CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209196Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL MEMO

CLINICAL STUDIES

NDA #:	209196
Drug Name:	SAR342434
Applicant:	Sanofi
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Roberto C Crackel, PhD
Concurring Reviewers:	Yun Wang, PhD, Acting Team Leader
Medical Division:	Metabolism and Endocrinology
Clinical Team:	Sonia Doi, MD, Medical reviewer William Chong, MD, Clinical team leader
Project Manager:	Callie CappelLynch

The following memo was written as an addendum to the statistical review for SAR342434 signed on 7 July 2017. The main purpose for this memo is to correct a typo and two demographic tables in Section 3.2.3. The corrections are as follows:

- At the top of page 13, EFC 13404 should read EFC 13403.

- The table below shows the original table as it appears on page 13. The number of randomized patients on the Humalog arm reads N=254, however it should be N=252.

Table 5: Patient disposition – Randomized population

	SAR342434 (N=253) n (%)	Humalog (N=254) n (%)
Randomized and not treated	0	0
Randomized and treated	253 (100)	252 (100)
Completed the main 6-month treatment period	228 (90.1)	230 (91.3)
Did not complete the main 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 during the main 6-month period		
Adverse event	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 serious adverse event (SAE)	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)

- The table below shows the corrected table.

Table 5: Patient disposition – Randomized population

	SAR342434 (N=253) n (%)	Humalog (N=252) n (%)
Randomized and not treated	0	0
Randomized and treated	253 (100)	252 (100)
Completed the main 6-month treatment period	228 (90.1)	230 (91.3)
Did not complete the main 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 during the main 6-month period		
Adverse event	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 serious adverse event (SAE)	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)

- The table below shows the original table as it appears on page 14. The table displays information for study EFC12619 when it should have been information for study EFC13403.

Table 6: Demographics and patient characteristics at baseline

	SAR342434 (N=253)	Humalog (N=254)	All (N=507)
Age (years)			
Mean (SD)	43.3 (14.5)	42.6 (13.9)	43.0 (14.2)
Age group [n(%)]			
< 65	226 (89.3)	237 (93.3)	463 (91.3)
≥ 65 to < 75	25 (9.9)	16 (6.3)	41 (8.1)
≥ 75	2 (0.8)	1 (0.4)	3 (0.6)
Gender [n(%)]			
Male	149 (58.9)	153 (60.2)	302 (59.6)
Female	104 (41.1)	101 (39.8)	205 (40.4)
Race [n(%)]			
Number	253	254	507
Caucasian / White	202 (79.8)	214 (84.3)	416 (82.1)
Black	16 (6.3)	8 (3.1)	24 (4.7)
Asian / Oriental	32 (12.6)	31 (12.2)	63 (12.4)
Other	3 (1.2)	1 (0.4)	4 (0.8)
Region-approved Humalog [n(%)]			
US-approved Humalog	139 (54.9)	140 (55.1)	279 (55.0)
EU-approved Humalog	114 (45.1)	114 (44.9)	228 (45.0)
Baseline HbA1c (%)			
Mean (SD)	8.07 (0.79)	7.99 (0.64)	8.03 (0.72)
Randomization of screening HbA1c [n(%)]			
< 8	99 (39.1)	99 (39.0)	198 (39.1)
> 8	154 (60.9)	155 (61.0)	309 (60.9)
Duration of T1DM (years)			
Mean (SD)	19.53 (12.63)	18.57 (11.99)	19.05 (12.31)

- The table below correctly displays information for study EFC13403.

Table 6: Demographics and patient characteristics at baseline

	SAR342434 (N=253)	Humalog (N=252)	All (N=505)
Age (years)			
Mean (SD)	62.1 (9.4)	62.8 (8.9)	62.5 (9.1)
Age group [n(%)]			
< 65	144 (56.9)	137 (54.4)	281 (55.6)
≥ 65 to < 75	89 (35.2)	93 (36.9)	182 (36.0)
≥ 75	20 (7.9)	22 (8.7)	42 (8.3)
Gender [n(%)]			
Male	136 (53.8)	132 (52.4)	268 (53.1)
Female	117 (46.2)	120 (47.6)	237 (46.9)
Race [n(%)]			
Caucasian / White	228 (90.1)	218 (86.5)	446 (88.3)
Black	14 (5.5)	17 (6.7)	31 (6.1)
Asian / Oriental	11 (4.3)	16 (6.3)	27 (5.3)
Other	0	1 (0.4)	1 (0.2)
Region-approved Humalog [n(%)]			
US-approved Humalog	122 (48.2)	120 (47.6)	242 (47.9)
EU-approved Humalog	131 (51.8)	132 (52.4)	263 (52.1)
Baseline HbA1c (%)			
Mean (SD)	7.99 (0.87)	8.03 (0.91)	8.01 (0.89)
Randomization of screening HbA1c [n(%)]			
< 8	105 (41.5)	104 (41.3)	209 (41.4)
> 8	148 (58.5)	148 (58.7)	296 (58.6)
Duration of T2DM (years)			
Mean (SD)	16.60 (7.93)	17.52 (8.67)	17.06 (8.31)

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/s/

ROBERTO C CRACKEL
07/26/2017

YUN WANG
07/26/2017

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 209196
Supplement #:	
Drug Name:	SAR342434
Indication(s):	A rapid-acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus
Applicant:	Sanofi
Date(s):	Stamp: 11/1/16
Review Priority:	Standard Review due date: 7/28/17
Biometrics Division:	II
Statistical Reviewer:	Roberto C. Crackel, PhD
Concurring Reviewers:	Yun Wang, PhD, Acting Team leader
Medical Division:	Metabolism and Endocrinology Products
Clinical Team:	Sonia Doi, MD, Medical reviewer William Chong, MD, Clinical team leader
Project Manager:	Callie CappelLynch

Keywords: Missing data, multiple imputation, subgroup analyses

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Brief introduction

On November 1st 2016, Sanofi submitted a new NDA for SAR342434 (insulin lispro [rDNA origin]), 100 Units/mL) solution for injection. SAR342434 solution for injection is developed as a follow-on product to Humalog (100 units/mL), and is intended to have the same indication, dosage form, route of administrations and dosing regimen. The submission included 2 randomized, open-label, 2-arm, parallel-group, active-controlled, 26-week, multi-center studies. The objective of studies EFC 12619 (6-month) and EFC 13403 were to demonstrate non-inferiority (non-inferiority margin of 0.3%) of SAR342434 versus Humalog in patients with type 1 and type 2 diabetes, respectively, with respect to change in HbA1c.

1.2 Primary efficacy results

The estimated difference in change in HbA1c between SAR342434 and Humalog is 0.06 with 95% CI of (-0.084, 0.197) for Study EFC 12619 (6-month) and -0.07 with a 95% CI: (-0.215, 0.067) for Study EFC 13403 from the protocol specified analysis.

There was a small amount of missing data in both studies. To address any potential impact of missing values, as sensitivity analysis, the statistical reviewer performed a "return to baseline" analysis, i.e., for patients without a week-26 HbA1c measurement. Missing week-26 HbA1c measurements were imputed multiple times centered around the patient's baseline HbA1c value plus an error term. The estimated difference in change in HbA1c between SAR342434 and Humalog is 0.06 with 95% CI of (-0.086, 0.202) for Study EFC 12619 (6-month) and -0.06 with a 95% CI: (-0.209, 0.090) for Study EFC 13403 from the return-to-baseline analysis.

1.3 Conclusions and recommendation

The results of the protocol specified analysis support the hypothesis that patients on the SAR342434 arm experience a similar reduction in HbA1c compared to patients on the Humalog arm. The results of the "return-to-baseline" analysis are consistent with the protocol specified analysis. Studies EFC 12619 (6-month) and EFC 13403 support the conclusion that SAR342434 is non-inferior to Humalog in reducing HbA1c for adult patients with Type 1 or Type 2 diabetes mellitus also using Insulin Glargine.

2 INTRODUCTION

2.1 Overview

On November 1st 2016, Sanofi submitted a new NDA (209196) for SAR342434. The submission included 2 randomized (1:1), open-label, 2-arm, parallel-group, active-controlled, 26-week, multi-center studies that enrolled patients with diabetes mellitus.

Study EFC 12619 (6-month) is titled, "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".

Study EFC 13403 is titled, "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".

This report will summarize the statistical review of the sponsor's methods at the primary endpoint as well as the results of thereviewer's analyses in addressing missing data.

2.1.1 Class and Indication

SAR342434, insulin lispro [recombinant DNA origin], is a human insulin analog produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of Escherichia coli (b) (4) as the production organism.

SAR342434 solution for injection is being developed in the EU as a biosimilar and in the US as a follow-on product to Humalog (100 units/mL, NDA 020563, (b) (4) and is intended to have the same indications, dosage form, route of administrations and dosing regimen. The active ingredient of SAR342434 solution is insulin lispro and its primary amino acid sequence is the same as that for the active ingredient of Humalog.

The proposed indication will be a rapid-acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus

2.1.2 Specific Studies Reviewed

Two randomized clinical trials were reviewed. Studies EFC12619 and EFC13403 were randomized (1:1), open-label, 2-arm, parallel-group, active-controlled, 26-week, multi-center studies that enrolled patients with diabetes mellitus also using Lantus. The population for study EFC12619 was patients with T1DM and the population for study EFC13403 were patients with T2DM.

Study EFC12619: At screening, patients were to be diagnosed with T1DM for at least 12-months, have an HbA1c value between 7% and 10%, treated with Lantus as basal insulin and insulin lispro (Humalog / Liprolog) or insulin aspart (NovoLog / NovoRapid) as rapid-acting mealtime insulin for at least 6 months.

Study EFC13403: At screening, patients were to be diagnosed with T2DM for at least 12-months, have an HbA1c value between 6.5% and 10%, treated with Lantus as basal insulin and insulin lispro (Humalog / Liprolog) or insulin aspart (NovoLog / NovoRapid) as rapid-acting mealtime insulin for at least 6 months.

2.2 Data Sources

The data and final study report were submitted electronically as an eCTD submission. The submission can be accessed at the following link:

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The following documents were used to support this review.

Document
Study Report Body
Statistical analysis plan
Protocol

All results presented in this review were based on data derived from the submitted datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There were no issues concerning the submission of data sets and files.

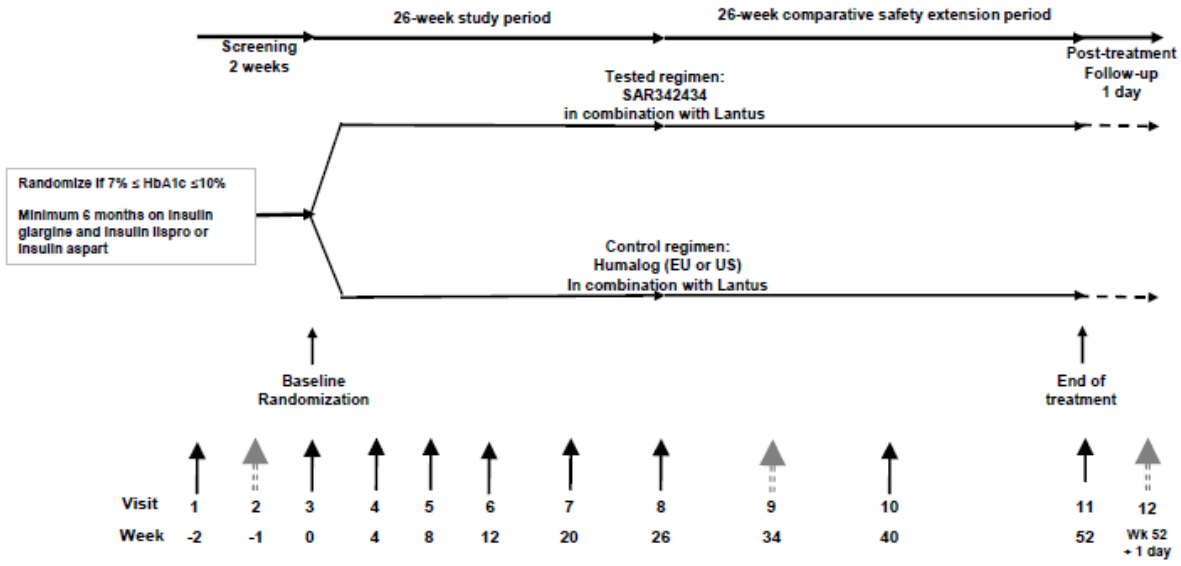
3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Studies EFC 12619 (6-month) and EFC 13403 were randomized, open-label, 2-arm, parallel-group, active-controlled, 26-week, multi-center studies to demonstrate non-inferiority of SAR342434 versus Humalog in patients with type 1 and type 2 diabetes, respectively (see figures below).

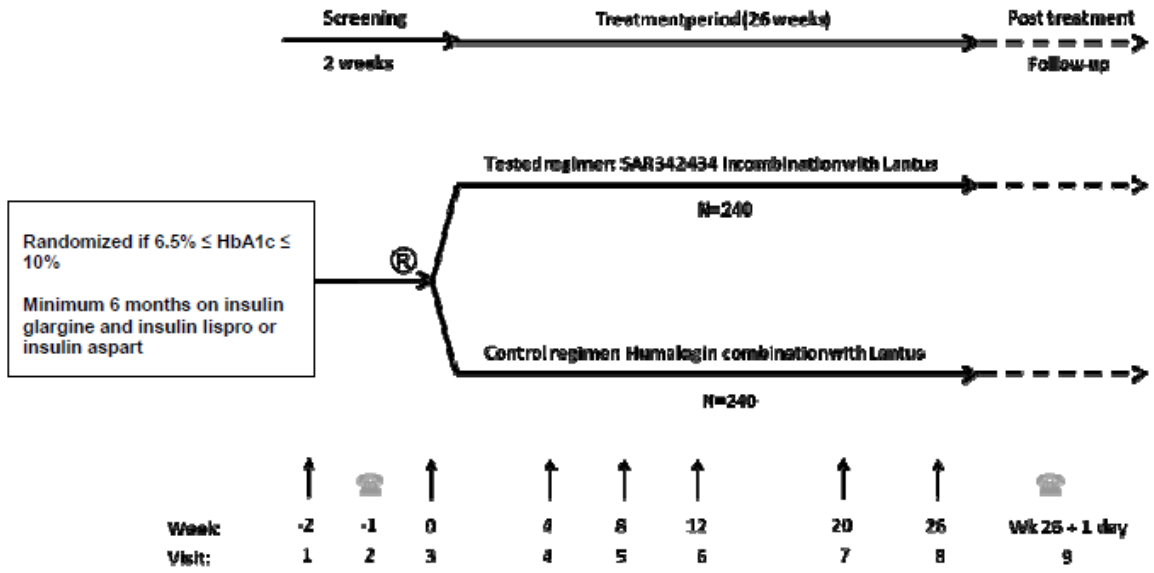
Study EFC 12619: A total of 507 patients were randomized in a 1:1 fashion to either SAR342434 or Humalog; 253 patients were randomized to SAR342434 and 254 to Humalog. Patients were stratified by screening HbA1c (< 8.0% or ≥ 8.0%), prior use of Humalog (Yes, No), and geographical region (Non-Japan, Japan). The trial spanned 89 centers in 8 countries. Landmark visits with respect to HbA1c and which were included in the primary efficacy analysis were baseline, week 12 and week 26.

Figure 1: Study design for EFC 12619



Study EFC 13403: A total of 505 patients were randomized in a 1:1 fashion to either SAR342434 or Humalog; 253 patients were randomized to SAR342434 and 252 to Humalog. Patients were stratified by screening HbA1c (< 8.0% or ≥ 8.0%) and prior use of Humalog (Yes, No). The trial spanned 103 centers in 12 countries. Landmark visits with respect to HbA1c and which were included in the primary efficacy analysis were baseline, week 12 and week 26.

Figure 2: Study design for EFC 13403



For studies EFC 12619 and EFC 13403, a sample size of 480 patients (240 patients per arm) was considered sufficient to ensure that the upper bound of the 2-sided 95% confidence interval would not exceed 0.3% with at least 90% power. A common standard deviation of 1.0% and true difference of 0% was assumed.

The primary efficacy endpoint was change in HbA1c from baseline to week 26 for both studies. There were no key secondary endpoints pre-specified for any labeling claim.

3.2.2 Statistical Methodologies

Protocol specified primary analyses

The study protocols specified that the change in HbA1c from baseline to week 26 would be analyzed using a mixed model for repeated measurements (MMRM). The model included fixed categorical effects of screening HbA1c (< 8.0% or screening ≥ 8.0%), prior use of Humalog (Yes, No), treatment group (SAR342434, Humalog), 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.

The protocol 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. Patients were analyzed in the treatment group to which they were randomized.

Reviewer's comment: The fixed categorical effect of geographical region (Japan, Non-Japan) was used in study EFC 12619 but not in EFC 13403.

Reviewer's comment: The MMRM only used patients who took one dose of study drug and had efficacy data from a post baseline landmark visit. In other words, randomized patients who withdrew before the next scheduled visit (week 12) are not included in the analysis. The statistical reviewer performed analyses based on all randomized patients regardless if any post baseline measurements were observed.

Statistical reviewer's primary analyses

To provide an unbiased comparison in all randomized patients regardless of adherence to treatment, patients should be followed after discontinuation to collect efficacy data. The use of such data in the primary analysis would be the preferred analysis.

However, collection of data after treatment discontinuation was minimal in both studies. In addition to the patients who did not contribute to the analysis, the pre-specified statistical methods rely on an assumption that HbA1c changes for those with missing data would be similar to those on the same treatment arm with complete data. This is likely not a reasonable assumption in that any effect of SAR342434 or Humalog may fade shortly after treatment discontinuation. Since these were active-controlled studies, we cannot partition and "wash-out" the effect of therapy. One way to compare the effect of SAR342434 with Humalog in all randomized patients regardless of adherence to treatment is to perform a multiple imputation analysis which models patients with missing week 26 measurements similar to their baseline

values. We refer to this analysis as a "return-to-baseline" analysis. Specifically, all patients, whether on SAR342434 or Humalog with missing week 26 HbA1c measurements will have their values imputed by drawing from a normal distribution centered around their baseline measurement with some random variation.

One hundred data sets were generated and an ANCOVA with the protocol specified factors and covariates was run on each data set and point estimates and standard errors were computed and the results combined to yield a multiple imputation point estimate and standard error (see appendix).

Reviewer's note: Besides the "return-to-baseline" analyses, the statistical reviewer also performed 3 additional analyses (see appendix) as further sensitivity analyses.

Protocol specified control of type-I error
A hierarchical step-down testing procedure described by Hochberg and Tamhane was applied to test the non-inferiority of Humalog over SAR342434 only if the non-inferiority of SAR342434 over Humalog (primary comparison) was demonstrated. No multiplicity adjustment was made for secondary endpoints as no statistical testing was performed.

Protocol specified analysis of secondary efficacy endpoints
Though not part of a formal testing scheme (and it appears that the sponsor will not seek a labelling claim), the sponsor performed an analysis that compares the difference in the proportion of patients that achieved an HbA1c measurement of less than 7% at week 26. A logistic regression was run where patients without week 26 data were considered as failures. The model included the treatment parameter (SAR342434, Humalog) and the stratification factors of screening HbA1c (< 8.0% or screening ≥ 8.0%), prior use of Humalog (Yes, No) and geographical region (Japan, Non-Japan) (study EFC 12619 only)

Reviewer's note: As a comparison, the statistical reviewer computed the proportion of responders in each of the 100 data sets in the "return-to-baseline" analysis and then averaged out these proportions.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Tables 1-6 below describe the analysis populations, patient disposition, demographics and patient characteristics at baseline.

Study EFC 12619: The percentage of patients who completed the 26-week treatment phase was slightly higher in the Humalog arm than in the SAR 342434 arm (95.7% vs. 93.7%,

respectively). The most common reason why patients discontinued treatment in both arms was due to "other" (12 on SAR 342434 and 7 on Humalog). There was 1 patient on SAR 342434 who discontinued due to an adverse event and 0 on Humalog. It is worth noting that 4 patients on Humalog discontinued treatment due to poor compliance to protocol while there were no patients on SAR 342534.

Study EFC 13403: The percentage of patients who completed the 26-week treatment phase was almost even both arms (91.3% for Humalog vs. 90.1% for SAR 342434). The most common reason why patients discontinued treatment in both arms was due to "other" (12 on each arm). Further, there were 7 patients on each arm that discontinued due to an adverse event.

Demographic and baseline characteristics are similar in both the SAR 342434 and Humalog arms for both studies.

EFC 12619:

Table 1: Analysis populations

	SAR342434 n (%)	Humalog n (%)	All n (%)
Randomized population	253 (100)	254 (100)	507 (100)
Efficacy population (ITT)	253 (100)	254 (100)	507 (100)
Safety population	252 (99.6)	254 (100)	506 (99.8)
Anti-insulin anitbody population	247 (97.6)	252 (99.6)	499 (98.4)

Table 2: Patient disposition – Randomized population

	SAR342434 (N=253) n (%)	Humalog (N=254) n (%)
Randomized and not treated	1 (0.4)	0
Randomized and treated	252 (99.6)	254 (100)
Completed the main 6-month treatment period	237 (93.7)	243 (95.7)
Did not complete the main 6-month treatment period	15 (5.9)	11 (4.3)
Subject's decision for treatment discontinuation	12 (4.7)	10 (3.9)
Reason for treatment discontinuation during the main 6-month period		
Adverse event	1 (0.4)	0
Lack of efficacy	1 (0.4)	0
Poor compliance to protocol	0	4 (1.6)
Hypoglycemia not reported as serious adverse event (SAE)	1 (0.4)	0
Other reasons	12 (4.7)	7 (2.8)
Status at last study contact for patients who prematurely discontinued the study during the main 6-month period		
Alive	12 (4.7)	8 (3.1)
Dead	1 (0.4)	0

Table 3: Demographics and patient characteristics at baseline

	SAR342434 (N=253)	Humalog (N=254)	All (N=507)
Age (years)			
Mean (SD)	43.3 (14.5)	42.6 (13.9)	43.0 (14.2)
Age group [n(%)]			
< 65	226 (89.3)	237 (93.3)	463 (91.3)
≥ 65 to < 75	25 (9.9)	16 (6.3)	41 (8.1)
≥ 75	2 (0.8)	1 (0.4)	3 (0.6)
Gender [n(%)]			
Male	149 (58.9)	153 (60.2)	302 (59.6)
Female	104 (41.1)	101 (39.8)	205 (40.4)
Race [n(%)]			
Number	253	254	507
Caucasian / White	202 (79.8)	214 (84.3)	416 (82.1)
Black	16 (6.3)	8 (3.1)	24 (4.7)
Asian / Oriental	32 (12.6)	31 (12.2)	63 (12.4)
Other	3 (1.2)	1 (0.4)	4 (0.8)
Region-approved Humalog [n(%)]			
US-approved Humalog	139 (54.9)	140 (55.1)	279 (55.0)
EU-approved Humalog	114 (45.1)	114 (44.9)	228 (45.0)
Baseline HbA1c (%)			
Mean (SD)	8.07 (0.79)	7.99 (0.64)	8.03 (0.72)
Randomization of screening HbA1c [n(%)]			
< 8	99 (39.1)	99 (39.0)	198 (39.1)
> 8	154 (60.9)	155 (61.0)	309 (60.9)
Duration of T1DM (years)			
Mean (SD)	19.53 (12.63)	18.57 (11.99)	19.05 (12.31)

EFC 13404:

Table 4: Analysis populations

	SAR342434 n (%)	Humalog n (%)	All n (%)
Randomized population	253 (100)	252 (100)	505 (100)
Efficacy population (ITT)	253 (100)	252 (100)	505 (100)
Safety population	253 (100)	252 (100)	505 (100)
Anti-insulin anitbody population	245 (96.8)	248 (98.4)	493 (97.6)

Table 5: Patient disposition – Randomized population

	SAR342434 (N=253) n (%)	Humalog (N=254) n (%)
Randomized and not treated	0	0
Randomized and treated	253 (100)	252 (100)
Completed the main 6-month treatment period	228 (90.1)	230 (91.3)
Did not complete the main 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 during the main 6-month period		
Adverse event	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 serious adverse event (SAE)	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)

Table 6: Demographics and patient characteristics at baseline

	SAR342434 (N=253)	Humalog (N=254)	All (N=507)
Age (years)			
Mean (SD)	43.3 (14.5)	42.6 (13.9)	43.0 (14.2)
Age group [n(%)]			
< 65	226 (89.3)	237 (93.3)	463 (91.3)
≥ 65 to < 75	25 (9.9)	16 (6.3)	41 (8.1)
≥ 75	2 (0.8)	1 (0.4)	3 (0.6)
Gender [n(%)]			
Male	149 (58.9)	153 (60.2)	302 (59.6)
Female	104 (41.1)	101 (39.8)	205 (40.4)
Race [n(%)]			
Number	253	254	507
Caucasian / White	202 (79.8)	214 (84.3)	416 (82.1)
Black	16 (6.3)	8 (3.1)	24 (4.7)
Asian / Oriental	32 (12.6)	31 (12.2)	63 (12.4)
Other	3 (1.2)	1 (0.4)	4 (0.8)
Region-approved Humalog [n(%)]			
US-approved Humalog	139 (54.9)	140 (55.1)	279 (55.0)
EU-approved Humalog	114 (45.1)	114 (44.9)	228 (45.0)
Baseline HbA1c (%)			
Mean (SD)	8.07 (0.79)	7.99 (0.64)	8.03 (0.72)
Randomization of screening HbA1c [n(%)]			
< 8	99 (39.1)	99 (39.0)	198 (39.1)
> 8	154 (60.9)	155 (61.0)	309 (60.9)
Duration of T1DM (years)			
Mean (SD)	19.53 (12.63)	18.57 (11.99)	19.05 (12.31)

3.2.4 Results and Conclusions

Protocol specified and reviewer's analysis of primary endpoint:

Based on the protocol specified analysis, the mean HbA1c reduction at week 26 was similar between SAR342434 and Humalog and non-inferiority was established (see Table 7 and 8 below) for studies 12619 and 13403.

Study 12619: The protocol specified estimated adjusted mean change from baseline for SAR342434 and Humalog was -0.42% and -0.47%, respectively, while the estimated difference was 0.06%. The estimated adjusted mean change from baseline based off the "return-to-baseline" analysis for SAR342434 and Humalog was -0.40% and -0.46%, respectively, and the estimated difference was 0.06%.Since the upper bound for the 95% C.I. for the difference does not exceed

0.3 and the lower bound does not exceed -0.3 (for the sponsor's and the return-to-baseline analysis), statistical evidence for non-inferiority is established.

Table 7: Study EFC 12619: Pre-specified primary and reviewer's sensitivity analysis of HbA1c at week 26 (ITT)

Sponsors analysis			***Reviewer's analysis***		
	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

Study 13403: The protocol specified estimated adjusted mean change from baseline for SAR342434 and Humalog was -0.92% and -0.85%, respectively, while the estimated difference was -0.07%. The estimated adjusted mean change from baseline based off the "return-to-baseline" analysis for SAR342434 and Humalog was -0.86% and -0.80%, respectively, and the estimated difference was -0.06%. Since the upper bound for the 95% C.I. for the difference does not exceed 0.3 and the lower bound does not exceed -0.3 (for the sponsor's and the return-to-baseline analysis), statistical evidence for non-inferiority is established.

Table 8: Study EFC 13403: Pre-specified primary and reviewer's sensitivity analysis of HbA1c at week 26 (ITT)

Sponsors analysis			***Reviewer's analysis***		
	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

Protocol specified and reviewer's analysis of proportion of patients with HbA1c < 7%

Study 12619: The estimated (unadjusted) proportion of patients achieving HbA1c less than 7% at week 26 under the sponsor's analysis was 22.5% and 21.7% for the SAR342434 and Humalog groups, respectively. The estimated odds ratio when comparing SAR342434 versus Humalog was estimated to be 1.06 (see table 9 below).

The **reviewer's** analysis of averaging the proportion of responders across the multiple imputed data sets was 23.5% and 22.2% for SAR 342434 and Humalog, respectively.

Table 9: Study 12619: 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.

Study 13403: The estimated (unadjusted) proportion of patients achieving HbA1c less than 7% at week 26 under the sponsor's analysis was 42.3% and 40.5% for the SAR342434 and Humalog groups, respectively. The estimated odds ratio when comparing SAR342434 versus Humalog was estimated to be 1.08 (see table 10 below).

The reviewer's analysis of averaging the proportion of responders across the multiple imputed data sets was 44.1% and 42.4% for SAR 342434 and Humalog, respectively.

Table 10: Study 13403: 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 MI 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.

Patient level residual standard deviation

Study EFC 12619: The estimated patient level residual variance and standard deviation from the sponsor's pre-specified analysis (MMRM) is 0.6227 and 0.7891, respectively. The average of the patient level residual variance and standard deviation from the "return-to-baseline" analysis is 0.6475 and 0.8047, respectively.

Study EFC 13403: The estimated patient level residual variance and standard deviation from the sponsor's pre-specified analysis (MMRM) is 0.6067 and 0.7789, respectively. The average of the patient level residual variance and standard deviation from the "return-to-baseline" analysis is 0.6796 and 0.8244, respectively.

Reviewer's note: The assumed standard deviation of 1.0% in the sample size calculation was overestimated for both studies.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section summarizes results from the analysis of the primary efficacy endpoint within subgroup levels. The subgroups explored by the reviewer are:

- Sex (females; males)
- Age (< 65 years; ≥ 65 years)
- Race (white; non-white)
- U.S. approved Humalog
- Continuous baseline HbA1c

4.1 Subgroup analyses results

Sponsor's analysis

The sponsor performed subgroup analyses based on race, sex, age, ethnicity, region approved Humalog, prior use of Humalog, geographical regions, duration of diabetes, baseline BMI, baseline eGFR, screening HbA1c, and concomitant use of SU/glinides.

Study EFC 12619 (6-month): No significant interactions (α=0.10) were found

Study EFC 13403: Significant interactions (α=0.10) were found for screening HbA1c (p=0.0458) and concomitant use of SU/glinides (p=0.0393). The model did not converge when testing for race.

Reviewer's analysis

Tables 11 and 12 shows the subgroup analyses performed by the reviewer in the following groups: sex, age, race, U.S. approved Humalog, and continuous baseline HbA1c. The model used in the analyses is the reviewer's "return-to-baseline" analyses (see Table 11 below). Interactions of the subgrouping variable with treatment were tested. A significant interaction was found for continuous baseline HbA1c (p=0.069) for study EFC 12619 at α=0.10 (to maintain consistency with what the sponsor used).

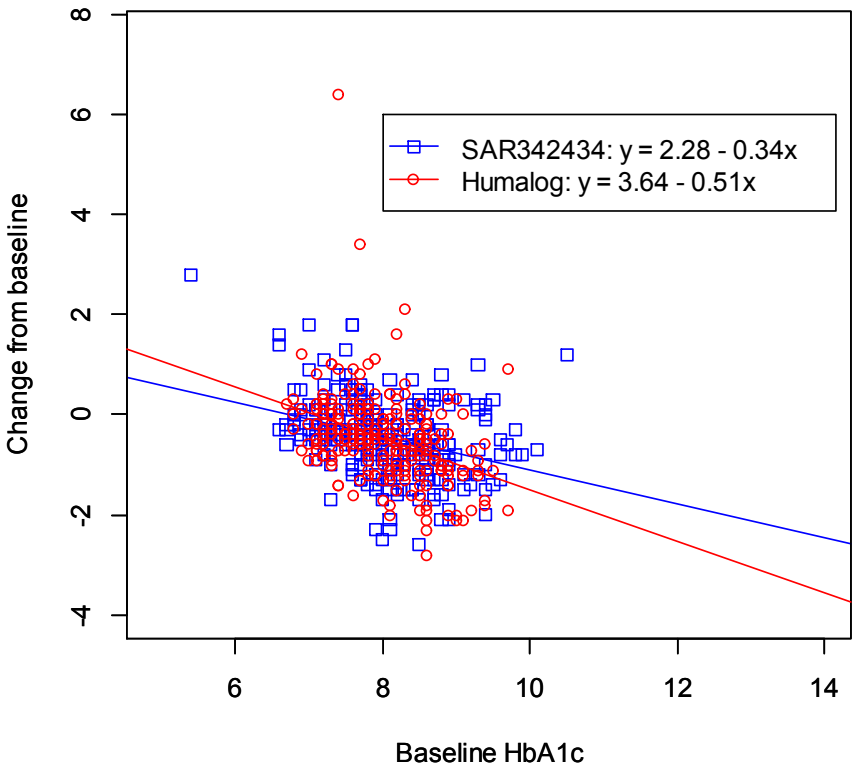
Table 11: EFC 12619: Reviewer's subgroup analysis of the primary efficacy endpoint, HbA1c

Sex				
	Males		**Females**	
	SAR 342434	**Humalog**	**SAR 342434**	**Humalog**
N	149	153	104	101
Adjusted mean change from baseline	-0.45	-0.44	-0.34	-0.5
SAR 342434 - Humalog	-0.01		0.16	
95% C.I.	(-0.19, 0.18)		(-0.07, 0.38)	
Test for interaction	p-value=0.269			
Age				
	> 65		**< 65**	
	SAR 342434	**Humalog**	**SAR 342434**	**Humalog**
N	27	17	226	237
Adjusted mean change from baseline	-0.6	-0.48	-0.38	-0.46
SAR 342434 - Humalog	-0.12		0.08	
95% C.I.	(-0.63, 0.39)		(-0.07, 0.23)	
Test for interaction	p-value=0.461			
Race				
	White		**Non-White**	
	SAR 342434	**Humalog**	**SAR 342434**	**Humalog**
N	202	214	51	40
Adjusted mean change from baseline	-0.46	-0.5	-0.18	-0.28
SAR 342434 - Humalog	0.04		0.1	
95% C.I.	(-0.12, 0.20)		(-0.24, 0.44)	
Test for interaction	p-value=0.748			
Region approved Humalog				
	U.S.		**Europe**	
	SAR 342434	**Humalog**	**SAR 342434**	**Humalog**
N	139	140	114	114
Adjusted mean change from baseline	-0.39	-0.39	-0.42	-0.55
SAR 342434 - Humalog	-0.01		0.14	
95% C.I.	(-0.20, 0.19)		(-0.08, 0.35)	
Test for interaction	p-value=0.341			
Baseline HbA1c				
N	507			
Test for interaction	p-value=0.069			

Table 12: EFC 13403: Reviewer's subgroup analysis of the primary efficacy endpoint, HbA1c

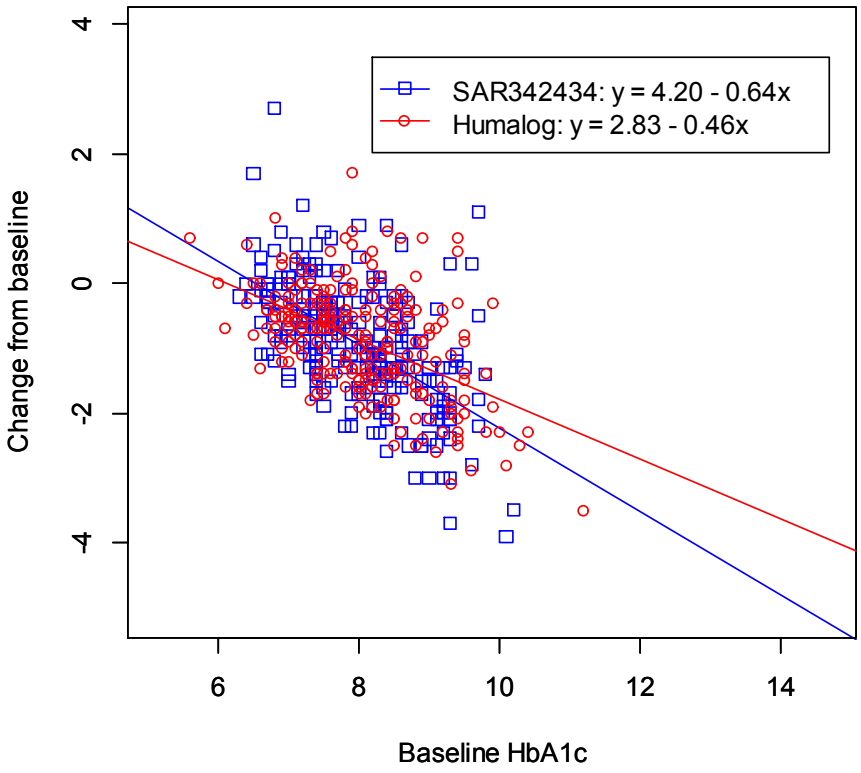
Sex				
	Males		**Females**	
	SAR 342434	**Humalog**	**SAR 342434**	**Humalog**
N	136	132	117	120
Adjusted mean change from baseline	-0.85	-0.78	-0.87	-0.82
SAR 342434 - Humalog	-0.07		-0.05	
95% C.I.	(-0.27, 0.14)		(-0.27, 0.17)	
Test for interaction	(p-value=0.929)			
Age				
	> 65		**< 65**	
	SAR 342434	**Humalog**	**SAR 342434**	**Humalog**
N	109	115	144	137
Adjusted mean change from baseline	-0.84	-0.84	-0.87	-0.77
SAR 342434 - Humalog	-0.01		-0.1	
95% C.I.	(-0.23, 0.22)		(-0.31, 0.10)	
Test for interaction	(p-value=0.533)			
Race				
	White		**Non-White**	
	SAR 342434	**Humalog**	**SAR 342434**	**Humalog**
N	228	218	25	34
Adjusted mean change from baseline	-0.89	-0.8	-0.61	-0.82
SAR 342434 - Humalog	-0.09		0.21	
95% C.I.	(-0.25, 0.07)		(-0.26, 0.67)	
Test for interaction	(p-value=0.235)			
Region approved Humalog				
	U.S.		**Europe**	
	SAR 342434	**Humalog**	**SAR 342434**	**Humalog**
N	122	120	131	132
Adjusted mean change from baseline	-0.82	-0.81	-0.89	-0.79
SAR 342434 - Humalog	-0.01		-0.11	
95% C.I.	(-0.23, 0.21)		(-0.31, 0.10)	
Test for interaction	(p-value=0.538)			
Baseline HbA1c				
N	505			
Test for interaction	(p-value=0.133)			

Figure 3: Study 12619: Scatter plots and regression lines



Scatter plots for SAR342434 and Humalog among the completers set
Regression lines computed using change from baseline as the dependent variable and baseline HbA1c as the independent variable

Figure 4: EFC 13403 Scatter plots and regression lines



Scatter plots for SAR342434 and Humalog among the completers set
Regression lines computed using change from baseline as the dependent variable and baseline HbA1c as the independent variable

Figures 3 and 4 are scatter plots of baseline HbA1c versus change from baseline using the completers for the SAR342434 and Humalog groups in studies EFC 12619 and EFC 13403, respectively. Regression lines were computed and superimposed over the scatter points.

For study EFC 12619, the difference in slopes is -0.17%, which means that for each increase of 1% in baseline HbA1c, the mean change in HbA1c from baseline for Humalog decreases 0.17% more than the mean change in HbA1c from baseline for SAR342434. For example, consider the following table:

Baseline value	Average change from baseline at week 26		
	SAR342434	Humalog	Humalog - SAR342434
7	-0.10	0.07	0.17
8	-0.44	-0.44	0
9	-0.78	-0.95	-0.17

For study EFC 13403, the difference in slopes is -0.18%, which means that for each increase of 1% in baseline HbA1c, the mean change in HbA1c from baseline for SAR342434 decreases 0.18% more than the mean change in HbA1c from baseline for Humalog. For example, consider the following table:

Baseline value	Average change from baseline at week 26		
	SAR342434	Humalog	SAR342434 - Humalog
7	-0.28	-0.39	0.11
8	-0.92	-0.85	-0.07
9	-1.56	-1.31	-0.25

5 SUMMARY AND CONCLUSIONS

5.1 Collective Evidence

On November 1st 2016, Sanofi submitted a new NDA for SAR342434 (insulin lispro [rDNA origin]), 100 Units/mL) solution for injection. The submission included 2 randomized, open-label, 2-arm, parallel-group, active-controlled, 26-week, multi-center studies. The objective of studies EFC 12619 (6-month) and EFC 13403 were to demonstrate non-inferiority (non-inferiority margin of 0.3%) of SAR342434 versus Humalog in patients with type 1 and type 2 diabetes, respectively, with respect to change in HbA1c.

5.2 Statistical Issues

The amount of missing data was relatively minimal. Below summarizes the amount of patients who discontinued in each treatment arm:

Study EFC 12619 (6-month):

	Randomized	Missing week 26 data	% Missing week 26 data
SAR342434	253	13	5.1
Humalog	254	8	3.1
Total	507	21	4.1

Study EFC 13403:

	Randomized	Missing week 26 data	% Missing week 26 data
SAR342434	253	22	8.7
Humalog	252	20	7.9
Total	505	42	8.3

- The protocol specified analysis was a mixed model repeated measurement (MMRM). The MMRM assumes that patients who discontinue therapy will behave similarly to those who continue. This is a strong and unverifiable assumption. One way of addressing missing data was to model a "return to baseline" for patients who discontinued therapy. This analysis

assumes that patients with missing week 26 HbA1c measurements would have had measurements similar to their baseline value. There was little difference in the results of my analysis compared to the protocol specified analysis. Therefore, missing data did not alter my conclusion that SAR342434 is non-inferior to Humalog in reducing HbA1c.

- The MMRM did not include the 11 patients who did not have a post-baseline measurement in the analysis in study EFC 12619 and the 20 patients who did not have a post-baseline measurement in study EFC 13403.

5.3 Primary efficacy results and conclusions:

The results of the protocol specified analysis support the hypothesis that patients on the SAR342434 arm experience a similar reduction in HbA1c compared to Humalog. There was a relatively small amount of missing data, however to address any impact of it, as sensitivity analysis, I performed an analysis that modeled a "return to baseline" for all patients without a week-26 HbA1c measurement. In addition, other sensitivity analyses were performed to further test robustness. The results of the "return-to-baseline" analysis did not change the conclusion in either study and so we are confident that even in the presence of missing data, SAR342434 is non-inferior to Humalog in reducing HbA1c. The results are summarized as follows:

Study EFC 12619 (6-month):

From the protocol specified analysis, the change in HbA1c is:

- 0.06 with a 95% CI: (-0.084 , 0.197)

From the "Return to Baseline" analysis, the change in HbA1c is:

- 0.06 with a 95% CI: (-0.086 , 0.202)

Study EFC 13403:

From the protocol specified analysis, the change in HbA1c is:

- -0.07 with a 95% CI: (-0.215 , 0.067)

From the "Return to Baseline" analysis, the change in HbA1c is:

- -0.060 with a 95% CI: (-0.209 , 0.090)

5.4 Labeling Recommendation

Since we are concerned with an analysis that utilizes all randomized patients, we are proposing that the estimated effect size in table 3 of section 14, should not report (b) (4) (b) (4) but rather the results of thereviewer's "return-to-baseline" analysis with footnotes detailing the method used.

The tables below are the sponsor's proposed table of results for the product label and the changes recommended by the reviewer for each study.

EFC 12619:

Table 13: Sponsor's recommended table

(b) (4)

Table 14: Reviewer's recommended table

(b) (4)

EFC 13403:

Table 15: Sponsor's recommended table

Table 16: Reviewer's recommended table

6 APPENDIX

Below describes the "return-to-baseline" analysis (Analyses 1) used in this review. As further sensitivity analyses, we modified Analyses 1 by adding a penalty of 0.3 (the non-inferiority margin) to the SAR342434 arm (Analyses 2). Analyses 3 returns patients with missing data back to baseline for those on SAR342434 but treats patients with missing data as missing at random for those on Humalog. Analyses 4 is similar to Analyses 3 but adds a penalty of 0.3 to patients on SAR342434.

Study design: HbA1c measurements were taken at baseline, week 12, and week 26

Analyses 1:

All available (on or off treatment) data for patients should be used.

For patients (SAR342434 and Humalog) with missing week 26 data, impute the week 26 measurement as follows:

$$Week\ 26 \sim N(Baseline, variance)$$

In regards to the $variance$, we suggest using $s^2\left(1+\frac{1}{n_c}\right)$ where s^2 is the pooled (SAR342434 and Humalog) variance of HbA1c week 28 measurements among completers, and n_c is the number of completers from both arms, but feel free to propose a different variance.

Analyses 2:

Perform Analyses 1, but for patients on SAR342434, impute the week 26 measurement as follows:

$$Week\ 26 \sim N(Baseline, variance) \ + \ 0.3$$

Analyses 3:

All available (on or off treatment) data for patients should be used.

For patients on SAR342434, impute the week 26 measurement as follows:

(b) (4)

Where $Baseline$ and $variance$ is the same as in Analyses 1 and 2

For patients on Humalog, impute week 26 measurements using a model that assumes MAR (e.g., a monotone regression pattern). Or perhaps fit 2 regression models using Humalog completers and impute as follows:

For a Humalog patient with only a baseline value, impute:

(b) (4)

Where n_{HC} is the number of Humalog completers.

For a Humalog patient with baseline and week 12 values, impute:

(b) (4)

Analyses 4:

Perform Analyses 3, but for patients on SAR342434, impute the week 26 measurement as follows:

(b) (4)

For each analysis, 100 data sets were generated, where an ANCOVA with the sponsor's pre-specified factors and covariates was run. Rubin's rule was then applied to obtain the LS Means and difference in LS Means estimates (with standard errors and confidence intervals).

Below are the results for each analysis:

EFC12619:

	LS Difference Estimate	C.I
Return to Baseline (Analyses 1)	0.058 (0.073)	(-0.086 , 0.202)
Return to Baseline with Penalty to SAR (Analyses 2)	0.072 (0.074)	(-0.073 , 0.218)
Return to Baseline and MAR (Analyses 3)	0.069 (0.073)	(-0.074 , 0.212)
Return to Baseline and MAR with Penalty to SAR (Analyses 4)	0.085 (0.074)	(-0.059 , 0.229)
Sponsor's MMRM	0.060 (0.071)	(-0.084 , 0.197)

	SAR	Humalog	
	LS Estimate	LS Estimate	LS Difference Estimate
Return to Baseline (Analyses 1)	-0.403 (0.052)	-0.461 (0.052)	0.058
Return to Baseline with Penalty to SAR (Analyses 2)	-0.390 (0.053)	-0.462 (0.052)	0.072
Return to Baseline and MAR (Analyses 3)	-0.404 (0.052)	-0.473 (0.051)	0.069
Return to Baseline and MAR with Penalty to SAR (Analyses 4)	-0.388 (0.053)	-0.472 (0.051)	0.085
Sponsor's MMRM	-0.420 (0.051)	-0.470 (0.050)	0.060

EFC13403:

	LS Difference Estimate	C.I
Return to Baseline (Analyses 1)	-0.060 (0.076)	(-0.209 , 0.090)
Return to Baseline with Penalty to SAR (Analyses 2)	-0.035 (0.077)	(-0.186 , 0.116)
Return to Baseline and MAR (Analyses 3)	-0.009 (0.074)	(-0.154 , 0.137)
Return to Baseline and MAR with Penalty to SAR (Analyses 4)	0.017 (0.076)	(-0.132 , 0.165)
Sponsor's MMRM	-0.070 (0.072)	(-0.215 , 0.067)

	SAR	Humalog	
	LS Estimate	LS Estimate	LS Difference Estimate
Return to Baseline (Analyses 1)	-0.859 (0.055)	-0.799 (0.054)	-0.060
Return to Baseline with Penalty to SAR (Analyses 2)	-0.836 (0.055)	-0.801 (0.055)	-0.035
Return to Baseline and MAR (Analyses 3)	-0.859 (0.053)	-0.850 (0.052)	-0.009
Return to Baseline and MAR with Penalty to SAR (Analyses 4)	-0.835 (0.054)	-0.851 (0.053)	0.017
Sponsor's MMRM	-0.920 (0.051)	-0.850 (0.051)	-0.070

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/s/

ROBERTO C CRACKEL
07/24/2017

YUN WANG
07/24/2017

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 209196
Related IND #:	120511
Product Name:	TRADENAME (insulin lispro) 100 unit per mL (U-100) is available as: 10 mL vials and 3 mL TRADENAME SoloStar prefilled pens
Indication(s):	Rapid-acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus
Applicant:	Sanofi
Dates:	Date submitted 11/1/16 Primary reviews due 7/28/17 PDUFA date 9/1/17
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Dr. Roberto Crackel
Concurring Reviewers:	Dr. Mark Rothmann
Medical Division:	ODEII, Diabetes
Clinical Team:	Sonia Doi William Chong
Project Manager:	Callie Cappel-Lynch

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
EFC12619	MC, R, OL, PG, AC trial (26 wks)	SAR342434/ 253 Humalog/ 254	Primary: Change in HbA1c Key Secondary:	
EFC13403	MC, R, OL, PG, AC (26 wks)	SAR342434/ 253 Humalog / 252	Primary: Change in HbA1c Key Secondary:	

* MC: multi-center, R: randomized, OL: open-label, PG: parallel group, AC: active controlled

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	**Designs are appropriate**
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	**Yes**
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	**N/A**
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	**No novel statistical methodology has been proposed**
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	**Yes**

3. Electronic Data Assessment

[*Note to Reviewer: The following section is meant to document the details as they pertain to the electronic data submitted in the application.*]

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	Study EFC12619: Application 209196 - Sequence 0000 - adhba1c Study EFC13403: Application 209196 - Sequence 0000 - adhba1c
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	ADaM
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	Adhba1c
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request	No

Content Parameter	Response/Comments
to be inspected and the rationale.	
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

[*Note to Reviewer: This information is needed or essential to be able to review the application.*]

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	X			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	X			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?

Yes

5. Comments to be Conveyed to the Applicant

No comments to be conveyed to the applicant at this time

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/s/

ROBERTO C CRACKEL
01/05/2017

MARK D ROTHMANN
01/05/2017
concur