be required for adequate glycemic control.

Long-term hyperglycemia and metabolic changes over the course of T1DM and T2DM increase the risk for macrovascular and microvascular complications. Results from the Diabetes Control and Complication Trial (DCCT)²⁻⁸, United Kingdom Prospective Diabetes Study (UKPDS)⁹⁻¹³ and the Kumamoto Study¹⁴ suggest that improved glycemic control (as measured by HbA1c) result in improved outcomes.

Rapid-acting insulin, such as insulin lispro is used as prandial therapy, in doses adjusted to the carbohydrate content to control blood glucose while avoiding hypoglycemia.

The Applicant has submitted a 505(b)(2) application that relies, in part, for approval on FDA's finding of safety and effectiveness for the listed drug (i.e., Humalog). The Applicant has satisfactorily established that such reliance is scientifically justified, based on comparative physicochemical tests and bioassay, nonclinical data, pharmacokinetic/pharmacodynamic (PK/PD) data, and clinical data (including an assessment of immunogenicity). Data from two Phase 3 clinical trials, one (EFC12619) in subjects with T1DM and one (EFC13403) in subjects with T2DM, show that the efficacy and safety profile of Admelog is similar to that of Humalog. The Applicant included both the US-approved Humalog and a non-US-approved insulin lispro

(1) CDC data: www.cdc.gov/chronicdisease/resources/publications/aag/diabetes.htm

(2) ADA data: www.diabetes.org/diabetes-basics/type-1/?loc=db-slabnav

(Humalog-EU) as comparators in the Phase 3 studies. Since the Agency can only rely upon the US-approved drug product, the Applicant has also provided a bridge between the EU-approved Humalog and US-approved Humalog.

2.1 Product Information

Insulin lispro is an insulin analog that differs from human insulin in that the amino acid proline at position B28 is replaced by lysine and the lysine in the position B29 is replaced by proline. The primary mechanism of action of insulins, including insulin lispro, is to lower blood glucose by stimulating peripheral glucose uptake in skeletal muscle and fat, and by inhibiting hepatic glucose production.

SAR342434 is an insulin lispro product proposed for use to improve glycemic control in patients with diabetes mellitus. This New Drug Application (NDA) relies, in part, on the Agency's findings of safety and effectiveness for Humalog (insulin lispro, solution for injection). The primary amino acid sequence of SAR342434 is the same as that of active ingredient of Humalog. Both, SAR342434 and Humalog are produced by recombinant DNA (rDNA) technology utilizing a non-pathogenic strain of *Escherichia coli* (*E. coli*).

2.2 Tables of Currently Available Treatments for Proposed Indications

The primary goal in the management of diabetes mellitus is to achieve near-normal levels of glucose control, which may require pharmacological therapy in addition to changes in life style. There are currently 12 pharmacological classes of medications approved in the US to treat diabetes. A listing of therapeutic options for the management of T1DM and/or T2DM is presented in Table 1. Many of these products are also approved as fixed combination drug products.

Table 1: Approved Therapeutic Options for the Management of Diabetes Mellitus*

Pharmacologic Class	Antihyperglycemic Drug Products
ALPHA-GLUCOSIDASE INHIBITORS	Acarbose; Meglitol
AMYLIN MIMETICS	Pramlintide
BIGUANIDES	Metformin
BILE ACID SEQUESTRANTS	Colesevelam
DOPAMINE-2 AGONISTS	Bromocriptine
DPP-4 INHIBITORS	Alogliptin; Linagliptin; Saxagliptin; Sitagliptin
GLP-1 RECEPTOR AGONISTS	Albiglutide; Dulaglutide; Exenatide; Exenatide extended-release; Liraglutide
INSULINS AND INSULIN ANALOGUES	Inhaled insulin human; Insulin aspart; Insulin detemir; Insulin glargine; Insulin glulisine; Insulin isophane (NPH); Insulin lispro; Insulin regular (human); Pre-mixed insulins (various)
MEGLITINIDES	Nateglinide; Repaglinide
SGLT-2 INHIBITORS	Canagliflozin; Dapagliflozin; Empagliflozin;
SULFONYLUREAS	Chlorpropamide; Glimepiride; Glipizide; Glipizide extended-release; Glyburide; Tolazamide; Tolbutamide
THIAZOLIDINEDIONES	Pioglitazone; Rosiglitazone;
BASAL INSULIN AND GLP-1 RECEPTOR AGONIST COMBINATIONS	Insulin degludec and liraglutide; Insulin glargine and lixisenatide

*Note that only insulins, insulin analogues, and amylin mimetics are approved for T1DM.

Source: Drugs@FDA: FDA Approved Drug Products (<http://www.accessdata.fda.gov/scripts/cder/daf/>)

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2

2.3 Availability of Proposed Active Ingredient in the United States

Insulin lispro was first approved on June 14, 1996 (NDA 020563) and it is indicated to improve glycemic control in adults and children with diabetes mellitus. It is currently available by prescription in a 100 unit/mL concentration, a 200 U/mL concentration, and in various pre-mixed insulin formulations.

2.4 Important Safety Issues with Consideration to Related Drugs

Hypoglycemia is the most common adverse reaction associated with the use of insulin products. Severe hypoglycemia can cause acute harm (e.g., falls, motor vehicle accidents or other injury), or lead to unconsciousness, convulsions, temporary or permanent impairment of brain function, or death¹⁵⁻¹⁷.

Immunogenicity allergic/hypersensitivity reactions are also a safety issue with insulins¹⁸. All insulin products can elicit the formation of insulin antibodies. Although uncommon, the presence of anti-insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose¹⁸.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

December 23, 2013: Pre-IND Type B Meeting requested. Written responses issued on February 21, 2014.

June 26, 2014: IND 120511 opened. "Study may proceed" letter issued on August 28, 2014.

October 6, 2014: End-of-phase 2 (EOP2) meeting held. Meeting minutes issued on November 7, 2014. (b) (4)

(b) (4)

February 13, 2015: Type C Meeting requested to discuss the comparative *in vitro* in-use stability study of insulin lispro and US Humalog used in pumps, and the outline of the proposed clinical study to compare the safety of insulin lispro and Humalog when used in external pumps (Study PDY13502). Written responses issued on April 27, 2015 included recommendations to conduct an appropriate study to support the use of SAR342434 with insulin pumps. In addition, the Agency suggested that the Sponsor use more than one type of insulin pump in the study.

July 22, 2015: The Sponsor submitted a reply to the Agency's EOP2 minutes and

requested additional clarifications to which the Agency issued a feedback on September 16, 2015.

September, 16 2015: The Agency issued a response to questions from the Sponsor and particularly addressed the anti-insulin antibody assay developed by the Sponsor as per FDA request at the EOP2 meeting.

October 2, 2015: The Sponsor responded to the FDA's comments issued in September 2015 and submitted amended trial protocols on November 10 and November 24, 2015 to which the Agency issued feedback comments on February 11, 2016.

On October 16, 2015 the Sponsor submitted a human factors study protocol to which the FDA issued comments on January 27, 2016.

March 23, 2016: Pre-NDA meeting. Meeting Minutes were issued on April 16, 2016, and included recommendations on reports of biocompatibility of the pen injector and constituent parts, on anti-insulin antibody assay, and a requirement to submit data from the completed extension period of study EFC12619 at the NDA submission.

April 20, 2016: The Sponsor requested a Type C meeting to obtain clarification on the impromptu discussion on insulin pumps that occurred after the Pre-NDA meeting. On June 10, 2016 the Agency issued a written response addressing the questions raised by the Sponsor. The Agency's comments to the Sponsor's clarification request on the regulatory pathway related to the insulin pumps used in the clinical trials and the implications for the application included the following points:

- In order to avoid an outstanding device issue the Sponsor's insulin product would have to be included in the labeling of at least one insulin pump. The 510(k) or PMA holder will need to request a labeling change for their device.
- It recommended that the submission of a device application to request its label revision should be timed such that its action would occur simultaneously with action for the NDA.
- A parallel review will be required for the pump systems to evaluate the requested labeling change for the 510(k) or PMA.

(b) (4)



2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Generally, the submission quality was adequate.

For the two clinical trials, 6 (2 domestic and 4 foreign) clinical sites were selected for clinical site inspection. Reasons for selecting these sites for inspection include: enrollment of large numbers of study subjects, higher than average AEs/SAEs, very low number AEs reported, financial disclosure, insufficient domestic data, and higher than average efficacy effect size. No significant concerns were identified during the site inspections conducted by the Division of Clinical Compliance Evaluation/Office of Scientific Investigations (DCCE/OSI). See memorandum signed by Dr. Cynthia Kleppinger, Dr. Janice Pohlman and Dr. Kassa Ayalew for details.

For the clinical pharmacology trials, the Division of New Drug Bioequivalence Evaluation/Office of Study Integrity and Surveillance (DNDBE/OSIS) recommended acceptance of bioequivalence data without an on-site inspection as the analytical and clinical sites listed in this NDA had recently been inspected and the inspectional outcome was classified as No Action Indicated (NAI).

3.2 Compliance with Good Clinical Practices

The Applicant states that all studies for this NDA application were conducted in compliance with Good Clinical Practices (GCP), and met the requirements of the Declaration of Helsinki as well as of applicable international laws and regulations of the countries where the studies were performed.

3.3 Financial Disclosures

Four studies (b) (6) were covered in the submitted financial disclosures. Only two clinical studies (b) (6) had clinical investigators with disclosable financial interests. The Applicant provided a list of investigators with disclosable financial interest (b) (6)

(b) (6)
See Table 2 below for financial disclosure details.

Table 2: Financial disclosure for clinical studies (b) (6)		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>666</u>		
Number of investigators who are Applicant employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>16</u>		
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: <u>None</u> Significant payments of other sorts: <u>16</u> Proprietary interest in the product tested held by investigator: <u>None</u> Significant equity interest held by investigator in sponsor of covered study: <u>None</u>		
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) <u>None</u>		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

Table completed using data submitted in the NDA package.

All disclosable financial interests were reported under the category of "Significant payments of other sorts", (b) (6)

(b) (6) Two investigators participating in study (b) (6) received the highest amounts: One received a total of \$202,470 (b) (6) and the other received a total of \$193,637 (b) (6). All the others received an amount below \$76,000.

Based upon my review of the disclosable financial interests, I do not have concerns that these payments could have introduced bias to the studies supporting this NDA. This conclusion is based on the following considerations:

- a) The percentage of investigators with reportable financial interests was about 2% (16 out of 666 investigators), which is relatively small. Investigators with

reportable financial interests were from sites that contributed (b) (6) of (b) (6) in study (b) (6) and (b) (6) of (b) (6) in study (b) (6). At my request, the Statistics reviewer re-analyzed the data excluding these sites and informed me that the results of efficacy were not altered.

- b) These studies were conducted as large multinational, multicentric, randomized clinical trials, which makes it less likely to be influenced by a small number of investigators.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

For a detailed discussion of the Chemistry, Manufacturing and Controls for SAR342434, see the reviews from the Office of Product Quality (OPQ). For detailed discussion of the to-be-marketed pen injector devices see the consult review from the Center for Devices and Radiological Health (CDRH), General Hospital Devices Branch (GHDB). The Applicant is also proposing use of SAR342434 in insulin pumps for continuous subcutaneous insulin infusion. A clinical study (study PDY13502) has been conducted in support of this route of administration. See the completed consult review from CDRH, Office of In Vitro Diagnostics and Radiological Health (OIR) for a detailed discussion.

Drug Substance: Insulin lispro, an analog of human insulin, differs from human insulin in the position of two amino acids. In insulin lispro, the proline at position B28 is replaced by lysine, and the lysine at position B29 is replaced by proline. The Applicant has produced insulin lispro (SAR342434) using rDNA technology with *Escherichia coli* (b) (4). See substance nomenclature in Table 3 and structure of amino acid sequence of insulin lispro in Figure 1.

Table 3: Substance Nomenclature

Compendial Names	Insulin lispro (Ph. Eur.)
	Insulin lispro (USP)
Chemical Name	28 ^B -L-Lysine-29 ^B -L-proline insulin (human)
Chemical Abstract Services (CAS) number	133107-64-9
Sponsor's code	SAR342434

Table completed using data submitted by the Applicant

Empirical Formula: C₂₅₇H₃₈₃N₆₅O₇₇S₆
Molecular Weight: 5808

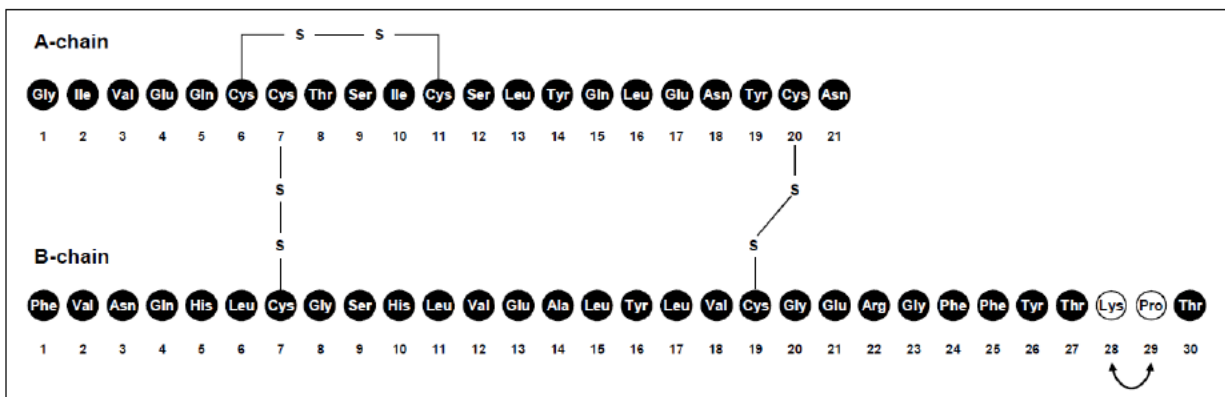


Figure 1: Structure of amino acid sequence of insulin lispro.

Excerpt from Figure 1, Drug-substance file submitted in Module 2 of the NDA. Arrow indicates the amino acid change (positions 28 and 29) from human insulin.

Drug Product: The SAR342434 drug product is manufactured as a sterile, aqueous, clear, and colorless solution which contains insulin lispro at a concentration of 100 U/mL and metacresol, glycerol, dibasic sodium phosphate, zinc oxide, sodium hydroxide, hydrochloric acid, and water for injection. The drug product used in the clinical trials was the to-be-marketed product. The drug product will be available in a 10 mL multi-use glass vial, and a 3 mL cartridge integrated into a disposable pen injector. The to-be-marketed pen-injector is based on the Applicant's currently marketed Solostar platform used with the applicant's insulin glargine products.

4.2 Clinical Microbiology

The Applicant included a description of the potential impurities originating from the expression system, as well as the processes utilized to identify the impurities and purify the drug substance. (b) (4)

(b) (4)

The Applicant states that the final drug substance complies with the limits of microbial contamination and endotoxin content set in accordance with the harmonized methods of the United States Pharmacopeia (USP) and the European Pharmacopoeia (Ph Eur) (b) (4)

See the microbiology review for detailed discussion.

4.3 Preclinical Pharmacology/Toxicology

For a detailed review of the Nonclinical Pharmacology/Toxicology studies, refer to the review by Dr. Daniel Minck.

The Applicant has submitted a limited number of studies comparing pharmacological actions and toxicology parameters between SAR342434 and Humalog (US and EU) to bridge SAR342434 to the approved insulin lispro product.

Nonclinical Pharmacology:

Three independent series of *in vitro* nonclinical pharmacology studies were conducted to demonstrate similarity between different batches of SAR342434 and batches of the insulin lispro product approved in the EU and the insulin lispro product approved in the US, as follows:

1. Studies supporting the clinical Phase 1 trial: Two batches of SAR342434 (Batch C1024625 used in study PDY12704 and batch SAR342434-12-009 used in the toxicology study) were compared to two batches of Humalog (Batch C000484-EU and batch A962891A-US) to test for similarity using *in vitro* assays to measure receptor affinity, activation and metabolic activity. Receptor affinity was measured for insulin receptor B (IR-B) and IGF-1 receptor (IGF-1R) by membrane receptor binding assays. Receptor activity was measured by autophosphorylation studies performed in cells overexpressing IR-B and IGF-1R. Insulin metabolic activity was compared between the batches of SAR342434 and the batches of Humalog using an assay to measure inhibition of lipolysis in adipocytes. The mitogenic activity was studied with ¹⁴C-thymidine incorporation in MCF-7 and SAOS-2 cells. The analysis of these studies demonstrated that the batches of SAR342434 (C1024625 and SAR342434-12-009) bound to IR-B and stimulated autophosphorylation and metabolic responses with a similar activity to the batches of Humalog (C000484-EU and A962891A-US) tested. The batches of SAR342434 and Humalog studied have also shown similar activities on IGF-1R binding, stimulation of autophosphorylation and of cell proliferation.
2. Studies supporting the clinical Phase 3 trials: The same studies conducted in the first series (above) were conducted with two batches of SAR342434 (C1024625 and C1033467) and two batches of Humalog (C079720-EU and C018505C-US) used in the clinical trials. Similarity of both batches of SAR342434 to Humalog EU and Humalog US was demonstrated by the results of all these series of studies.
3. Studies conducted to comply with European Medicines Agency (EMA) guideline on nonclinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues: Four batches each, SAR342434 (Batches C1033467, 5F006, 5F007, and 5F008), Humalog EU (C079720, C224081, C350360, C278315) and Humalog US (C018505C, C0152074A, C257286C, and C087535A) were compared in a side-by-side biological similarity assessment using a set of *in vitro* pharmacodynamics studies. These studies included: Binding affinity and binding kinetics of IR subtype A (IR-A) and IR subtype B (IR-B), IGF-1R binding, autophosphorylation activity of IR-B, IR-A, and IGF-1R, inhibition of lipolysis, stimulation of glucose uptake, gene regulation of

glucose-6 phosphatase, and determination of mitogenic potency. Results of these studies demonstrated that batches of SAR342434 and batches of Humalog EU and Humalog US included in this study had similar binding affinity and autophosphorylation activity to IR-B, IR-A, similar binding kinetics in regards to IR-B and IR-A; and similar metabolic activity and mitogenic potency.

Toxicology:

The Applicant states that the SAR342434 formulation used in the toxicology studies is the same as that used in all clinical studies and is the same as the to-be-marketed formulation. The toxicology program was comprised of two 1-month repeated dose studies performed in rats (one with Humalog-EU comparator and the other with Humalog-US comparator) and a local tolerability study performed in rabbits.

1. Repeated dose study in rats (SAR342434 vs. Humalog EU, and SAR342434 vs. Humalog US): Subcutaneous injections (twice daily) of SAR342434 or Humalog at doses of 0, 10, 50 and 200 U/kg/day were administered to rats for one month. Toxicological evaluations included: clinical observations, body weight, food consumption, ophthalmologic examination, mortality rate, and laboratory analysis (blood glucose, hematology, coagulation, clinical chemistry and urinalysis). A sub-group of animals was designated for toxicokinetic determinations and assessment of anti-insulin antibodies (AIA). Post-mortem tissue microscopy was performed for animals that received 0 and 200 U/kg/day of SAR342434 or Humalog (EU and US). Staining of mammary gland tissue with Ki-67 was performed to evaluate the mitogenic effect of the compounds tested. Findings from these studies are summarized below:
 - a. SAR342434 vs. Humalog (EU and US) toxicokinetic study - The Applicant reported that the exposure values ($C_{\max,1}$ and AUC_{0-8}) for equivalent doses of SAR342434 and Humalog were similar for both Humalog EU and Humalog US. The Applicant noted a high variability within groups and pointed out that the study was designed with only three rats/time point, non-serial sampling and different animals per analyte. Regarding gender, the only difference observed was a higher exposure at $C_{\max,1}$ in females compared to males with SAR342434 in the SAR342434 vs. Humalog US study. No difference was observed with Humalog EU.
 - b. The AIA was measured at Study Day 29, and a similar percentage of AIA-positive animals was observed for equivalent doses of SAR342434 and its reference product (Humalog EU). The Applicant reported that at least two thirds of the animals were positive for AIA, and that the percentage of AIA-positive animals increased in a dose-dependent fashion. It was noted that the percentage of AIA-positive animals was higher in the female groups. AIA was positive in 100% of the females treated with SAR342434 and with Humalog

EU at 200 U/kg/day, and in 94.4 % of females treated with Humalog US at 200 U/kg/day.

- c. In the toxicological evaluation of SAR342434 and Humalog EU, three drug-related deaths were reported. Two moribund rats were euthanized: One at Day 24 on SAR342434 dose of 50 U/kg/day, and the other at Day 29 on Humalog EU dose of 200 U/kg/day. One animal on 200 U/kg/day Humalog EU was found dead in the cage at Day 30, and the microscopic findings of multifocal cerebral vacuolization were compatible with death caused by acute hypoglycemic shock. In the study with Humalog US, two premature treatment-related deaths were reported, both with SAR342434 at 50 U/kg/day. The Applicant considered that these two animal deaths were unlikely to be related to drug alone, since no clinical signs of toxicity related to SAR342434 at 50 and 200 U/kg/day were observed.
- d. The expected pharmacological effects of insulin (dose-dependent lowering of blood glucose and the increase in food consumption and body weight) were similar between SAR342434 and Humalog (EU and US). Relevant findings were restricted to hypoglycemia-related death and microscopic changes in brain and liver compatible with severe hypoglycemia. No significant differences between these two compounds were observed in any of the parameters studied including clinical, laboratory and microscopic evaluations. No mammary gland tissue proliferation was observed with SAR342434 or Humalog (EU and US). NOAEL was determined based on hypoglycemia-related deaths observed in each study. The differences in NOAEL noted between the two toxicology studies may be explained by the fact that in study TSA1505 the NOAEL was determined based on one single animal (out of 10) per group. The values are presented in the Table 4 below:

Table 4: NOAEL of SAR342434 in comparison with Humalog US and with Humalog EU (Subcutaneous repeat-dose toxicity studies in rats)

Study Number		SAR342434	Humalog
TSA1505	SAR342434 vs. Humalog EU	10 U/kg/day	50 U/kg/day
TSA1519	SAR342434 vs. Humalog US	200 U/kg/day	200 U/kg/day

Table generated adapted from data submitted the toxicology summary, Table 2.

2. Local tolerance study in rabbits with SAR342434 and Humalog EU: SAR342434 was administered at 100 U/mL to 4 groups of rabbits (3 animals/group), via subcutaneous (SC, 0.1 mL), intravenous (IV, 0.5 mL), paravenous (PV, 0.1 mL) or intramuscular (IM, 0.5 mL) injection. Each rabbit was dosed by a combination of IM and PV or IV and SC routes. Another 4 groups of rabbits received Humalog EU

following the same design. NaCl (0.9%) solution was injected contralaterally as control for IM and SC routes, and injected via IV or PV at both ears in 3 additional groups of rabbits. Assessments included: examination of local injection site, clinical signs of toxicity, changes in body weight, mortality, and microscopic examination of injection sites at necropsy. The Applicant reported that in comparison with saline and the reference drug Humalog EU, administration of SAR342434 via SC, IV, PV and IM was well-tolerated.

Overall, the nonclinical studies conducted appear to support similarity between batches of SAR342434 and batches of Humalog (EU and US origin) that were used.

4.4 Clinical Pharmacology

For a detailed review of the Clinical Pharmacology studies, refer to the review by Dr. Sze Lau.

4.4.1 Mechanism of Action

Insulin lispro is a human insulin analogue that increases peripheral glucose uptake in skeletal muscle and fat. Insulin binds to the insulin receptor and stimulates tyrosine-kinase activity promoting receptor autophosphorylation, and subsequent recruitment of intracellular signaling molecules. This event initiates a cascade of intracellular reactions leading to a number of metabolic and mitogenic effects that include the translocation of glucose transporters to the cell surface, promoting glucose uptake. Activation of other pathways by insulin stimulates the synthesis of glycogen, protein, and lipids in muscle, adipose tissue, liver and other tissues¹⁹.

4.4.2 Pharmacodynamics

The Applicant conducted a clamp study (PDY12704) in T1DM patients intended to bridge SAR342434 and Humalog (EU and US). PDY12704 was a cross-over, double blind, euglycemic clamp study in T1DM patients, following a Williams design for comparison of 3 formulations, 6 sequences and 3 periods. This study evaluated AUC, AUC_{last} and C_{max} to demonstrate that the pharmacokinetic profiles of SAR342434, Humalog EU and Humalog US were all similar. The PD endpoint used for comparison of the three insulin products was the body weight standardized glucose infusion rate (GIR) vs. the time curve from 0 to 12 hours post-administration of insulin lispro (GIR-AUC_{0-12h}). Analysis of this parameter demonstrated that the PD characteristics of SAR342434, Humalog EU and Humalog US were similar. These results are summarized in Table 5.

Table 5: Treatment effect on GIR-AUC_{0-12h} - Point estimates of treatment ratio with 90% and 95% confidence intervals.

Parameter	Treatment ratio	Estimate	90% CI	95% CI
GIR-AUC _{0-12h} (mg/kg)	SAR342434 vs Humalog US	1.00	(0.94 to 1.07)	(0.93 to 1.08)
	SAR342434 vs Humalog EU	1.06	(0.97 to 1.15)	(0.95 to 1.17)
	Humalog US vs Humalog EU	1.05	(0.98 to 1.14)	(0.96 to 1.15)

Source: Excerpted from Table 3, Clinical Overview file submitted by the Applicant.

To satisfy the updated EMA guidelines, the Applicant also provided results based on the maximum smoothed body weight standardized glucose infusion rate (GIR_{max}) as a secondary PD endpoint. The data submitted support similarity of GIR_{max} between SAR342434, Humalog EU and Humalog US, and are presented in Table 6.

Table 6: Treatment effect on GIR_{max} - Point estimates of treatment ratios with 90% and 95% confidence intervals.

Parameter	Treatment ratio	Estimate	90% CI	95% CI
GIR _{max} (mg/kg/min)	SAR342434 vs Humalog US	1.04	(0.98 to 1.10)	(0.96 to 1.12)
	SAR342434 vs Humalog EU	1.07	(0.99 to 1.14)	(0.98 to 1.16)
	Humalog US vs Humalog EU	1.03	(0.95 to 1.10)	(0.94 to 1.12)

Source: Excerpted from Table 4, Clinical Overview file submitted by the Applicant.

4.4.3 Pharmacokinetics

Individual PK parameters (C_{max}, AUC_{last} and AUC) were measured in Study PDY12704 after a single subcutaneous injection of 0.3 U/kg of SAR342434, Humalog US and Humalog EU. The statistical analysis of the data submitted by the Applicant and summarized in Table 7 below support similarity in PK profile between SAR342434 and Humalog US, between SAR342434 and Humalog EU, and between Humalog US and Humalog EU.

Table 7: Statistical analyses of primary pharmacokinetic parameters INS-C_{max}, INS-AUC_{last}, and INS-AUC - Point estimates of treatment ratio with 90% confidence intervals.

Parameter	Treatment ratio	Estimate	90% CI
INS-C _{max} (pg/mL)	SAR342434 vs Humalog US	0.97	(0.89 to 1.05)
	SAR342434 vs Humalog EU	0.96	(0.89 to 1.04)
	Humalog US vs Humalog EU	0.99	(0.94 to 1.03)
INS-AUC _{last} (pg.h/mL)	SAR342434 vs Humalog US	0.95	(0.91 to 0.99)
	SAR342434 vs Humalog EU	0.97	(0.94 to 1.01)
	Humalog US vs Humalog EU	1.03	(1.00 to 1.05)
INS-AUC (pg.h/mL)	SAR342434 vs Humalog US	0.95	(0.92 to 0.99)
	SAR342434 vs Humalog EU	0.97	(0.94 to 1.00)
	Humalog US vs Humalog EU	1.02	(1.00 to 1.05)
PGM=PRODOPS/SAR342434/PDY12704/CSR/REPORT/PGM/pk_equivstat_k.sas OUT=REPORT/OUTPUT/pk_eq_pp_int_k_t_2_i.rtf (19SEP2013 - 15:07)			

Source: Excerpted from Table 2, Clinical Overview file submitted by the Applicant.

4.5 Device Constituent

The Center for Devices and Radiological Health (CDRH) was consulted to review one of the proposed commercial presentations of SAR342434, which consists of a 3-mL insulin lispro cartridge assembled in a disposable pen injector. The pen-injector proposed for use with SAR342434 is a mechanical device based on the Applicant's SoloStar pen-injector platform, and it is designed to deliver multiple doses of variable volume. The same SoloStar pen-injector platform has been used with Lantus (Insulin Glargine, 100 U/mL) since April 2000 and with Apidra (Insulin Glulisine, 100 U/mL) since February 2009. See the CDRH consultant review for a detailed discussion.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant submitted two Phase 3 studies: EFC12619 in patients with T1DM and EFC1343 in patients with T2DM to compare safety and efficacy of SAR342434 to US-approved Humalog and to EU-approved Humalog. Immunogenic response (anti-insulin antibody) and its influence on efficacy and safety were also assessed in both these trials. An additional safety study (PDY13502) was conducted in patients with T1DM to assess the incidence of infusion set occlusions with continuous subcutaneous insulin infusion devices. A list of the relevant clinical trials for this application is presented in Table 8 below.

Table 8: Listing of Clinical Trials Submitted in Support of NDA 209196.

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Studies to Bridge Efficacy and Safety of SAR342434 and the reference drug Humalog</i>							
EFC12619	Multinational, multicenter, open-label, randomized, parallel-group, controlled. Comparator: Humalog US in the US and Japan; Humalog EU in Europe	Injected subcutaneously before and/or immediately after meals, if needed. Admin. device: SoloStar for SAR342434, and KwikPen for Humalog.	Primary endpoint: HbA1c (%) change from baseline to week 26	Main period: 6 months, with 6-month safety extension	SAR342434: 253 subjects and Humalog: 254 subjects	Adult subjects with T1DM on Lantus, in combination with mealtime insulin analog for at least 6 months prior to the study, with screening HbA1c between 7% and 10%	89 centers, 15 countries
EFC13403	Multinational, multicenter, open-label, randomized, parallel-group, controlled. Comparator: Humalog US in the US; Humalog EU in Europe, Turkey, South Korea, Argentina, Chile and Colombia	Injected subcutaneously before and/or immediately after meals, if needed. Admin. device: SoloStar for SAR342434, and KwikPen for Humalog.	Primary endpoint: HbA1c (%) change from baseline to week 26	6 months	SAR342434: 253 subjects and Humalog: 252 subjects	Adult subjects with T2DM on Lantus, in combination with mealtime insulin analog for at least 6 months prior to the study, with screening HbA1c between 6.5% and 10%	103 centers, 15 countries

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Sonia Doi, MD, PhD
NDA 209196
Admelog (Insulin lispro)

<i>Safety Study on Infusion Sets</i>							
PDY13502	Randomized, open-label, comparative 2-treatment arm, 2-period crossover. Comparator: Humalog US	Continuous subcutaneous insulin infusion (CSII), using Medtronic with 3 ml reservoir or Animas Vibe or One Touch Ping pump.	Primary endpoint: Incidence of infusion set occlusions, defined as failure to correct hyperglycemia by insulin bolus via CSII	2 x 4 weeks	27 subjects	Adult subjects with T1DM on CSII	2 centers

Table generated with data submitted in Table 1, Clinical Overview

5.2 Review Strategy

In approaching this review, the two efficacy and safety trials (trial EFC12619 and EFC13403) were considered separately as they were conducted in different patient populations. Additionally, efficacy and safety were considered in greater detail for the comparison of SAR342434 with the US approved insulin lispro product.

My discussion of efficacy will primarily summarize the applicant's reported efficacy results. The FDA efficacy review has been completed by Dr. Roberto Crackel. See Dr. Crackel's review for a detailed discussion of the FDA's efficacy findings.

5.3 Discussion of Individual Studies/Clinical Trials

Key features of trial EFC12619 and EFC13403 will be discussed here. An additional clinical trial to support administration via continuous subcutaneous insulin infusion (trial PDY13502) was conducted in patients with T1DM to assess the incidence of infusion set occlusions with continuous subcutaneous insulin infusion devices. This study will also be briefly described here. For additional discussion of trial PDY13502, see the consult review from CDRH/OIR.

5.3.1 EFC12619, Phase 3 Trial in patients with T1DM

Study Title:

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

Primary Objective:

The primary objective of this study was to demonstrate non-inferiority of SAR342434 in comparison to approved insulin lispro, as measured by change in HbA1c from baseline to week 26 in patients with T1DM, on Lantus as a background basal insulin treatment.

Secondary Objectives:

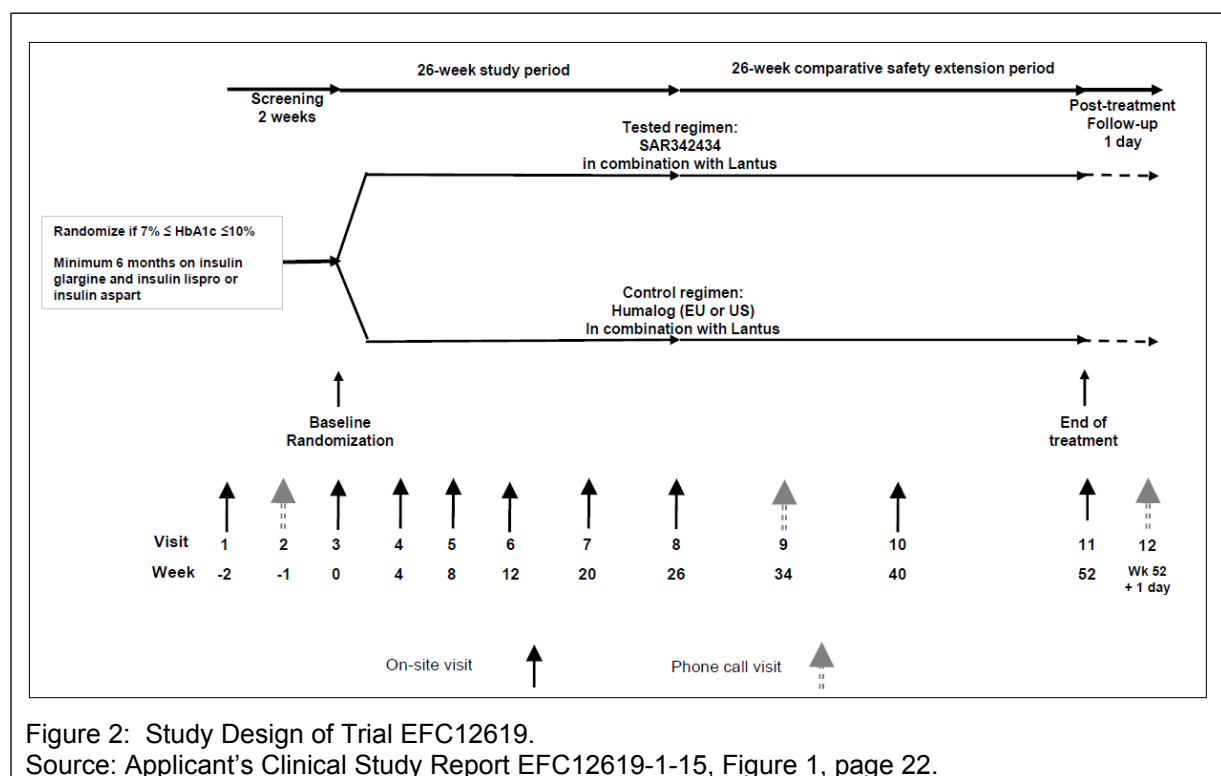
Secondary objectives were to compare SAR342434 to Humalog in terms of safety including immunogenicity, and other efficacy variables.

Study Design:

Study EFC12619 was a multicenter, multinational, open-label, randomized, active-controlled, 2-arm parallel-group study to compare SAR342434 to Humalog in T1DM

adult patients treated with insulin glargine as basal insulin over a period of 6 months for efficacy and safety evaluation, with a 6-month safety extension period, and 1-day post-treatment follow-up.

The basic study plan was to randomize patients with T1DM on treatment with insulin glargine as basal insulin for at least 6 months prior to the screening visit, to receive subcutaneous injection of either SAR342434 or approved insulin lispro immediately before meals, and occasionally after meals for a period of 6 months (26 weeks), in addition to the basal insulin administered once daily. A diagram of the study design is presented in Figure 2 below.



Subjects:

A total of 506 subjects were randomized 1:1 to receive either SAR342434 or Humalog. The randomization was stratified by the screening values of HbA1c (< 8.0%; ≥8.0%), prior use of Humalog/Liprolog (Yes; No), and geographical region (non-Japan; Japan). A central interactive voice response system/interactive web response system (IVRS/IWRS) generated the patient randomization list and allocation of patients to the treatment groups.

Inclusion Criteria included:

Adult patients diagnosed with T1DM for at least 12 months and treated with Lantus as basal insulin and Humalog/Liprolog or NovoLog/NovoRapid (at least 3 times daily, i.e., before meals) in the 6 months prior to the screening visit.

Exclusion Criteria included:

- HbA1c <7% or >10% at screening
- BMI ≥ 35 kg/m²
- Diabetes other than T1DM
- Post-pancreatectomy
- Post pancreas and/or islet cell transplantation
- Less than 1 year on continuous insulin treatment
- Use of insulin pump in the last 6 months before screening
- Use of glucose lowering agents other than insulin including use of non-insulin injectable peptides in the last 6 months prior to screening
- Use of insulin other than insulin glargine (Lantus) and Humalog/Liprolog⁽³⁾ or NovoLog/NovoRapid as part of a multiple injection regimen in the last 6 months prior to screening visit.
- Patients on twice daily Lantus who were unwilling to switch to once daily insulin glargine
- Hypoglycemia unawareness in the last 6 months before the screening visit
- History of severe hypoglycemia requiring treatment by emergency room admission or hospitalization in the last 6 months before screening
- Hospitalization for diabetic ketoacidosis (DKA) in the last 6 months before screening
- Laboratory findings at the screening visit of:
 - Alanine aminotransferase (ALT) or aspartate aminotransaminase (AST) >3 upper limit of normal (ULN).
 - Total bilirubin >1.5X ULN (except in case of Gilbert's syndrome)
 - Positive test for hepatitis B and/or hepatitis C
 - Positive serum pregnancy test
- Patients under conditions/situations that either can impact the evaluation of the primary endpoint (e.g., hemoglobinopathy) or preclude patient's safe participation in the study.
- No exam by an ophthalmologist/optometrist within 12 months of screening for patients with retinopathy or within 24 months for those with no evidence of retinopathy.
- Patients who had impaired renal function with creatinine clearance < 30 mL/min or an eGFR <30 mL/min/1.73 m²

(b) (4)

- Uncontrolled treated/untreated severe hypertension
- Patients with severe or unstable hepatic, gastrointestinal, cardiovascular, respiratory, neurological, psychiatric, hematological, renal, endocrine, dermatological disease, active malignant tumor, other major systemic disease or patients with short life expectancy or any other medical condition that might interfere with the evaluation of the study medication according to investigator's medical judgement.
- History of myocardial infarction, stroke or heart failure requiring hospitalization within the last 3 months prior to screening
- Known history of drug or alcohol abuse within 6 months prior to screening
- Use of systemic glucocorticoids, except topical applications or inhaled forms, greater than replacement dose for one week or more within 3 months prior to the time of screening.

Treatments administered:

After screening, T1DM patients were randomized 1:1 to receive either SAR342434 or Humalog in addition to continuing Lantus once daily. Patients received either SAR342434 (3 mL cartridges with 100 U/mL solution) in the SoloStar disposable prefilled pen or the approved insulin lispro (3 mL cartridges with 100 U/mL solution) in the KwikPen disposable pre-filled pen. The non-investigational drug Lantus (insulin glargine) was a mandatory background basal insulin treatment for all patients in the study, and was supplied as a SoloStar pen.

SAR342434 or the approved insulin lispro were self-administered as subcutaneous injection immediately (within 5-10 minutes) before starting a meal (breakfast, lunch, dinner, any additional meal and snacks), and occasionally after a meal, if necessary. Patients were to record the basal dose of insulin and all the bolus doses in their e-diary, and the data were then transferred to the clinical database.

The dose of SAR342434 or of the approved insulin lispro administered was determined by the pre-meal self-measure plasma glucose (SMPG) and the size or carbohydrate content of the meal, and was adjusted at the discretion of the Investigator to meet a target of 2-hour postprandial SMPG in the range of 120 to 160 mg/dL, while avoiding hypoglycemia.

Lantus was adjusted to meet a fasting, pre-prandial SMPG in the range of 80 to 130 mg/dL without hypoglycemia. The dose of Lantus was up-titrated if the median of fasting, pre-prandial SMPG values of the previous 3-4 days was greater than the recommended target (i.e., 80-130 mg/dL) or the individual pre-specified target. The increase in dose was not to exceed 10% of the daily dose of Lantus. Reduction and adjustments in the doses of Lantus were done with the occurrence of any hypoglycemia, at the discretion of the Investigator.

No formal algorithm was used for insulin titration. An internal titration review team, blinded to treatment was established to review compliance with the treat to target goals and to monitor titration of both the basal insulin Lantus and the adjustments of bolus insulin doses.

Endpoints:

Primary Efficacy Endpoint: Change in HbA1c from baseline to Week 26.

Secondary Efficacy Endpoints:

- Anti-insulin antibodies (AIA) measured in both arms, SAR342434 and approved insulin lispro (positive/negative status and titers at each sampling)
- The percentage of patients with HbA1c<7% at Week 26
- Change in FPG from baseline to Week 26
- Change in the mean 24-hour plasma glucose based on the 7-point SMPG profile from baseline to Week 26
- Change in postprandial plasma glucose excursions from baseline to Week 26

Main Efficacy Assessments:

For efficacy assessments, HbA1c and fasting plasma glucose (FPG) were measured at several visits during the main 6-month period. During the 6-month safety extension period, HbA1c and FPG measurements were performed at week 40 and week 52.

- HbA1c and FPG were measured by a central laboratory.
- SMPG was recorded at fasting pre-breakfast, 7-point SMPG, 3-point SMPG, and SMPG at episodes of symptomatic hypoglycemia.

For further details please refer to **Section 6 – Review of Efficacy**.

Safety Assessments:

The main safety assessments are listed below. For a more detailed discussion, please refer to **Section 7 – Review of Safety**.

- Events of hypoglycemia, as defined by the American Diabetes Association and FDA.
- Adverse Events, including injection site reactions and hypersensitivity
- Results of anti-insulin antibody determinations
- Results of laboratory tests
- Records of vital signs
- Electrocardiogram (ECG)

Statistical Methods:

A total of 507 patients with T1DM were randomized in a 1:1 fashion to either SAR342434 treatment (253 patients) or Humalog treatment (254 patients). The primary efficacy endpoint tested the non-inferiority of SAR342434 to Humalog measured by HbA1c change from baseline to week 26 at 0.3% non-inferiority margin.

5.3.2 EFC13403, Phase 3 Trial on patients with T2DM

Study Title:

Six-month, Randomized, Open-label, Parallel-group Comparison of the Insulin Analog SAR342434 to Humalog in Adult Patients With Type 2 Diabetes Mellitus also Using Insulin Glargine

Primary Objective:

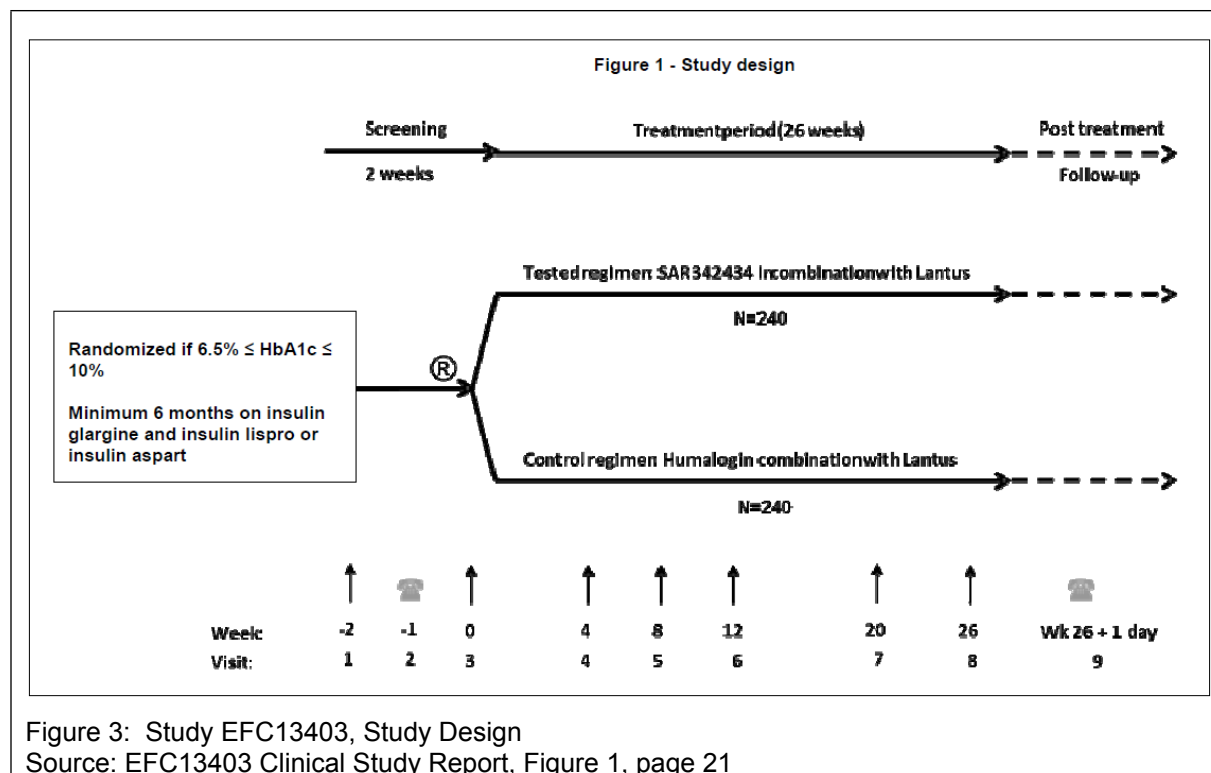
The primary objective of this study was to demonstrate non-inferiority of SAR342434 in comparison to the approved insulin lispro, as measured by change in HbA1c from baseline to week 26 in patients with T2DM, on insulin glargine as a background basal insulin treatment.

Secondary Objectives:

Secondary objectives were to compare SAR342434 to the approved insulin lispro in terms of safety including immunogenicity, and other efficacy variables.

Study Design:

This was a multicenter, multinational, open-label, randomized, active-controlled, 2-arm, parallel-group study to compare SAR342434 to the approved insulin lispro in patients with T2DM on insulin glargine as basal insulin therapy. A diagram of the study design is presented in Figure 3 below.



Subjects:

A total of 505 subjects were randomized 1:1 to either SAR342434 or approved insulin lispro. The randomization was stratified by the screening values of HbA1c ($< 8.0\%$; $\geq 8.0\%$), prior use of Humalog/Liprolog (Yes; No), and geographical region (non-Japan; Japan). A central interactive voice response system/interactive web response system (IVRS/IWRS) generated the patient randomization list and allocation of patients to the treatment groups.

Inclusion Criteria included:

Adult patients diagnosed with T2DM for at least 12 months and treated with Lantus as basal insulin and Humalog/Liprolog or NovoLog/NovoRapid (at least 3 times daily, i.e., before meals) in the 6 months prior to the screening visit.

Exclusion Criteria included:

- HbA1c $< 6.5\%$ or $> 10\%$ at screening
- Diabetes other than T2DM
- Use of insulin pump in the 6 months prior to screening
- Use of insulin other than Lantus and Humalog/Liprolog or NovoLog/NovoRapid in the 6 months prior to screening

- Use of Humalog/Liprolog or Novolog/NovoRapid less than 3 times daily, i.e., before each main meal
- Use of non-insulin injectable peptides in the 6 months preceding the screening visit
- BMI ≥ 40 kg/m² at screening
- History of hypoglycemia unawareness in the period of 6-months preceding the screening visit
- History of severe hypoglycemia requiring admission to Emergency Room or hospitalization in the 6-month period preceding screening
- History of hospitalization for DKA in the 6-month period preceding screening
- Abnormal laboratory findings at the screening visit:
 - ALT or AST $>3X$ ULN
 - Total bilirubin $>1.5X$ ULN
 - Positive test for Hepatitis B and or Hepatitis C
 - Positive serum test for pregnancy
- Patients under conditions/situations that either can impact the evaluation of the primary endpoint (e.g., hemoglobinopathy) or preclude patient's safe participation in the study.
- No exam by an ophthalmologist/optometrist within 12 months of screening for patients with retinopathy or within 24 months for those with no evidence of retinopathy.
- Patients who had impaired renal function with creatinine clearance < 30 mL/min or an eGFR <30 mL/ min/1.73 m²
- Uncontrolled treated/untreated severe hypertension
- Patients with severe or unstable hepatic, gastrointestinal, cardiovascular, respiratory, neurological, psychiatric, hematological, renal, endocrine, dermatological disease, active malignant tumor, other major systemic disease or patients with short life expectancy or any other medical condition that might interfere with the evaluation of the study medication according to investigator's medical judgement.
- History of myocardial infarction, stroke or heart failure requiring hospitalization within the last 3 months prior to screening
- Known history of drug or alcohol abuse within 6 months prior to screening
- Use of systemic glucocorticoids, except topical applications or inhaled forms, greater than replacement dose for one week or more within 3 months prior to the time of screening.

Treatments administered:

- All patients received Lantus once daily as basal insulin.
- SAR342434 or the approved insulin lispro was injected subcutaneously immediately before meals and snacks.
- The dose of SAR342434 or of the approved insulin lispro administered was determined by the pre-meal SMPG and the size or carbohydrate content of the meal,

and was adjusted at the discretion of the Investigator to meet a target of 2-hour postprandial SMPG in the range of 120 to 160 mg/dL, while avoiding hypoglycemia.

- Lantus was adjusted to achieve a fasting and pre-prandial SMPG in the range of 80 to 130 mg/dL.
- The dose of Lantus was up-titrated if the median of fasting, pre-prandial SMPG values of the previous 3-4 days was greater than the recommended target (i.e., 80-130 mg/dL) or the individual pre-specified target. The increase in dose should not exceed 10% of the daily dose of Lantus.
- No formal algorithm was used for insulin titration. An internal titration review team, blinded to treatment was established to review compliance and to monitor insulin titration.

Endpoints:

Primary Efficacy Endpoint: Change in HbA1c from baseline to Week 26.

Main Secondary Efficacy Endpoints:

- Anti-insulin antibodies (AIA) measured in both arms, SAR342434 and Humalog (positive/negative status and titers at each sampling)
- The percentage of patients with HbA1c<7% at Week 26
- Change in FPG from baseline to Week 26
- Change in the mean 24-hour plasma glucose based on the 7-point SMPG profile from baseline to Week 26
- Change in postprandial plasma glucose excursions from baseline to Week 26

Main Efficacy Assessments:

For efficacy assessments, HbA1c and fasting plasma glucose (FPG) were measured at several visits during the main 6-month period. During the 6-month safety extension period, HbA1c and FPG measurements were performed at week 40 and week 52.

- HbA1c and FPG were measured by a central laboratory.
- Self-measured plasma glucose (SMPG) was recorded at fasting pre-breakfast, 7-point SMPG, 3-point SMPG, and SMPG at episodes of symptomatic hypoglycemia.

For further details please refer to **Section 6 – Review of Efficacy**.

Safety Assessments:

The main safety assessments are similar to those conducted in the EFC12619 trial. For a more detailed discussion, please refer to **Section 7 – Review of Safety**.

Statistical Methods:

A total of 505 patients with T2DM were randomized in a 1:1 fashion to either SAR342434 treatment (253 patients) or Humalog treatment (252 patients). The primary efficacy endpoint tested the non-inferiority of SAR342434 to Humalog measured by HbA1c change from baseline to week 26 at a non-inferiority margin of 0.3%.

5.3.3 PDY13502, Insulin Pump study in patients with T1DM

This study will be briefly described here. For additional discussion of trial PDY13502, see the consult review from CDRH/OIR.

Study Title: A randomized, 2X4 week, active-controlled, open-label, 2 treatment arm, 2 period cross-over study assessing the safety of SAR342434 and Humalog used in continuous subcutaneous insulin infusion (CSII) in adult patients with type 1 diabetes mellitus.

Primary Objective: To assess the safety of SAR342434 and of the approved insulin lispro when used in external pumps in terms of the incidence of infusion set occlusions.

Secondary Objectives: To assess safety by determining the intervals for infusion set changes, the incidence of insulin pump alarms for infusion set occlusion, the infusion set occlusions observed and recorded by patient in the patient diary, the adverse and serious events, and the incidence of hypoglycemic events.

Study Design: This was an open-label, randomized, active-controlled, 2 x 4 weeks cross-over study.

Subjects: A total of 27 patients with T1DM were randomized into 2 groups. The first group (13 patients) received SAR342434 for the first 4-week period and the approved insulin lispro for the second 4-week period, and the second group (14 patients) received the approved insulin lispro in the first period followed by SAR342434 in the second period.

Inclusion criteria included:

- Adult patients with T1DM
- Demonstration of successful use of insulin pump and performance of at least 4 blood glucose check per day
- Compliance with SMPG 4-times per day.

Exclusion criteria included:

- HbA1c level $\geq 8.5\%$ at screening
- Use of oral glucose-lowering agents or injectable glucose-lowering agents other than insulin during the 3 months before screening

- Hospitalization for DKA in the last 6 months before screening
- Hypoglycemic unawareness in the last 6 months before screening
- History of severe hypoglycemia requiring emergency room admission for treatment in the last 6 months prior to screening
- Use of investigational drug(s) within 3 months or 5 half-lives, whichever is longer, prior to screening.

Treatment Administration:

The investigational medical product (IMP) was administered at a basal rate and in bolus doses via the patient's own insulin infusion pump. The pumps used in this study were Medtronic 530G Model 751, other Medtronic models with a 3 mL reservoir, Animas Vibe or One Touch Ping.

Each patient continued using the same basal and bolus infusion rate that they were using prior to enrolling in the study. During the study, the dose was individually titrated by the Investigator as needed to achieve pre-prandial glucose in the range of 70 – 130 mg/dL, and a postprandial glucose <180 mg/dL.

Endpoints:

The main safety endpoint was infusion set occlusion, defined as failure to correct hyperglycemia (plasma glucose ≥ 300 mg/dL) by insulin bolus via the insulin pump.

Safety Assessment:

The safety assessment for this study included:

- Safety parameters related to the risk of infusion set occlusion.
- Hypoglycemia.
- Adverse events (AEs) and serious adverse events (SAEs) including bruising at the infusion site, injection site and hypersensitivity reactions.
- Laboratory data.
- Vital signs including body weight.

Safety parameters related to the risk of infusion set occlusions:

Plasma glucose was monitored by SMPG four times daily. If the plasma glucose was ≥ 300 mg/dL, the patient was to administer an insulin bolus via insulin pump and monitor plasma glucose every 30 minutes until the value had fallen by at least 50 mg/dL and to <300 mg/dL. Failure to lower plasma glucose by at least 50 mg/dL within 60 minutes of the insulin bolus via the insulin pump was considered an infusion set occlusion and a criterion for replacing the infusion set and changing the infusion site.

Patients were instructed to document the primary reasons for the infusion set change under the following categories:

- Scheduled infusion set change (3 days from the last infusion set change, or change required to refill pump reservoir).

- Unexplained plasma glucose concentration ≥ 300 mg/dL that was not reduced by at least 50 mg/dL within 60 minutes of an insulin bolus via the insulin pump.
- Visual infusion set occlusion.
- Pain or swelling at infusion site.
- Pump alarm for infusion set occlusion.
- Other.

The main safety parameter related to the risk of infusion set occlusion was defined as failure to correct hyperglycemia (plasma glucose ≥ 300 mg/dL) by insulin bolus via the insulin pump. The secondary safety parameters were: average interval for infusion set changes, insulin pump alarms for infusion set occlusion, and patient observation of infusion set occlusion.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication of SAR342434 is to improve glycemic control in adults and children with diabetes mellitus.

6.1.1 Methods

The efficacy evaluation came from the two pivotal phase 3 trials. Efficacy findings were considered separately. There was no pooling for efficacy. The Applicant analysis of HbA1c change from baseline to week 26 used a mixed model for repeated measurements (MMRM). As per Applicant's protocol, the specified primary efficacy population is the intent-to-treat (ITT) population, which included all randomized patients, irrespective of compliance with the study protocol and procedures.

6.1.2 Demographics

Study EFC12619: A total of 507 patients with T1DM were randomized to SAR342434 (253) or to Humalog (254) and 506 patients were exposed to the study drug.

Study EFC13403: A total of 505 patients with T2DM were randomized to receive either SAR342434 (253) or Humalog (252) and all patients were exposed to the study drug.

The average age was 42.9 years in the T1DM study population and 62.5 years in the T2DM population. The majority of the subjects were white in both trials (82% in EFC12619 and 88% in EFC13403). Both trials were conducted in 8 countries and the US was the largest region among those included in the studies.

The baseline demographics of subjects in the two pivotal trials EFC12619 (T1DM) and EFC13403 (T2DM) are presented in Table 9.

Table 9: Baseline Demographics of Randomized Populations of Trials EFC12619 (T1DM) and EFC13403 (T2DM)

Demographic Parameters	EFC12619 (T1DM)		EFC13403 (T2DM)	
	SAR342434 (N=252) n(%)	Humalog (N=254) n(%)	SAR342434 (N=253) n(%)	Humalog (N=252) n(%)
SEX				
Male	148 (58.7)	153 (60.2)	136 (53.8)	132 (52.4)
Female	104 (41.3)	101 (39.8)	117 (46.2)	120 (47.6)
AGE				
Mean years (SD)	43.2 (14.5)	42.6 (13.9)	62.1 (9.4)	62.8 (8.9)
Median (years)	43	42	63	64
Min, Max (years)	18, 83	18, 84	35, 88	38, 86
AGE GROUP				
< 65	225 (89.3)	237 (93.3)	144 (56.9)	137 (54.4)
>= 65 < 75	25 (9.9)	16 (6.3)	89 (35.2)	93 (36.9)
>= 75	2 (0.8)	1 (0.4)	20 (7.9)	22 (8.7)
RACE				
White	201 (79.8)	214 (84.3)	228 (90.1)	218 (86.5)
Black	16 (6.3)	8 (3.1)	14 (5.5)	17 (6.7)
Asian	32 (12.7)	31 (12.2)	11 (4.3)	16 (6.3)
American Indian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	3 (1.2)	1 (0.4)	0 (0.0)	1 (0.4)
ETHNICITY				
Hispanic	17 (6.7)	10 (3.9)	43 (17.0)	47 (18.7)
Non-Hispanic	235 (93.3)	244 (96.1)	210 (83.0)	205 (81.3)
GEOGR				
Eastern Europe	68 (27.0)	88 (34.6)	67 (26.5)	58 (23.0)
Rest of the World	31 (12.3)	30 (11.8)	32 (12.6)	37 (14.7)
United States	108 (42.9)	110 (43.3)	122 (48.2)	120 (47.6)
Western Europe	45 (17.9)	26 (10.2)	32 (12.6)	37 (14.7)

Table generated using data submitted by Applicant in CSR files of Study EFC12619 and Study EFC13403.

Overall, no clinical meaningful differences were observed between SAR342434 and Humalog in the demographic parameters analyzed for study EFC12619 and study EFC13403.

6.1.3 Subject Disposition

In the Study EFC12619, 12-month period, one of the patients randomized to SAR342434 did not receive treatment, but was included in the ITT population for efficacy analysis. The percentage of patients discontinued was similar between treatment arms: 10.3% in the SAR342434 group vs. 7.5% in the Humalog group. The most common reasons for discontinuation were "other reasons" (21 patients in the SAR342434 group and 10 patients in the Humalog group).

(b) (6)

(b) (6)

Table 10: Patient disposition for study EFC12619, 12-month period

	SAR342434 (N=253)	Humalog (N=254)
Randomized and not treated	1 (0.4%)	0
Randomized and treated	252 (99.6%)	254 (100%)
Completed the whole study treatment period	226 (89.3%)	235 (92.5%)
Did not complete the whole study treatment period	26 (10.3%)	19 (7.5%)
Subject's decision for treatment discontinuation	21 (8.3%)	15 (5.9%)
Reason for treatment discontinuation during the whole study period		
Adverse event ^a	2 (0.8%)	2 (0.8%)
Lack of efficacy	1 (0.4%)	0
Poor compliance to protocol	1 (0.4%)	7 (2.8%)
Hypoglycemia not reported as SAE ^b	1 (0.4%)	0
Other reasons	21 (8.3%)	10 (3.9%)
Status at last study contact		
Alive	252 (99.6%)	254 (100%)
Dead	1 (0.4%)	0
SAE: Serious adverse event		
^a Including serious hypoglycemia reported as SAE		
^b For non-serious events		
Note: Percentages are calculated using the number of patients randomized as denominator		
PGM=PRODOPS/SAR342434/EFC12619/CSR_01/REPORT/PGM/dis_std_dispo_r_t.sas OUT=REPORT/OUTPUT/dis_std_dispo_r_t.trf		
(17AUG2016 - 9:01)		

Source: Table excerpted from Study EFC12619 – 12 month CSR, Table 5.

In Study EFC13403 with T2DM patients, the percentage of patients who discontinued the study prematurely was similar between the treatment arms: 9.9% for SAR342434 and 8.7% for Humalog. Three patients in the SAR342434 group discontinued the study due to a site closure, but were included in the ITT and safety populations.

The most common reason for discontinuation was “other reasons”, with a similar percentage of patients between the two treatment arms: 4.7% for SAR342434 and 4.8% for Humalog. Under the “other reason” category, the most frequent reported reasons were: patient decision and consent withdrawal. The percentage of patients discontinued under the category of adverse events was the same in SAR342434 (2.8%) and Humalog (2.8%) groups. (b) (6)

In the SAR342434 group, other relevant adverse events reported include pneumonia, cardiopulmonary arrest, pancreatitis, and one patient with multiple events (non-malignant gliosis, cerebral hematoma, sinus vein thrombosis and pulmonary embolism). In the Humalog group, other relevant events reported include

pancreatic carcinoma, bladder cancer with metastasis, cardiorespiratory insufficiency, and biliary hepatic litiasis. There were 4 deaths (1 in the SAR342434 group and 3 in the Humalog group). **See Section 7.3.1 Deaths** for a detailed discussion. Patient disposition for study EFC13403 is shown in Table 11 below.

Table 11: Patient disposition for study EFC13403

	SAR342434 (N=253)	Humalog (N=252)
Randomized and not treated	0	0
Randomized and treated	253 (100%)	252 (100%)
Completed the 6-month treatment period	228 (90.1%)	230 (91.3%)
Did not complete the 6-month treatment period	25 (9.9%)	22 (8.7%)
Subject's decision for treatment discontinuation	15 (5.9%)	16 (6.3%)
Reason for treatment discontinuation		
Adverse event ^a	7 (2.8%)	7 (2.8%)
Lack of efficacy	2 (0.8%)	1 (0.4%)
Poor compliance to protocol	4 (1.6%)	2 (0.8%)
Hypoglycemia not reported as SAE ^b	0	0
Other reasons	12 (4.7%)	12 (4.8%)
Status at last study contact		
Alive	252 (99.6%)	249 (98.8%)
Dead	1 (0.4%)	3 (1.2%)

SAE: Serious adverse event
^a Including serious hypoglycemia reported as SAE
^b For non-serious events
 Note: Percentages are calculated using the number of patients randomized as denominator
 PGM=PRODOPS/SAR342434/EFC13403/CSR/REPORT/PGM/dis_std_dispo_m6_r_t.sas OUT=REPORT/OUTPUT/dis_std_dispo_m6_r_t.rtf
 (31MAY2016 - 10:01)

Source: Excerpted from Study EFC13403, CSR, Table 4.

My review of patient disposition for study EFC12619 and EFC13403 did not identify any imbalances between treatment arms in the percentage of patients who discontinued the study prematurely. Also, a review of the reasons listed for permanent discontinuation, including the content of narratives did not raise a concern that the study drug was causing harm leading to permanent discontinuation.

6.1.4 Analysis of Primary Endpoint(s)

The primary objective in both studies was to demonstrate that the upper bound of the 2-sided 95% CI of the difference between SAR342434 and Humalog treatments was <0.3%. The MMRM analysis used by the Applicant did not include randomized patients

who withdrew before the next scheduled visit (week 12). To provide for unbiased comparison in all randomized patients regardless of adherence to treatment, the statistical reviewer performed the “return-to-baseline” analysis. The results of the “return-to-baseline” analysis are consistent with the protocol specified analysis and support the finding that the mean HbA1c change from baseline to week 26 is similar between SAR342434 and Humalog, and that the non-inferiority margin of <0.3% was met in both, study EFC12619 (T1DM) and study EFC13403 (T2DM). The results from the analyses performed by the Sponsor and by the Statistical Reviewer are illustrated in Table 12 (for EFC12619) and Table 13 (for EFC13403), excerpted from the Statistical Review. See Dr. Crackel’s review for a complete discussion of the FDA efficacy analysis.

Table 12: Study EFC12619 - Mean change HbA1c from baseline to week 26

<u>Sponsors analysis</u>			<u>Reviewer's analysis</u>		
	SAR 342434	Humalog		SAR 342434	Humalog
N	247	249	N	253	254
Change from Baseline at week 26	-0.42	-0.47	Change from Baseline at week 26	-0.403	-0.461
SAR 342434 - Humalog	0.06		SAR 342434 - Humalog	0.058	
95% C.I.	(-0.084, 0.197)		95% C.I.	(-0.086, 0.202)	

ITT: Intention-to-Treat; all randomized patients
Protocol specified analysis is based on the Mixed Model for Repeated Measurement with the fixed categorical effects of treatment group (SAR342434, Humalog), screening HbA1c (< 8.0% or screening ≥ 8.0%), prior use of Humalog (Yes, No), geographical region (Japan, Non-Japan), visit (Week 12, Week 26), and treatment-by-visit interaction as well as the continuous fixed covariates of baseline HbA1c and baseline HbA1c-by-visit interaction.
FDA analysis is based on multiple imputation using ANCOVA with the same factors and covariates used by the sponsor

Source: Excerpted from the Statistical Review, Table 7.

Table 13: Study EFC13403 - Mean change HbA1c from baseline to week 26

<u>Sponsors analysis</u>			<u>Reviewer's analysis</u>		
	SAR 342434	Humalog		SAR 342434	Humalog
N	239	249	N	253	252
Change from Baseline at week 26	-0.92	-0.85	Change from Baseline at week 26	-0.859	-0.799
SAR 342434 - Humalog	-0.07		SAR 342434 - Humalog	-0.06	
95% C.I.	(-0.215, 0.067)		95% C.I.	(-0.209, 0.090)	

ITT: Intention-to-Treat; all randomized patients
Protocol specified analysis is based on the Mixed Model for Repeated Measurement with the fixed categorical effects of treatment group (SAR342434, Humalog), screening HbA1c (< 8.0% or screening ≥ 8.0%), prior use of Humalog (Yes, No), visit (Week 12, Week 26), and treatment-by-visit interaction as well as the continuous fixed covariates of baseline HbA1c and baseline HbA1c-by-visit interaction.
Reviewer's analysis is based on multiple imputation using ANCOVA with the same factors and covariates used by the sponsor

Source: Excerpted from the Statistical Review, Table 8.

6.1.5 Analysis of Secondary Endpoints(s)

Since there were no key secondary endpoints pre-specified for any labeling claim, no multiplicity controlled statistical testing was performed for secondary endpoints. The Applicant performed an exploratory analysis of the difference in the proportion of patients in the SAR342434 group vs. Humalog group that achieved HbA1c level <7% at week 26. The statistical reviewer computed the proportion of responders of the 100 data sets in the “return-to-baseline” analysis and averaged out the proportions. The results obtained by Dr. Crackel’s analysis supported the Applicant’s findings, as illustrated in Table 14 (for EFC12619) and Table 15 (for EFC13403), excerpted from the Statistical Review. See Dr. Crackel’s review for complete information.

Table 14: Study EFC12619 - Pre-specified secondary and sensitivity analysis of patients achieving HbA1c < 7.0% at week 26

Sponsor's Analysis	SAR342434		Humalog		Treatment Comparison SAR342434 vs. Humalog	
	N	%	N	%	Odds Ratio	95% CI
HbA1c < 7.0%	57	22.5	55	21.7	1.06	(0.685 , 1.632)
HbA1c ≥ 7.0%	196	77.5	199	78.3		
Total	253		254			
Reviewer's MI Analysis	SAR342434		Humalog			
Average of Proportion of subjects with HbA1c < 7.0%	23.5		22.2			

Protocol specified analysis is based on a Logistic Regression with the fixed categorical effects of treatment group (SAR342434, Humalog), screening HbA1c (< 8.0% or screening ≥ 8.0%), prior use of Humalog (Yes, No) and geographical region (Japan, Non-Japan). Sponsor considered patients with missing week 26 data as non-responders.

Source: Excerpted from the Statistical Review, Table 9.

Table 15: EFC13403 - Pre-specified secondary and sensitivity analysis of patients achieving HbA1c < 7.0% at week 26

Sponsor's Analysis	SAR342434		Humalog		Treatment Comparison SAR342434 vs. Humalog	
	N	%	N	%	Odds Ratio	95% CI
HbA1c < 7.0%	107	42.3	102	40.5	1.08	(0.748 , 1.566)
HbA1c ≥ 7.0%	146	57.7	150	59.5		
Total	253		252			
Reviewer's MII Analysis	SAR342434		Humalog			
Average of Proportion of subjects with HbA1c < 7.0%	44.1		42.4			

Protocol specified analysis is based on a Logistic Regression with the fixed categorical effects of treatment group (SAR342434, Humalog), screening HbA1c (< 8.0% or screening ≥ 8.0%) and prior use of Humalog (Yes, No. Sponsor considered patients with missing week 26 data as non-responders.

Source: Excerpted from the Statistical Review, Table 10.

6.1.6 Other Endpoints

Other efficacy variables were measured in the extension period of the study EFC12619, with T1DM patients and included change in HbA1c from baseline to week 52. The results presented by the Applicant for the extension period of study EFC12619 support the similarity demonstrated in the analysis of the primary endpoint for the 26-week period of study EFC12619 and study EFC13403. A summary of the applicant's findings for change in HbA1c (%) from baseline to week 52 is shown in Table 16.

Table 16: Summary of change in HbA1c (%) from baseline to week 52 using MMRM analysis – ITT population

HbA1c (%)	SAR342434 (N=253)	Humalog (N=254)
Baseline		
Number	247	250
Mean (SD)	8.08 (0.78)	8.00 (0.64)
Median	8.00	7.95
Min : Max	5.4 : 10.5	6.7 : 9.7
Week 52		
Number	230	237
Mean (SD)	7.80 (0.98)	7.71 (0.96)
Median	7.60	7.60
Min : Max	5.3 : 11.4	5.8 : 15.4
Change from baseline to Week 52		
Number	230	237
Mean (SD)	-0.25 (0.89)	-0.29 (0.94)
Median	-0.30	-0.30
Min : Max	-2.7 : 3.4	-3.1 : 8.0
LS Mean (SE) ^a	-0.22 (0.057)	-0.30 (0.056)
95% CI	(-0.336 to -0.112)	(-0.409 to -0.187)
LS Mean difference (SE) vs Humalog ^a	0.07 (0.080)	
95% CI	(-0.084 to 0.232)	
MMRM=Mixed-effect model for repeated measures		
^a MMRM with treatment group (SAR342434, Humalog), randomization strata of screening HbA1c (<8.0, ≥8.0%), prior use of Humalog (Yes, No) and geographical region (Japan, Non-Japan), visit (Week 12, Week 26, Week 40 and Week 52) and treatment-by-visit interaction as fixed categorical effects, and baseline HbA1c value and baseline HbA1c value-by-visit interaction as continuous fixed covariates.		
Note: Descriptive statistics are performed on patients included in the MMRM analysis		
PGM=PRODOPS/SAR342434/EFC12619/CSR_01/REPORT/PGM/mmrms_t.sas OUT=REPORT/OUTPUT/eff_mmrms_hba1cp_wk52_i_t_i.rtf (17AUG2016 - 9:01)		

Source: Excerpted from Study EFC12619 – 12 month CSR, Table 12.

6.1.7 Subpopulations

Dr. Crackel performed analyses of the efficacy primary endpoint on the following subgroups: sex (females; males), age (<65 years; ≥65 years), race (white; non-white), US approved Humalog, and continuous baseline HbA1c. The reviewer used the model of “return-to-baseline” analyses and the interactions of the subgrouping variable with treatment were tested. No significant interactions were found with any of the subgroup variables, except for continuous baseline HbA1c (p=0.069) for study EFC12619 at

$\alpha=0.10$ (to maintain consistency with what the sponsor used), meaning that as baseline HbA1c increases the difference in the change from baseline varies ($p=0.069$).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No specific studies were performed for dosing recommendations. The dose of the insulin lispro product administered is to be adjusted individually.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See discussion of efficacy results evaluated at week 52 in **Section 6.1.6 Other Endpoints**.

6.1.10 Additional Efficacy Issues/Analyses

N/A

7 Review of Safety

Safety Summary

7.1 Methods

Because T1DM and T2DM are diseases of different pathophysiology and safety signals may be different, I analyzed the safety presented for individual studies instead of pooled data. Data from the phase 2 study (PDY13502) were reviewed and safety signals were included in the appropriate section. The majority of my discussion in this section will focus on the safety findings from trial EFC12619 and trial EFC13403. Findings from trial PDY13502 will be discussed in **Section 7.4.5 Special Safety Studies**, as well as in the consult review from CDRH/OIR.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety data come from the phase 3 clinical trials EFC12619 and EFC13403. Clinical trial EFC12619 was conducted with T1DM patients and trial EFC13403 was conducted with T2DM patients. Additional safety data to support continuous subcutaneous insulin infusion with SAR342434 come from Trial PDY13502. For a more detailed discussion of these studies, see **Section 5 – Sources of Clinical Data**.

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were defined by the Applicant as any untoward medical occurrence in a patient administered a pharmaceutical product, and not necessarily having a causal relationship with the received treatment.

Serious adverse events (SAEs) were defined as any untoward medical occurrence that at any dose:

- Resulted in death, or
- Was life-threatening (risk of death at the time of the event), or
- Required inpatient hospitalization or prolongation of existing hospitalization, or
- Resulted in persistent or significant disability/incapacity, or
- Was a congenital anomaly/birth defect, or
- Was a medically important event.

Each AE was coded according to MedDRA low level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT) and associated primary system organ class (SOC). The MedDRA versions used to code adverse events for the clinical studies in this application are listed below:

- EFC12619 and EFC13403 phase 3 trials - MedDRA version 18.1
- PDY13502 – MedDRA 19.0

The Allergic Reaction Assessment Committee (ARAC) was set up with experts in the field of hypersensitivity reactions to adjudicate all allergic or possible allergic events occurring during the studies. Members of the ARAC team were independent from the Applicant and Investigators and were blinded to the studies. The ARAC reviewed cases of hypersensitivity and allergic reactions reported to determine the nature and diagnosis of the events and to assess the possible existence of a correlation between the antibody titer with efficacy and with immunological or hypersensitivity reactions.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Trial EFC12619 was conducted with T1DM patients and trial EFC13403 was conducted with T2DM patients. Because T1DM and T2DM are distinct diseases, the safety evaluation was performed with data from each trial separately and not using pooled data.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Adequacy of Overall Clinical Experience

Overall, the total number of T1DM and T2DM subjects exposed to the IMP, the duration of exposure, and the design of clinical trials appear reasonable to support the safety analysis of the application.

Demographics

A summary of the subject demographics and clinical characteristics of the trial population for trials EFC12619 and EFC13403 is presented in Table 10 (Section 6.1.2). The safety population appears adequately representative of the US diabetes population and thus, it seems reasonable to derive the safety finding of this review to the risk/benefit assessment of SAR342434.

The cumulative exposure and the cumulative duration of treatment in days were similar between SAR342434 and the comparator for each Phase 3 study (EFC12619, 12 months and EFC13403, 6 months). The percentage of patients by category of cumulative duration of study was comparable between the T1DM study and the T2DM study. See Table 17 below.

Table 17: Exposure to IMP for the 12-month treatment period for EFC12619 and EFC13403 trials – Safety population

	EFC12619 – 12 month		EFC13403 – 6 month	
	SAR342434 (N=252)	Humalog (N=254)	SAR342434 (N=253)	Humalog (N=252)
Cumulative exposure (patient years)	237.11	241.93	116.99	119.50
Duration of treatment (days) Mean (SD)	345.0 (67.1)	353.5 (48.7)	172.3 (35.0)	176.0 (26.5)
Cumulative duration of treatment by category Number of patients [n (%)]				
Missing duration	1 (0.4)	4 (1.6)	5 (2.0)	4 (1.6)
≥1 day	251 (99.6)	250 (98.4)	248 (98.0)	248 (98.0)
>4 weeks	248 (98.4)	250 (98.4)	243 (96.0)	246 (97.6)
>8 weeks	245 (97.2)	250 (98.4)	238 (94.1)	244 (96.8)
>12 weeks	245 (97.2)	247 (97.2)	234 (92.5)	242 (96.0)
>20 weeks	242 (96.0)	243 (95.7)	228 (90.1)	235 (93.3)
>25 weeks	-	-	221 (87.4)	224 (88.9)
>26 weeks	239 (94.8)	241 (94.9)	77 (30.4)	66 (26.2)
>34 weeks	233 (92.5)	238 (93.7)	-	-
>40 weeks	230 (91.3)	237 (93.3)	-	-
>51 weeks	222 (88.1)	226 (89.0)	-	-
>52 weeks	85 (33.7)	100 (39.4)	-	-

Source: Table generated with data from EFC12619-12 month, CSR table 18 and EFC13403, CSR table 17. IMP: Investigational Medicinal Product.

7.2.2 Explorations for Dose Response

Insulins in both trials EFC12619 and EFC13403 were titrated to glycemic targets. Explorations for dose response are not applicable.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

Routine clinical testing included the safety assessments and is described in **Section 5 – Sources of Clinical Data**.

7.2.5 Metabolic, Clearance, and Interaction Workup

See **Section 4.4 – Clinical Pharmacology**

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Hypoglycemia is the major adverse event associated with insulin use. Hypoglycemia is reviewed in **Section 7.3.5 – Submission Specific Primary Safety Concerns**.

Immune reactions are also potential adverse events observed with insulin use. Immunogenicity was assessed by anti-insulin antibody (AIA) measurements and is discussed in **Section 7.3.5 – Submission Specific Primary Safety Concerns and Section 7.4.6 – Immunogenicity**.

7.3 Major Safety Results

7.3.1 Deaths

There were a total of 6 deaths reported in the SAR342434 program (2 with SAR342434, 4 with Humalog), including the safety study for infusion set occlusion: 5 deaths were reported during treatment and one post-treatment. A summary of deaths is presented in Table 18.

Table 18: Summary of deaths reported during the SAR342434 development program

TRIAL	EFC12619		EFC13403		PDY15302 (pump)	
	SAR342434	Humalog	SAR342434	Humalog	SAR342434	Humalog
Treatment period	1	0	1	2	0	1
Post-treatment	0	0	0	1	0	0

Table generated with data submitted by the Applicant in the CSR of Study EFC12619, EFC13403 and Study13502

All 5 patients who died during and after the Phase 3 trials had

(b) (6)

(b) (6)

(b) (6)

There was only one death reported in the trial with T1DM patients. According to the narrative, (b) (6)

(b) (6)

One death was reported during the Study PDY13502 with T1DM patients and was attributed to (b) (6)

(b) (6)

After reviewing the narratives of each death reported, I agree with the Investigator/Applicant assessment that all 5 deaths reported in the phase 3 trials were unrelated to the study drug. The relevant data reported for deaths in the SAR342434 program is summarized in Table 19.

(b) (6)

Overall, my review of the data does not suggest an increased risk of death with SAR342434 compared to Humalog.

7.3.2 Nonfatal Serious Adverse Events

Study EFC12619 (T1DM): The number of patients with non-fatal serious TEAEs in the study with T1DM patients was similar between the two treatment groups. The total number of serious TEAEs reported during the 12-month period was 20 (7.9%) patients in the SAR342434 and 19 (7.5%) patients in the Humalog group. No imbalance was noted between patients treated with SAR342434 and patients treated with Humalog in any of the TEAE categories reported. A summary of serious TEAEs reported in the 12-month treatment period of the EFC12619 trial (T1DM patients) coded by SOC and by PT is presented in Table 20.

Table 20: Total number of patients (%) with serious TEAEs during the 12 month period of study EFC 12619 (T1DM) coded by SOC and by PT

SOC	PT	EFC1219 (T1DM) – 12 m	
		SAR342434	HUMALOG
Infections and Infestations		1(0.4%)	3(1.2%)
	Cellulitis	1(0.4%)	1(0.4%)
	Gastroenteritis viral	0	2(0.8%)
Neoplasms Benign, Malignant and Unspecified		1(0.4%)	0
	Uterine leiomyoma	1(0.4%)	0
Metabolism and nutrition disorders		4(1.6%)	6(2.4%)
	Diabetic ketoacidosis	1(0.4%)	2(0.8%)
	Hyperkalemia	0	1(0.4%)
	Hypokalemia	0	1(0.4%)
	Diabetes mellitus inadequate control	0	1(0.4%)
	Hypoglycemia	3(1.2%)	3(1.2%)
Nervous System Disorders		9(3.6%)	8(3.1%)
	Cerebral infarction	1(0.4%)	0
	Cerebrovascular accident	1(0.4%)	0
	Migraine	1(0.4%)	0
	Hypoglycemic coma	0	1(0.4%)
	Hypoglycemic unconsciousness	6(2.4%)	6(2.4%)
	Dizziness	1(0.4%)	0
	Hypoglycemic seizure	0	1(0.4%)
	Cerebral ventricle dilation	0	1(0.4%)
Cardiac Disorders		1(0.4%)	1(0.4%)
	Atrial fibrillation	0	1(0.4%)
	Acute myocardial	1(0.4%)	0

SOC	PT	EFC1219 (T1DM) – 12 m	
		SAR342434	HUMALOG
	infarction		
Respiratory, Thoracic and Mediastinal Disorders		0	1(0.4%)
	Pneumothorax	0	1(0.4%)
Gastrointestinal Disorders		2(0.8%)	1(0.4%)
	Enterocolitis hemorrhagic	1(0.4%)	0
	Abdominal pain	0	1(0.4%)
	Vomiting	1(0.4%)	0
Hepatobiliary Disorders		1(0.4%)	0
	Cholangitis	1(0.4%)	0
Musculoskeletal and Connective Tissue Disorders		1(0.4%)	0
	Osteoarthritis	1(0.4%)	0
Renal and Urinary Disorders		0	1(0.4%)
	Acute kidney injury	0	1(0.4%)
Pregnancy, Puerperium and Perinatal Conditions		0	1(0.4%)
	Abortion threatened	0	1(0.4%)
Reproductive System and Breast Disorders		0	1(0.4%)
	Ovarian cyst	0	1(0.4%)
General Disorders and Administration Site Conditions		1(0.4%)	0
	Cardiac death	1(0.4%)	0
Injury, Poisoning and Procedural Complications		4(1.6%)	6(2.4%)
	Joint injury	1(0.4%)	0
	Clavicle fracture	0	1(0.4%)
	Radius fracture	0	1(0.4%)
	Spinal compression fracture	0	1(0.4%)
	Rib fracture	0	2(0.8%)
	Accidental overdose	3(1.2%)	2(0.8%)
	Wrong drug administered	0	1(0.4%)

SOC	PT	EFC1219 (T1DM) – 12 m	
		SAR342434	HUMALOG
Surgical and Medical Procedures		0	1(0.4%)
	Gastrectomy	0	1(0.4%)
Social Circumstances		0	1(0.4%)
	Pregnancy of partner	0	1(0.4%)

Source: Table adapted from data presented in EFC12619 CSR, Table 25; MedDRA version 19.0

Serious TEAEs involving hypoglycemia were coded at the MedDRA PT level as Hypoglycemia (SOC of Metabolism and Nutrition Disorders), Hypoglycemia unconsciousness, Hypoglycemia seizure and Hypoglycemia coma (SOC of Nervous System Disorders). Severe hypoglycemia was reported as SAE in 8 patients in the SAR342434 group with a total of 9 events and in 8 patients in the Humalog group with a total of 11 events. The number of patients reported with severe hypoglycemia events stratified by symptoms was balanced between the two treatment groups. (b) (6)

(b) (6)

(b) (6)

Table 21: Summary of the number of patients reported with severe hypoglycemia in the EFC12619 trial (12 month period)

SOC	PT	EFC1219 (T1DM)	
		SAR342434 252	Humalog 254
Metabolism and Nutrition Disorders	Hypoglycemia	3 (1.2%)	3 (1.2%)
	Hypoglycemic unconsciousness	6 (2.4%)	6 (2.4%)
Nervous System Disorders	Hypoglycemia seizure	0	1 (0.4%)
	Hypoglycemia coma	0	1 (0.4%)

Table generated with data reported in Study EFC12619, 12-month CSR, Section 11.4.2

For a complete review of hypoglycemia events including those reported in the dedicated hypoglycemia forms please see **Section 7.3.5 - Submission Specific Primary Safety Concerns**.

There were a few reports of diabetic ketoacidosis (DKA) in this study. DKA was reported as serious TEAE in 1 patient in the SAR342434 group and in 2 patients in the Humalog group, suggesting that the risk for DKA in patients exposed to SAR342434 was similar to the risk of patients exposed to Humalog.

Study EFC13403 (T2DM): The percentage of patients with non-fatal serious TEAEs in the study with T2DM patients was lower in the SAR342434 group than in the Humalog group. There were 14 (5.5%) patients in the SAR342434 treatment arm and 27 (10.7%) patients in the Humalog treatment arm. Among the TEAEs reported in this study, events were balanced between treatment groups, except for Cardiac Disorders (coded by SOC), which was reported for 3 (1.2%) patients in SAR342434 and 11 (4.4%) patients in the Humalog arm. A summary of serious TEAEs reported in the EFC13403 trial (T2DM patients) is presented in Table 22.

Table 22: Total number of patients (%) with serious TEAEs during the 6 month period of study EFC 13403 (T2DM) coded by SOC and by PT

SOC	PT	EFC13403 (T2DM)	
		SAR342434	HUMALOG
Infections and Infestations		2(0.8%)	2(0.8%)
	Pneumonia	2(0.8%)	1(0.4%)
	Urinary tract infection	0	1(0.4%)
Neoplasms Benign, Malignant and Unspecified		1(0.4%)	3(1.2%)
	Adenocarcinoma of colon	0	1(0.4%)
	Pancreatic carcinoma	0	1(0.4%)
	Bladder transitional cell carcinoma	1(0.4%)	0
	Metastatic carcinoma of the bladder	0	1(0.4%)
Metabolism and nutrition disorders		0	4(1.6%)
	Diabetic ketoacidosis	0	1(0.4%)
	Hypokalemia	0	1(0.4%)
	Hypoglycemia	0	2(0.8%)
Nervous System Disorders		4(1.6%)	2(0.8%)
	Gliososis	1(0.4%)	0
	Cerebrovascular accident	0	1(0.4%)
	Hypoglycemic unconsciousness	2(0.8%)	0
	Syncope	0	1(0.4%)
	Hypoglycemic seizure	0	1(0.4%)
	Carpal tunnel syndrome	1(0.4%)	0
Eye Disorders		1(0.4%)	0
	Cataract	1(0.4%)	0
	Vitreous hemorrhage	1(0.4%)	0
Ear and Labyrinth Disorders		1(0.4%)	0

SOC	PT	EFC13403 (T2DM)	
		SAR342434	HUMALOG
	Vertigo positional	1(0.4%)	0
Cardiac Disorders		3(1.2%)	11(4.4%)
	Bundle branch block left	0	1(0.4%)
	Atrial fibrillation	0	2(0.8%)
	Sinus bradycardia	0	1(0.4%)
	Cardio-respiratory arrest	1(0.4%)	0
	Coronary artery disease	0	1(0.4%)
	Angina pectoris	0	3(1.2%)
	Myocardial infarction	0	1(0.4%)
	Cardiac failure	0	1(0.4%)
	Cardiac failure chronic	1(0.4%)	0
	Cardiac failure congestive	1(0.4%)	2(0.8%)
	Cardiopulmonary failure	0	1(0.4%)
	Ischemic cardiomyopathy	1(0.4%)	0
Vascular Disorders		0	2(0.8%)
	Hypotension	0	1(0.4%)
	Deep vein thrombosis	0	1(0.4%)
Respiratory, Thoracic and Mediastinal Disorders		2(0.8%)	1(0.4%)
	Chronic obstructive pulmonary disease	1(0.4%)	0
	Pulmonary embolism	0	1(0.4%)
	Respiratory failure	1(0.4%)	0
Gastrointestinal Disorders		2(0.8%)	2(0.8%)
	Pancreatitis	2(0.8%)	0
	Gastric erosive	0	1(0.4%)
	Intestinal perforation	0	1(0.4%)
Hepatobiliary Disorders		0	1(0.4%)
	Bile duct stone	0	1(0.4%)
Musculoskeletal and Connective Tissue Disorders		0	2(0.8%)
	Cervical spinal stenosis	0	1(0.4%)
	Back pain	0	1(0.4%)
General Disorders and Administration Site Conditions		0	1(0.4%)
	Non-cardiac chest pain	0	1(0.4%)

Source: Table adapted from data presented in EFC13403 CSR, Table 24; MedDRA version 19.0

Overall, my review of the SAEs does not suggest a difference in the safety profile of SAR342434 compared to the approved insulin lispro.

7.3.3 Dropouts and/or Discontinuations

From the total number of T1DM patients who were randomized and treated in study EFC12619 (252 in SAR342434 group and 254 in Humalog group), the percentage of patients that discontinued treatment during the 12-month period was 10.3% in SAR342434 group and 7.5% in the Humalog group. Although these percentages are numerically different, two analyses performed by the Statistics review demonstrated that the percentage of patients that discontinued treatment was not statistically different between the two treatment groups: One analysis showed that the confidence interval (-0.02, 0.08) contains zero and a second analysis resulted in a p-value of 0.267.

From the number of patients who did not complete the 12-month treatment period, 15 of 26 patients in the SAR342434 group and 11 of 19 patients in the Humalog group (approximately 58% in both arms) discontinued the treatment during the main 6-month period. The most frequent reason for treatment discontinuation was reported as “Other reasons” (8.3% for SAR342434 and 3.9% for Humalog). The most common reason reported under “Other reasons” was patient decision or consent withdrawal. “Other reasons” also included 3 patients in the SAR342434 group and 1 patient in the Humalog group that were discontinued due to a site closure, and this contributed to the slightly higher number of SAR342434-treated compared to Humalog-treated patients reported under this category. Discontinuations due to adverse events including serious hypoglycemia accounted for 2 patients in each treatment arm, and 1 patient with non-serious hypoglycemia in SAR342434 arm. There was 1 case of death in the SAR342434 group that was reported as permanent discontinuation under “Other reasons”.

In the EFC13403 trial, 25 out of 253 (9.9%) T2DM patients in the SAR342434 group and 22 out of 252 (8.7%) patients in the Humalog group discontinued the treatment. The most frequent reason for discontinuation was reported as “Other reasons” that accounted for 12 patients in each of the treatment groups. The most common reported “other reason” reported was patient decision or consent withdrawal. “Other reasons” also included 2 patients in each treatment group reported as “lost-to-follow up” and 3 patients in the SAR342434 group that were discontinued due to a site closure. There were 7 patients in each treatment group that were discontinued due to adverse events including serious hypoglycemia, and there was 1 patient discontinued due to non-serious hypoglycemia in the Humalog group. There were 4 deaths reported in this trial, with 1 in the SAR342434 group and 3 in the Humalog group.

7.3.4 Significant Adverse Events

Significant adverse events not meeting the criteria for serious events that were identified by the Applicant include: alanine aminotransferase increase, pregnancy, symptomatic overdose with IMP/NIMP, injection site reactions, and hypersensitivity reactions,. Please note that injection site reactions and hypersensitivity reactions are reviewed under **Section 7.3.5 - Submission Specific Primary Safety Concerns**.

Alanine aminotransferase (ALT) increase:

Liver function tests including AST, ALT, ALP and total bilirubin were performed to assess possible drug induced toxicity as part of study procedures on Day 1 (baseline) and Week 26 (end of study period 1 for study EFC12619 and end of study EFC13403) or Week 52 (end of extension period for EFC12619). A review of these data did not raise concerns related to drug-induced ALT increase. As detailed below, no imbalances were observed between treatment arms in the number of patients with elevated ALT (1 patient in each treatment arm in study EFC12619 and no patients reported in study EFC13403). Also, the narratives did not show evidence of relatedness between SAR342434 and ALT level increase.

Two patients were reported with elevated serum ALT in the Study EFC12619 (T1DM): 1 patient in the SAR342434 group had an (b) (6) on day 231 of treatment, and 1 patient in the Humalog group was reported with an (b) (6) from an unknown cause as per site information on day 363 of treatment. Three months after the first reporting of elevated ALT, the last know value was (b) (6). The investigator considered the event as related to IMP and related to NIMP, but the Applicant assessed the event as unrelated to IMP and unrelated to NIMP. The information provided by the narrative on this patient appears insufficient for a definitive conclusion of relatedness to IMP/NIMP. In addition, 1 patient in the Humalog group was reported with total bilirubin (b) (6). See additional information on ALT and bilirubin in **Section 7.4.2 - Laboratory Findings**.

In Study EFC13403, no TEAE of increased ALT level was reported.

Pregnancy:

Three patients were reported with pregnancy during the Study EFC12619. One patient in the SAR342434 group was found to be pregnant on day 324 of treatment. Miscarriage was reported about 10 days later with an estimated duration of gestation of 5 to 6 weeks. In the Humalog group, there were two patients found to be pregnant: one at day 336 of treatment and another at day 133 of treatment, with no apparent complications related to IMP. In addition, pregnancy was reported in female partners of 3 male study patients in the Humalog group. One pregnancy was reported as SAE because the patient's female partner was hospitalized for imminent abortion.

No pregnancy was reported during the Study EFC13403.

Symptomatic overdose with IMP/NIMP:

In this NDA, SAR342434 and Humalog (US or EU) are considered investigational medicinal products (IMP) and the basal insulin glargine is considered non-investigational medicinal product (NIMP). Events of symptomatic overdose (accidental or intentional) with IMP or NIMP were captured from the electronic case report form (e-CRF) records. Events of IMP/NIMP overdose suspected by the Investigator or spontaneously notified by the patient, that resulted in clinical symptoms and/or signs of insulin overdose and that were considered a “significant overdose” by the Investigator were to be recorded as an adverse event of special interest (AESI), with immediate notification “Symptomatic overdose (accidental or intentional)”. Only events that fulfilled the criteria for SAE were listed as SAE. Asymptomatic IMP/NIMP overdose (accidental or intentional) was recorded as AE, but was not included in this analysis. .

During the 12-month period of Study EFC12619, accidental symptomatic overdose was reported in 3 patients on SAR342434 and in 2 patients in the Humalog group. In all these 5 patients, the accidental overdose was considered as related to the IMP and considered serious. In 2 patients (one from each treatment group), the overdose resulted in hypoglycemic unconsciousness. There was one event caused by mistakenly injecting 30 units of IMP instead of basal insulin. In one patient from the Humalog group, the dose of IMP was reduced because the patient changed the eating behavior, but none of the events led to permanent IMP discontinuation.

In the Study EFC13403, symptomatic overdose was reported in 1 patient from the Humalog group, who injected the IMP twice by mistake. Overdose with NIMP was reported in 1 patient in the SAR3242434 group. In both cases, the event was accidental and the patients recovered without complications.

My review of the symptomatic IMP/NIMP overdose events reported with T1DM and T2DM patients did not identify any imbalance in the incidence or intensity of events between treatment arms. Examination of the narratives suggests that most events were caused by inappropriate dosing of insulin for the meal intake (skipping meal or miscalculating meal carbohydrate content). There were a few errors of injecting the wrong dose or the wrong type of insulin (basal insulin instead of insulin lispro). The cause of NIMP overdose was unclear.

Overall, my review of the data does not suggest that there are clinically meaningful differences between SAR342434 and the approved insulin lispro with respect to the above discussed significant adverse events.

7.3.5 Submission Specific Primary Safety Concerns

This section includes review of the following submission specific primary safety concerns: Hypoglycemia, injection site reactions and hypersensitivity reactions.

Hypoglycemia

For both phase 3 studies, all hypoglycemia events were reported on a dedicated reporting page of the e-CRF. Hypoglycemia events were not reported as AEs, unless they met the criteria for SAE, in which case they were reported in both the SAE form and hypoglycemia dedicated form. SMPG was the method used as biochemical confirmation of hypoglycemia.

Hypoglycemia was categorized and defined as:

- **Severe hypoglycemia:** an event requiring assistance of another person to administer carbohydrate, glucagon or other resuscitative actions. Neurological symptoms such as seizure, unconsciousness or coma without plasma glucose measurement were considered induced by hypoglycemia if a neurological recovery was attributable to measures to restore plasma glucose to normal.
- **Documented symptomatic hypoglycemia:** an event with clinical symptoms of hypoglycemia that did not require active assistance, with a documented plasma glucose ≤ 70 mg/dl or < 54 mg/dl. Plasma glucose level during a hypoglycemic event was to be documented by using a glucometer device (SMPG) before the intake of carbohydrates whenever possible and the plasma glucose value was then transferred to the e-diary.
- **Asymptomatic hypoglycemia:** an event with measured plasma glucose ≤ 70 mg/dl, but without clinical symptoms of hypoglycemia.
- **Severe and/or confirmed hypoglycemia:** an event classified as severe or with measured plasma glucose ≤ 70 mg/dl or < 54 mg/dl. This category includes hypoglycemia of any of the three categories above.
- **Probable symptomatic hypoglycemia:** an event with clinical symptoms of hypoglycemia, but without measured plasma glucose concentration.
- **Relative hypoglycemia:** an event with clinical symptoms of hypoglycemia and a measured plasma glucose > 70 mg/dl.

The number of patients with at least one event of hypoglycemia was similar between SAR342434 and Humalog treatment groups in the trial with T1DM patients and also in the trial with T2DM patients. No imbalances were noted in any of the categories and sub-categories of hypoglycemia. A summary of the number of patients that reported at least one hypoglycemia during the 12-month treatment period of EFC12619 and EFC13403 trials is presented in the Table 23 below:

Table 23: Number (%) of patients with at least one hypoglycemia event during the treatment period.

Type of hypoglycemia n(%)	EFC12619 – 12 month (T1DM)		EFC13403 (T2DM)	
	SAR342434 (N=252)	Humalog (N=254)	SAR342434 (N=253)	Humalog (N=252)
Any hypoglycemia	250 (99.2%)	254 (100%)	173 (68.4%)	188 (74.6%)
Severe hypoglycemia	34 (13.5%)	34 (13.4%)	6 (2.4%)	4 (1.6%)
Documented symptomatic hypoglycemia				
≤3.9 mmol/L (70 mg/dL)	220 (87.3%)	228 (89.8%)	152 (60.1%)	167 (66.3%)
< 3.0 mmol/L (54 mg/dL)	177 (70.2%)	193 (76.0%)	73 (28.9%)	69 (27.4%)
Asymptomatic hypoglycemia				
≤3.9 mmol/L (70 mg/dL)	245 (97.2%)	248 (97.6%)	89 (35.2%)	94 (37.3%)
< 3.0 mmol/L (54 mg/dL)	195 (77.4%)	209 (82.3%)	26 (10.3%)	32 (12.7%)
Severe and/or confirmed hypoglycemia				
≤3.9 mmol/L (70 mg/dL)	249 (98.8%)	254 (100%)	169 (66.8%)	183 (72.6%)
< 3.0 mmol/L (54 mg/dL)	229 (90.9%)	241 (94.9%)	89 (35.2%)	84 (33.3%)
Probable symptomatic hypoglycemia				
Relative hypoglycemia	27 (10.7%)	25 (9.8%)	9 (3.6%)	16 (6.3%)
>3.9 mmol/L (70 mg/dL)	17 (6.7%)	17 (6.7%)	22 (8.7%)	33 (13.1%)

Source: Adapted from Table 19 of EFC12619 – 12 month CSR and Table 18 of EFC13403 CSR.

Cases of severe hypoglycemia were recorded by Investigators according to patients responding “yes” to requiring assistance of another person during hypoglycemic events. As noted by the Applicant, “required assistance” included assistance in hypoglycemia events without neuroglycopenic symptoms and without a record of plasma glucose < 50 mg/dl. For that reason, a *post-hoc* analysis of severe hypoglycemia was performed including as criteria the presence of seizure, coma or unconsciousness and/or measured plasma glucose < 50 mg/dl. After the *post-hoc* analysis, the number of patients with severe hypoglycemia was reduced in both trials. The number of patients with at least one episode of severe hypoglycemia with neurological symptoms (coma, seizure or unconsciousness) and/or a measurement of plasma glucose by SMPG <50 mg/dl was similar between SAR342434 and Humalog treatments arms within each trial, as illustrated in Table 24.

Table 24: Number (%) of patients with at least one severe hypoglycemia event with coma, seizure or unconsciousness, and/or SMPG <50 mg/dl in trial EFC12619 and trial EFC13403.

n(%)	EFC12619 – 12 month (T1DM)		EFC13403 (T2DM)	
	SAR342434 (N=252)	Humalog (N=254)	SAR342434 (N=253)	Humalog (N=252)
Severe hypoglycemia as per investigator (required assistance =YES)	34 (13.5%)	34 (13.4%)	6 (2.4%)	4 (1.6%)
With neuroglycopenic symptoms	5 (2.0%)	7 (2.8%)	1 (0.4%)	0
With SMPG<50 mg/dL	13 (5.2%)	15 (5.9%)	0	0
With neuroglycopenic symptoms and/or SMPG<50 mg/dL	14 (5.6%)	20 (7.9%)	1 (0.4%)	0

Source: Adapted from EFC12619-12 month, AE-data file, page 97, and from EFC13403 AE-data file, page 99.

The initial assessment of the reported event-rate of severe hypoglycemia suggested an increased risk with SAR342434 compared to Humalog in T1DM patients (1.21 events per patient-year with SAR342434 vs. 0.31 events per patient-year with Humalog). Upon examination of the data, the Applicant noted that the higher event rate of severe hypoglycemia in the SAR342434 group in trial EFC12619 was due to a single patient reporting required assistance multiple times with no associated neuroglycopenic events. This patient had a background of psychiatric disorders and reported requiring third-party assistance, but there was no evidence of neuroglycopenia or records of hospitalization associated with any of these events. The data was re-analyzed with exclusion of this patient and the hypoglycemia event rate resulted in a value comparable with that of Humalog (see Table 25 below). I reviewed the narrative of the patient with multiple reports of severe hypoglycemia and I agree with the Applicant's approach of excluding this patient from the analysis.

Table 25: Number of hypoglycemia events (rate per patient-year) in trial EFC12619 and trial EFC13403.

Number of events (rate per patient-year)	EFC12619		EFC13403	
	All hypoglycemia		All hypoglycemia	
	SAR342434 (N=252)	Humalog (N=254)	SAR342434 (N=253)	Humalog (N=252)
Total patient-years	237.92	245.24	118.69	121.23
Severe hypoglycemia as per investigator (=assistance required YES)	175 (0.74)	70 (0.29)	9 (0.08)	4 (0.03)
With neuroglycopenic symptoms ^a	6 (0.03)	9 (0.04)	1 (0.01)	0
With SMPG <50 mg/dL	50 (0.21)	23 (0.09)	0	0
With neuroglycopenic symptoms ^a and/or SMPG <50 mg/dL	51 (0.21)	30 (0.12)	1 (0.01)	0

^a Coma, seizure, or unconsciousness

Source: EFC12619, AE Data File, page 98 and EFC13403 AE Data File, page 100

Upon my review of hypoglycemia events reported in the studies with T1DM and T2DM patients, I found no significant differences between SAR342434 and Humalog in the number of patients with hypoglycemia, severity of hypoglycemia or the number of event per patient-year.

Injection site reactions:

Injection site reactions were captured by examining the AE forms and dedicated allergic event forms, in addition to assessing the ARAC diagnosis of cases reviewed. The applicant used the following MedDRA searches to identify injection site reactions: Under HLG "Administration site reactions" and HLTs "Administration site reactions not elsewhere classified (NEC)", "Injection site reactions", "Infusion site reactions" and "Application and instillation site reactions", and excluding HLTs "Implant and catheter site reactions" and "Vaccination site reactions". The MedDRA terms used to identify injection site reactions appear appropriate.

During the whole 12-month treatment period of study EFC12619, the incidence of injection site reactions was the same in the SAR342434 group and the Humalog group, with 3 patients (1.2%) reported in each treatment arm. All reactions were reported as of mild/moderate intensity and none led to IMP discontinuation. All 3 injection site reactions observed in the SAR342434 group and 1 observed in the Humalog group were considered as related to the IMP.

The percentage of patients with injection site reactions in study EFC13403 was similar between the treatment arms: 1 patient (0.4%) with 2 events in the SAR342434 group and 4 patients (1.6%) with one event each in the Humalog group. None of the events were considered serious or led to discontinuation of the IMP. The injection site reactions of the patient in the SAR342434 and of 3 out of 4 patients in the Humalog group were considered as related to the IMP. The reactions were transitory, except in one patient in the Humalog group in whom the injection site pain was considered as not resolved at the end of the study. There were a few injection site reactions considered by the Investigator as related to the IMP: 3 patients in the SAR342434 group and 1 patient in the Humalog group.

Overall, my review of injection site reactions reported during the T1DM and T2DM clinical trials suggests that the incidence, intensity, duration and relatedness of the reaction to IMP in the SAR342434 group were similar to those experienced by patients in the Humalog group.

Hypersensitivity reactions:

Allergic reactions to insulin or its analogs have been reported to occur in approximately 0.1-3% of insulin-treated diabetic patients^{20,21} with hypersensitivity reactions ranging from local injection site reactions to life-threatening anaphylaxis²²⁻²⁴.

Hypersensitivity reactions were captured by examining the records in the e-CRF AE pages and dedicated allergic event forms, in addition to assessing the ARAC diagnosis of the hypersensitivity cases reviewed. To identify hypersensitivity reactions, the Applicant used the following MedDRA searches to identify hypersensitivity reactions: Angioedema standardized MedDRA query (SMQ) [Narrow], Severe cutaneous adverse reactions SMQ [Broad], Hypersensitivity SMQ [Broad and Narrow] and excluding PTs related to administration, application, injection and infusion sites. HLT “Anaphylactic Responses” were included in the SMQs. The MedDRA terms used to identify hypersensitivity reactions appear appropriate.

In the study with T1DM patients, hypersensitivity reactions were reported in 6.0% of patients in the SAR342434 group and in 6.3% of patients in the Humalog group. One case of hypersensitivity reaction in SAR342434 was considered as related to IMP by the Investigator, but the ARAC adjudicated this adverse event as not an allergic reaction. At day 3 of treatment, the patient developed a generalized itching reaction after SAR342434 injection, and recovered within 3 days. The anti-insulin antibody titer was negative at screening and remained negative throughout the treatment. The hypersensitivity reactions observed were reported as of mild or moderate intensity, and none led to discontinuation of the IMP. The list of hypersensitivity reactions at the PT level reported in the SAR342434 group appears similar to that of the Humalog group, as illustrated in Table 26.

Table 26: Number of patients (%) with hypersensitivity reactions in Study EFC12619

Preferred Term n(%)	SAR342434 (N=252)		Humalog (N=254)	
	All	Related	All	Related
Any hypersensitivity reactions	15 (6.0%)	1 (0.4%)	16 (6.3%)	0
Asthma	3 (1.2%)	0	0	0
Conjunctivitis allergic	2 (0.8%)	0	0	0
Drug hypersensitivity	2 (0.8%)	0	0	0
Eczema	2 (0.8%)	0	1 (0.4%)	0
Hypersensitivity	2 (0.8%)	1 (0.4%)	1 (0.4%)	0
Rash	2 (0.8%)	0	2 (0.8%)	0
Conjunctivitis	1 (0.4%)	0	1 (0.4%)	0
Dermatitis contact	1 (0.4%)	0	1 (0.4%)	0
Seasonal allergy	1 (0.4%)	0	2 (0.8%)	0
Acquired epidermolysis bullosa	0	0	1 (0.4%)	0
Blister	0	0	1 (0.4%)	0
Eosinophil count increased	0	0	1 (0.4%)	0
Erythema	0	0	1 (0.4%)	0
Rash pustular	0	0	1 (0.4%)	0
Rhinitis allergic	0	0	1 (0.4%)	0
Stomatitis	0	0	1 (0.4%)	0
Urticaria	0	0	1 (0.4%)	0

TEAE: Treatment emergent adverse event, PT: Preferred term, IMP: Investigational medicinal product
MedDRA dictionary: MEDDRA 19.0
n (%) = number and percentage of patients with at least one TEAE linked to hypersensitivity reaction
Note: Table sorted by decreasing frequency of PT based on incidence in the SAR342434 treatment group
PGM=PRODOPS/SAR342434/EFC12619/CSR_01/REPORT/PGM/ae_localtol_hypers_relation_m12_s_t.sas
OUT=REPORT/OUTPUT/ae_hypers_relation_s_t_i.rtf (18AUG2016 - 6:13)

Source: Excerpted from EFC12619-12 month CSR, Table 28.

The ARAC adjudicated 6 hypersensitivity events in the SAR342434 group and 8 events in the Humalog group. From the 6 events in the SAR342434 group, none were adjudicated as allergic reaction, and 6 events were adjudicated as not allergic reaction, with 1 event considered related to IMP. From the 8 events in the Humalog group, 2 events were adjudicated as allergic reactions and 6 events as not allergic reactions, with none of these events considered related to the IMP.

Analysis of hypersensitivity reactions by subgroup, including by region (Humalog US and Humalog EU) did not show relevant differences between treatment arms. It is noteworthy that some subgroups were too small to allow a definitive comparative conclusion (e.g., race subgroups).

In the study with T2DM, 4.0% of patients in the SAR342434 group and 3.6% of patients in the Humalog group were reported with hypersensitivity reaction. Two events of

hypersensitivity reactions were considered by the Investigator as related to the IMP: 1 patient (pruritus) in the SAR342434 treatment arm and 1 patient (erythema) in the Humalog treatment arm. One case of hypersensitivity reaction was reported as respiratory failure in a patient in the SAR342434 group on day 27 of treatment. This event occurred during a biopsy procedure for gliosis, and was assessed as unrelated to IMP or to NIMP. Two events of hypersensitivity reaction were not identifiable by MedDRA search because the PT of the event did not correspond to the terms included in the MedDRA search. These events were reported on the dedicated allergic reaction AE form and adjudicated by ARAC. Most events were considered of mild or moderate intensity. A listing of symptoms reported at the PT level does not show relevant differences between SAR342434 and Humalog treatment arms, and is presented in Table 27.

Table 27: Number of patients (%) with hypersensitivity reactions in Study EFC13403.

Preferred Term n(%)	SAR342434 (N=253)		Humalog (N=252)	
	All	Related	All	Related
Any hypersensitivity reactions	10 (4.0%)	1 (0.4%)	9 (3.6%)	1 (0.4%)
Dermatitis contact	2 (0.8%)	0	0	0
Blister	1 (0.4%)	0	0	0
Dermatitis	1 (0.4%)	0	1 (0.4%)	0
Dermatitis allergic	1 (0.4%)	0	0	0
Lip swelling	1 (0.4%)	0	0	0
Pruritus	1 (0.4%)	1 (0.4%)	2 (0.8%)	0
Respiratory failure	1 (0.4%)	0	0	0
Rhinitis allergic	1 (0.4%)	0	0	0
Seasonal allergy	1 (0.4%)	0	0	0
Asthma	0	0	1 (0.4%)	0
Erythema	0	0	1 (0.4%)	1 (0.4%)
Eye swelling	0	0	1 (0.4%)	0
Face oedema	0	0	1 (0.4%)	0
Mouth swelling	0	0	1 (0.4%)	0
Rash	0	0	3 (1.2%)	0

TEAE: Treatment emergent adverse event, PT: Preferred term, IMP: Investigational medicinal product
MedDRA dictionary: MEDDRA 18.1
n (%) = number and percentage of patients with at least one TEAE linked to hypersensitivity reaction
Note: Table sorted by decreasing frequency of PT based on incidence in the SAR342434 treatment group
PGM=PRODOPS/SAR342434/EFC13403/CSR/REPORT/PGM/ae_localtol_relation_s_t.sas
OUT=REPORT/OUTPUT/ae_hypers_relation_m6_s_t_i.rtf (13JUN2016 - 14:29)

Source: Excerpted from EFC13403 CSR, Table 27.

The ARAC adjudicated 8 hypersensitivity events (7 patients) in the SAR342434 group and 8 events (6 patients) in the Humalog group. From the 8 events in the SAR342434 group, 4 were adjudicated as allergic reactions and unrelated to IMP, and 4 were

adjudicated as not allergic reactions with 2 considered related to IMP. From the 8 events in the Humalog group, 3 events were adjudicated as allergic reaction and unrelated to IMP and 5 events were adjudicated as not allergic reaction, with 1 event considered related to IMP. Subgroup analysis for hypersensitivity reactions was not informative due to the low number of events.

Overall, the percentage of patients reporting hypersensitivity reactions in both studies was balanced between the treatment arms. I did not find evidence to suspect that SAR342434 differs from Humalog in the incidence or the intensity of hypersensitivity reactions.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The common adverse events reported in patients with T1DM appear to be similar to those reported in patients with T2DM. In both patient populations, common adverse events were similar when comparing SAR342434 and the approved insulin lispro. The most common adverse effects reported in both studies (EFC12619 and EFC13403) were in the system organ class (SOC) of infections and infestations, with the preferred term (PT) of nasopharyngitis, which were mapped from the verbatim terms of cold, common cold, cold symptoms and head cold. Headache was the second most common adverse event in both T1DM and T2DM patients. An analysis by study will be detailed below.

Study EFC12619 (T1DM): The adverse events reported during the 12-month study period of the study with T1DM patients were balanced between SAR342434 and Humalog groups. The most frequently reported TEAEs at the primary SOC level were infections and infestations with 32.5% patients in the SAR342434 group and 31.9% patients in the Humalog group. See Table 28 for a list of TEAEs by primary SOC.

Table 28: TEAEs by primary SOC reported in Study EFC12619, 12-month period.

Primary System Organ Class	SAR342434 N=252	Humalog N=254
Infections and infestations	82 (32.5%)	81 (31.9%)
Musculoskeletal and connective tissue disorders	24 (9.5%)	20 (7.9%)
Nervous system disorders	24 (9.5%)	20 (7.87%)
Injury, poisoning and procedural complications	18 (7.1%)	26 (10.2%)
Gastrointestinal disorders	17 (6.8%)	27 (10.6%)
Respiratory, thoracic and mediastinal disorders	14 (5.6%)	9 (3.5%)
Skin and subcutaneous tissue disorders	13 (5.2%)	15 (5.9%)
General disorders and administration site conditions	12 (4.8%)	6 (2.4%)
Metabolism and nutrition disorders	7 (2.8%)	8 (3.2%)
Psychiatric disorders	7 (2.8%)	6 (2.4%)

Primary System Organ Class	SAR342434 N=252	Humalog N=254
Cardiac disorders	6 (2.9%)	3 (1.2%)
Eye disorders	6 (2.9%)	5 (2.0%)
Immune system disorders	6 (2.9%)	4 (1.6%)
Reproductive system and breast disorders	5 (2.0%)	2 (0.8%)
Investigations	5 (2.0%)	7 (2.8%)
Surgical and medical procedures	4 (1.6%)	7 (2.8%)
Vascular disorders	4 (1.6%)	8 (3.2%)
Ear and labyrinth disorders	3 (1.2%)	1 (0.4%)
Renal and urinary disorders	2 (0.8%)	2 (0.8%)
Congenital, familial and genetic disorders	1 (0.4%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4%)	3 (1.2%)
Blood and lymphatic system disorders	1 (0.4%)	1 (0.4%)
Pregnancy, puerperium and perinatal conditions	1 (0.4%)	3 (1.2%)
Hepatobiliary disorders	1 (0.4%)	0 (0.0%)
Endocrine disorders	0 (0.0%)	1 (0.4%)
Product issues	0 (0.0%)	1 (0.4%)
Social circumstances	0 (0.0%)	4 (1.6%)

Table generated by clinical reviewer using JReview

At the HLT level, the most common were upper respiratory tract infection (23.0% for SAR342434 and 18.5% for Humalog), followed by musculoskeletal and connective tissue pain and discomfort (4.4% for SAR342434 and 3.1% for Humalog). At the PT level, nasopharyngitis (13.1% in the SAR342434 group and 11.0% in the Humalog group) was the most common TEAE reported followed by upper respiratory tract infection (6.0% in the SAR342434 group and 5.5% in the Humalog group). The percentage of patients with TEAEs considered by the Investigator as related to the drug treatment was similar between SAR342434 [14 (5.6%)] and Humalog [10 patients (3.9%)] groups, and included hypoglycemia. A list of TEAEs at the PT level with an incidence >1% was generated from data submitted by the Applicant and is presented in Table 29. My review of TEAEs reported at a lower percentage ($\leq 1\%$) did not identify any relevant issue.

Table 29: TEAEs at the PT level reported in Study EFC12619, 12 month period

Dictionary Derived Term (PT)	SAR342434 N=252	Humalog N=254
Nasopharyngitis	33 (13.1%)	28 (11.0%)
Upper respiratory tract infection	15 (5.9%)	14 (5.5%)
Bronchitis	7 (2.8%)	5 (2.0%)
Headache	7 (2.8%)	6 (2.4%)
Gastroenteritis	7 (2.8%)	7 (2.8%)
Back pain	7 (2.8%)	3 (1.2%)
Hypoglycemic unconsciousness	6 (2.4%)	6 (2.4%)
Pharyngitis	6 (2.4%)	5 (2.0%)

Dictionary Derived Term (PT)	SAR342434 N=252	Humalog N=254
Sinusitis	5 (2.0%)	4 (1.6%)
Cough	5 (2.0%)	2 (0.8%)
Influenza	4 (1.6%)	1 (0.4%)
Dizziness	4 (1.6%)	1 (0.4%)
Diarrhea	3 (1.2%)	3 (1.2%)
Influenza like illness	3 (1.2%)	1 (0.4%)
Depression	3 (1.2%)	3 (1.2%)
Arthralgia	3 (1.2%)	4 (1.6%)
Hypertension	3 (1.2%)	5 (2.0%)
Asthma	3 (1.2%)	0 (0.0%)
Ligament sprain	3 (1.2%)	2 (0.8%)
Osteoporosis	3 (1.2%)	0 (0.0%)
Vomiting	3 (1.2%)	5 (2.0%)
Hypoglycemia	3 (1.2%)	4 (1.6%)
Lipohypertrophy	3 (1.2%)	1 (0.4%)
Muscle strain	3 (1.2%)	1 (0.4%)
Musculoskeletal pain	3 (1.2%)	3 (1.2%)
Cystitis	3 (1.2%)	1 (0.4%)
Onychomycosis	3 (1.2%)	1 (0.4%)
Accidental overdose	3 (1.2%)	5 (2.0%)
Acute sinusitis	3 (1.2%)	1 (0.4%)
Nausea	2 (0.8%)	3 (1.2%)
Gastroenteritis viral	2 (0.8%)	4 (1.6%)
Abdominal pain	2 (0.8%)	3 (1.2%)
Gastritis	2 (0.8%)	3 (1.2%)
Dental caries	1 (0.4%)	4 (1.6%)
Pain in extremity	1 (0.4%)	3 (1.2%)
Tooth extraction	1 (0.4%)	3 (1.2%)
Tooth infection	0 (0.0%)	3 (1.2%)
Arthropod bite	0 (0.0%)	2 (0.8%)
Pregnancy of partner	0 (0.0%)	3 (1.2%)
Contusion	0 (0.0%)	3 (1.2%)

Table generated from data submitted by the Applicant, including TEAEs reported in an incidence of >1.0% in any treatment arm.

The output in Table 28 and Table 29 is in agreement with data presented by the Applicant. No clinically significant differences were noted between the incidence of TEAEs reported for SAR342434 and Humalog treatment arms in patients with T1DM.

Adverse events by subgroups

In my review of the common adverse events subgroup analyses, I found no evidence of differences between T1DM patients in the SAR342434 group and Humalog group for any of the subgroups. It is of note that the small number of patients in some subgroups,

such as age ≥ 75 years, did not allow for a conclusive comparison between the treatment arms.

The subgroup analysis by region-approved (US-approved Humalog vs. EU-approved Humalog) shows that the overall incidence of TEAEs was similar in each region:

- US-approved Humalog: 61.2% in SAR342434 group vs. 66.4% in Humalog group
- EU-approved Humalog: 46.0% in SAR342434 group vs. 42.1% in Humalog group

Additionally, I reviewed the terms by region and found the types of TEAEs to be similar between treatments for each region.

Study EFC13403 (T2DM): Similarly to the report for trial EFC12619 (T1DM), the most frequently reported TEAEs in the trial with T2DM patients coded at the primary SOC level were Infections and infestations (20.2% in the SAR342434 group and 16.3% in the Humalog group). A table of TEAEs by primary SOC comparing SAR342434 and Humalog generated using JReview (Table 30) is in agreement with data presented by the Applicant.

Table 30: TEAEs by primary SOC reported in Study EFC13403

Primary System Organ Class	SAR342434 N=253	Humalog N=252
Infections and infestations	51 (20.2%)	41 (16.3%)
Nervous system disorders	23 (9.1%)	19 (7.5%)
Musculoskeletal and connective tissue disorders	22 (8.7%)	21 (8.3%)
Gastrointestinal disorders	22 (8.7%)	23 (9.1%)
Injury, poisoning and procedural complications	15 (5.9%)	9 (3.6%)
General disorders and administration site conditions	12 (4.7%)	14 (5.6%)
Skin and subcutaneous tissue disorders	9 (3.6%)	10 (4.0%)
Respiratory, thoracic and mediastinal disorders	9 (3.6%)	13 (5.2%)
Vascular disorders	8 (3.2%)	6 (2.4%)
Investigations	8 (3.2%)	7 (2.8%)
Cardiac disorders	6 (2.4%)	14 (5.6%)
Eye disorders	4 (1.6%)	6 (2.4%)
Metabolism and nutrition disorders	3 (1.2%)	11 (4.4%)
Psychiatric disorders	3 (1.2%)	8 (3.2%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (1.2%)	3 (1.2%)
Blood and lymphatic system disorders	3 (1.2%)	3 (1.2%)
Surgical and medical procedures	2 (0.8%)	1 (0.4%)
Immune system disorders	2 (0.8%)	0 (0.0%)
Endocrine disorders	1 (0.4%)	1 (0.4%)
Ear and labyrinth disorders	1 (0.4%)	2 (0.8%)
Reproductive system and breast disorders	1 (0.4%)	1 (0.4%)
Renal and urinary disorders	1 (0.4%)	3 (1.2%)
Congenital, familial and genetic disorders	0 (0.0%)	1 (0.4%)
Hepatobiliary disorders	0 (0.0%)	4 (1.6%)

Table generated from data submitted by reviewer using JReview.

The most frequently reported TEAEs by HLT were upper respiratory tract infection (8.7% for SAR342434 and 6.0% for Humalog) and musculoskeletal and connective tissue pain and discomfort (4.7% for SAR342434 and 4.4% for Humalog). At the PT level, the most common TEAEs reported were nasopharyngitis (4% in the SAR342434 group and 2% in the Humalog group). The percentages of patients with TEAEs reported at the PT level presented by the Applicant were confirmed by the reviewer's analysis and are shown in Table 31 for TEAEs with incidence >1.0% in any treatment arm. My review of TEAEs reported at a lower percentage ($\leq 1\%$) did not identify any relevant issue.

Table 31: TEAEs at the PT level reported in Study EFC13403

Dictionary Derived Term	SAR342434 N=253	Humalog N= 252
Nasopharyngitis	10 (4.0%)	5 (2.0%)
Musculoskeletal pain	6 (2.4%)	3 (1.2%)
Headache	6 (2.4%)	5 (2.0%)
Diarrhea	5 (2.0%)	4 (1.6%)
Bronchitis	5 (2.0%)	5 (2.0%)
Influenza	5 (2.0%)	5 (2.0%)
Edema peripheral	5 (2.0%)	3 (1.2%)
Back pain	4 (1.6%)	5 (2.0%)
Sinusitis	4 (1.6%)	2 (0.8%)
Accidental overdose	4 (1.6%)	4 (1.6%)
Urinary tract infection	4 (1.6%)	6 (2.4%)
Cough	4 (1.6%)	5 (2.0%)
Hypertension	4 (1.6%)	2 (0.8%)
Arthralgia	3 (1.2%)	3 (1.2%)
Carpal tunnel syndrome	3 (1.2%)	0 (0.0%)
Fall	3 (1.2%)	0 (0.0%)
Pharyngitis	3 (1.2%)	2 (0.8%)
Pneumonia	3 (1.2%)	3 (1.2%)
Weight increased	3 (1.2%)	3 (1.2%)
Upper respiratory tract infection	3 (1.2%)	5 (2.0%)
Vomiting	3 (1.2%)	2 (0.8%)
Nausea	3 (1.2%)	1 (0.4%)
Contusion	3 (1.2%)	1 (0.4%)
Angina pectoris	2 (0.8%)	3 (1.2%)
Pain in extremity	2 (0.8%)	4 (1.6%)
Dizziness	2 (0.8%)	3 (1.2%)

Table generated from data submitted by the Applicant using JReview including TEAEs reported in an incidence of >1.0% in any treatment arm.

The output in both tables (Table 30 and Table 31) is in agreement with data presented by the Applicant. No clinically significant differences were noted between the incidence of TEAEs reported for SAR342434 and Humalog treatment arms in patients with T2DM.

Adverse events by subgroups

I reviewed the results of the common adverse events subgroup analysis performed by the Applicant for the study EFC13403, and I agree with the Applicant's findings that there were no outstanding differences between treatment arms in any of the subgroups. However, it should be noted that the small number of patients other than Caucasian in the race category did not allow for a conclusive comparison between treatment arms in racial subgroups.

The subgroup analysis by region-approved (US-approved Humalog vs. EU-approved Humalog) shows that the overall incidence of TEAEs was similar in each region:

- US-approved Humalog: 52.5 % in SAR342434 group vs. 48.3% in Humalog group
- EU-approved Humalog: 41.2 % in SAR342434 group vs. 37.9% in Humalog group

Additionally, I reviewed the terms by region and found the types of TEAEs to be similar between treatments for each region.

7.4.2 Laboratory Findings

Clinical laboratory tests included: hematology and clinical chemistry (lipid profile, electrolytes, renal function and liver function). Samples for laboratory analyses were collected at Day 1 (baseline) and at the end of the treatment period (Week 26 for study EFC13403 or Week 26 and 52 for study EFC12619 short and extension periods, respectively), and were analyzed as change from baseline values. For patients who discontinued prematurely, the last sample was collected in the first visit after the last dose of IMP.

As per protocol, Potentially Clinically Significant Abnormality (PCSA) values were defined as abnormal values of clinical laboratory tests and vital signs considered clinically relevant by the Applicant according to predefined criteria/thresholds based on literature review and. The number of all patients with at least one PCSA during the on-treatment period, including non-scheduled or repeated evaluations was used as the numerator for the on-treatment PCSA percentage. Laboratory data considered as PCSA were reported and specified whether they were related to serious TEAEs or if led to permanent IMP discontinuation.

In addition, the Investigator was to monitor, document and manage the following specific abnormalities, according to specific guidance provided by the Sponsor (a flowchart of the guidance for each one of these abnormalities can be found in the Appendix A of the Clinical Protocol for EFC12619 and EFC13403):

- Neutropenia

- Thrombocytopenia
- Acute renal insufficiency
- Increase in ALT levels
- Suspicion of rhabdomyolysis

Hematology Parameters:

No imbalance was noted in the hematology findings between treatment arms in either EFC12619 (T1DM) or EFC13403 (T2DM). PCSA was defined for each hematologic parameter (US units) as follows:

- Hemoglobin ≤ 11.5 g/dL or ≥ 18.5 g/dL (male); ≤ 9.5 g/dL or ≥ 16.5 g/dL (female)
- Hematocrit $\leq 37\%$ or $\geq 55\%$ (male); $\leq 32\%$ or $\geq 50\%$ (female)
- Erythrocytes $\geq 6.0 \times 10^6/\mu\text{L}$
- Platelets $< 100 \times 10^3/\mu\text{L}$ or $\geq 700 \times 10^3/\mu\text{L}$
- Total leukocytes $< 3.0 \times 10^3/\mu\text{L}$ (Non-Black); $< 2.0 \times 10^3/\mu\text{L}$ (Black) or $\geq 16.0 \times 10^3/\mu\text{L}$
- Neutrophils $< 1.50 \times 10^3/\mu\text{L}$ (Non-Black); $< 1.00 \times 10^3/\mu\text{L}$ (Black)
- Lymphocytes $> 4.00 \times 10^3/\mu\text{L}$
- Monocytes $> 0.70 \times 10^3/\mu\text{L}$
- Basophils $> 0.10 \times 10^3/\mu\text{L}$
- Eosinophils $> 0.500 \times 10^3/\mu\text{L}$ or $> \text{ULN}$ (If $\text{ULN} \geq 0.500 \times 10^3/\mu\text{L}$)

No PCSA in hematology was reported as a serious TEAE or leading to permanent IMP discontinuation. A summary of change from baseline of hematology parameters is presented in Table 32.

Table 32: Hematology parameters (Change from baseline) - Study EFC12619, 12-month period and Study EFC13403

Parameters (Conventional US units)	Change from baseline	EFC12619 – 12 month		EFC13403	
		SAR342434 (N=252)	Humalog (N=254)	SAR342434 (N=252)	Humalog (N=254)
Hemoglobin (g/dL)					
	N	221	230	224	227
	Mean (SD)	-0.07 (0.74)	-0.06 (1.01)	-0.01 (0.85)	0.00 (0.78)
	Median	-0.10	-0.10	0.00	0.00
Hematocrit (%)					
	N	221	229	224	227
	Mean (SD)	-0.39 (2.38)	-0.17 (2.89)	-1.00 (3.11)	-1.07 (2.72)
	Median	0.00	0.00	-1.30	-1.10
Erythrocytes ($10^6/\mu\text{L}$)					
	N	221	230	224	227
	Mean (SD)	4.75 (0.47)	4.76 (0.45)	0.01 (0.31)	0.00 (0.26)
	Median	4.70	4.70	0.00	0.00
Platelets ($10^3/\mu\text{L}$)					

Parameters (Conventional US units)	Change from baseline	EFC12619 – 12 month		EFC13403	
		SAR342434 (N=252)	Humalog (N=254)	SAR342434 (N=252)	Humalog (N=254)
	N	220	230	223	224
	Mean (SD)	-4.38 (44.10)	-1.71 (44.06)	3.09 (42.52)	7.15 (37.98)
	Median	0.00	0.00	4.00	6.00
Leukocytes (10 ³ /uL)					
	N	221	230	224	227
	Mean (SD)	6.16 (1.76)	6.18 (1.92)	0.33 (1.52)	0.19 (1.13)
	Median	5.93	5.83	0.29	0.26

Table adapted from clinical laboratory data submitted (CSR-EFC12619 and CSR-EFC13403).

Lipid Parameters:

The lipid parameters were similar between treatment arms in either EFC12619 (T1DM) or EFC13403 (T2DM). PCSA was defined for lipid parameters as follows (US units):

- Total Cholesterol ≥ 298.8 mg/dL
- Triglycerides ≥ 407.1 mg/dL

No PCSA in lipid profile was reported as serious TEAE or leading to permanent IMP discontinuation. A summary of change from baseline of lipid parameters is presented in Table 33.

Table 33: Lipid parameters (Change from baseline) - Study EFC12619, 12-month period and Study EFC13403

Parameters (Conventional US units)	Change from baseline	EFC12619 – 12 month		EFC13403	
		SAR342434 (N=252)	Humalog (N=254)	SAR342434 (N=253)	Humalog (N=252)
Cholesterol (mg/dL)					
	N	216	225	215	216
	Mean (SD)	-2.89 (28.12)	0.83 (30.12)	1.06 (36.78)	4.60 (32.68)
	Median	-5.21	2.32	0.00	1.00
HDL Cholesterol (mg/dL)					
	N	216	225	214	216
	Mean (SD)	-1.55 (9.65)	-1.41 (10.11)	-1.19 (7.24)	-0.58 (7.28)
	Median	-0.39	-1.93	-1.00	-1.00
LDL Cholesterol Calculated (mg/dL)					
	N	216	223	202	211
	Mean (SD)	-1.82 (24.87)	1.13 (24.55)	3.10 (31.68)	5.75 (28.79)
	Median	4.70	4.70	3.00	4.00
Triglycerides (mg/dL)					
	N	216	225	215	216
	Mean (SD)	2.49 (37.53)	4.23 (52.86)	-2.13 (92.29)	-2.13 (92.29)
	Median	1.77	2.65	1.00	-2.50

Table adapted from clinical laboratory data submitted (CSR-EFC12619 and CSR-EFC13403).

Clinical Chemistry Parameters:

There were no relevant changes from baseline to the last on-treatment value on electrolytes in T1DM and T2DM patients. PCSA was defined for electrolytes as follows (US units):

- Sodium ≤ 129 mEq/L or ≥ 160 mEq/L
- Potassium < 3.0 mEq/L or ≥ 5.5 mEq/L

A PCSA of high potassium (≥ 5.5 mmol/L) associated with a serious TEAE was reported in one T1DM patient in the Humalog group, and a PCSA of low potassium (< 3.0 mmol/L) associated with a serious TEAE was reported in one T1DM patient and in one T2DM patient, both in the Humalog treatment group.

- A T1DM patient (on Humalog) experienced hyperkalemia (6.4 mmol/L) on Day 186 while hospitalized for diabetic ketoacidosis. The patient recovered and was discharged on the following day.
- A T1DM patient (on Humalog) experienced hypokalemia (2.9 mmol/L) on Day 58, which was treated with intravenous fluid and potassium replacement. Of note, this patient was taking hydrochlorothiazide, which may have contributed to the patient's potassium depletion. The patient recovered and was discharged from hospital.

- A T2DM patient (on Humalog) experienced serious AE of severe intensity reported as hypokalemia (blood level not reported) on Day 177 of study. The narrative does not contain any detailed information in regards to the symptoms that the patient experienced. The patient recovered and was discharged from the hospital.

Renal Function Tests:

There were no relevant changes from baseline to the last on-treatment value on any renal function parameters in either treatment group of Study EFC12619 and Study EFC13403. The results of renal function tests are summarized in Table 34 below.

Table 34: Renal function tests (Change from baseline) - Study EFC12619, 12-month period and Study EFC13403

Parameters (Conventional US units)	Change from baseline	EFC12619 – 12 month		EFC13403	
		SAR342434 (N=252)	Humalog (N=254)	SAR342434 (N=253)	Humalog (N=252)
GFR* (mL/min/1.73m ²)					
	N	222	229	225	227
	Mean (SD)	-1.48 (11.89)	-0.81 (11.01)	0.01 (0.16)	-0.01 (0.19)
	Median	0.00	0.00	0.00	1.00
Creatinine (mg/dL)					
	N	222	229	225	227
	Mean (SD)	0.01 (0.11)	0.01 (0.09)	-1.12 (9.27)	-1.72 (10.20)
	Median	1.00	1.00	-1.00	-1.00
Calculated creatinine clearance (mL/min)					
	N	222	229	221	223
	Mean (SD)	0.30 (14.60)	1.02 (12.91)	-1.04 (8.66)	-0.72 (7.61)
	Median	0.45	0.93	-1.00	0.00

Table adapted from clinical laboratory data submitted (CSR-EFC12619 and CSR-EFC13403).

*Serum GFR derived 4-variable MDRD Equation.

Decreases in creatinine clearance, although more frequent in T2DM patients than in T1DM, were balanced between treatment groups in both trials.

PCSA for renal function was defined by the following parameters (US units):

- Creatinine ≥ 1.70 mg/dL (Adults); $\geq 30\%$ from baseline or $\geq 100\%$ from baseline
- Creatinine clearance < 30 mL/min (severe renal impairment); ≥ 30 - < 50 mL/min (moderate renal impairment) or ≥ 50 - ≤ 80 mL/min (mild renal impairment)

In the T1DM trial (EFC12619), from the total number of patients 5 (2.1%) patients in the SAR342434 group and 4 (1.6%) in the Humalog group met the criteria for PCSA of creatinine $\geq 30\%$ change from baseline. For the parameter creatinine clearance, the percentage of patients with renal impairment was balanced between the treatment arms, with a higher percentage in the category of mild renal impairment (creatinine

clearance ≥ 50 - ≤ 80 mL/min). There were no patients with severe renal impairment (creatinine clearance < 30 mL/min) at baseline or during the treatment period.

Three PCSAs were reported as TEAEs: 1 in the SAR342434 group with blood creatinine increased, and 2 in the Humalog group with creatinine clearance decreased. These events were reported as non-serious and of mild intensity. A serious TEAE of acute kidney injury was reported for one T1DM patient in the Humalog group while hospitalized for severe diabetic ketoacidosis associated with hyperkalemia. The patient recovered without complications.

In the T2DM trial (EFC13403), 11 (4.6%) patients in the SAR342434 group and 7 (2.9%) patients in the Humalog group had creatinine values ≥ 1.7 mg/dL. From the total number of patients, 10 (4.2%) in the SAR342434 group and 11 (4.6%) in the Humalog group met the criteria for PCSA of creatinine $\geq 30\%$ change from baseline. The number of patients with PCSAs for creatinine clearance was similar between the treatment arms, and most had a mild renal impairment (creatinine clearance between 50 and 80 mL/min): 58 (24.3%) in the SAR342434 group and 63 (26.5%) in the Humalog group. One patient in the SAR342434 group had an estimated clearance creatinine of 25 mL/min at screening and was randomized by mistake. According to the exclusion criteria, patients with creatinine clearance < 30 mL/min should not enter the study. This case was reported as major deviation. The level of creatinine clearance remained stable throughout the study and the patient completed the study with no report of complications.

Liver Function Tests:

Liver enzymes (ALT, AST and ALP) and bilirubin were measured to assess the possible occurrence of drug induced liver toxicity.

PCSA for liver function parameters were defined as follows:

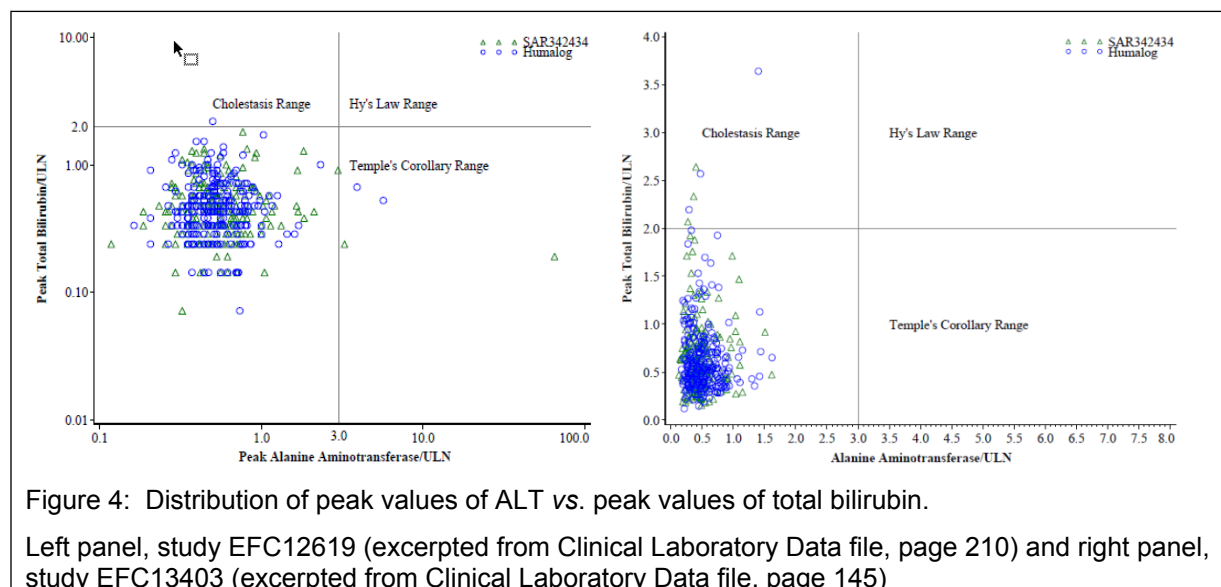
- ALT $> 3X$ ULN and $\leq 5X$ ULN; $> 5X$ ULN and $\leq 10X$ ULN; $> 10X$ ULN and $\leq 20X$ ULN; or $> 20X$ ULN
- ASP $> 3X$ ULN and $\leq 5X$ ULN; $> 5X$ ULN and $\leq 10X$ ULN; $> 10X$ ULN and $\leq 20X$ ULN; or $> 20X$ ULN
- ALP $> 1.5X$ ULN
- Total bilirubin $> 1.5X$ ULN or $> 2X$ ULN
- ALT and total bilirubin (TBILI) ALT $> 3X$ ULN and TBILI $> 2X$ ULN
- Conjugated and total bilirubin $> 35\%$ and TBILI $> 1.5X$ ULN

In the 12-month period of the EFC12619 study, 1 (0.4%) patient in the SAR342434 group and 3 (1.2%) patients in the Humalog group had PCSA for total bilirubin. However, the number of patients with bilirubin values available to measure change in bilirubin was low (15 in SAR342434 and 13 in Humalog group). There was one patient (patient No. 012619-276-008-004) in the SAR342434 treatment arm with PCSA values for ALT and AST $> 20X$ ULN on day 231 of treatment due to Hepatitis E. There were no

chronic complications and the patient completed the study. One patient in the Humalog treatment arm had a PCSA value of ALT $>5X$ ULN and $\leq 10X$ ULN reported one day after the last IMP (Day 365). The ALT value was $5.68X$ ULN and the AST value was $4.35X$ ULN, with normal values of alkaline phosphatase and of total bilirubin. The highest ALT value ($7.25X$ ULN) was recorded 22 days after the first measurement. The last measurement measured was performed approximately at 5 months in the follow-up period and the ALT value was $1.68X$ ULN. The patient remained asymptomatic during the whole ALT elevation period and the cause of abnormal ALT was reported by the Investigator as unknown. The Applicant assessed this event as unrelated to IMP and unrelated to NIMP, but from the reviewer point-of-view the relationship of this case with IMP/NIMP remains unclear. One T1DM patient (012619-276-002-008) in the SAR342434 group was reported with an SAE of cholangitis on Day 129 of treatment. The patient recovered and was not discontinued from the study.

In Study EFC13403, 6 patients (2.5%) in each treatment group had PCSA for total bilirubin. No patients had PCSA for ALT or for AST.

There were no records of patients that met the criteria for Hy's Law. Distribution of peak values of ALT vs. peak values of total bilirubin for study EFC12619 and EFC13403 is represented in the Figure 4.



Overall, the values of liver enzymes were similar between treatment arms in the study with T1DM patients and in the study with T2DM patients. The results of liver function tests are summarized in Table 35.

Table 35: Liver function parameters (Change from baseline) - Study EFC12619, 12-month period and Study EFC13403

Parameters (Conventional US units)	Change from baseline	EFC12619 – 12 month		EFC13403	
		SAR342434 (N=252)	Humalog (N=254)	SAR342434 (N=253)	Humalog (N=252)
Bilirubin (mg/dL)					
	N	221	229	225	227
	Mean (SD)	-0.00 (0.25)	-0.00 (0.22)	0.01 (0.16)	-0.01 (0.19)
	Median	0.00	0.00	0.00	1.00
ALT (U/L)					
	N	221	229	225	227
	Mean (SD)	1.16 (13.26)	2.27 (16.02)	-1.12 (9.27)	-1.72 (10.20)
	Median	1.00	1.00	-1.00	-1.00
AST (U/L)					
	N	220	228	221	223
	Mean (SD)	0.89 (10.73)	1.40 (12.70)	-1.04 (8.66)	-0.72 (7.61)
	Median	1.00	0.00	-1.00	0.00
Alkaline Phosphatase (U/L)					
	N	22	229	221	223
	Mean (SD)	0.32 (13.04)	2.28 (13.52)	3.67 (17.14)	1.52 (15.74)
	Median	0.00	1.00	3.00	1.00

Table adapted from clinical laboratory data submitted (CSR-EFC12619 and CSR-EFC13403).

7.4.3 Vital Signs

Small changes were observed in systolic and diastolic blood pressure and in heart rate in both T1DM and T2DM patients during the on-treatment period.

In the Study EFC12619, the mean value of maximum changes observed during the 12-month study period was: -1.7 mmHg for systolic blood pressure, -0.5 mmHg for diastolic blood pressure, and +1.2 bpm for heart rate in the SAR342434 group, and -2.2 mmHg for systolic blood pressure, -0.7 mmHg for diastolic blood pressure, and +1.5 bpm for heart rate in the Humalog group.

In the EFC13403 clinical trial, the maximum value of mean changes reported over the course of the treatment period was: +3.4 mmHg for systolic blood pressure, +0.7 mmHg for diastolic blood pressure, and +0.2 bpm for heart rate in the SAR342434 group, and +0.8 mmHg for systolic blood pressure, -0.7 mmHg for diastolic blood pressure, and +0.8 bpm for heart rate in the Humalog group.

The Applicant defined PCSA of vital signs for patients who met the following criteria at least once during the treatment:

- Systolic blood pressure (sitting) ≤ 95 mmHg and decrease from baseline ≥ 20 mmHg; or ≥ 160 mmHg and increase from baseline ≥ 20 mmHg
- Diastolic blood pressure (sitting) ≤ 45 mmHg and decrease from baseline ≥ 10 mmHg; or ≥ 110 mmHg and increase from baseline ≥ 10 mmHg

- Heart rate ≤ 50 bpm and decrease from baseline ≥ 20 bpm; or ≥ 120 bpm and increase from baseline ≥ 20 bpm

The number of patients with vital signs values that met the criteria for PCSAs of blood pressure and heart rate was relatively low in both studies, as represented in Table 36.

Table 36: Vital signs PCSAs – Study EFC12619, 12-month period and Study EFC13403

Vital Sign Parameters PCSA criteria n/N1(%)	EFC12619 – 12 month		EFC13403	
	SAR342434 (N=252)	Humalog (N=254)	SAR342434 (N=253)	Humalog (N=252)
Systolic Blood Pressure (sitting)				
≤ 95 mmHg and decrease from baseline ≥ 20 mmHg	9/250 (3.6%)	2/253 (0.8%)	3/248 (1.2%)	2/248 (0.8%)
≥ 160 mmHg and increase from baseline ≥ 20 mmHg	8/250 (3.2%)	10/253 (4.0%)	19/248 (7.7%)	17/248 (6.9%)
Diastolic blood pressure (sitting)				
≤ 45 mmHg and decrease from baseline ≥ 10 mmHg	1/250 (0.4%)	1/253 (0.4%)	0/248	0/248
≥ 110 mmHg and increase from baseline ≥ 10 mmHg	0/250	0/253	1/248 (0.4%)	1/248 (0.4%)
Heart rate				
≤ 50 bpm and decrease from baseline ≥ 20 bpm	4/250 (1.6%)	0/253	1/248 (0.4%)	1/248 (0.4%)
≥ 120 bpm and increase from baseline ≥ 20 bpm	0/250	1/253 (0.4%)	1/248 (0.4%)	0/248

Table adapted from data submitted by the Applicant in EFC12619 - Other Safety file and EFC13403 - Other Safety file.

Based on my review of vital signs, I believe that the results of blood pressure and heart rate reported for patients in the SAR342434 group were similar to those reported for patients in the Humalog group in both, study EFC12619 and study EFC13403.

7.4.4 Electrocardiograms (ECGs)

A 12-lead ECG was recorded at screening and at the end of the study. The ECG trace recorded at the last visit was compared to the trace of the ECG recorded at the screening visit. The assessment of the ECG was performed by the Investigator and was recorded as “normal” or “abnormal”/“clinically significant”/“clinically not significant”. No other assessment of ECG abnormalities was performed.

There were 4 T1DM patients reported with a clinically significant abnormal ECG during the on-treatment period: 3 (1.2%) in the SAR342434 group and 1 (0.4%) in the Humalog group. In the study with T2DM patients, there were a total of 5 patients with a clinically significant abnormal ECG: 1 (0.4%) in the SAR342434 group and 4 (1.7%) patients in the Humalog group. The number of patients with abnormal ECG is summarized in

Table 37. There was no apparent relationship between the ECG abnormality incidence and the IMP/NIMP.

Table 37: Number of patients with abnormal ECG status (compared to baseline ECG trace) in Study EFC12619 and Study EFC13403.

ECG baseline status ECG post-baseline	EFC12619 – 12 month		EFC13403	
	SAR342434 (N=252)	Humalog (N=254)	SAR342434 (N=253)	Humalog (N=252)
Total*				
Normal/Missing	165/244 (67.6%)	171/244 (70.1%)	111/231 (48.1%)	119/234 (50.9%)
Abnormal, not clinically significant	76/244 (31.1%)	72/244 (29.5%)	119/231 (51.5%)	111/234 (47.4%)
Abnormal, clinically significant	3/244 (1.2%)	1/244 (0.4%)	1/231 (0.4%)	4/234 (1.7%)
Normal/Missing				
Normal/Missing	154/191 (80.6%)	159/192 (82.8%)	81/97 (83.5%)	94/104 (90.4%)
Abnormal, not clinically significant	34/191 (17.8%)	33/192 (17.2%)	16/97 (16.5%)	10/104 (9.6%)
Abnormal, clinically significant	3/191 (1.6%)	0/192	0/97	0/104
Abnormal, not clinically significant				
Normal/Missing	11/52 (21.2%)	11/50 (22.0%)	29/133 (21.8%)	22/124 (17.7%)
Abnormal, not clinically significant	41/52 (78.8%)	39/50 (78.0%)	103/133 (77.4%)	99/124 (79.8%)
Abnormal, clinically significant	0/52	0/50	1/133 (0.8%)	3/124 (2.4%)

Table adapted from data submitted by the Applicant in EFC12619 - Other Safety file and EFC13403 -- Other Safety file.

*Regardless of baseline status

The percentage of patients with clinically significant ECG abnormality in both studies was very low, and the incidence of this abnormality did not show a trend towards SAR342434 in comparison with Humalog.

7.4.5 Special Safety Studies/Clinical Trials

In order to evaluate infusion set occlusions, the applicant conducted study PDY13502. The patients randomized for this study were to demonstrate proficiency with the use of insulin pump and to utilize their own pumps. Medtronic pumps (81.5%) and the Animas Vibe pumps (18.5%) were used by patients in the study.

The primary objective of Study PDY13502 was to assess the incidence of infusion set occlusions with SAR342434 and Humalog when using external pumps. The Applicant

defined infusion set occlusions as failure to correct hyperglycemia (plasma glucose ≥ 300 mg/dL) by insulin bolus via the insulin pump (excluding malfunction).

Out of the 27 patients, a total of 6 (24%) patients reported at least one infusion set occlusion: 4 (14.8%) patients experienced infusion set occlusions during the SAR342434 period and during the Humalog period, and 2 patients reported infusion set occlusions during the SAR342434 period only. There was 1 patient exposed to Humalog in period 2 of the study with no data collected in regards to infusion set occlusion. Two patients in the SAR342434 group were not exposed/not evaluated. Data is summarized in Table 38, and the risk estimate and risk difference of SAR342434 to the approved insulin lispro is presented in Table 39.

Table 38: Number of patients with or without infusion set occlusions during the on-treatment period (safety population)

SAR342434				
Number of patients with infusion set occlusions				
Humalog	YES	NO	Not exposed/evaluable	Total
Number of patients with infusion set occlusions				
YES	4	0	0	4
NO	2	18	2	22
Not exposed/evaluable	0	1	0	1
Total	6	19	2	27
Infusion set occlusion defined as failure to correct hyperglycemia by insulin bolus via the insulin pump (excluding pump malfunction)				
Patient (b) (6) exposed to Humalog in period 2 but without data with regards to infusion set change and hyperglycemia event collected for this period, is counted in the corresponding "Not exposed/evaluable" line/column				
PGM=PRODOPS/SAR342434/PDY13502/CSR/REPORT/PGM/ae_saf_main_cross_s_t.sas OUT=REPORT/OUTPUT/ae_saf_main_cross_s_t.i.rtf (13JUL2016 - 10:24)				

Source: Table excerpted from Study PDY13502, CSR file submitted by the Applicant.

Table 39: Number (%) of patients with at least one infusion set occlusion

	SAR342434 (N=25)	Humalog (N=27)
At least one infusion set occlusion ^a	6 (24.0%)	4 (14.8%)
Risk estimate ^b	22.5%	14.6%
95% CI	[6.66% ; 38.29%]	[1.60% ; 27.52%]
Risk Difference vs Humalog ^b	7.9 %	
95% CI	[-1.90% ; 17.73%]	
CI: confidence interval		
^a Infusion set occlusion defined as failure to correct hyperglycemia by insulin bolus via the insulin pump (excluding pump malfunction)		
^b Repeated measures model using a binomial regression and an identity-link function, including fixed categorical effects for treatment, period and sequence. Risks within each treatment group, risk difference and their 95% CIs provided using the adjusted LSmean estimates of the treatment effect.		
Patient (b) (6) was exposed to Humalog in period 2 but no data with regards to infusion set change and hyperglycemia event was collected for this period		
PGM=PRODOPS/SAR342434/PDY13502/CSR/REPORT/PGM/ae_saf_main_par1_s_t.sas OUT=REPORT/OUTPUT/ae_saf_main_par1_s_t.rtf (17JUN2016 - 9:36)		

Source: Excerpted from Study PDY 13502, CSR, Table 12

The difference between the number of patients with at least one infusion set occlusion in SAR342434 group and in the Humalog group was 2 patients, resulting in 24% (6/25) patients with infusion set occlusions while receiving SAR342434 and 14.8% (4/27) while receiving Humalog. The risk difference of SAR342434 to Humalog was 7.9%, and the risk estimate was 22.5% for SAR342434 and 14.6% for Humalog. The risk estimate for SAR342434 and for Humalog was tested by the Statistics review and the difference between the two arms is considered not significant as the confidence interval contains zero.

The total number of infusion set occlusion events was 23, with 14 reported with SAR342434 and 9 with Humalog. There were 4 patients reporting more than a single occlusion event, with the maximum of 4 occlusions reported per patient. See distribution of events per patient in Table 40 below.

Table 40: Number of infusion set occlusion events per patient.

Patient ID	# of occlusions while receiving SAR432434	# of occlusions while receiving Humalog	Total # of occlusions
(b) (6)	4	4	8
	3	3	6
	3	1	4
	2	0	2
	1	1	2
	1	0	1
Total	14	9	23
a Treatment sequence: Humalog/SAR342434			
b Treatment sequence: SAR342434/Humalog			
Source document for the table is in 16-2-7-ae-data [16.2.7.4] .			

Source: Excerpt from PDY13502, Table15 of CSR, page 51.

There were also reports of other causes for infusion set occlusion: two patients reported insulin pump alarm for infusion set occlusion during SAR342434 infusion, and 1 patient reported observation of infusion set occlusion (bent catheter) twice, one with SAR342434 and the other with Humalog infusion. See Table 41.

Table 41: Number (%) of patients with any infusion set occlusion.

	SAR342434 (N=25)	Humalog (N=27)
Patient with infusion set occlusion defined as failure to correct hyperglycemia ^a	6 (24.0%)	4 (14.8%)
Patient with insulin pump alarm for infusion set occlusion	2 (8.0%)	0
Patient observation of infusion set occlusion	1 (4.0%)	1 (3.7%)
Patient with any infusion set occlusion (combined endpoint) ^b	8 (32.0%)	5 (18.5%)
a Infusion set occlusion defined as failure to correct hyperglycemia by insulin bolus via the insulin pump (excluding pump malfunction)		
b Infusion set occlusion defined as failure to correct hyperglycemia by insulin bolus via the insulin pump (excluding pump malfunction), or insulin pump alarm for infusion set occlusion, or patient observation of infusion set occlusion		
Patient (b) (6) was exposed to Humalog in period 2 but no data with regards to infusion set change and hyperglycemia event was collected for this period		
PGM=PRODOPS/SAR342434/PDY13502/CSR/REPORT/PGM/ae_saf_sec_par_pat_s_t.sas OUT=REPORT/OUTPUT/ae_saf_sec_par_pat_s_t.i.rtf (17JUN2016 - 9:40)		

Source: Excerpt from PDY13502, Table 16 of CSR, page 52

In the SAR342434 group, there were 3 patients (23.1%) in the first period and 3 patients (25.0%) in the second period with at least one infusion set occlusion, while in the Humalog group, there were 3 patients (21.4%) in the first treatment period and 1 (7.7%) in the second period. The differences observed between treatment periods in the two groups was not considered statistically significant (p=0.14). However, the sample size was insufficient to determine small differences.

To account for events that could have been missed by the primary objective criteria, the Applicant performed sensitivity analyses of infusion set occlusions using hyperglycemia data derived from failure to correct hyperglycemia (plasma glucose ≥ 300 mg/dL) within 60 minutes after insulin bolus. The criteria included:

- All hyperglycemia events (blood glucose ≥ 300 mg/dL) with a decrease of blood glucose value ≤ 50 mg/dL at 60 minutes post insulin bolus via the insulin pump, excluding those due to pump malfunction.
- All events of infusion set occlusion documented by the patient in the e-CRF with “unexplained plasma glucose” as the primary reason and “infusion set occlusion” in the specified field.
- The 60 min post-bolus (via the insulin pump) blood glucose measurement was missing and the 30 min post-bolus measurement showed a decrease of ≤ 50 mg/dL.
- Post-bolus blood glucose data collected after an infusion set change were not included in the analysis.

Results from the sensitivity analysis showed that there were more infusion set occlusion events reported by patients with SAR342434 infusion than with Humalog infusion: 12 (48%) patients and 23 events with SAR342434 vs. 8 (29.6%) patients, 17 events with Humalog. The rate of events per month calculated as mean $\pm$ SD was 0.95 ± 1.52 for SAR342434 and 0.68 ± 1.40 for Humalog. Although the sensitivity analysis for set infusion occlusions showed a higher incidence of set occlusions for SAR342434 than for Humalog, the relevance is unclear due to the small sample size. See also the discussion of infusion set occlusions by the CDRH consultants.

7.4.6 Immunogenicity

Immunogenicity is a concern for any peptide product. Assessments for anti-insulin antibodies (AIAs) were performed as part of the assessment of safety. In the study EFC12619, with T1DM patients (duration of 52 weeks), AIA assessment was performed at Day 1, at Week 4, Week 12, Week, Week 40 and Week 52. In the study EFC13403, with T2DM patients (duration of 26 weeks), AIA assessment was performed at Day 1, at Week 4, Week 12, and Week 26. For patients who discontinued the study prematurely, blood sample for AIA was drawn at the end-of-treatment assessment. According to the protocol, samples were to be collected 8 hours after the administration of either the SAR342434 or Humalog at the earliest.

Immunogenicity variables measured were:

- AIA status: positive or negative
- AIA titer
- Cross-reactivity to insulin glargine
- Cross-reactivity to insulin glargine metabolite M1
- Cross-reactivity to human insulin

The occurrence of AIA was categorized as:

- Patients with treatment-emergent AIAs - defined as patients with treatment-induced or treatment-boosted AIAs.
 - Treatment-induced AIAs - defined as patients without pre-existing AIA or with missing baseline AIA value that had at least one positive AIA measurement at any time during the on-treatment period.
 - Treatment-boosted AIAs - defined as patients with pre-existing AIAs that had at least one AIA sample with titer increase of 4-fold or more compared to baseline at any time during the on-treatment period.
- Patients without treatment-emergent AIAs - defined as patients without treatment-induced and without treatment-boosted AIAs.
- Inconclusive patients were those who could not be unquestionably classified as patients without treatment-emergent AIAs.

The AIA prevalence, measured by the percentage of patients with detectable AIA titer in at least one time point during the treatment was similar between the SAR342434 and Humalog groups in both trials. In the trial with T1DM patients, the highest titer observed during the treatment period was 1:512 (1 patient) in the SAR342434 group and 1:256 in the Humalog group (1 patient). In the trial with T2DM patients, the highest titer observed during treatment was 1:256 in both treatment arms. The small or no difference in the highest AIA titer observed and in the number of patients that experienced the high titer level between the two treatment arms in studies with T1DM and with T2DM patients suggest that the antigenicity of SAR342434 is similar to that of Humalog.

The impact of AIAs on efficacy (evaluated by HbA1c and insulin dose), and on safety parameters, including hypoglycemia, hypersensitivity, injection site reactions, TEAEs and SAEs, was analyzed for each treatment group (SAR342434 and Humalog) in the T1DM and T2DM trials.

Impact of AIA on efficacy parameters

The Applicant assessed the impact of presence of AIA and of AIA titer on HbA1c and daily insulin dose by treatment arm in both studies EFC12619 and EFC13403.

Study EFC12619 (T1DM):

The mean changes in HbA1c from baseline to week 52 were similar in the 2 treatment groups (SAR342434 and Humalog), regardless of the treatment emergent AIA status (positive/negative). A summary of changes in HbA1c (%) from baseline to week 52 by treatment-emergent AIA (anti-insulin antibody population) is shown in Table 42.

Table 42: Correlation of HbA1c with treatment-emergent AIA (EFC12619)

HbA1c (%)	Treatment-emergent AIA			
	Yes ^a		No	
	SAR342434 (N=56)	Humalog (N=61)	SAR342434 (N=192)	Humalog (N=191)
p-value (treatment-by-subgroup interaction) = 0.4212				
Baseline				
Number	56	61	188	189
Mean (SD)	8.18 (0.74)	7.97 (0.64)	8.05 (0.79)	8.01 (0.64)
Median	8.05	7.80	8.00	8.00
Min : Max	6.8 : 9.8	6.7 : 9.4	5.4 : 10.5	6.8 : 9.7
Week 52				
Number	51	60	177	177
Mean (SD)	7.92 (1.05)	7.66 (0.91)	7.77 (0.96)	7.72 (0.98)
Median	7.90	7.70	7.60	7.60
Min : Max	6.3 : 11.3	5.8 : 11.8	5.3 : 11.4	5.9 : 15.4
Change from baseline to Week 52				
Number	51	60	177	177
Mean (SD)	-0.23 (0.84)	-0.29 (0.84)	-0.26 (0.91)	-0.29 (0.97)
Median	-0.30	-0.40	-0.30	-0.30
Min : Max	-2.2 : 3.4	-1.8 : 3.6	-2.7 : 3.1	-3.1 : 8.0
LS Mean (SE) ^b	-0.14 (0.121)	-0.33 (0.114)	-0.25 (0.066)	-0.29 (0.065)
95% CI	(-0.381 to 0.096)	(-0.558 to -0.111)	(-0.376 to -0.118)	(-0.414 to -0.157)
LS mean difference (SE) vs Humalog ^b	0.19 (0.166)		0.04 (0.093)	
95% CI	(-0.135 to 0.519)		(-0.143 to 0.220)	

AIA=Anti-insulin antibody, MMRM=Mixed-effect model for repeated measures

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

b MMRM with treatment group (SAR342434, Humalog), randomization strata of screening HbA1c (<8.0, ≥8.0%), prior use of Humalog (Yes, No), visit (Week 12, Week 26, Week 40 and Week 52), treatment-by-visit interaction, AIA subgroup, AIA subgroup-by-treatment interaction, AIA subgroup-by-visit interaction and

AIA subgroup-by-visit-by-treatment interaction as fixed categorical effects, and baseline HbA1c value and baseline HbA1c value-by-visit interaction as continuous fixed covariates

Descriptive statistics are performed on patients included in the MMRM analysis

PGM=PRODOPS/SAR342434/EFC12619/CSR_01/REPORT/PGM/mmr_aia_subgrp_s_t.sas

OUT=REPORT/OUTPUT/osa_mmr_hba1c_p_52_aia_ontrt_i_t_i.rtf (06SEP2016 - 9:01)

Source: Excerpted from Study EFC12619-12 month CSR, Table 34.

From the data presented, there was no evidence that the presence of treatment-emergent AIA had any impact on mealtime insulin dose or on total daily insulin dose. A summary of changes from baseline to week 52 of daily insulin doses adapted from data submitted by the Applicant is presented in Table 43.

Table 43: Summary of daily insulin dose (U/kg) expressed as change from baseline to week 52 by treatment-emergent AIA (AIA population), Study EFC12619

Average daily insulin dose (U/kg)	Treatment-emergent AIA			
	YES		NO	
	SAR342434 N=56	Humalog N=61	SAR342434 N=192	Humalog N=191
BASAL INSULIN Change from baseline to Week 52				
Number	42	54	157	155
Mean (SD)	0.138 (0.781)	0.044 (0.071)	0.021 (0.069)	0.002 (0.061)
Median	0.021	0.021	0.014	-0.002
MEALTIME INSULIN Change from baseline to Week 52				
Number	39	54	153	149
Mean (SD)	0.007 (0.123)	0.010 (0.099)	0.021 (0.115)	0.006 (0.106)
Median	-0.005	-0.006	0.016	0.013
TOTAL INSULIN Change from baseline to Week 52				
Number	39	52	152	148
Mean (SD)	0.028 (0.168)	0.054 (0.122)	0.042 (0.126)	0.007 (0.127)
Median	0.019	0.032	0.039	0.002

Table adapted from data presented in Table 35 of Study EFC12619-12 month, CSR.

Changes from baseline to week 52 in basal insulin dose were found slightly higher in both treatment groups in patients with treatment-emergent AIA than in patients without treatment-emergent AIA. The difference was particularly noted in the SAR342434 group (mean of 0.138 U/kg for SAR342434 vs. mean of 0.044 U/kg for Humalog), and the Applicant attributed this increase to a data entry error reporting an increase in insulin from baseline at week 52 of 324 U (5.05 U/kg) for one patient (b) (6).

(b) (6) This error was noted after database lock and it was then confirmed that the correct values entered into the database should have been 36 U instead of 360 U at week 20, at week 34, at week 40 and at week 52, and should have been 36 U instead of 246 U at week 26. I reviewed the AIA data for this patient and found that the treatment-emergent AIA was negative at baseline, turning positive only at week 4 (titer 1:2) and returning to negative results in the subsequent visits. Based on these results, I find unlikely that AIA antibodies would explain an increase of insulin doses required for this patient. If AIAs were not blocking the insulin from binding the insulin receptors, then the high doses of insulin reported should have caused a severe hypoglycemia event. There were no severe hypoglycemia events reported for this patient, supporting the

Applicant's explanation that an entry error accounts for the high insulin doses recorded. Analyses of data were performed with inclusion of the doses incorrectly reported. The applicant did not conduct analyses excluding the insulin dose data for this patient. The scatter plot analyses showed no correlation between AIA titers (regardless of treatment-emergent AIA status) with total insulin dose or with change in HbA1c from baseline to week 52.

Study EFC13403 (T2DM): The mean changes in HbA1c from baseline to week 26 in SAR342434 treatment group were similar to those in Humalog treatment group, regardless of the treatment-emergent AIA status, as illustrated in Table 44.

Table 44: Correlation of HbA1c with treatment-emergent AIA (EFC13403)

HbA1c (%)	Treatment-emergent AIA			
	Yes ^a		No	
	SAR342434 (N=46)	Humalog (N=36)	SAR342434 (N=199)	Humalog (N=211)
p-value (treatment-by-subgroup interaction) = 0.6927				
Baseline				
Number	45	36	191	208
Mean (SD)	7.92 (0.87)	7.92 (0.93)	8.02 (0.86)	8.04 (0.91)
Median	7.70	7.95	8.00	8.00
Min : Max	6.4 : 9.7	5.6 : 9.4	6.3 : 10.2	6.0 : 11.2
Week 26				
Number	45	35	183	196
Mean (SD)	7.08 (0.83)	7.25 (1.02)	7.05 (0.86)	7.15 (0.86)
Median	7.00	7.10	7.00	7.05
Min : Max	5.5 : 9.2	5.4 : 9.6	5.5 : 10.8	5.3 : 10.1
Change from baseline to Week 26				
Number	45	35	183	196
Mean (SD)	-0.84 (0.77)	-0.71 (0.85)	-0.96 (1.02)	-0.90 (0.84)
Median	-0.80	-0.60	-1.00	-0.80
Min : Max	-2.5 : 0.8	-2.5 : 0.8	-3.9 : 2.7	-3.5 : 1.7
LS mean (SE) ^b	-0.88 (0.117)	-0.74 (0.132)	-0.93 (0.057)	-0.86 (0.055)
95% CI	(-1.111 to -0.651)	(-0.995 to -0.477)	(-1.045 to -0.819)	(-0.972 to -0.755)
LS mean difference (SE) vs Humalog ^b	-0.15 (0.176)		-0.07 (0.080)	
95% CI	(-0.492 to 0.201)		(-0.225 to 0.088)	
AIA=Anti-insulin antibody, MMRM=Mixed-effect model for repeated measures				
^a Patients with pre-existing AIAs that were boosted to a significant higher titer (at least 4-fold increase) compared to baseline, or patients without pre-existing AIA (or missing baseline) and with at least one positive AIA sample				
^b MMRM with treatment group (SAR342434, Humalog), randomization strata of screening HbA1c (<8.0, ≥8.0%), prior use of Humalog (Yes, No), visit (Week 12, Week 26), treatment-by-visit interaction, AIA subgroup, AIA subgroup-by-treatment interaction, AIA subgroup-by-visit interaction and AIA subgroup-by-visit-by-treatment interaction as fixed categorical effects, and baseline HbA1c value and baseline HbA1c value-by-visit interaction as continuous fixed covariates				
Descriptive statistics are performed on patients included in the MMRM analysis				
PGM=PRODOPS/SAR342434/EFC13403/CSR/REPORT/PGM/mmm_aia_subgrp_s_lsas OUT=REPORT/OUTPUT/osa_mmm_hba1c_p_26_aia_ontr_l_t_i.rtf (08JUN2016 - 10:38)				

Source: Excerpted from Study EFC13403 CSR, Table 33.

Daily insulin (basal, mealtime and total) dose were similar between treatment arms for patients with or without treatment-emergent AIA. The mean changes in insulin doses from baseline to week 26 were also comparable between treatment arms in the subgroups of patients with treatment-emergent AIA and patients without treatment-emergent AIA. These results are presented in Table 45 below.

Table 45: Summary of daily insulin dose (U/kg) expressed as change from baseline to week 26 by treatment-emergent AIA (AIA population), Study EFC13403.

Average daily insulin dose (U/kg)	Treatment-emergent AIA			
	YES		NO	
	SAR342434 N=46	Humalog N=36	SAR342434 N=199	Humalog N=211
BASAL INSULIN Change from baseline to Week 26				
Number	40	31	156	186
Mean (SD)	0.073 (0.092)	0.067 (0.088)	0.084 (0.142)	0.071 (0.127)
Median	0.051	0.056	0.053	0.047
MEALTIME INSULIN Change from baseline to Week 26				
Number	41	32	156	185
Mean (SD)	0.044 (0.164)	0.100 (0.280)	0.098 (0.218)	0.077 (0.243)
Median	0.053	0.037	0.062	0.053
TOTAL INSULIN Change from baseline to Week 26				
Number	40	31	156	184
Mean (SD)	0.123 (0.205)	0.179 (0.296)	0.184 (0.314)	0.147 (0.299)
Median	0.130	0.087	0.118	0.112

Table adapted from data presented in Table 34 of Study EFC13403, CSR.

There was no evidence from the data presented in the application to suggest an impact of treatment-emergent AIA elevated titers and change in HbA1c from baseline to last on-treatment measurement or change in daily insulin doses from baseline to last on-treatment measurement in patients with T1DM and patients with T2DM.

Impact of AIAs on safety parameters

There was no evidence that the presence of treatment-emergent AIA had an impact on the incidence of hypoglycemia events in either study EFC12619 (T1DM) or study EFC13403 (T2DM). The percentage of patients with at least one hypoglycemia event reported was similar between the SAR342434 group and the Humalog group for all the categories of hypoglycemia across subgroups defined by treatment-emergent hypoglycemia in the studies with T1DM and T2DM patients. See Table 46.

Table 46: Number of patients with severe hypoglycemia reported during the study by treatment-emergent AIA subgroup

	EFC12619		EFC13403	
	SAR342434	Humalog	SAR342434	Humalog
With treatment-emergent AIA	10/56	6/61	0/46	1/36
Without treatment-emergent AIA	23/192	28/191	6/199	2/211

Table generated from data reported in study EFC12619, 12-month CSR and in study EFC13403 CSR

The status of treatment-emergent AIA did not appear to influence the incidence of TEAEs reported in any of the two phase 3 trials (EFC12619 and EFC13403). The percentage of common TEAEs reported was similar in both treatment groups with treatment-emergent AIA (SAR342434: 53.6% and Humalog: 52.5%) and with no treatment-emergent AIA (SAR342434: 55.2% and Humalog: 57.1%) in the trial with T1DM patients. In the trial with T2DM patients, the percentage of patients with TEAEs and treatment-emergent AIA was slightly higher in the SAR342434 group (45.7%) than in the Humalog group (38.9%). The percentage of patients with common TEAEs and no treatment-emergent AIA was also similar between the two treatment groups (43.2% for SAR342434 and 43.6% for Humalog). In study EFC12619 (T1DM), the majority of patients with hypersensitivity reactions were those without treatment-emergent AIAs. A similar trend was observed in the study EFC13403 (T2DM). There was no evidence of relationship between the treatment-emergent AIAs and hypersensitivity reactions or injection site reactions, as illustrated in a combined table below (Table 47).

Table 47: Number of patients with hypersensitivity reactions and injection site reactions by treatment-emergent AIA in study EFC12619 and study EFC13403.

Number of patients (%)	Treatment-emergent AIA		Treatment-emergent AIA	
	YES		NO	
	EFC12619			
	SAR342434 N=56	Humalog N=61	SAR342434 N=192	Humalog N=191
Any hypersensitivity reaction	1 (1.8%)	2 (3.3%)	14 (7.3%)	14 (7.3%)
Any injection reaction	0	2 (3.3%)	3 (1.6%)	1 (0.5%)
	EFC13403			
	SAR342434 N=46	Humalog N=36	SAR342434 N=199	Humalog N=211
Any hypersensitivity reaction	1 (2.2%)	1 (2.8%)	8 (4.0%)	8 (3.8%)
Any injection reaction	1 (2.2%)	1 (2.8%)	0	3 (1.4%)

Table adapted from Table 36, in Study EFC12619-12 month CSR and Table 35, Study EFC13403 CSR.

The percentage of patients with SAEs and common TEAEs by treatment-emergent AIA was similar between SAR342434 and Humalog groups, with no evidence of a trend between the type of common TEAEs and the treatment-emergent AIA status in Study EFC12619 (T1DM). Similar results were observed in the Study EFC13403 with T2DM patients.

8 Postmarket Experience

Currently, there is no postmarketing experience with SAR342434.

9 Appendices

9.1 Literature Review/References

1. Guidance for Industry. Diabetes mellitus — Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Silver Spring, MD: Food and Drug Administration, December, 2008. (Accessed February 20, 2017, at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf>).
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9.2 Labeling Recommendations

Labeling recommendations include correction in the percentage of patients with positive AIA at baseline in Section 6 and removing (b) (4)

(b) (4) Additionally, the values should be updated to be consistent with the FDA statistical reviewer's findings. Sections 5 and 6 mirror the respective sections of the

approved insulin lispro label and with exception of the recommended change in AIA production, the presented safety data is acceptable.

9.3 Advisory Committee Meeting

Not applicable. No Advisory Committee was held to discuss this Application.

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/s/

SONIA D DOI
08/14/2017

WILLIAM H CHONG
08/14/2017

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: NDA209196 Applicant: Sanofi

Stamp Date: 11/01/2016

Drug Name: Insulin Lispro

NDA/BLA Type: 505(b)(2)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	x			The Application was submitted using eCTD format.
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm)	x			Proposed product labeling conforms to the final rule governing the "Requirements On Content and Format of Labeling for Human Prescription Drug and Biological Products" released on January 24, 2006, and is consistent with product labeling for the listed drug (i.e., HUMALOG).
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
10.	Has the applicant submitted a benefit-risk analysis for the product?	x			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(2)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?				Insulin lispro (HUMALOG), NDA020563
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?	x			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Describe the scientific bridge (e.g., BA/BE studies)	x			The Sponsor claims similarity between SAR342434 and HUMALOG based on the following studies: Analytical studies of the product; two 1-month toxicity studies (rats) and one tolerability study (rabbits); a 3-way crossover clinical pharmacology study (T1DM) to support PK/PD similarity of SAR342434, HUMALOG-US and HUMALOG-EU; a 6- and 12-month comparative study (T1DM) and a 6-month comparative study in T2DM patients to assess efficacy and safety similarity.
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Treatment Arms: Location in submission:			x	Insulin dosing is individualized to a patient's needs. There is no specific dose.
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Indication: SAR342434 is a rapid-acting human insulin analog indicated to improve glycemic control in children and adults with diabetes mellitus. Pivotal Study #1: EFC12619, randomized trial, open-label, 2-arm parallel group, comparative study in T1DM patients also using LANTUS, with an extension of 6-months. In the main 6-month period, 252 patients (SAR342434) and 254 patients (HUMALOG) were studied. In the 12-month period, 252 patients (SAR342434) and 254 patients (HUMALOG) were studied. Pivotal Study #2: EFC13403, randomized trial, open-label, 2-arm parallel group, 6-month comparative study in T2DM patients	x			Two Phase 3 studies (EFC12619 and EFC13403) were conducted to support that administration of SAR342434 by subcutaneous injection had similar efficacy on glycemic control and safety profile as HUMALOG in patients with T1DM and T2DM.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	(SAR342434, n=253; HUMALOG, n=252).				
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			Populations and trial designs (e.g., endpoints and durations) are acceptable for this 505(b)(2) application.
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			The mean change in HbA1c from baseline to week 26 was the primary endpoint agreed upon for pivotal studies in the pre-NDA meeting
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		x		Patients enrolled in both pivotal studies were primarily from the U.S. (EFC12619: 43.0% and EFC13403: 47.9%)
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
21.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	x			
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dosage (or dosage range) believed to be efficacious?	x			In study EFC12619, 252 patients received SAR342434 in the main 6-month period, and 252 patients in the 12-month period. In study EFC13403, 253 patients received SAR342434.
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
25.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the	x			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	new drug belongs?				
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			As requested by the FDA in the pre-NDA meeting, the Sponsor submitted: the full 12-month completed data of EFC12619.
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			The Sponsor has submitted a PREA Exemption Statement, which was agreed upon in the pre-NDA meeting (04/16/2016).
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm)?		x		SAR342434 has not been studied in pregnancy and lactation. The Sponsor makes reference to the information provided in sections 8.1 and 8.3 of the US Prescribing Information for Humalog.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	The Sponsor states that neither SAR342434 nor HUMALOG has a known profile of drug abuse, and we find this reasonable.
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		x		Patients enrolled in both pivotal studies were primarily from North America (EFC12619:43.0% and EFC13403:47.9%)
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
35.	Has the applicant submitted datasets in the format agreed to	x			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	previously by the Division?				
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
37.	Are all datasets to support the critical safety analyses available and complete?	x			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES__

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Sponsor should submit updated information to comply with the new PLLR section 8.3 (impairment of fertility)

Reviewing Medical Officer	Date
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Clinical Team Leader	Date
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SONIA D DOI
12/23/2016

WILLIAM H CHONG
12/23/2016