CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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 REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 206538
Drug Name:	HOE901-U300 (insulin glargine 300 U/mL)
Indication(s):	To improve glycemic control in adults with diabetes mellitus
Applicant:	Sanofi-Aventis
Date(s):	Stamp date: 4/25/2014
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
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Keywords:	NDA reviews, clinical studies, mixed models, endpoint analysis/LOCF

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AHA:	antihyperglycemic agents
ANCOVA:	analysis of covariance
BMI:	body mass index
CDC:	Centers for Disease Control and Prevention
CGM:	continuous glucose monitoring
CI:	confidence interval
CMH:	Cochran-Mantel-Haenszel
CSR:	clinical study report
FPG:	fasting plasma glucose
HbA1c:	glycated hemoglobin A1C
IMP:	investigational medicinal product
IQR:	interquartile range
LOCF:	Last Observation Carried Forward
mITT:	Modified intention-to-treat
MMRM:	Mixed Model with Repeated Measurements
OAD:	oral antihyperglycemic drugs
SAP:	statistical analysis plan
SD:	standard deviation
SE:	standard error
SMPG:	self-monitored plasma glucose
T1DM:	type 1 diabetes mellitus
T2DM:	type 2 diabetes mellitus

1 EXECUTIVE SUMMARY

HOE901-U300 (insulin glargine 300 U/mL) is a human insulin analog product. The proposed indication of HOE901-U300 is improvement in glycemic control in adults with diabetes mellitus. It is supplied as a solution for injection. HOE901-U300 (proposed trade name: Toujeo® SoloStar®) currently is not approved in any country.

In this application, Sanofi-Avantis submitted a report assessing the glucose-lowering efficacy and the associated risk of hypoglycemia of HOE901-U300 when compared to Lantus (insulin glargine 100 U/mL) in the treatment of adult patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM). (b) (4)

Four multicenter, open-label, active controlled Phase 3 studies and two sub-studies were reviewed as a part of this submission. All main trials were randomized, multi-center trials in patients with diabetes mellitus. Three of those main studies were in patients with Type 2 diabetes (T2DM) and one study in Type 1 diabetes (T1DM). The primary endpoint in all four main studies was change from baseline to Month 6 in HbA1c. The main secondary endpoint was occurrence of nocturnal hypoglycemia. Additional trial extensions (sub-studies) were designed to explore the efficacy of HOE901-U300 when adaptable versus fixed dosing intervals were examined. The finding of non-inferiority of HOE901-U300 was consistent across all four main studies.

Statistical Issues and Findings

The shortcomings of this submission include:

1. The sponsor did not provide any clarification or reasoning for the choice of the non-inferiority margin. The choice of the noninferiority margin is an important part of study design and it is not clear whether the margin of 0.4% of HbA1c would be appropriate for the studies in T2DM as well as in the study in T1DM.

2. Difficulty in interpretation of analysis of adaptable versus fixed dosing intervals.

3. Handling of the missing data.

4. A problematic definition of nocturnal hypoglycemia (which could potentially result in introduction of exclusion bias and inaccurate assessment of the events due to the fact that the patient might have been asleep).

5. The results for individual races other than white are not robust because the small number of non-white subjects. The racial distribution of patients with Type 2 diabetes in the US includes two to five times the percentage of Black or African American patients that were in the studies.

6. Selection of study population that does not adequately represent US population of subjects with diabetes mellitus

My recommendations regarding these shortcomings are as follows:

1. After careful examination of submissions involving insulin-type products (such as Insulin detemir), I noticed that the noninferiority margin of 0.4% of HbA1c is consistent with previously approved submissions. My review of the statistical analysis found that HOE901-U300 is not inferior when compared to Lantus and therefore effective in treatment of diabetes mellitus, assuming the noninferiority margin of 0.4. Based on precedents, this meets the requirement, although justification of noninferiority margins should be provided in submissions.
2. (b) (4)
3. Regarding missing data, the sponsor suggested to use MMRM analysis to handle missing data. In my view, MMRM is not the appropriate tool for examination of missing data impact. The concern is mitigated by the fact that LOCF and MMRM gave similar results to each other in all four studies. In my view, LOCF is even less appropriate than MMRM. However, the fact that two different approaches yielded similar results coupled with the fact that the amount of missing data was not overwhelmingly large allows me to conclude that the handling of missing data probably did not have a large impact on results and therefore should not be a primary decisive factor in this application.
4. Regarding the definition of nocturnal hypoglycemia, I defer my opinion to the clinical reviewers.
5. The lack of robust race-specific results leads me to recommend a disclaimer in the label stating that although the trends in noninferiority were similar among different races, sample sizes were too small to produce robust conclusions for non-whites. Population-level statistics could be computed from those for individual races, except the sample sizes of non-white races were too small. The same label disclaimer as recommended for item 5 could also serve as a suitable remedy for this matter.

2 INTRODUCTION

2.1 Overview

Insulin glargine (HOE901-U300) is indicated in diabetes mellitus where treatment with insulin is required. Insulin glargine, like human insulin, acts via the human insulin receptor system. The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism.

The submission is based on results from the main 6-month on-treatment period of 4 multinational, open-label, randomized, controlled, Phase 3 studies in patients with T1DM (EFC12456) and T2DM (EFC11628, EFC11629 and EFC12347). In these Phase 3 studies, the objectives were to demonstrate that HOE901-U300 is as effective as Lantus in terms of HbA1c reduction.

This submission contains data on all subjects/patients exposed to HOE901-U300 in completed studies or completed 6-month main study periods (EFC11628, EFC11629, EFC12347 and EFC12456) and the 16-week exploratory CGM study PDY12777. The study PDY12777 is not covered in this review.

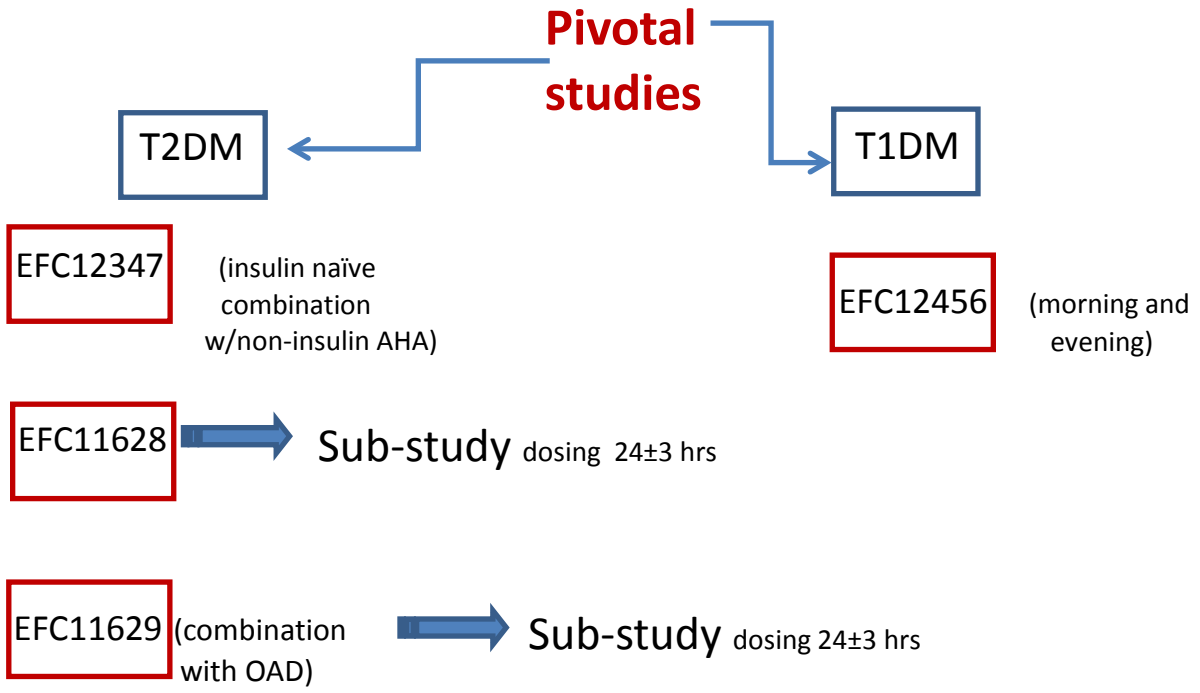
The Phase 3 program included 4 pivotal Phase 3 studies to assess the efficacy and safety of HOE901-U300 in patients with T1DM and T2DM; EFC11628, EFC11629 and EFC12347 in T2DM and study EFC12456 in T1DM. These studies were designed as randomized, controlled studies in a broad range of patient populations requiring insulin treatment, including insulin-naïve patients with T2DM not adequately controlled on non-insulin AHA (EFC12347) or insulin-pretreated T2DM patients, where the basal insulin was given in combination with mealtime insulin (EFC11628) or in combination with OADs (EFC11629) or patients with T1DM (EFC12456). The comparator in all studies was Lantus (insulin glargine 100 U/mL).

Results from two 3-month administration sub-studies embedded in the extension periods of studies EFC11628 and EFC11629 in patients with T2DM are submitted in support of the efficacy and safety of HOE901-U300 when administered at intervals up to 3 hours earlier or later than the patient's usual 24-hour injection interval.

The sponsor presented efficacy data by study for the 4 Phase 3 studies. The results of pooled analysis of studies EFC11629 and EFC12347 in T2DM were also presented.
Regarding pooled analysis, the sponsor states the following "Pooling efficacy data from the 4 Phase 3 studies was not considered appropriate due to differences between studies in the insulin regimens (basal insulin in combination with mealtime insulin or in combination with non-insulin AHA), and in the type of diabetes mellitus."

A schematic description of the submission is presented below.

Figure 1. A schematic description of the submission



The study population consisted of adult patients at least 18 years of age with a screening HbA1c in the range of ≥7.0 to ≤10.0% for insulin-pretreated patients (EFC11628, EFC11629, EFC12456) and ≥7.0 to ≤11.0% in insulin-naïve patients (EFC12347).

Patients with T1DM had to be on basal insulin in combination with a mealtime insulin for at least one year, insulin-naïve T2DM patients had to have a known history of T2DM for at least one year and pretreatment with non-insulin AHA for 6 months (EFC12347), T2DM patients pretreated with basal insulin in combination with OAD had to be receiving this insulin regimen for at least 6 months (EFC11629), and patients with T2DM on basal insulin in combination with a mealtime insulin had to be on this regimen for at least 1 year (EFC11628). In studies EFC11628 and EFC11629 in T2DM patients pretreated with basal insulin, the daily basal insulin dose had to be at least 42 U.

The description of each trial is presented below:

Table 1. List of all studies included in analysis

	Phase and Design	Treatment Period	Region	Randomization	# of Subjects per Arm	Study Population
EFC12456	Phase 3 multicenter, open-label, parallel group design	6 months	North America, Europe, Japan	1:1:1:1 HOE901-U300 morning injection HOE901-U300 evening injection Lantus morning injection Lantus evening injection	HOE901-U300: 274 Lantus: 275	T1DM on basal insulin in combination with mealtime insulin analog
EFC11628	Phase 3 multicenter, open-label, parallel group design	6 months	North America, South America, Europe, South Africa	1:1 HOE901-U300 Lantus	HOE901-U300: 404 Lantus: 403	T2DM on basal insulin in combination with mealtime insulin analog
EFC11628 sub-study		3 months (Month 6 – Month 9 extension period)		1:1 at fixed 24-hour intervals at intervals of 24±3 hours	Fixed intervals: 53 Adaptable intervals: 56	Patients randomized and treated with HOE901-U300 during the main study period
EFC11629	Phase 3 multicenter, open-label, parallel group design	6 months	North America, South America, Europe, South Africa	1:1 HOE901-U300 Lantus	HOE901-U300: 404 Lantus: 407	T2DM on basal insulin in combination with OAD
EFC11629 sub-study		3 months (Month 6 – Month 9 extension period)		1:1 at fixed 24-hour intervals at intervals of 24±3 hours	Fixed intervals: 44 Adaptable intervals: 45	Patients randomized and treated with HOE901-U300 during the main study period
EFC12347	Phase 3 multicenter, open-label, parallel group design	6 months	North America, Europe, Japan	1:1 HOE901-U300 Lantus	HOE901-U300: 439 Lantus: 439	Insulin-naïve T2DM not adequately controlled on non-insulin AHA

2.2 Data Sources

Overview documents:
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\\cdsesub1\evsprod\NDA206538\0000\m2\27-clin-sum\summary-clin-efficacy-diabetes.pdf

Labeling:
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Statistical analysis plan (SAP):
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Efficacy reports:
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Electronic analysis datasets:
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SAS codes:
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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

This submission is in electronic common technical document (eCTD) format.
Study datasets were provided as SAS XPORT transport files. The analysis datasets were joinable by unique identifier (SUBJID). The datasets were in good organization. Define.pdf file was clear enough. The reported analysis results were in good quality. The reviewer's analysis on the primary and secondary efficacy endpoints gives approximately the same results as those reported in the clinical study report (CSR). The submission included SAPs for each of the studies.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The studies utilized a common core protocol that standardized most aspects of the study design, including the comparator Lantus (insulin glargine 100 U/mL).

The sample sizes were determined by sponsor for the 4 pivotal Phase 3 studies with 99% power to detect differences of 0.4% in the change in HbA1c from baseline to week 26 (month 6) between HOE901-U300 and Lantus. This calculation assumed a common standard deviation of 1.3%. I recalculated the sample size and arrived at the number that was close to the number provided by the sponsor, i.e. my sample size was n=390 per group.

The primary efficacy endpoint for all four main studies was change from baseline to Month 6 in HbA1c. A stepwise closed testing approach was used. The first endpoint was the noninferiority which was tested with a noninferiority margin of 0.4% HbA1c. The second primary endpoint was superiority of HOE901-U300 over Lantus. The second primary endpoint was tested only if noninferiority was demonstrated. The primary endpoints (month 6) were examined using one-sided test at level $\alpha = 0.025$.

In the two substudies during the extension periods of EFC11628 and EFC11629 comparing adaptable versus fixed dosing intervals, the primary endpoint was the mean change in HbA1c from Month 6 (= baseline of substudy) to Month 9 (= endpoint of substudy) of the main study.

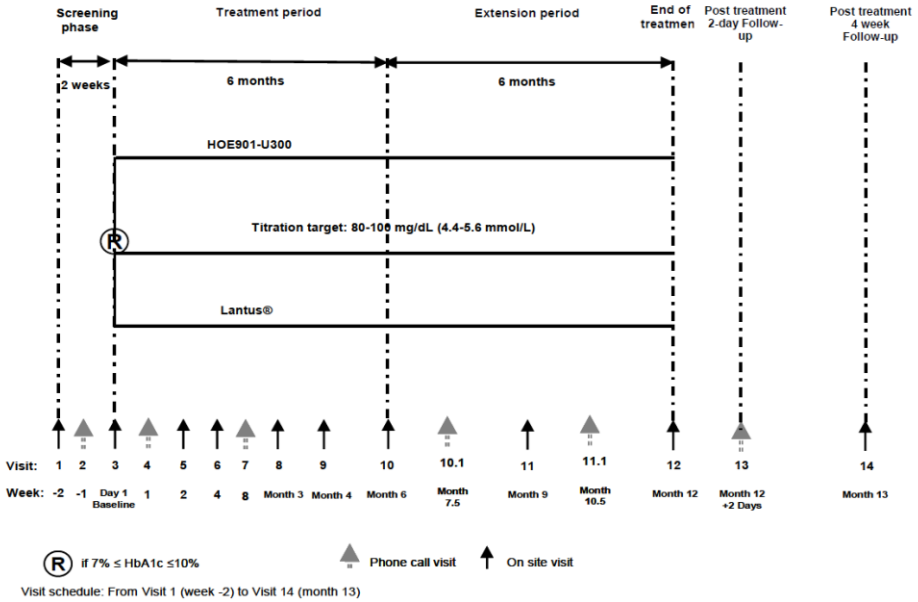
The key secondary efficacy endpoints in all main studies were occurrence of nocturnal hypoglycemia, change in pre-injection plasma glucose, and change in variability of pre-injection plasma glucose.

Efficacy analysis sets were defined by the sponsor as the following:

The primary efficacy population is the **mITT population**, which includes all randomized patients who received at least one dose of the open label IMP, and have both a baseline assessment and at least one post baseline assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures.

A schematic description of each of the study schemes is presented below:

Figure 2. Studies EFC11628 and EFC11629



Both studies (EFC11628 and EFC11629) are comprised of the following periods:

- An up-to 2-week screening period
- A 6-month open-label, randomized treatment period comparing HOE901-U300 to Lantus while maintaining the mealtime short-acting insulin analogue in study EFC11628 or the oral antihyperglycemic drug(s) in study EFC11629
- A 6-month randomized, comparative safety extension period while maintaining the study treatment plus the mealtime insulin in study EFC11628 or plus the oral antihyperglycemic treatment in study EFC11629

Figure 3. Study EFC12347

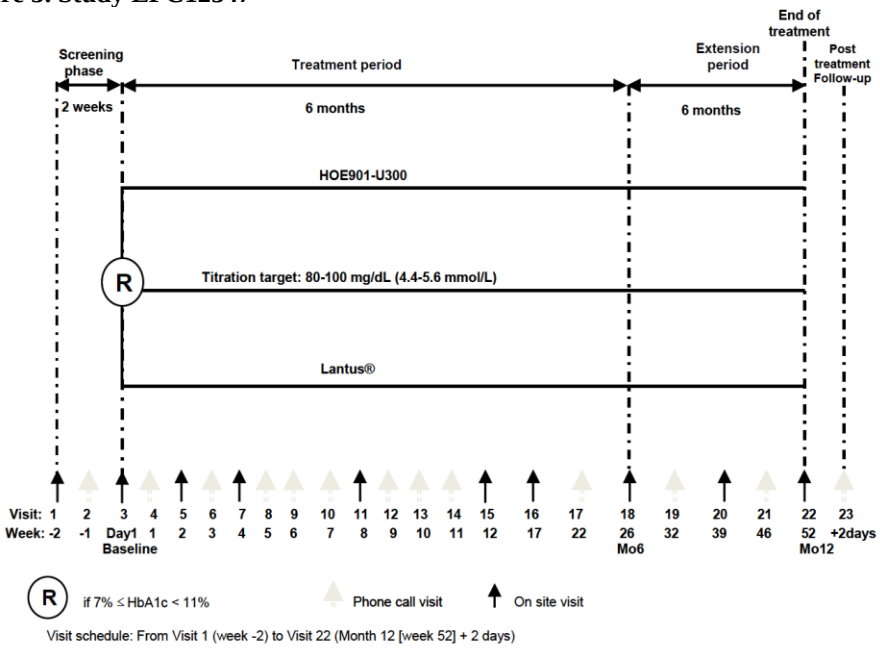
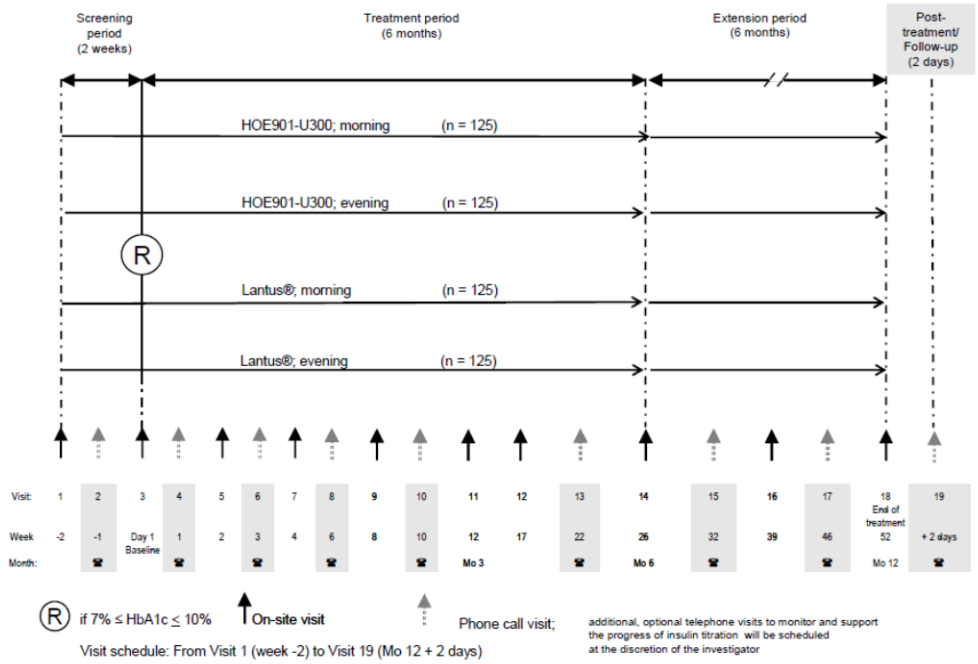


Figure 4. Study EFC12456



Similarly to studies EFC11628 and EFC11629, the timelines for studies EFC12347 and EFC12456 consisted of 2-week screening period, a 6-month open-label, randomized treatment period comparing HOE901-U300 to Lantus, and a 6-month randomized, comparative safety extension period.

Potential issues of the submission that might impact the interpretation of the outcomes:

1. *Study population*

A visualized racial distribution is presented in Figure 1. The graph shows that 78% or more of subjects in each trial were white (between 78 and 94 percent of each study). In contrast, the percentage of black or African American subjects ranged between 4.4 and 11, and Asian between 1.2 to 8.7. I estimated the distribution of patients with diabetes using 2010 census data and diabetes information provided by diabetes.org. My results based on the data of these three races (White, African American and Asian, which comprise 90% of the US population) show that 22% of all patients with diabetes are Black or African American. Similarly, about 6% of patients with diabetes are Asian. Therefore, the study composition makes it difficult to apply the results to the US population of diabetes patients. Application to patients of particular races is of greater interest. The number of study participants by race is listed in Table 3, while in section 3.2.1, I show that the number of study participants required to show noninferiority is 390. Although 390 African American study participants may not be a realistic goal, having a population better reflecting the diversity of the US population with diabetes would lend more credence to applicability to the US market. One way to handle this issue is to make a note about it in the label.

Figure 5. Racial distribution within each study

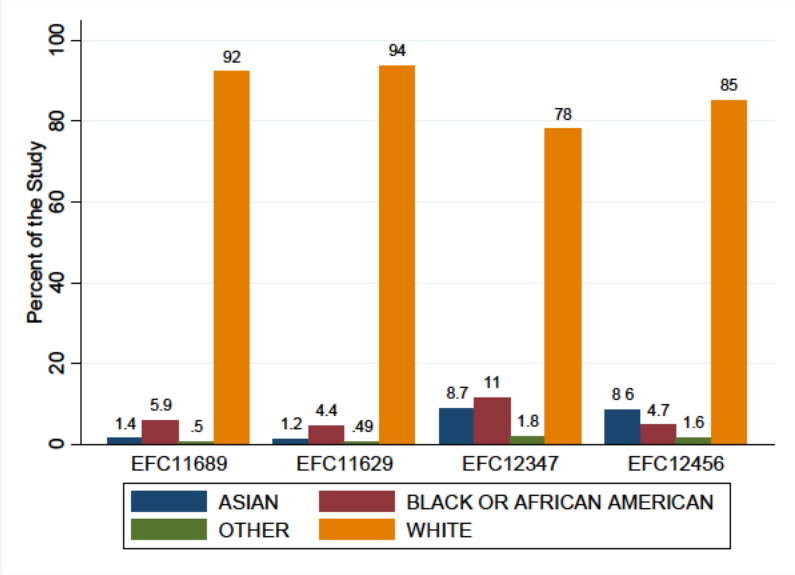


Table 2. Racial distribution of patients with diabetes in the US

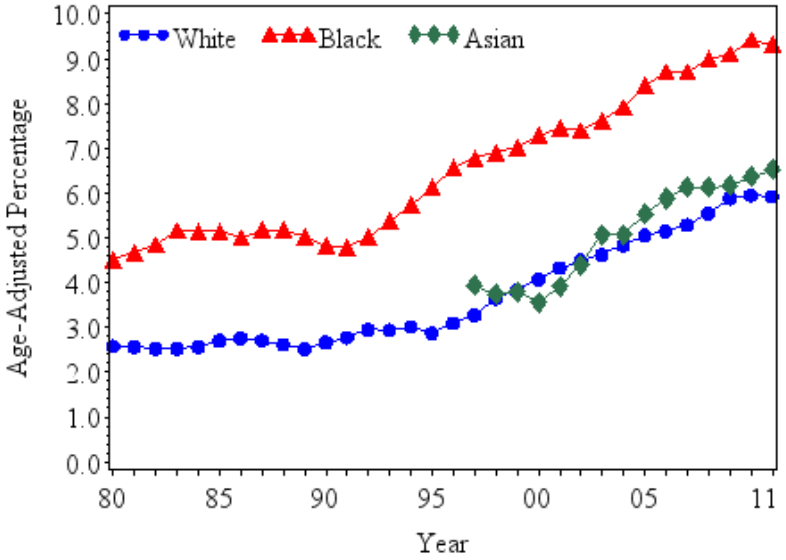
Race	Number of people in the US*	Prevalence of diabetes (%)**	Estimated number of people with diabetes	Estimated percent of total number of people with diabetes (%)§
White American	223,553,265	7.6	16,990,048.14	72.45
African American	38,929,319	13.2	5,138,670.108	21.91
Asian American	14,674,252	9.0	1,320,682.68	5.63
Total			23,449,400.93	

*based on the publication "Overview of Race and Hispanic Origin: 2010" (PDF). Retrieved 2013-05-08. US Census Bureau March 2011

**based on website diabetes.org http://www.diabetes.org/diabetes-basics/statistics/ last assessed on January 16, 2015

§ based on ratios involving only these three races

Figure 6. Age-Adjusted Percentage of Civilian, Noninstitutionalized Population with Diagnosed Diabetes, by Race, United States, 1980–2011 (CDC)



Data source: http://www.cdc.gov/diabetes/statistics/prev/national/figbyrace.htm

2. *Flexible intervals between injections*

The sponsor defined intervals between injections in the following way:

"…patients were randomized to either continue once daily injections every 24 hours (fixed dosing interval) or to inject once daily at intervals of 24±3 hours (adaptable dosing interval) when they so wished, using the maximum intervals at least twice per week."

It is hard to understand the patterns of 3 hour delays and it is not clear how often the subjects in the fixed dose group had alterations in timing of their injections.

3. *Definition of nocturnal hypoglycemia*

Hypoglycemia was defined by the sponsor as:
"Severe and/or confirmed (≤ 3.9 mmol/L [70 mg/dL]) nocturnal hypoglycemia (reported between 00:00 and 05:59 hours) between Week 9 and Month 6."

It could potentially become an issue since the study participant might not have recognized that the levels of glucose dropped during the night and therefore the incidence of hypoglycemia might be underreported.

Hypothesis testing procedure
Superiority of HOE901-U300 over Lantus was tested in a pre-specified order of priority only if noninferiority of HOE901-U300 versus Lantus was demonstrated for the primary endpoint (hierarchical testing strategy). Specifically, to assess noninferiority, the upper bound of the two-sided 95% CI for the difference in the mean change in HbA1c from baseline to endpoint between HOE901-U300 and Lantus is compared with the predefined noninferiority margin of 0.4% HbA1c. Noninferiority is demonstrated if the upper bound of the two-sided 95% CI of the difference between HOE901-U300 and Lantus on mITT population is <0.4%.
Only if noninferiority of HOE901-U300 versus Lantus has been demonstrated, the sponsor proceeded to test superiority of HOE901-U300 over Lantus. The superiority of HOE901-U300 over Lantus is demonstrated if the upper bound of the two-sided 95% CI for the difference in the mean change in HbA1c from baseline to endpoint between HOE901-U300 and Lantus on mITT population is <0.
The tests for the primary endpoint (month 6) is performed one-sided at level $\alpha = 0.025$.

3.2.2 Statistical Methodologies

Primary Analysis
In the amended statistical analysis plan for studies EFC11628 (Edition I) and EFC11629 (Edition II), the sponsor indicated that the primary analysis is going to be performed using an analysis of covariance (ANCOVA) model with treatment, strata of screening HbA1c (<8.0 and ≥8.0%), and country as fixed effects and using the HbA1c baseline value as a covariate.
Similarly, the primary analyses for the both sub-studies, was supposed to be done using the ANCOVA model using Last Observation Carried Forward (LOCF) imputation.

For the studies EFC11628 and EFC11629, the sponsor indicated that sensitivity analyses will include the longitudinal data analysis Mixed Model with Repeated Measurements (MMRM).

In contrast, according to the Statistical Analysis Plans for studies EFC12347 and EFC12456, the change in HbA1c from baseline to endpoint (Month 6) was analyzed using a Mixed Model for Repeated Measurements (MMRM) approach under the missing at random framework.

All primary efficacy analyses were based on the modified intent-to-treat (mITT) population.

(b) (4)

The sponsor provided datasets that included indicator variables for the observations utilized in LOCF analysis in all main studies. The observations used in MMRM analyses were identified by the sponsor only in studies EFC12347 and EFC12456. Similarly, the sponsor provided SAS codes for longitudinal data analyses only for those two studies. I performed my own MMRM analysis for the studies EFC11628 and EFC11629. My results were close to the results provided by the sponsor. I was also able to verify all LOCF analyses.

A stepwise closed testing approach was used for the primary efficacy variable to assess noninferiority and superiority sequentially:

- Step 1 proceeds to assess noninferiority of HOE901-U300 versus Lantus. Non-inferiority is demonstrated if the upper bound of the two-sided 95% CI of the difference between HOE901-U300 and Lantus on mITT population is <0.4%.

- Only if noninferiority of HOE901-U300 versus Lantus has been demonstrated, step 2 is proceeded to test superiority of HOE901-U300 over Lantus. The superiority of HOE901-U300 over Lantus is demonstrated if the upper bound of the two-sided 95% CI for the difference in the mean change in HbA1c from baseline to endpoint between HOE901-U300 and Lantus on mITT population is <0.

The tests for the primary endpoint (month 6) is performed one-sided at level $\alpha = 0.025$.

Secondary efficacy analysis

The main secondary objectives of these two studies are to compare HOE901-U300 and Lantus in terms of:

- occurrence of **nocturnal hypoglycemia**;

  Endpoint: proportion of patients with at least one nocturnal hypoglycemia between start of week 9 and endpoint (month 6), indicated as severe and/or confirmed by plasma glucose ≤ 70 mg/dL (3.9 mmol/L) that occurred between 00:00 and 05:59 hours, is analyzed as the first main secondary endpoint on the mITT population. The analysis was performed using Cochran-Mantel-Haenszel (CMH) method with treatment as a factor and stratified on strata of screening HbA1c (<8.0 and ≥8.0%).

- change in **pre-injection plasma glucose**;

  The analysis was performed using an ANCOVA model with treatment, strata of screening HbA1c (<8.0 and ≥8.0%), and country as fixed effects and using the pre-injection SMPG baseline value as a covariate.

- change in **variability of pre-injection plasma glucose**;

  The analysis was performed using an analysis of variance (ANOVA) model with treatment, strata of screening HbA1c (<8.0 and ≥8.0%), and country as fixed effects.

Additional secondary objectives include:

- a comparison of HOE901-U300 and Lantus in terms of reaching target HbA1c values and controlled plasma glucose (all and reaching target without hypoglycemia);
- a comparison of HOE901-U300 and Lantus in terms of treatment satisfaction of patients with T2DM;

• a comparison of HOE901-U300 and Lantus in terms of the frequency of occurrence and diurnal distribution of hypoglycemia (symptomatic, asymptomatic, nocturnal, severe, probable and relative);
• an assessment of the safety and tolerability (including development of anti-insulin antibodies) of HOE901-U300.

Statistical analysis issues:

1. *Missing data*

Subjects who had data at baseline and week 26, but observations at week 26 were not included in the analysis [LOCF analysis: study EFC11628 n=13, study EFC11629 n=12, study EFC12347 n=8, study EFC12456 n=12; MMRM analysis: study EFC12347 n=24, study EFC12456 n=11]. A more detailed description of missing data is located in the results section of this review.

The sponsor addressed some of the missing data issues by conducting the sensitivity analyses based on MMRM.

In my view, the MMRM analysis does not completely solve the issue of missing data since the MMRM model assumes that subjects with missing HbA1C values at the end of the study may be characterized by those with measurements. Such an assumption could lead to a clinically meaningless treatment effect just based on the outcomes from the statistical model.
To examine the impact of rescue medications (rescue therapy was permitted in studies EFC11629 and EFC12347) , the sponsor proposed the following analyses:

a. In study EFC11629 only: analysis based on all scheduled HbA1c measurements during the main 6-month treatment period, to assess the impact of rescue medication. Any unscheduled measurements are excluded from the analysis. A multilevel model with random slopes and intercepts, proposed by White, et al , is used to adjust for the effect of rescue medication. The model includes fixed-effect factors for treatment, visit, treatment-by-visit interaction, randomization strata of screening HbA1c (<8.0, ≥8.0%), country, baseline HbA1c-by-visit interaction, and the number of days spent on rescue medications. The multilevel model is implemented via PROC MIXED. The treatment group has two levels (HOE901-U300 and Lantus) and the visit factor (with nominal visits) has two levels (visit 8 [week 12] and visit 10 [month 6]). Parameters are estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom are estimated using Kenward-Roger approximation by fitting values from all post-randomization visits in the main 6-month treatment period (1).

b. 6-months completers analysis: A sensitivity analysis is conducted with the 6-month completers (i.e., all patients who complete the main 6-month period of treatment and do not start rescue therapy before 6 months in study EFC11629 only) using the month 6 values and the same ANCOVA model described in the above section.

c. Penalized LOCF analysis: it is derived from the primary LOCF analysis (with censoring at first initiation of rescue medication) as follows: for those patients who do not have a valid assessment of HbA1c at month 6 (due to dropout and/or initiation of rescue

medication before month 6), the endpoint is imputed as LOCF + Δ (Δ >0) for HOE901-U300 group and LOCF – Δ for Lantus group. This amounts to applying a penalty Δ to the experimental group and a bonus Δ to the control group. The greatest value of Δ preserving noninferiority is searched for.

2. *MMRM analysis and SAS codes (label) [studies EFC11628 and EFC11629]*

According to the SAP documentation for both trials (EFC11628 and EFC11629), MMRM was not supposed to be the main method for the primary analysis. In contrast, for studies EFC12347 and EFC12456 MMRM was planned to be the main method for the HbA1c analysis. (b) (4)

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The studies included 549 randomized patients with T1DM and 2496 randomized patients with T2DM; 717 (23.5%) patients were aged 65 years or older, 1872 (75.0%) patients with T2DM had a body mass index (BMI) of at least 30 kg/m² and 488 (16%) patients had some degree of renal impairment (GFR [MDRD] ≤60 mL/min). The majority of the patients were Caucasian/white (n=2667; 87.6%), other ethnicities were represented by n=210 (6.9%) Black, n=144 (4.7%) Asian/Oriental, and n=463 (15.2%) Hispanic. Geographical areas included North America, South America, Europe, South Africa, and Japan. The Kaplan-Meier curves depicting a detailed description of drop out patterns for each study is presented in Appendix A.

Table 3. Demographic data

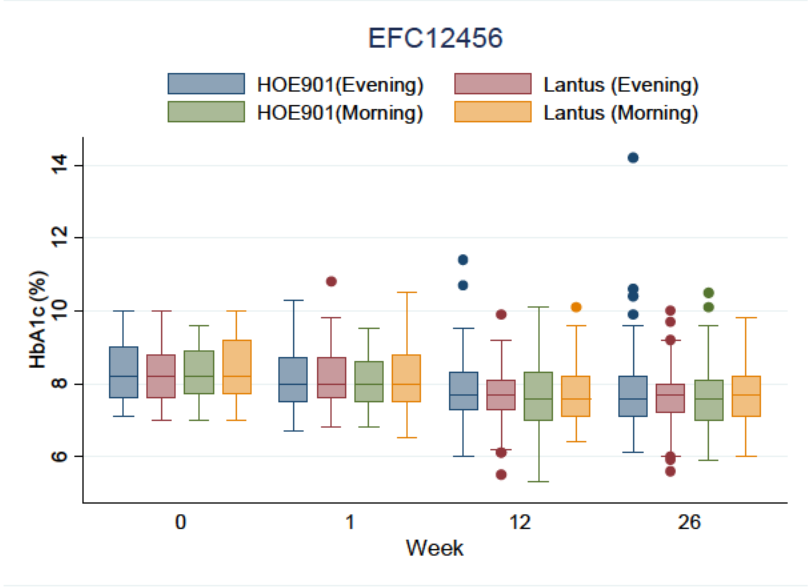
	T1DM	T2DM		
	EFC12456	**EFC11628**	**EFC11629**	**EFC12347**
Number of patients	N=549	N=807	N=811	N=878
Age (years; mean	47.3 (13.7)	60.0 (8.6)	58.2 (9.2)	57.7 (10.1)
≥ 65 years (%)	55 (10.0%)	246 (30.4%)	190 (23.4%)	226 (25.7)
Male, N (%)	313 (57.0%)	427 (52.9%)	372 (45.9%)	507 (57.7%)
Weight (kg;	81.8 (18.7)	106.3 (20.8)	98.3 (21.6)	95.3 (22.9)
BMI (kg/m² mean;	27.6 (5.1)	36.6 (6.4)	34.8 (6.4)	33.0 (6.7)
≥ 30 kg/m²	153 (27.9%)	699 (86.6%)	614 (75.7%)	559 (63.6%)
GFR (MDRD) < 60 mL/min/1.73m²	67 (12.2%)	188 (23.3%)	114 (14.1%)	119 (13.6%)
Duration of diabetes	21.0 (12.9)	15.8 (7.5)	12.6 (7.0)	9.8 (6.4)
≥ 10 years	431 (78.9%)	633 (78.4%)	501 (61.9%)	372 (42.7%)
Total insulin dose prior to study (U/kg; mean) in the last 7 days prior to	0.719 (0.262)	1.197 (0.466)	0.671 (0.238)	NA
Caucasian/white	467 (85.1%)	745 (92.3%)	761 (93.8%)	685 (78.0%)
Asian/Oriental	47 (8.6%)	11 (1.4%)	10 (1.2%)	76 (8.7%)
Black	26 (4.7%)	47 (5.8%)	36 (4.4%)	101 (11.5%)
Hispanic	26 (4.7%)	51 (6.3%)	193 (23.8%)	193 (22.0%)

SD=Standard deviation; N=number; GFR= Glomerular filtration rate; MDRD= Modification of diet in renal disease (MDRD) formula; NA = not applicable.

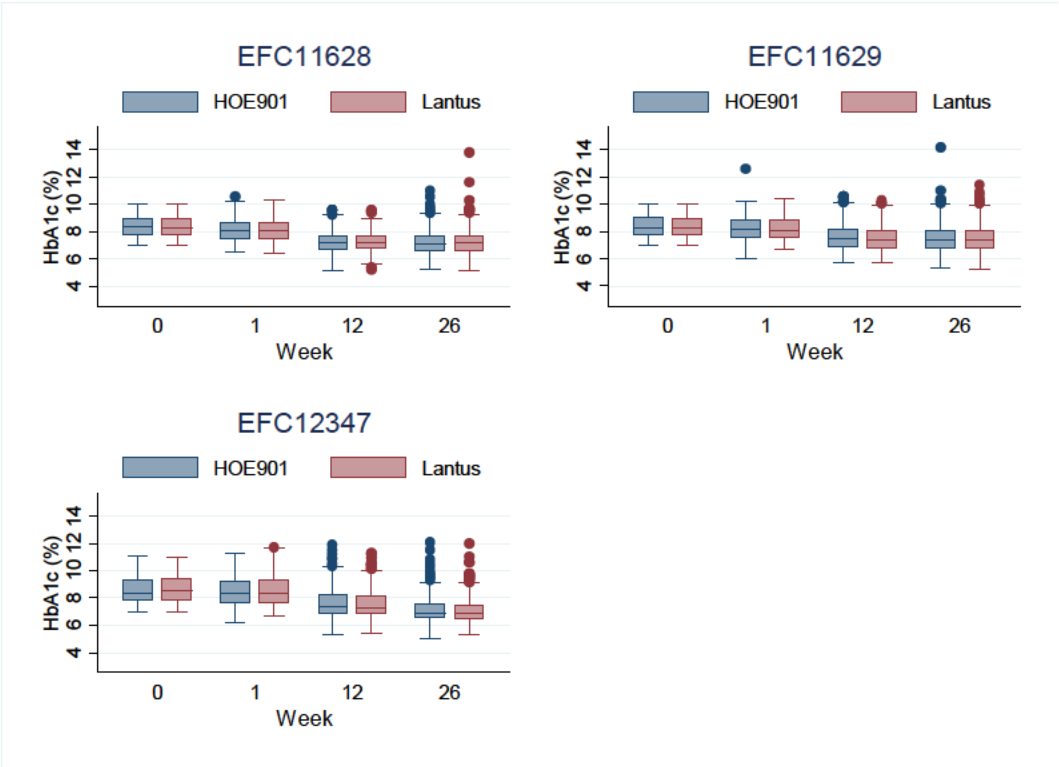
A graphical comparison of baseline age and HbA1c between the arms within each trial revealed that the differences between arms were not significant within each study. Overall, subjects diagnosed with T1DM were younger than subjects diagnosed with T2DM. Please see figures below.

Figure 7. Distributions of HbA1c

A. Distributions of HbA1c (longitudinal data) in subjects with T1DM

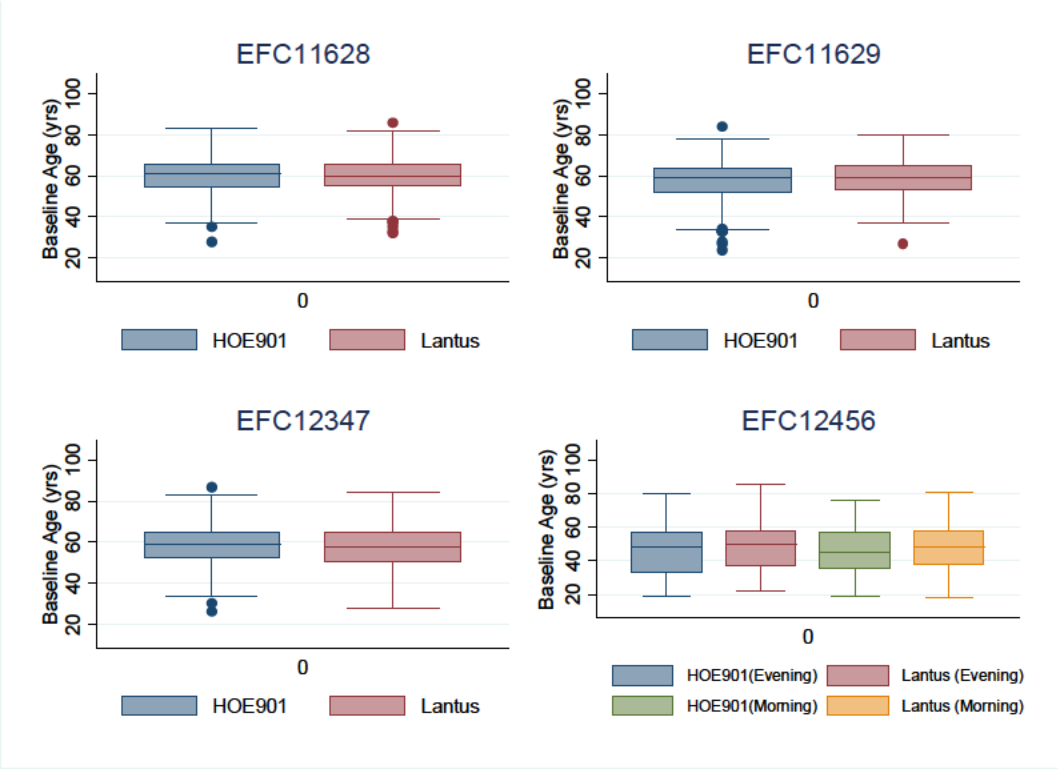


A. Distributions of HbA1c (longitudinal data) in subjects with T2DM



Legend for figure 7 (A and B): Each graph represents a different study. Each box represents a distribution of HbA1c before and during treatment period in a separate study arm. The name of each study arm is presented in the legend. A) Subjects Type 1 diabetes. B) Subjects with Type 2 diabetes. Boxes represent the 25th to 75th percentiles (interquartile range = IQR); horizontal lines within boxes, the median values; and vertical lines, 1.5 times the IQR. The circles represent outliers. Outliers are data points exceeding 1.5 times the IQR.

Figure 8. Baseline age by trial arm



Legend for figure 8 (A and B): Each subgraph represents a different study. Each box represents a distribution of baseline age in a separate study arm. The name of each study arm is presented in the legend. A) Subjects Type 1 diabetes. B) Subjects with Type 2 diabetes. Boxes represent the 25th to 75th percentiles (interquartile range = IQR); horizontal lines within boxes, the median values; and vertical lines, 1.5 times the IQR. The circles represent outliers. Outliers are data points exceeding 1.5 times the IQR.

A visualized racial distribution is presented in Figure 5 (section 3.2.1). The graph shows that more than 78% of subjects in each trial were white. The racial distribution within all studies does not reflect a distribution of US population dignosed with diabetes. According to CDC, the majority of subjects diagnosed with diabetes were African American.

3.2.4 Results and Conclusions

Missing data analysis

Since the data were analyzed using both, LOCF and MMRM methods, I examined the missing data patterns in relationship to those methods. My results are presented in the tables 3-6. The left side of the tables contains information on the number of subjects who completed the study, i.e. subjects who had baseline and visit 26 observations, how many of those subjects were included in the sponsor's analysis. The right side of those tables contains information on the length of the follow-up identifying the subjects who did not complete the study.

Table 4. Missing data EFC11628

Total n=804 HOE n=404 Lantus n=400	Visit 26+baseline available in dataset*	LOCF (sponsor)	Last observation included in LOCF analysis		
				Week26+baseline not present*	Week26+baseline present*
All subjects	739	785	Day 1	1	0
			Week 12	16	13
			Week 26	0	726
			Early treatment end	29	0
HOE901-U300	369	391			
			Week 12	9	7
			Week 26	0	362
			Early treatment end	13	0
Lantus	370	394			
			Day 1	1	0
			Week 12	7	6
			Week 26	0	364
			Early treatment end	16	0

*in the dataset;

Table 5. Missing data EFC11629

Total n=808 HOE n=403 Lantus n=405	Visit 26+baseline available in dataset*	LOCF (sponsor)	Last observation included in LOCF analysis		
				Week26+baseline not present*	Week26+baseline present*
All subjects	727	778	Day 1	2	0
			Week 12	19	12
			Week 26	4	674
			Early treatment end	28	39†
HOE901-U300	363	386			
			Day 1	1	0
			Week 12	7	7
			Week 26	2	333
			Early treatment end	15	21
Lantus	364	392			
			Day 1	1	0
			Week 12	12	5
			Week 26	2	341
			Early treatment end	13	18

Table 6. Missing data EFC12347

Total n=862 HOE n=432 Lantus n=430	Visit 26+baseline available in dataset*	LOCF (sponsor)	Included in MMRM
All subjects	728	817	796
HOE901-U300	371	410	402
Lantus	357	407	394

LOCF Analysis

Total n=862 HOE n=432 Lantus n=430 All subjects	Visit 26+baseline available in dataset	LOCF (sponsor)	Last observation included in LOCF analysis		
				Week26+baseline not present	Week26+baseline present
All subjects	728	817	Day 1	1	0
			Week 12	30	8
			Week 26	0	703
			Early treatment end	58	14
HOE901-U300	371	410			
			Day 1	0	0
			Week 12	13	3
			Week 26	0	360
			Early treatment end	26	6
Lantus	357	407			
			Day 1	1	0
			Week 12	17	5
			Week 26		343
			Early treatment end	32	8

MMRM analysis

Total n=862 HOE n=432 Lantus n=430 All subjects	Visit 26+baseline available in dataset*	MMRM (sponsor)	Last observation included in MMRM analysis		
				Week26+baseline not present*	Week26+baseline present*
All subjects	728	796	Week 12	47	20
			Week 26	0	703
			Early treatment end	22	4
HOE901-U300	371	402	Week 12	20	9
			Week 26	0	360
			Early treatment end	11	2
Lantus	357	394	Week 12	27	11
			Week 26	0	343
			Early treatment end	11	2

Table 7. Missing data EFC12456

Total n=546 HOE (evening)n=138 HOE (morning) n=135 Lantus (evening) n=139 Lantus (morning) n =134	Visit 26+baseline available in dataset*	LOCF (sponsor)**	Included in MMRM**
All subjects	463	**522**	**499**
HOE901-U300	**230**	**258**	**247**
evening	117	128	124
morning	113	130	123
Lantus	**233**	**264**	**252**
evening	119	133	126
morning	114	131	126

*Subjects who had data on visit 26 and had a non-missing baseline HbA1c

** Subjects included in the sponsor's analysis

Total n=862 HOE n=432 Lantus n=430 All subjects	Visit 26+baseline available in dataset*	LOCF (sponsor)**	Last observation included in LOCF analysis		
				Week26+baseline not present*	Week26+baseline present*
All subjects	463	**522**	Day 1	1	**0**
			Week 12	17	**10**
			Week 26	0	**451**
			Early treatment end	42	**0**
HOE901-U300	**230**	**258**		29	**229**
evening	117	128	Day 1	0	**0**
			Week 12	3	**3**
			Week 26		**112**
			Early treatment end	9	**0**
morning	113	130	Day 1	1	**0**
			Week 12	6	**1**
			Week 26		**112**
			Early treatment end	10	**0**
Lantus	**233**	**264**		31	**233**
evening	119	133	Day 1	0	**0**
			Week 12	3	**3**
			Week 26	0	**116**
			Early treatment end	11	**0**
morning	114	131	Day 1	0	**0**
			Week 12	5	**3**
			Week 26	0	**111**
			Early treatment end	12	**0**

MMRM analysis

Total n=546 HOE (evening)n=138 HOE (morning) n=135 Lantus (evening) n=139 Lantus (morning) n =134	Study Arm	Visit 26+baseline available in dataset	MMRM (sponsor)	Last observation included in MMRM analysis		
					MMRM not present	MMRM present
All subjects		463[§]	499			
				Week 12	24	11
				Week 26	0	451
				Early treatment end	13	0
HOE901-U300	Evening	117	124			
				Week 12	4	4
				Week 26	0	112
				Early treatment end	4	0
	Morning	113	123			
				Week 12	8	1
				Week 26	0	112
				Early treatment end	2	0
Lantus	Evening	119	126			
				Week 12	4	3
				Week 26	0	116
				Early treatment end	3	0
	Morning	114	126			
				Week 12	8	3
				Week 26	0	111
				Early treatment end	4	0

[§]One subject had both, baseline and visit 26 data, but was not included in MMRM analysis

Primary efficacy analysis

For the primary analysis, the data were examined in two ways: using LOCF and longitudinal approach. Within each study the results obtained using LOCF were in the same direction as the results obtained using longitudinal data. A detailed summary of the outcomes is presented in the tables below.

Although the sponsor did not provide a justification for the choice of the noninferiority margin stating only that margin was pre-defined, I carefully examined previously approved submissions that involved insulin-type products (such as Insulin detemir). In those submissions I encountered that the noninferiority margin of 0.4% of HbA1c is consistent with previously approved

medications. Based on a margin of 0.4%, the noninferiority of HOE901-U300 compared with Lantus was shown when the upper bound of the 95% CI was below 0.4%. This was achieved in all four studies. The results were similar when morning and night groups were compared among subjects with T1DM (study EFC12456).
The superiority of HOE901-U300 to Lantus was not identified in any of the studies.

Summary of mean change in HbA_{1c} (%) from baseline to endpoint (Month 6) in the Phase 3 studies mITT population

Table 8. Primary Analysis study EFC11628

Analysis descripti	**Primary Analysis**			
Analysis population and time point description	Modified intention-to-treat (mITT) population – change from baseline to endpoint (Month 6, LOCF)			
Descriptive statistics, point estimate, and effect estimate	Primary endpoint	Comparison groups	HOE901-U300 (N=404)	Lantus (N=400)
	LOCF analysis: HbA1c (%)	n	391	394
		Endpoint (Month 6): Mean	7.25 (0.85)	7.28 (0.92)
		Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-0.83 (0.060) [-0.946, -0.709]	-0.83 (0.061) [-0.944 , -0.706]
		Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus [95% CI]	-0.002 (0.056) [-0.112, 0.107]	
	Longitudinal analysis***			
Descriptive statistics, point estimate, and effect estimate	Longitudinal analysis: HbA1c (%)	n	384	384
		Endpoint (Month 6): Mean (SD)	7.24(0.85)	7.26(0.92)
		Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-0.89(0.041) [-0.975, -0.813]	-0.87(0.041) [-0.956, -0.794]
		Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus	-0.02(0.058) [-0.134,0.095]	

*** This is reviewer's analysis. The results are close to the values in the label. The sponsor did not provide information on the choice of observations for the longitudinal analysis. SAS codes were also not provided.

Table 9. Primary Analysis study EFC11629

Analysis descriptio	**Primary Analysis**			
Analysis population and time point description	Modified intention-to-treat (mITT) population – change from baseline to endpoint (Month 6, LOCF)			
Descriptive statistics, point estimate, and effect estimate	Primary endpoint	Comparison groups	HOE901-U300 (N=403)	Lantus (N=405)
	LOCF analysis: HbA1c (%)	n	386	392
		Endpoint (Month 6): Mean (SD)	7.57 (1.02)	7.56 (1.04)
		Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-0.57 (0.094) [-0.756, 0.387]	-0.56 (0.093) [-0.744,-0.379]
		Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus [95% CI]	-0.01 (0.066) [-0.139, 0.119]	
	Longitudinal analysis***			
		n	378	383
Descriptive statistics, point estimate, and effect estimate	Longitudinal analysis: HbA1c (%)	Endpoint (Month 6): Mean (SD)	7.53(1.02)	7.52(1.00)
		Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-0.74(0.048) [-0.831,-0.644]	-0.72(0.047) [-0.809, -0.623]
		Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus	-0.02(0.067) [-0.154,0.11]	

*** This is reviewer's analysis. The results are close to the values in the label. The sponsor did not provide information on the choice of observations for the longitudinal analysis. SAS codes were also not provided.

Table 10. Primary Analysis study EFC12347

Analysis descriptio	**Primary Analysis**			
Analysis population and time point description	Modified intention-to-treat (mITT) population – change from baseline to endpoint (Month 6, LOCF)			
Descriptive statistics, point estimate, and effect estimate	Primary endpoint	Comparison groups	HOE901-U300 (N=432)	Lantus (N=430)
	LOCF analysis: HbA1c (%)	n	410	406
		Endpoint (Month 6): Mean (SD)	7.20(1.12)	7.19(1.04)
		Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-1.53(0.086) (-1.695, -1.359)	-1.55(0.084) (-1.711,-1.381)
		Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus [95% CI]	0.019(0.071) (-0.121, 0.158)	
	Longitudinal analysis			
	Longitudinal analysis: HbA1c (%)	n	365	350
		Endpoint (Month 6): Mean (SD)	7.08 (0.96)	7.05 (0.95)
		Change from baseline to endpoint (Month 6): LS mean (SE) [95%	-1.42 (0.047) [-1.511,-1.326]	-1.46 (0.048) [-1.555, 1.367]
		Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus [95% CI]	0.04 (0.067) [-0.090, 0.174]	

Table 11. Primary Analysis study EFC12456

Analysis descriptio	**Primary Analysis**			
Analysis population and time point description	Modified intention-to-treat (mITT) population – change from baseline to endpoint (Month 6, LOCF)			
Descriptive statistics, point estimate, and effect estimate	Primary endpoint	Comparison groups	HOE901-U300 (N=273)	Lantus (N=273)
	LOCF analysis: HbA1c (%)	n	258	264
		Endpoint (Month 6): Mean (SD)	7.6(1.00)	7.7(0.80)
		Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-0.416(0.078) [-0.57, -0.261]	-0.466(0.08) [-0.622, -0.311]
		Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus [95% CI]	0.05(0.068) [-0.082, 0.184]	
	Longitudinal analysis			
Descriptive statistics, point estimate, and effect estimate	Longitudinal analysis: HbA1c (%)	n	225	229
		Endpoint (Month 6): Mean (SD)	7.70 (0.99)	7.68 (0.80)
		Change from baseline to endpoint (Month 6): LS mean (SE)	-0.40 (0.051) [-0.501,0.299]	-0.44 (0.051) [-0.543,0.344]
		Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus	0.04 (0.072) [-0.098, 0.185]	

Table 12. Primary Analysis study EFC12456

Analysis descriptio	**Primary Analysis**					
Analysis population and time point description	Modified intention-to-treat (mITT) population – change from baseline to endpoint (Month 6, LOCF)					
	Longitudinal analysis					
Descriptive statistics, point estimate, and effect estimate	Primary endpoint	Comparison groups	HOE901-U300 (N=273)		Lantus (N=273)	
			morning	evening	morning	evening
	Longitudinal analysis: HbA1c (%)	n	112	113	115	114
		Endpoint (Month 6): Mean (SD)	7.63 (0.91)	7.78 (1.06)	7.73 (0.84)	7.62 (0.74)
		Change from baseline to endpoint (Month 6): LS mean (SE) [95% CI]	-0.48 (0.072) [-0.618, -0.334]	-0.32 (0.072) [-0.466, -0.182]	-0.41 (0.071) [-0.551, -0.271]	-0.48 (0.072) [-0.617, -0.334]
		Change from baseline to endpoint (Month 6): LS mean difference (SE) morning versus evening	-0.15 (0.102) [-0.353 to 0.049]			
		Change from baseline to endpoint (Month 6): LS mean difference (SE) HOE901-U300 versus Lantus	Morning: -0.07 (0.102) [-0.265 to 0.135]		Evening: 0.15 (0.102) [-0.049 to 0.352]	

The sponsor conducted the sensitivity analyses described in the methods section. The results of those analyses were similar to the primary analysis.
I examined the missing data patterns in both LOCF and MMRM scenarios. The missing data patterns were similar in both arms. The detailed results of my findings are presented in the table located in Appendix A.

Analysis of secondary efficacy endpoints

1. Hypoglycemia

   I examined the raw data counts of any hypoglycemia events and nocturnal hypoglycemia events during the entire study period.

Overall, the mean number of any hypoglycemia events (within study arm) ranged between 18.61 and 51.5 per subject. The numbers of any events during the entire period of study were rather similar when HOE901-U300 and Lantus arms were compared. Subjects with T1DM had on average higher number of those events (a mean of 51.49 and 50.49 events in the HOE901-U300 arms and 46.53 and 46.11 in the Lantus arms). The lead time (number of days) to first event was slightly higher in HOE901-U300 arms. The number of events with sever hypoglycemia were much smaller. Interestingly among subjects with T1DM, the number of severe hypoglycemia events was much larger among subjects who took their insulin (HOE901-U300 or Lantus) in the evening. This might have to do with the fact that those were subjects with T1DM who also used meal time insulin during the day.

Table 13. Hypoglycemia

Study	Study arm	Total number of events during treatment	Number of *subjects* with any hypoglycemia events (% of all subjects in the arm)	Average number of any hypoglycemia events *per subject* Mean (std)	Lead time to first event Mean (std)	Number of events of severe hypoglycemia (% of all severe events within the arm)
EFC 11628	HOE901-U300 (Evening)	5138	337(83.42%)	34.27(25.26)	34.62(40.28)	53(1.03%)
	Lantus (Evening)	5430	356(89%)	33.79(48)	26.28(30.18)	47(0.87%)
EFC 11629	HOE901-U300 (Evening)	2750	287(71.22%)	25.61(19.7)	45.71(39.9)	5(0.18%)
	Lantus (Evening)	3675	321(79.26%)	27.49(20.5)	34.41(32.63)	12(0.33%)
EFC12347	HOE901-U300 (Evening)	1431	216(50%)	18.81(23.94)	62.26(44.43)	4(0.28%)
	Lantus (Evening)	1787	241(56.05%)	18.61(15.07)	58.01(42.38)	4(0.22%)
EFC12456	HOE901-U300 (Evening)	4927	128(92.75)	51.49(38.42)	12.02(19.24)	21(0.43%)
	HOE901-U300 (Morning)	5006	128(94.81)	50.49(37.95)	14.13(21.64)	9(0.18%)
	Lantus (Evening)	4792	131(94.24)	46.53(33.15)	8.86(14.83)	32(0.67%)
	Lantus (Morning)	4588	127(94.24)	46.11(35.63)	13.11(26.53)	11(0.24%)

When only nocturnal hypoglycemia was examined, the numbers of events were much smaller (table below). The number of subjects who had the nocturnal events was slightly higher among patients on Lantus than among patients on HOE901-U300. Similarly, the lead time to the first nocturnal hypoglycemia event was longer for subjects on Lantus. The smallest number of subjects who had nocturnal hypoglycemia was among the participants from the study EFC12347 (20.37% in the HOE901-U300 arm and 24.42% in the Lantus arm). In contrast, the highest percentage of subjects who had nocturnal

hypoglycemia was among subjects with T1DM in the study EFC12456 (69.6% to 72.66% of subjects had a nocturnal event during the study). The numbers of severe nocturnal hypoglycemia events were very small in both arms (no severe nocturnal events were registered in both arms of study EFC12347 and in HOE901-U300 arm in study EFC11629), therefore no robust conclusions could be made based on these data.

Table 14. Nocturnal Hypoglycemia

Study	Study arm	Total number of events during treatment	Nocturnal Event (00:00-05:59) (% of all events during treatment)	Number of *subjects* with nocturnal events (% of all subjects with events within the arm)	Average number of nocturnal events *per subject* Mean (std)	Lead time to first event Mean (std)	Number of events of severe nocturnal hypoglycemia (% of all severe events within the arm)
EFC 11628	HOE901-U300 (Evening)	4491	646(12.58%)	183(45.3%)	9.75(6.81)	59.35(49.22)	12(22.64%)
	Lantus (Evening)	4545	883(16.27%)	240(60%)	10.78(7.31)	52.97(45.1)	15(31.91%)
EFC 11629	HOE901-U300 (Evening)	2750	379(13.78%)	123(30.52%)	11.14(12.09)	67.4(47.2)	0
	Lantus (Evening)	3675	766(20.84%)	169(41.73%)	13.38(8.31)	45.11(45.34)	2(16.67%)
EFC12347	HOE901-U300 (Evening)	1431	295(20.61%)	88(20.37%)	9.15(7)	85.69(48)	0
	Lantus (Evening)	1787	281(15.72%)	105(24.42%)	7.64(6.82)	83.76(49.62)	0
EFC12456	HOE901-U300 (Evening)	4927	533(10.82%)	97(70.29%)	11.06(8.75)	71.94(54.02)	9(42.86%)
	HOE901-U300 (Morning)	5006	493(9.85%)	94(69.63%)	11.28(8.36)	71.76(47.4)	1(11.11%)
	Lantus (Evening)	4791	607(12.67%)	101(72.66%)	12.58(13.06)	59.01(48.49)	3(9.38%)
	Lantus (Morning)	4588	567(12.36%)	95(70.9%)	13.33(9.77)	60.98(49.06)	4(36.36%)

2. Change in pre-injection SMPG from baseline to endpoint (Month 6)
   In all 4 pivotal studies, the least square (LS) mean change from baseline to endpoint (Month 6) in average pre injection SMPG was similar in the HOE901-U300 and Lantus groups

3. Change in variability of pre-injection SMPG from baseline to endpoint (Month 6)
   The variability of pre-injection SMPG, calculated as mean of coefficient of variation over at least 3 SMPG measurements during the 7 days preceding the visit, decreased from baseline to endpoint (Month 6) similarly in the HOE901-U300 and Lantus treatment

groups in EFC12456 and EFC11628. In study EFC11629 variability decreased more in the HOE901-U300 group than Lantus group.

4. Change in FPG from baseline to endpoint (Month 6)
   In all 4 pivotal studies, FPG had decreased in the HOE901-U300 and Lantus groups at endpoint (Month 6).

5. 8-point SMPG profile
   Eight-point profiles were comparable between treatment groups at baseline in all 4 studies and had decreased similarly at all time points and at endpoint (Month 6) in both treatment groups.

6. 24-hour average plasma glucose
   In all 4 studies, 24-hour average plasma glucose based on the 8-point SMPG profile was comparable between the treatment groups and had decreased similarly in the HOE901-U300 and Lantus group at Month six.

Efficacy in morning and evening injection

In study EFC12456, conducted in patients with T1DM, patients were randomized to receive HOE901-U300 or Lantus once daily in the morning (any time prior to breakfast until lunch) or evening (anytime immediately prior to the evening meal until bedtime).
At the end of the 6-month treatment period in the study EFC12456, HbA1c had decreased similarly in the morning injection groups of HOE901-U300 and Lantus, whereas a smaller decrease was seen in the HOE901-U300 evening injection group compared with the Lantus evening injection group (Table 12). Comparing morning and evening injection groups within the HOE901-U300 group, the morning injection resulted in a larger decrease of HbA1c than the evening injection, although the LS mean difference between HOE901-U300 morning and evening injection group was not clinically relevant.

Substudies: Adaptable administration intervals

According to the sponsor, at the end of the 3-month study period, the efficacy analyses in terms of LS mean change from baseline in HbA1c and FPG showed comparable results for the 2 dosing interval regimens in both substudies (HbA1c, LS mean difference between flexible and fixed dosing intervals, substudy EFC11628: 0.05%, 95% CI: -0.189 to 0.298]; EFC11629: 0.13%, 95% CI: -0.152 to 0.415) (2.7.3 [Table 29]). Eight-point SMPG profiles (mean at each time point) and pre-injection SMPG during the 3-month substudy period were also generally similar between groups. In both dosing interval regimen groups, the average daily basal and total insulin doses remained stable during the 3-month comparative regimen period.

Table 15. Sub-study EFC11628

Analysis descripti	**Primary Analysis**			
Analysis population and time point description	Modified intention-to-treat (mITT) population – change from baseline to endpoint (Month 6, LOCF)			
Descriptive statistics, point estimate, and effect estimate	Primary endpoint	Comparison groups	HOE901-U300 Adaptable (N=55)	HOE901-U300 Fixed (N=53)
	LOCF analysis: HbA1c (%)	n	55	51
		Endpoint (Month 9): Mean (SD)	7.25 (0.96)	7.14 (0.96)
		Change from baseline (Month 6) to endpoint (Month 9): LS mean (SE) [95% CI]	0.21(0.111) [-0.011, 0.429]	0.16(0.12 [-0.084, 0.394]
		Change from baseline (Month 6) to endpoint (Month 9): LS mean difference (SE) HOE901-U300 versus Lantus	0.05(0.123) [-0.189, 0.298]	

Table 16. Sub-study EFC11629

Analysis descripti	**Primary Analysis**			
Analysis population and time point description	Modified intention-to-treat (mITT) population – change from baseline to endpoint (Month 6, LOCF)			
Descriptive statistics, point estimate, and effect estimate	Primary endpoint	Comparison groups	HOE901-U300 Adaptable (N=)	HOE901-U300 Fixed (N=)
	LOCF analysis: HbA1c (%)	n	40	37
		Endpoint (Month 9): Mean (SD)	7.47 (0.87)	7.49 (1.11)
		Change from baseline (Month 6) to endpoint (Month 9): LS mean (SE) [95% CI]	-0.12 (0.151) [-0.422, 0.183]	-0.25 (0.162) (-0.574, 0.072)
		Change from baseline (Month6) to endpoint (Month 9): LS mean difference (SE) HOE901-U300 versus Lantus	0.13 (0.142) (-0.152, 0.415)	

3.3 Evaluation of Safety

Safety events were reviewed by Dr. Tania Condarco from Medical Division of Metabolism and Endocrinology Products. Readers are referred to Dr. Condarco's review for this section.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The subgroup analysis was performed using a mixed effects model that included the term for the subgroup and interactions between subgroup and treatment, subgroup and time, and a 3-way interaction for subgroup, treatment, and time.

Overall in all 4 studies EFC12456, EFC11628, EFC11629 and EFC12347, the treatment effect (mean change in HbA1c from baseline to endpoint (Month 6)) of HOE901-U300 versus Lantus

was consistent across tested subgroups defined by baseline/screening factors such as age, gender, race, ethnicities, and geographical area. These findings might not be robust for individual races other than white because the number of Black or African American and Asian patients were very small. A similar issue could be seen in the age-specific analysis for the subjects of age 75 or older.
The detailed results of the subgroup analyses are presented in Appendix B.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The noninferiority of HOE901-U300 to Lantus in change in HbA1c from baseline to endpoint was shown across all main studies. Based on the predefined noninferiority margin of 0.4%, the noninferiority of HOE901-U300 compared with Lantus was shown as the upper bound of the 95% CI was below 0.4%. In study EFC12456 in T1DM, similar efficacy was observed for HOE901-U300 in comparison with Lantus for both morning and evening injections.

I have a concern regarding the following aspects of this submission:

1. The choice of the noninferiority margin was not justified by the sponsor. Just from the text of the submission, it is not clear whether this margin is appropriate in studies involving subjects with Type 1 or Type 2 diabetes. Although the sponsor did not justify the choice of the margin, after I examined previously approved submissions involving insulin-type products (such as Insulin detemir), I encountered that the noninferiority margin of 0.4% of HbA1c is consistent with previously approved submissions.

2. Data comparing adaptive and fixed intervals for injection of HOE901-U300 are hard to interpret since it is not clear how reliable data based on fixed time of observation were. (b) (4)

3. Definition of hypoglycemia and nocturnal hypoglycemia is problematic since it may introduce exclusion bias and thus underreport the number of hypoglycemia events. Although, exclusion bias could be considered as a statistical concern, in this circumstance a clinical component might be more important in interpretation of hypoglycemia events, therefore I defer my opinion to the clinical reviewers.

4. Selection of study population that does not adequately represent US population of subjects with diabetes mellitus. Because the sample sizes of non-white patients were small, some of the analyses might not produce robust findings. Therefore I would suggest putting a disclaimer in the label clarifying that issue.

5.2 Labeling Recommendations

Below are high-level recommendations for the label included with the NDA submission:

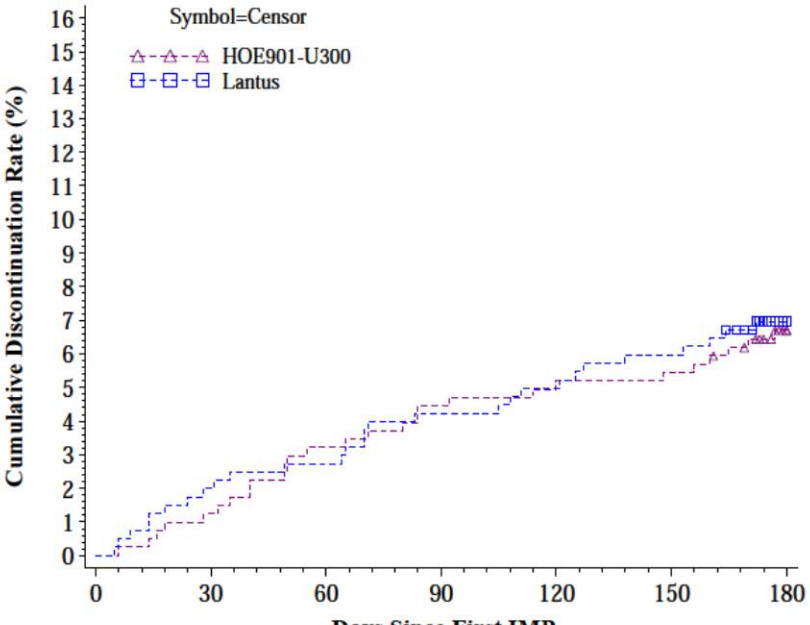
The results of the sub-studies examining the effects of flexible and fixed time intevals of the drug administration were difficult to interpret (it is not clear how reliable data based on fixed time of observation were). (b) (4)

The lack of robust race-specific results leads me to recommend a disclaimer in the label stating that although the trends in noninferiority were similar among different races, sample sizes were too small to produce robust conclusions for non-whites.

Appendix A

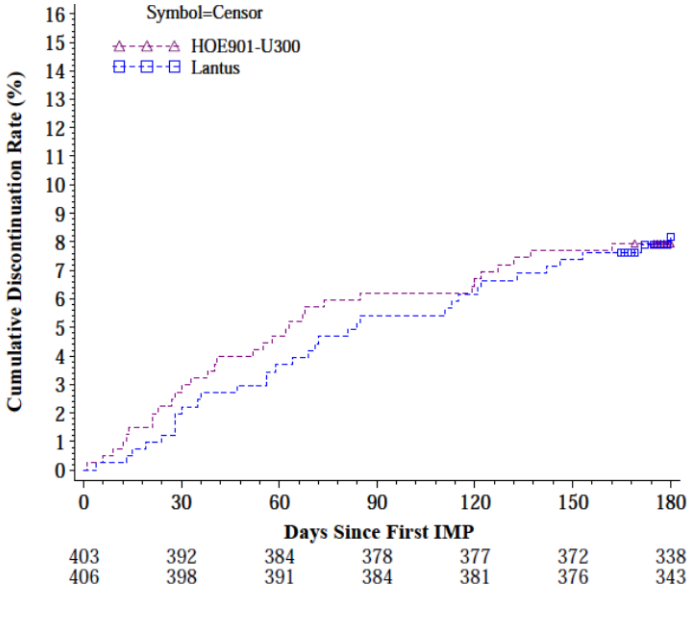
Kaplan-Meier plot of time to treatment discontinuation due to any reason during the main treatment period
Randomized and treated population

Figure 9. Kaplan-Meier plot EFC11628



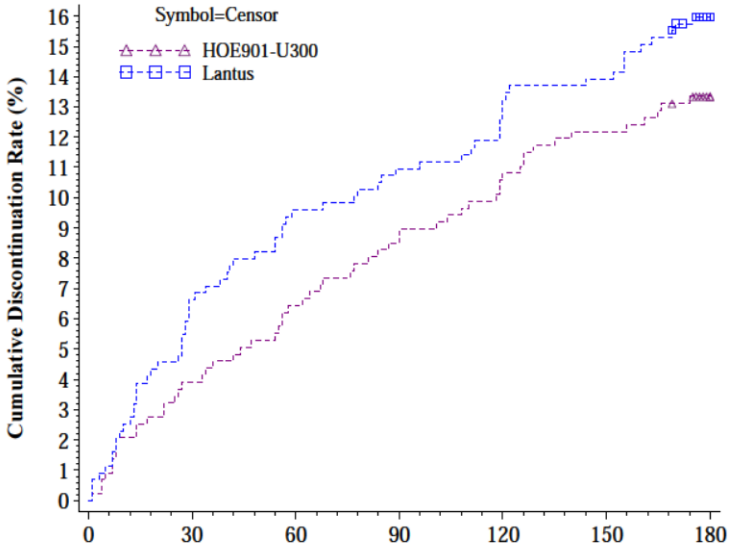
Number at Risk							
HOE901-U300	404	399	391	386	384	382	335
Lantus	402	394	391	385	382	378	333

Figure 10. Kaplan-Meier plot EFC11629



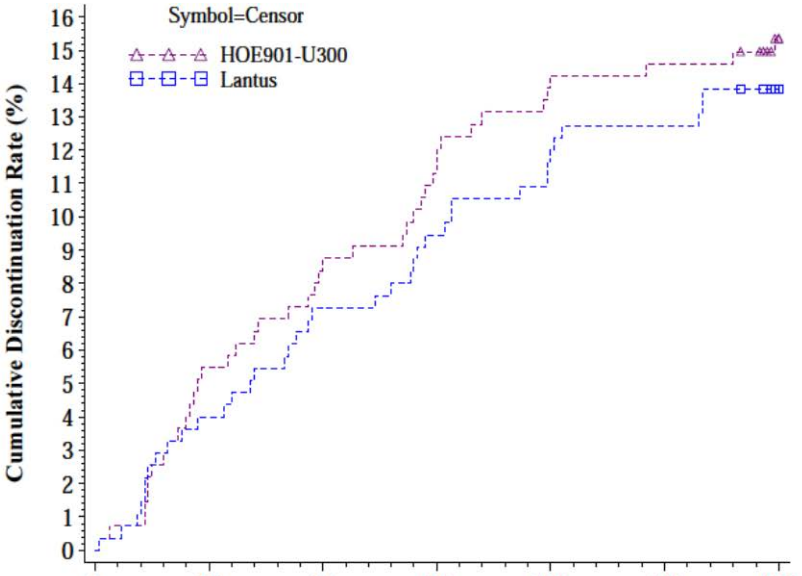
Number at Risk							
HOE901-U300	403	392	384	378	377	372	338
Lantus	406	398	391	384	381	376	343

Figure 11. Kaplan-Meier plot EFC12347



Number at Risk							
HOE901-U300	435	418	407	398	389	382	357
Lantus	438	409	396	390	383	377	334

Figure 12. Kaplan-Meier plot EFC12456



Number at Risk							
HOE901-U300	274	259	251	243	236	234	215
Lantus	275	264	255	249	243	240	224

Appendix B

Table 17. Subgroup analysis by age

Age Group	Number of subjects	Baseline	Month 6 (MMRM)	Change from baseline to Month 6 endpoint (MMRM)		
		Mean	Mean	LS Mean (SE)	Difference (SE)	95% CI
Study EFC11628						
Age Group(years) <65 H0E901-U300	277	8.19	7.24	-0.92 (0.049)	-0.08 (0.069)	(-0.219, 0.054)
Lantus	282	8.22	7.33	-0.84 (0.049)		
Age Group(years) [65-75[H0E901-U300	114	8.02	7.24	-0.84 (0.079)	0.08 (0.113)	(-0.140, 0.302)
Lantus	105	7.97	7.15	-0.92 (0.081)		
Age Group(years) ≥75 H0E901-U300	13	7.78	7.04	-0.91 (0.227)	0.22 (0.334)	(-0.435, 0.876)
Lantus	13	7.66	6.81	-1.13 (0.246)		
Study EFC11629						
Age Group(years) <65	317	8.28	7.47	-0.74 (0.054)	-0.03 (0.077)	(-0.178 to 0.126)
Lantus	303	8.25	7.49	-0.71 (0.055)		
Age Group(years) [65-75[H0E901-U300	79	8.24	7.47	-0.76 (0.112)	-0.13 (0.154)	(-0.429 to 0.175)
Lantus	87	8.15	7.53	-0.63 (0.105)		
Age Group(years) ≥75 H0E901-U300	7	8.08	7.60	-0.33 (0.394)	0.54 (0.486)	(-0.413 to 1.494)
Lantus	15	8.00	7.23	-0.87 (0.284)		
Study EFC 12347						
Age Group(years) <65 H0E901-U300	269	8.55	7.12	-1.39 (0.055)	0.08 (0.078)	(-0.076, 0.231)
Lantus	260	8.66	7.06	-1.47 (0.056)		
Age Group(years) [65-75[H0E901-U300	79	8.30	6.95	-1.48 (0.102)	-0.01 (0.144)	(-0.290, 0.276)
Lantus	77	8.38	6.97	-1.48 (0.103)		
Age Group(years) ≥75 H0E901-U300	17	8.51	6.93	-1.60 (0.222)	-0.33 (0.329)	(-0.974, 0.318)
Lantus	13	8.17	7.22	-1.27 (0.243)		

Study EFC12456						
Age Group(years) <65 H0E901-U300 **<65**	204	8.15	7.72	-0.39 (0.054)	0.07 (0.076)	(-0.077, 0.223)
Lantus	208	8.11	7.66	-0.46 (0.054)		
Age Group(years) [65-75[H0E901-U300	16	7.96	7.49	-0.58 (0.195)	-0.35 (0.278)	(-0.897, 0.195)
Lantus	16	8.29	7.94	-0.23 (0.197)		
Age Group(years) ≥75 H0E901-U300	5	7.86	7.64	-0.61 (0.443)	-0.33 (0.572)	(-1.450, 0.796)
Lantus	5	7.78	7.66	-0.28 (0.361)		

Table 18. Subgroup analysis by gender

Gender	**Number of subjects**	**Baseline**	**Month 6 (MMRM)**	**Change from baseline to Month 6 endpoint (MMRM)**		
Treatment group		**Mean**	**Mean**	**LS Mean (SE)**	**Difference (SE)**	**95% CI**
Study EFC11628						
Gender : Male H0E901-U300	217	8.15	7.31	-0.84 (0.056)	0.09 (0.080)	(-0.068 , 0.247)
Lantus	208	8.10	7.20	-0.93 (0.057)		
Gender : Female H0E901-U300	187	8.10	7.15	-0.97 (0.060)	-0.16 (0.084)	(-0.329, 0.002)
Lantus	192	8.18	7.34	-0.81 (0.059)		
Study EFC11629						
Gender : Male H0E901-U300	187	8.23	7.42	-0.78 (0.070)	-0.07 (0.101)	(-0.270, 0.126)
Lantus	184	8.16	7.43	-0.71 (0.072)		
Gender : Female H0E901-U300	216	8.31	7.52	-0.69 (0.067)	-0.00 (0.093)	(-0.186, 0.179)
Lantus	221	8.26	7.54	-0.69 (0.064)		
Study EFC12347						
Gender : Male H0E901-U300	207	8.44	6.99	-1.47 (0.063)	0.03 (0.088)	(-0.144, 0.203)
Lantus	208	8.56	7.01	-1.50 (0.062)		
Gender : Female H0E901-U300	158	8.56	7.19	-1.35 (0.072)	0.05 (0.104)	(-0.149, 0.258)
Lantus	142	8.61	7.09	-1.41 (0.075)		

Study EFC12456						
Gender : Male H0E901-U300	125	8.07	7.69	-0.39 (0.069)	0.06 (0.095)	(-0.125, 0.250)
Lantus	136	8.09	7.67	-0.45 (0.066)		
Gender : Female H0E901-U300	200	8.21	7.72	-0.42 (0.078)	0.02 (0.112)	(-0.201, 0.238)
Lantus	93	8.16	7.70	-0.44 (0.080)		

Table 19. Subgroup analysis by race

Race	**Number of subjects**	**Baseline**	**Month 6 (MMRM)**	**Change from baseline to Month 6 endpoint (MMRM)**		
Treatment group		**Mean**	**Mean**	**LS Mean (SE)**	**Difference (SE)**	**95% CI**
Study EFC11628						
Caucasian/White H0E901-U300	371	8.12	7.21	-0.92 (0.043)	-0.04 (0.060)	(-0.155, 0.082)
Lantus	371	8.12	7.24	-0.89 (0.043)		
Black H0E901-U300	26	8.34	7.51	-0.66 (0.164)	-0.10 (0.238)	(-0.571, 0.365)
Lantus	21	8.28	7.65	-0.56 (0.173)		
Asian/Oriental* H0E901-U300	6	7.90	7.52	-0.51 (0.323)	0.15 (0.480)	(-0.792, 1.091)
Lantus	5	7.98	7.42	-0.65 (0.354)		
Study EFC11629						
Caucasian/White H0E901-U300	377	8.25	7.44	-0.75 (0.050)	-0.03 (0.070)	(-0.169, 0.107)
Lantus	381	8.21	7.47	-0.72 (0.049)		
Black H0E901-U300	20	8.41	7.71	-0.57 (0.220)	0.15 (0.333)	(-0.506, 0.800)
Lantus	16	8.05	7.39	-0.71 (0.249)		
Asian/Oriental* H0E901-U300	3	8.07	7.60	-0.80 (0.598)	-0.94 (0.704)	(-2.325, 0.439)
Lantus	7	8.90	8.73	0.15 (0.372)		
Study EFC12347						
Caucasian/White H0E901-U300	289	8.50	7.07	-1.43 (0.053)	0.06 (0.076)	(-0.087, 0.212)
Lantus	271	8.59	7.04	-1.49 (0.055)		
Black H0E901-U300	35	8.54	7.21	-1.30 (0.152)	0.06 (0.205)	(-0.347, 0.459)
Lantus	42	8.74	7.15	-1.35 (0.138)		
Asian/Oriental H0E901-U300	35	8.13	6.91	-1.50 (0.155)	-0.13 (0.223)	(-0.567, 0.310)
Lantus	31	8.15	6.96	-1.37 (0.162)		
Other* H0E901-U300	6	9.37	7.82	-1.17 (0.37)	0.12 (0.515)	(-0.888, 1.136)

Lantus	6	9.04	7.25	-1.30 (0.364)		
Study EFC12456						
Caucasian/White H0E901-U300	189	8.09	7.69	-0.39 (0.056)	0.01 (0.078)	(-0.140, 0.167)
Lantus	195	8.09	7.70	-0.40 (0.055)		
Black* H0E901-U300	9	8.12	7.80	-0.37 (0.246)	0.05 (0.353)	(-0.640, 0.746)
Lantus	10	7.98	7.61	-0.42 (0.253)		
Asian/Oriental H0E901-U300	23	8.42	7.80	-0.47 (0.163)	0.48 (0.236)	(0.015, 0.942)
Lantus	21	8.49	7.40	-0.95 (0.172)		
Other* H0E901-U300	4	8.30	7.48	-0.88 (0.452)	-1.13 (0.632)	(-2.370, 0.114)
Lantus	3	8.15	8.43	0.25 (0.442)		

*Findings might not be robust since the number of subjects was small

Table 20. Subgroup analysis by geographic region

Geographic region	**Number of subjects**	**Baseline**	**Month 6 (MMRM)**	**Change from baseline to Month 6 endpoint (MMRM)**		
Treatment group		**Mean**	**Mean**	**LS Mean (SE)**	**Difference (SE)**	**95% CI**
Study EFC11628						
Northern America H0E901-U300	206	8.11	7.27	-0.85 (0.058)	-0.02 (0.082)	(-0.185, 0.136)
Lantus	206	8.10	7.30	-0.82 (0.058)		
Western Europe H0E901-U300	33	7.83	7.31	-0.70 (0.150)	-0.03 (0.208)	(-0.439, 0 376)
Lantus	31	8.08	7.46	-0.67 (0.145)		
Rest of the world H0E901-U300	18	8.37	7.43	-0.82 (0.194)	0.03 (0.259)	(-0.479, 0.538)
Lantus	22	8.30	7.37	-0.85 (0.171)		
Study EFC11629						
Northern America H0E901-U300	174	8.26	7.35	-0.85 (0.073)	-0.14 (0.100)	(-0.333, 0.061)
Lantus	193	8.12	7.44	-0.72 (0.069)		
Western Europe H0E901-U300	40	7.88	7.09	-0.90 (0.155)	-0.48 (0.218)	(-0.908, -0.052)
Lantus	42	8.28	7.82	-0.42 (0.154)		
Eastern Europe H0E901-U300	122	8.28	7.51	-0.72 (0.085)	0.18 (0 125)	(-0.068, 0.422)
Lantus	103	8.25	7.31	-0.90 (0.091)		
Rest of the world H0E901-U300	67	8.51	7.95	-0.33 (0.122)	0.15 (0.170)	(-0.185, 0.483)
Lantus	67	8.42	7.76	-0.48 (0.119)		

Study EFC12347						
Northern America H0E901-U300	252	8.52	7.15	-1.34 (0.056)	0.08 (0.081)	(-0.079, 0.238)
Lantus	240	8.65	7.09	-1.42 (0.058)		
Western Europe H0E901-U300	26	8.44	6.89	-1.59 (0.180)	0.20 (0.254)	(-0.301, 0.696)
Lantus	25	8.16	6.61	-1.79 (0.180)		
Eastern Europe H0E901-U300	62	8.56	6.98	-1.58 (0.116)	-0.10 (0.164)	(-0.417, 0.226)
Lantus	62	8.70	7.12	-1.48 (0.116)		
Rest of the world H0E901-U300	25	8.02	6.78	-1.24 (0.69)	-0.20 (0.262)	(-0.716, 0.315)
Lantus	23	7.98	6.91	-1.01 (0.74)		
Study EFC12456						
Northern America H0E901-U300	147	8.09	7.74	-0.34 (0.063)	0.08 (0.091)	(-0.101, 0.255)
Lantus	139	8.06	7.66	-0.41 (0.065)		
Western Europe H0E901-U300	20	7.86	7.42	-0.51 (0.177)	-0.25 (0.233)	(-0.712, 0.204)
Lantus	27	8.24	7.99	-0.25 (0.150)		
Eastern Europe H0E901-U300	35	8.30	7.63	-0.59 (0.133)	-0.16 (0.179)	(-0.512, 0.190)
Lantus	43	8.04	7.65			
Rest of the world H0E901-U300	23	8.42	7.80	-0.47 (0.163)	0.47 (0.239)	(-0.005, 0.935)
Lantus	20	8.52	7.44	-0.94 (0.177)		

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/s/

ANNA E KETTERMANN
01/26/2015

MARK D ROTHMANN
01/26/2015
I concur

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 206538 **Applicant:** Sanofi-aventis U.S. LLC **Stamp Date:** 4/25/2014

Drug Name: insulin glargine [rDNA origin] injection, 300 units/mL **NDA/BLA Type:**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	x			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

Comments for the 74-day letter:

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

The applicant provided SAS codes for calculations involving only primary endpoint (HbA1C). There were no SAS codes submitted supporting other endpoints. Additionally, SAS program codes were not provided for any of the sub studies. Please provide SAS programs for all efficacy endpoints that will appear in the product label.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Anna Kettermann	6/5/2014
Reviewing Statistician	Date
Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANNA E KETTERMANN
06/16/2014

MARK D ROTHMANN
06/16/2014
I concur