

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205692Orig1s000**

**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 #:** 205-692 / No. 0000

**Supplement #:**

**Drug Name:** (b) (4) (insulin glargine [rDNA origin] for injection in a disposable delivery) strength and dosage form U100

**Indication(s):** (b) (4) of adult and pediatric patients with type 1 diabetes mellitus (T2DM) or adult patients with type 2 diabetes mellitus (T2DM) (b) (4)

**Applicant:** Eli Lilly

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**Review Priority:** Standard

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## 1 EXECUTIVE SUMMARY

Studies ABEB and ABEC showed non-inferiority of LY2963016 to Lantus in HbA1c change from baseline to Week 24. The +0.22% (T1DM) and +0.17% (T2DM) upper confidence limits of the treatment differences +0.11% (T1DM) and +0.05 (T2DM), respectively, were less than the 0.4% non-inferiority margin (NIM) (Tables 1 & 2).

The subgroup of LY2963016 vs. US-approved Lantus showed the following:

**T1DM:** The +0.19% [+0.02, +0.36] between treatment difference [95% CI] in HbA1c change from baseline to week 24 showed that the criterion was met for LY2963016 being non-inferior to US-approved Lantus (the upper limit of the CI of +0.36% < +0.4%). The criterion was also met for LY2963016 being inferior to US-approved Lantus (the lower limit of the above confidence interval of +0.02% > 0) (p=0.028).

**T2DM:** The +0.01 [-0.15, +0.18] between treatment difference [95% CI] in HbA1c change from baseline to week 24 showed that LY2963016 was non-inferior to Lantus in patients with T2DM.

**Table 1 ANCOVA\* results of HbA1c (%) change from baseline to Week 24 (LOCF) - ABEB**

Treatment n	ABEB T1DM		US subgroup		EU subgroup	
	LY2963016 n=267	Lantus n=267	LY2963016 n=98	US Lantus n=96	LY2963016 n=169	EU Lantus n=171
LSM Baseline (SE)	7.86 (0.09)	7.90 (0.09)	7.76 (0.12)	7.73 (0.12)	7.85 (0.11)	7.93 (0.12)
LSM Change (SE)	-0.35 (0.05)	-0.46 (0.05)	-0.22 (0.06)	-0.41 (0.06)	-0.46 (0.07)	-0.53 (0.08)
Treatment difference [95% CI], p-value**	<b>+0.11 [-0.002, +0.22] p=0.055</b>		<b>+0.19 [+0.02, +0.36] p=0.028</b>		<b>+0.07 [-0.08, +0.21] p=0.345</b>	

\*Model includes treatment, country and time of baseline basal insulin injection (daytime or evening/bedtime) as fixed effects and baseline HbA1c as covariate

\*\* p-values are for testing for a difference

**Table 2 ANCOVA\* results of HbA1c change (%) from baseline to Week 24 (LOCF) - ABEC**

Treatment n	ABEC		US subgroup**		EU subgroup	
	LY n=369	Lantus n=375	LY n=205	US Lantus n=213	LY n=164	EU Lantus n=162
LSM Baseline (SE)	8.32 (0.08)	8.28 (0.08)	8.34 (0.09)	8.20 (0.09)	8.26 (0.10)	8.32 (0.10)
LSM Change (SE)	-1.29 (0.06)	-1.34 (0.06)	-1.27 (0.07)	-1.28 (0.07)	-1.25 (0.09)	-1.36 (0.09)
Treatment difference [95% CI], p-value <sup>a</sup>	<b>+0.05 [-0.07, +0.17] p=0.40</b>		<b>+0.01 [-0.16, +0.18] p=0.90</b>		<b>+0.11 [-0.07, +0.29] p=0.23</b>	

\*Model includes treatment, country, sulfonylurea use and time of baseline basal insulin injection (daytime or evening/bedtime) as fixed effects and baseline HbA1c as covariate

\*\*No country in the model for US subgroup analysis

<sup>a</sup> p-values are for testing for a difference

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## 2 INTRODUCTION

### 2.1 Overview

This 505(b)(2) application for LY2963016 (insulin glargine, a long-acting basal insulin analogue) relies partly on FDA's findings of safety and effectiveness of the listed reference drugs, Lantus (insulin glargine; Sanofi-Aventis, NDA 21081 approved April 20, 2000) and Lantus SoloStar pen (approved April 25, 2007). The two Phase 3 clinical studies used both US-approved Lantus (US and Puerto Rico sites) and EU-approved Lantus (all other sites, European Union, Mexico and Japan). The review presents the overall study and the subgroup results of US-approved Lantus and the EU-approved Lantus. Two studies, ABEB and ABEC, were conducted, one in type 1 diabetes mellitus (T1DM) patients and the other in type 2 diabetes mellitus (T2DM) patients (Tables 3 and 4).

#### Studies included in analysis

**Table 3 Study ABEB**

ABEB – T1DM	Dose regimen	Inclusion criteria	Duration & # of patients
Phase 3, prospective, randomized, multicenter, 2-arm, active control, open-label, parallel, 24-week treatment study with a 28-week active control, open label extension period and 4-week posttreatment follow-up in patients with T1DM.	<b>Test: LY2963016 QD, SC.</b> LY2963016 was started at the same dose and administered at same timing (i.e., daytime or nighttime) as the patient's prestudy QD basal insulin and individually titrated. <b>Control: US- or EU-approved LANTUS® QD, SC.</b> LANTUS® was started at the same dose and administered at same timing (i.e., daytime or nighttime) as the patient's prestudy QD basal insulin and individually titrated.	Males and females with T1DM ≥1 year, aged ≥18, BMI ≤35 kg/m <sup>2</sup> , HbA1c ≤11%, on basal-bolus insulin therapy for ≥1 year. Basal insulin must be QD injection of NPH, LANTUS®, or detemir ≥3 months prior to study entry and combined with mealtime injections of human regular insulin, insulin analog lispro, aspart, or glulisine.	52 weeks 24-week treatment: 536 randomized 509 completed US-approved Lantus subgroup: 195 randomized 180 completed 28-week extension: 490 completed US-approved Lantus subgroup: 167 completed extension

The primary objective of Study ABEC was to test the hypothesis that LY2963016 QD was noninferior to LANTUS® QD in HbA1c change from baseline to 24 weeks using a 0.4% NIM, when used in combination with OAMs.

**Table 4 Study ABEC**

ABEC – T2DM	Dose regimen	Inclusion criteria	Duration & # of patients
Phase 3, randomized, multicenter, 2-arm, active control, double-blind, parallel, 24-week treatment, and 4-week posttreatment follow-up study in adult patients with T2DM.	<p><b>Test: LY2963016 QD, SC:</b>            Patients on prestudy LANTUS®: Starting LY2963016, at same dose as prestudy LANTUS® QD basal and individual titrated.            Insulin-naïve patients: Starting LY2963016 QD 10-U dose and individually titrated.</p> <p><b>Control: US- or EU-approved LANTUS® QD, SC;</b>            Patients on prestudy LANTUS®: Starting LANTUS® QD, at same dose as prestudy LANTUS® and individually titrated.</p> <p>Insulin-naïve patients: Starting LANTUS® QD 10-U dose and individually titrated</p>	Patients with T2DM, aged ≥18, with BMI ≤45 kg/m <sup>2</sup> , and on ≥2 OAMs (with or without LANTUS®) for ≥12 weeks prior to study entry. Insulin-naïve patients: HbA1c between ≥7.0% and ≤11.0%. Prestudy LANTUS® patients: HbA1c ≤11.0%.	24 weeks  759 randomized 662 completed  US-approved Lantus subgroup: 360 randomized 295 completed

## 2.2 Data Sources

Study report (10/18/2013):

<\\cdsesub1\evsprod\nda205692\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-1-and-type-2-diabetes\5351-stud-rep-contr\i4l-mc-abeb\abeb-04-body.pdf> (T1DM)

<\\cdsesub1\evsprod\nda205692\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-1-and-type-2-diabetes\5351-stud-rep-contr\i4l-mc-abeb\abeb-04-body-addendum.pdf> (US subgroup)

<\\cdsesub1\evsprod\nda205692\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-1-and-type-2-diabetes\5351-stud-rep-contr\i4l-mc-abec\abec-04-body.pdf> (T2DM)

<\\cdsesub1\evsprod\nda205692\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-1-and-type-2-diabetes\5351-stud-rep-contr\i4l-mc-abec\abec-04-body-addendum.pdf> (US subgroup)

Electronic analysis datasets:

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<\\cdsesub1\evsprod\nda205692\0000\m5\datasets\i4l-mc-abec\analysis\legacy\datasets>

Statistical analysis plan (SAP):

<\\cdsesub1\evsprod\nda205692\0008\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-1-and-type-2-diabetes\5351-stud-rep-contr\i4l-mc-abeb\abeb-sap.pdf>

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Labeling amendment:

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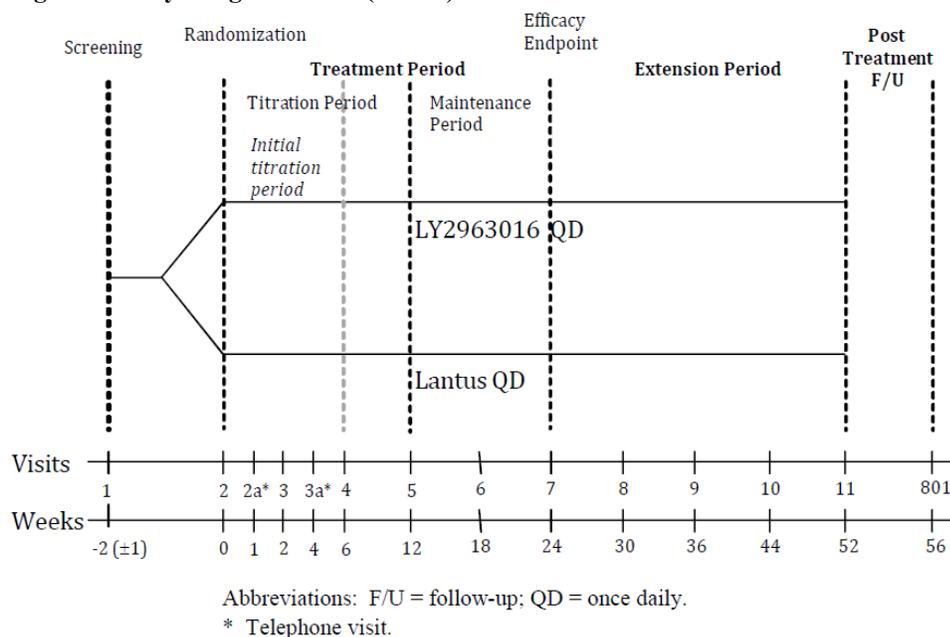
### 3 STATISTICAL EVALUATION

#### 3.1 Evaluation of Efficacy Study ABEB (T1DM)

##### 3.1.1 Study Design and Endpoints

Study ABEB was a randomized, multinational, multicenter, active-controlled, open-label, 24-week treatment study in patients with type 1 diabetes mellitus (T1DM) with an active-controlled 28-week extension and 4-week posttreatment follow-up. Figure 1 displays the study design.

Figure 1 Study design – T1DM (ABEB)



HbA1c was evaluated at visits 1 (screening), 2 (randomization), 4 (week 6), 5 (week 12) and 7 (week 24, efficacy endpoint) and visits 9 (week 36), 11 (week 52) and post-treatment follow up (week 56).

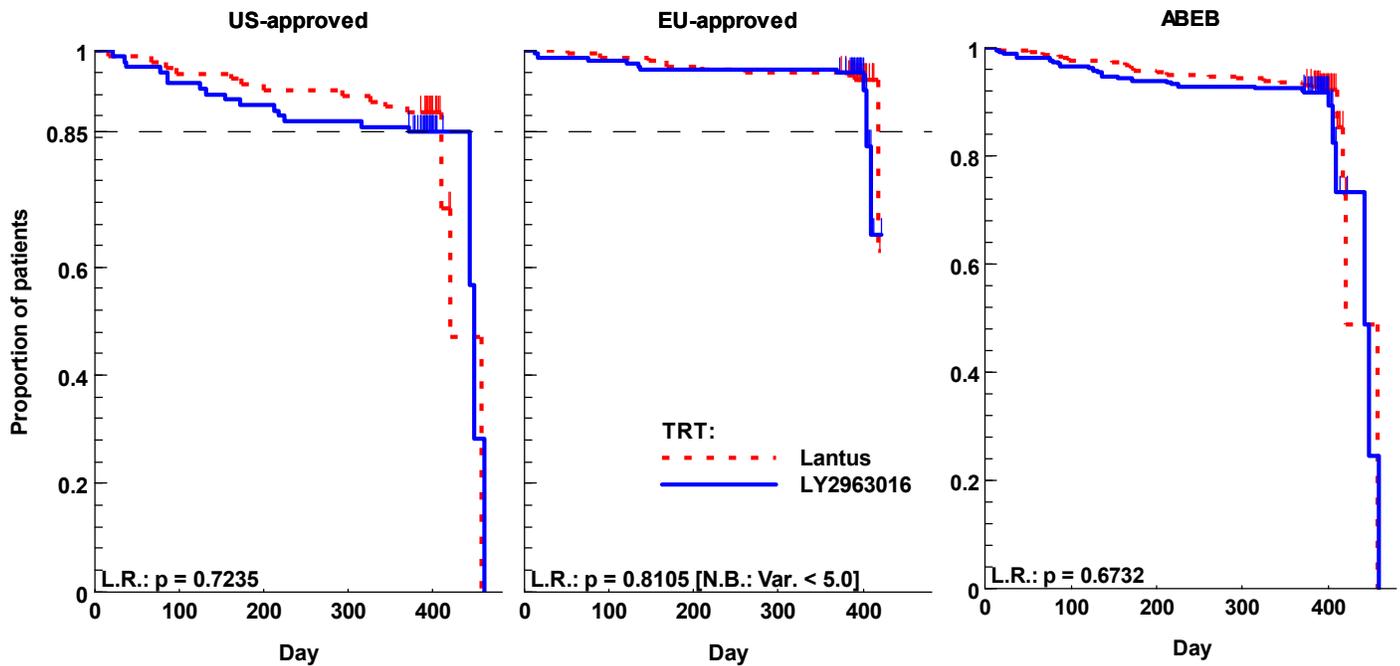
The primary efficacy variable was HbA1c change from baseline to Week 24 or last postbaseline observation carried forward (LOCF). End point (Treatment Phase) is defined as the last non missing HbA1c for visit greater than or equal to 3 (week 2) and less than or equal to 7 (week 24). Study ABEB does not have Week 2 HbA1c evaluation.

The inclusion criteria for patients were: at least 18 years of age at screening, had a diagnosis of T1DM based on the WHO diagnostic criteria, had diabetes for at least 1 year at screening, had an HbA1c value  $\leq 11.0\%$ , had been on basal-bolus insulin therapy for at least 1 year prior to screening. Basal insulin was required to be QD injection of NPH, LANTUS<sup>®</sup>, or detemir for at least 3 months (90 days) prior to screening and combined with mealtime injections of human regular insulin, or insulin analog lispro, aspart, or glulisine and had a body mass index (BMI)  $\leq 35$  kg/m<sup>2</sup>.

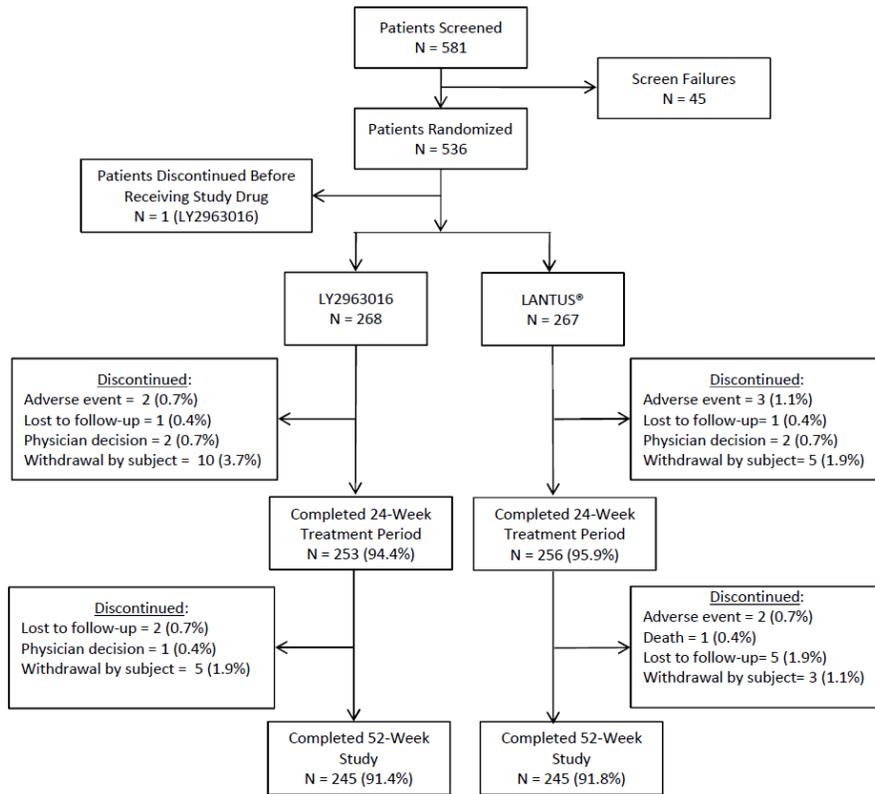
### 3.1.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 536 patients were randomized. Figure 2 displays proportion of all randomized patients on study over time. Figure 3 displays patient disposition from screen to Week 24 (primary efficacy timepoint) and Week 52 for the Full Analysis Set (FAS) population (Sponsor's Figure ABEB.10.1.). Patient 1306, randomized to LY2963016 group discontinued (lost to follow-up) before receiving study drug was not in the FAS. The completion rates were approximately 95% at Week 24 and 92% at Week 52. Table 5 presents disposition in treatment phase for all randomized patients, and US- and EU-approved Lantus subgroups in the treatment phase. Approximately 84% of US-approved Lantus subgroup completed week 24.

**Figure 2 Kaplan Meier curves for proportion of patients on study – All randomized patients**



**Figure 3 Patient disposition – Study ABEB**



**Table 5 ABEB Patient disposition – all randomized treatment phase**

	US-approved Lantus		EU-approved Lantus		ABEB	
	LY	Lantus	LY	Lantus	LY	Lantus
n	100	96	169	171	269	267
Completed	82 (82%)	82 (85%)	159 (94%)	161 (94%)	241 (90%)	243 (91%)
Discontinued	18 (18%)	14 (15%)	10 (6%)	10 (6%)	28 (10%)	24 (9%)
Adverse Event	1 (1%)	1 (1%)	1 (0.6%)	4 (2.3%)	2 (0.7%)	5 (1.9%)
Death	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Entry Criteria Not Met	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lost To Follow-Up	5 (5%)	5 (5.2%)	2 (1.2%)	3 (1.8%)	7 (2.6%)	8 (3%)
Physician Decision	2 (2%)	0 (0%)	1 (0.6%)	2 (1.2%)	3 (1.1%)	2 (0.7%)
Withdrawal By Subject	10 (10%)	7 (7.3%)	6 (3.6%)	1 (0.6%)	16 (5.9%)	8 (3%)

Table 6 and 7 present patient demographics and baseline characteristics, respectively for the FAS population. The overall mean age was 41 years. The majority of patients were less than 65 years in age (95%) and White (75%). More than half of the patients were male (58%). Patient characteristics were generally similar between treatment groups.

**Table 6 – Demographics – FAS**

	US approved		EU approved		ABEB	
	LY n=99	Lantus n=96	LY n=169	Lantus n=171	LY n=268	Lantus n=267
Age (years)						
Mean (SD)	43 (14)	47 (12)	40 (13)	38 (13)	41 (14)	41 (13)
Median [min, max]	42 [18, 69]	49 [22, 69]	38 [18, 81]	36 [20, 72]	40 [18, 81]	41 [20, 72]
Age group n (%)						
< 65 years	94 (95%)	91 (95%)	160 (95%)	165 (96%)	254 (95%)	256 (96%)
≥ 65 years	5 (5%)	5 (5%)	9 (5%)	6 (4%)	14 (5%)	11 (4%)
Gender n (%)						
Male	67 (68%)	57 (59%)	88 (52%)	98 (57%)	155 (58%)	155 (58%)
Female	32 (32%)	39 (41%)	81 (50%)	73 (43%)	113 (42%)	112 (42%)
Race n (%)	n=98	n=96				
Caucasian	89 (91%)	94 (98%)	108 (64%)	107 (63%)	197 (74%)	201 (75%)
Black	8 (8%)	2 (2%)	1 (0.6%)	0	9 (3%)	2 (0.7%)
Asian	0	0	49 (29%)	51 (30%)	49 (18%)	51 (19%)
American Indian or Alaskan native	0	0	11 (7%)	12 (7%)	11 (4%)	12 (5%)
Multiple	1 (1%)	0	0	1 (0.6%)	1 (0.4%)	1 (0.4%)
Ethnic group	n=99	n=95	n=169	n=171	n=268	n=266
Hispanic	2 (2%)	1 (1%)	9 (5%)	9 (5%)	11 (4%)	10 (4%)
Non-Hispanic	96 (97%)	94 (99%)	81 (48%)	76 (44%)	177 (66%)	170 (64%)
Not applicable (for sites not located in the US)	1 (1%)	0	79 (47%)	86 (50%)	80 (30%)	86 (32%)
Country n(%)						
United States	99 (100%)	96 (100%)			99 (37%)	96 (36%)
Belgium			12 (7%)	11 (6%)	12 (5%)	11 (4%)
Germany			26 (15%)	28 (16%)	26 (10%)	28 (11%)
Greece			15 (9%)	13 (8%)	15 (6%)	13 (5%)
Hungary			14 (8%)	16 (9%)	14 (5%)	16 (6%)
Japan			49 (29%)	51 (30%)	49 (18%)	51 (19%)
Mexico			17 (10%)	19 (11%)	17 (6%)	19 (7%)
Poland			18 (11%)	17 (10%)	18 (7%)	17 (6%)
Romania			18 (11%)	16 (9%)	18 (7%)	16 (6%)
Duration of T1DM (years)						
Mean (SD)	19.5(12.2)	21.1(12.8)	14.3(9.8)	14 (8.6)	16.2 (11)	16.6 (10.8)
Median [min, max]	18.3 [2.3, 54.3]	18.6 [1.1, 55.2]	12.5 [1.0, 51.4]	12.5 [1.4, 41.4]	14.3 [1, 54.3]	15.2 [1.1, 55.2]

	US approved		EU approved		ABEB	
	LY n=99	Lantus n=96	LY n=169	Lantus n=171	LY n=268	Lantus n=267
Duration of diabetes group in years; n(%)						
≤10	26 (26%)	18 (19%)	62 (37%)	66 (39%)	88 (33%)	84 (32%)
>10	73 (74%)	78 (81%)	107 (63%)	105 (61%)	180 (67%)	183 (69%)

**Table 7 – Baseline characteristics – FAS**

Baseline variables	US approved		EU approved		All	
	LY2963016 n=99	Lantus n=96	LY2963016 n=169	Lantus n=171	LY2963016 n=268	Lantus n=267
<b>HbA1c (%)</b>						
<b>Mean (SD)</b>	7.7 (1.1)	7.7 (1.1)	7.8 (1.2)	7.8 (1.0)	7.8 (1.1)	7.8 (1.0)
<b>Median [min, max]</b>	7.7 [5.7, 10.7]	7.7 [5.2, 10.3]	7.7 [4.8, 11.5]	7.8 [5.3, 10.3]	7.7 [4.8, 11.5]	7.7 [5.2, 10.3]
<b>HbA1c (%) Group; n (%)</b>						
< 8.5%	74 (75%)	73 (76%)	129 (76%)	124 (73%)	203 (76%)	197 (74%)
≥ 8.5%	25 (25%)	23 (24%)	40 (24%)	47 (27%)	65 (24%)	70 (26%)
<b>Body Weight (kg)</b>						
<b>Mean (SD)</b>	82 (17)	82 (16)	72 (16)	71 (14)	76 (17)	75 (15)
<b>Median [min, max]</b>	82 [51, 115]	82 [49, 120]	72 [42, 118]	70 [43, 110]	75 [42, 118]	73 [43, 120]
<b>BMI (kg/m<sup>2</sup>)</b>						
<b>Mean (SD)</b>	27 (4)	27 (4)	25 (3)	25 (4)	26 (4)	25 (4)
<b>Median [min, max]</b>	27 [19, 38]	27 [20, 35]	24 [19, 36]	24 [17, 35]	25 [17, 38]	25 [19, 36]
<b>Basal insulin; n(%)</b>						
<b>Lantus</b>	84 (85%)	88 (92%)	134 (79%)	146 (85%)	218 (81%)	234 (88%)
<b>Detemir</b>	11 (11%)	7 (7%)	13 (8%)	13 (8%)	24 (9%)	20 (7%)
<b>Insulin</b>	4 (4%)	1 (1%)	22 (13%)	12 (7%)	26 (10%)	13 (5%)
<b>Time of basal insulin injection; n(%)</b>	n=99	n=96	n=169	n=171	n=268	n=267
<b>Daytime</b>	28 (28%)	27 (28%)	23 (14%)	21 (12%)	51 (19%)	48 (18%)
<b>Evening/Bedtime</b>	71 (72%)	69 (72%)	146 (86%)	150 (88%)	217 (81%)	219 (82%)
<b>Short acting insulin; n(%)</b>						
<b>Lispro</b>	51 (52%)	42 (44%)	73 (43%)	79 (46%)	124 (46%)	121 (45%)
<b>Aspart</b>	37 (37%)	41 (43%)	67 (40%)	65 (38%)	104 (39%)	106 (40%)
<b>Glulisine</b>	6 (6%)	7 (7%)	14 (8%)	13 (8%)	20 (7%)	20 (7%)
<b>Insulin</b>	5 (5%)	5 (5%)	14 (8%)	14 (8%)	19 (7%)	19 (7%)
<b>Insulin Human</b>	0	1 (1%)	0	0	0	1 (0.4%)
<b>Basal insulin dose</b>	n=98	n=96	n=169	n=171	n=267	n=267
<b>Mean (SD)</b>	30 (16)	27 (13)	22 (10)	21 (10)	25 (13)	23 (12)
<b>Median [min, max]</b>	25 [6, 100]	26 [3, 100]	20 [1, 50]	20 [2, 60]	22 [1, 100]	22 [2, 100]
<b>Short acting insulin</b>	n=96	n=96	n=168	n=171	n=264	n=267
<b>Mean (SD)</b>	31 (21)	27 (17)	30 (14)	31 (17)	31 (17)	29 (17)
<b>Median [min, max]</b>	28 [0, 94]	24 [4, 87]	28 [4, 100]	29 [2, 137]	28 [0, 100]	28 [2, 137]

### 3.1.3 Statistical Methodologies

The primary analysis model was an analysis of covariance model (ANCOVA) with treatment, country, time of basal insulin injection (daytime, evening/bedtime) as fixed effects and baseline HbA1c as a covariate. The plan of pooling country with less than 10 patients in similar geographic region was not necessary because all participating countries had at least 10 patients. Secondary efficacy variables included change in HbA1c from baseline to 6, 12, 24, 36, and 52 weeks, 7-point SMBG, daily basal insulin dose, Lispro insulin dose, total daily insulin dose (basal plus lispro bolus doses), weight and body mass index (BMI). The proportions of patients achieving HbA1c target values (HbA1c < 7.0% and ≤ 6.5%) using Fisher's Exact test.

The analysis of the continuous secondary efficacy variables used the same ANCOVA model as the primary efficacy endpoint. Missing data was imputed by the last-observation-carried forward methodology.

### 3.1.4 Results and Conclusions

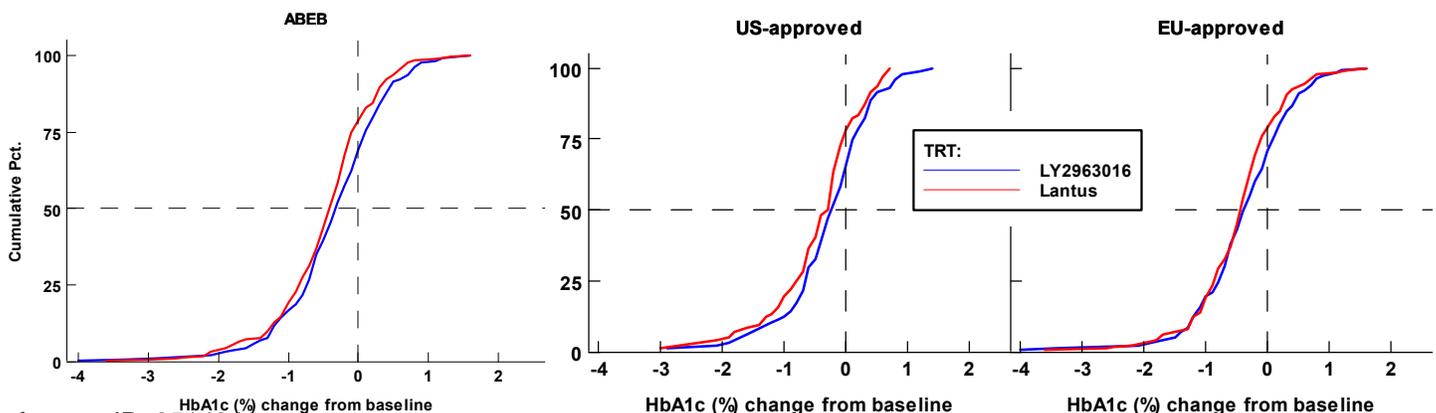
#### Primary efficacy endpoint: HbA1c (%) change from baseline to week 24 (LOCF)

The cumulative distribution (Fig. 4), the boxplots (Fig. 5) and the descriptive statistics (Table 8) showed that Lantus consistently had a little more reduction in HbA1c change from baseline to week 24 (LOCF) than LY2963016.

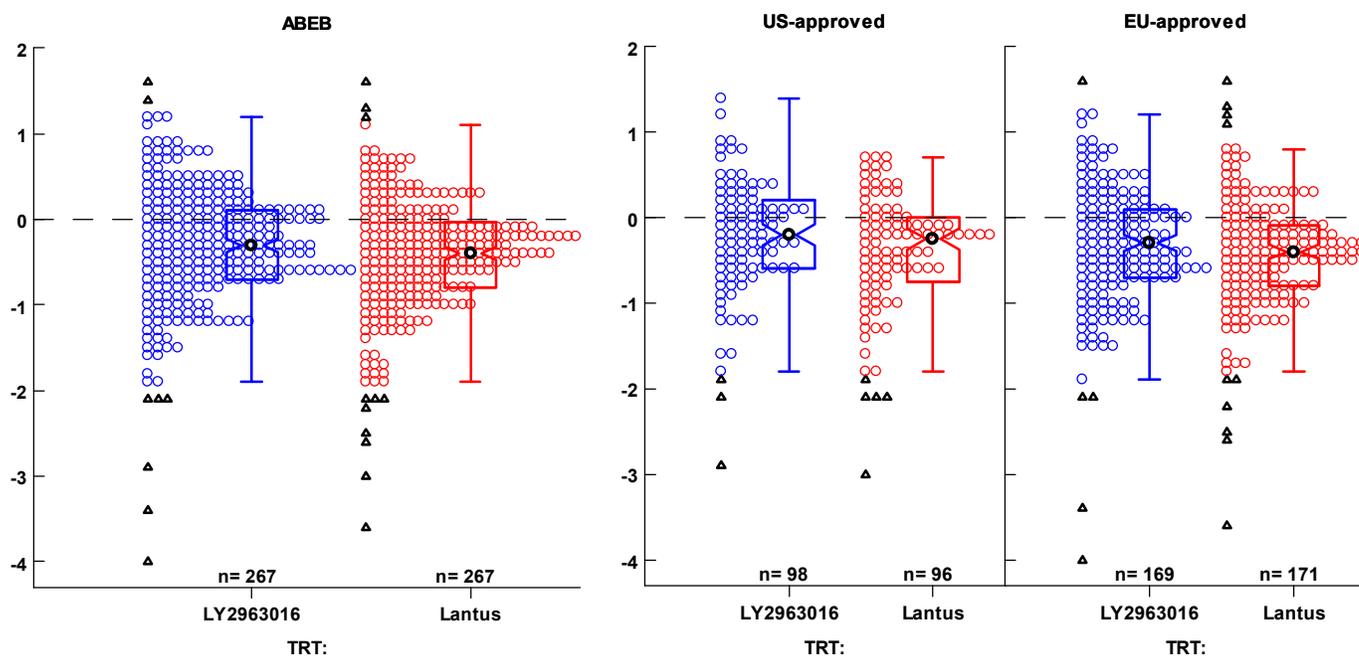
**Table 8 Descriptive statistics of HbA1c change from baseline to week 24 (LOCF)**

	Treatment	N	Variable	Mean	(SD)	Median	Min	Max
ABEB	LY2963016	267	BL	7.75	(1.14)	7.7	4.8	11.5
			chg	-0.32	(0.74)	-0.3	-4	1.6
	Lantus	267	BL	7.79	(1.03)	7.7	5.2	10.3
			chg	-0.43	(0.71)	-0.4	-3.6	1.6
US-approved	LY2963016	98	BL	7.75	(1.11)	7.7	5.7	10.7
			chg	-0.25	(0.70)	-0.2	-2.9	1.4
	Lantus	96	BL	7.72	(1.05)	7.65	5.2	10.3
			chg	-0.43	(0.71)	-0.25	-3	0.7
EU-approved	LY2963016	169	BL	7.76	(1.16)	7.7	4.8	11.5
			chg	-0.36	(0.76)	-0.3	-4	1.6
	Lantus	171	BL	7.83	(1.02)	7.8	5.3	10.3
			chg	-0.44	(0.71)	-0.4	-3.6	1.6

**Figure 4 Cumulative distribution of HbA1c (%) change from baseline to week 24 (LOCF)**



**Figure 5 Boxplots of HbA1c (%) change from baseline to week 24 (LOCF)**



Results from ANCOVA showed that treatment difference in HbA1c change from baseline to week 24 was +0.11% with an upper 95% CI of +0.22% (<0.4% and <0.3% margins). For US subgroup, the +0.36% upper 95% CI was <0.4% NIM. The criteria of inferior to Lantus was met also due to the +0.02% lower 95% CI excluded 0 (p=0.028) (Table 9).

**Table 9 ANCOVA\* results of HbA1c (%) change from baseline to Week 24 (LOCF) - ABEB**

Treatment n	ABEB T1DM		US subgroup		EU subgroup	
	LY2963016 n=267	Lantus n=267	LY2963016 n=98	US Lantus n=96	LY2963016 n=169	EU Lantus n=171
LSM Baseline (SE)	7.86 (0.09)	7.90 (0.09)	7.76 (0.12)	7.73 (0.12)	7.85 (0.11)	7.93 (0.12)
LSM Change (SE)	-0.35 (0.05)	-0.46 (0.05)	-0.22 (0.06)	-0.41 (0.06)	-0.46 (0.07)	-0.53 (0.08)
Treatment difference [95% CI], p-value <sup>a</sup>	+0.11 [-0.002, +0.22] p=0.055		+0.19 [+0.02, +0.36] p=0.028		+0.07 [-0.08, +0.21] p=0.345	

\*Model includes treatment, country and time of baseline basal insulin injection (daytime or evening/bedtime) as fixed effects and baseline HbA1c as covariate

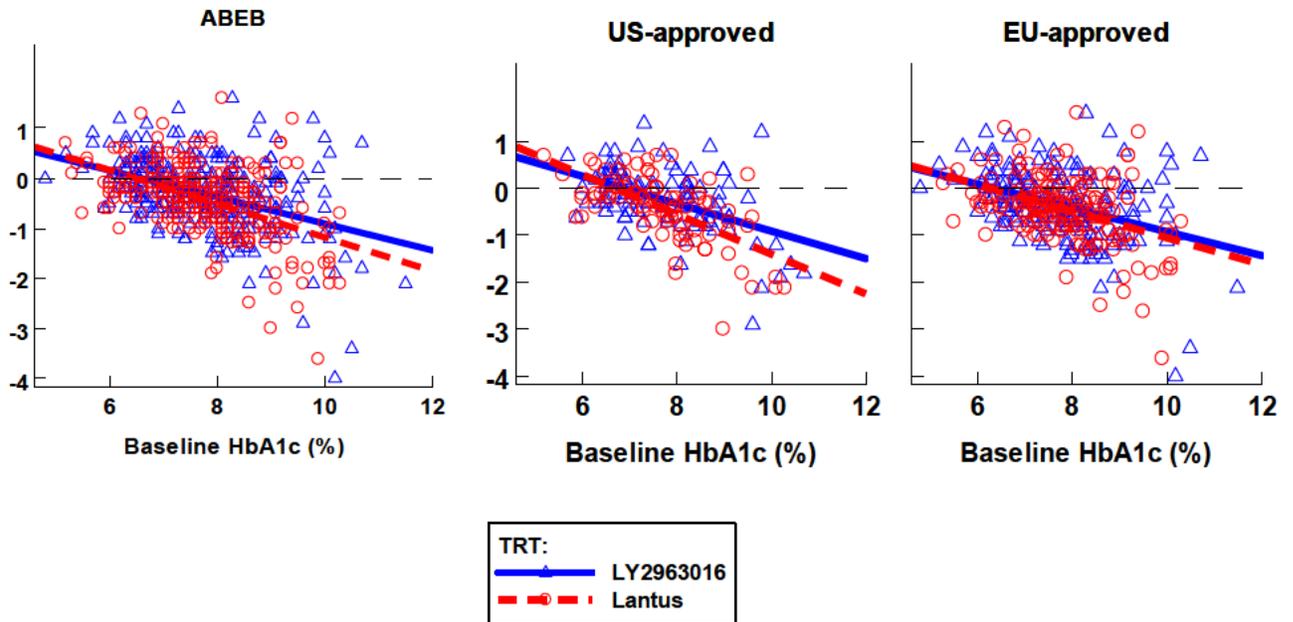
<sup>a</sup>p-values are for testing for a difference

The overall treatment-by-baseline HbA1c interaction was not significant (p=0.22). P-value for treatment-by-baseline HbA1c interaction was 0.10 for US-approved Lantus subgroup and it was 0.68 for EU-approved Lantus subgroup. Note that these interaction tests examine whether the

difference in treatment effects of LY2963016 and Lantus depends on baseline HbA1c. These tests do not provided information on whether the treatment effect of LY2963016 relative to placebo depends on baseline HbA1c.

Figure 6 displays regression of HbA1c change from baseline to week 24 by baseline HbA1c. For US-approved Lantus subgroup, the vertical distance between treatment groups increases as baseline increases.

**Figure 6 HbA1c change from baseline to Week 24 by baseline HbA1c - LOCF**



**Secondary efficacy variables**

**1. 7-point SMBG profiles at Week 24**

The SMBG was collected at 7 time points (pre-meal for each meal, 2 hours after morning and midday meals, bedtime and 3 AM). Table 10 presents descriptive statistics of the 7-point SMBG.

**Table 10 Baseline and change from baseline to week 24 (LOCF) of 7-point SMBG (mg/dL)**

Study ABEB		LY2963016			Lantus		
7-point SMBG		n	Mean (SD)	[Min, Max]	n	Mean (SD)	[Min, Max]
MORNPRE	Baseline	266	151 (54)	[57, 343]	264	148 (54)	[48, 367]
	Change		-8.6 (56)	[-191, 137]		-8.8 (55)	[-217, 135]
MORNPP	Baseline	263	161 (52)	[65, 326]	262	170 (56)	[61, 356]
	Change		-1.9 (62)	[-216, 187]		-14.9 (58)	[-226, 183]
MIDDYPRE	Baseline	266	142 (45)	[53, 328]	265	147 (47)	[64, 321]
	Change		-0.18 (54)	[-156, 202]		-4.3 (52)	[-193, 141]
MIDDYPP	Baseline	264	164 (55)	[68, 397]	264	159 (52)	[61, 308]
	Change		-9.1 (60)	[-188, 184]		-4.5 (57)	[-199, 148]
EVENPRE	Baseline	264	160 (59)	[52, 419]	264	159 (54)	[60, 385]
	Change		-3.4 (62)	[-275, 198]		-5.7 (62)	[-221, 169]
BEDTIME	Baseline	266	167 (60)	[59, 385]	264	169 (57)	[50, 427]
	Change		-10.1 (66)	[-214, 175]		-2.8 (60)	[-215, 166]
AM3	Baseline	262	149 (54)	[31, 352]	257	151 (52)	[42, 351]
	Change		-7.3 (59)	[-220, 139]		-1.1 (54)	[-199, 168]

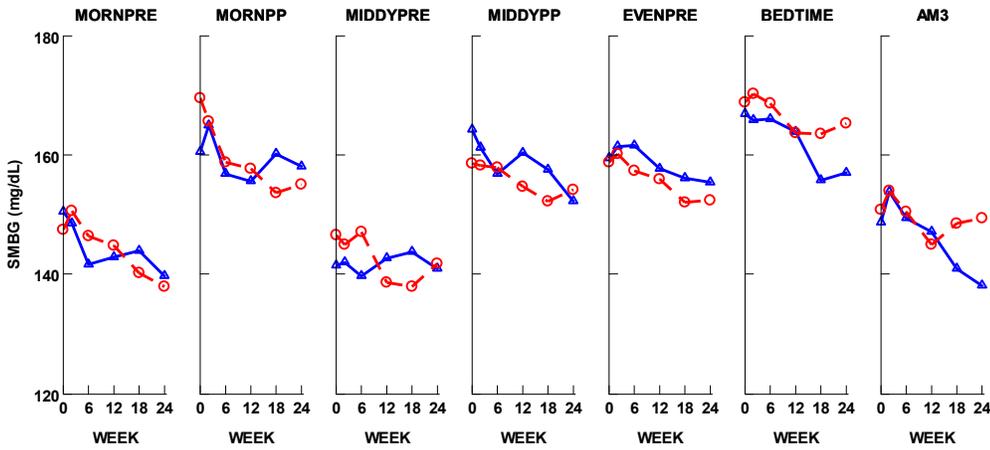
**US-, EU-approved Lantus subgroup**

	US-approved						EU-approved						
	LY2963016			Lantus			LY2963016			Lantus			
	n	Mean SD	Min, Max										
MORNPRE	Baseline	99	165 (58)	[64, 343]	95	150 (53)	[48, 335]	167	142 (50)	[57, 301]	169	146 (55)	[53, 367]
	Change	99	-13.2 (63)	[-191, 137]	95	-6.4 (59)	[-217, 135]	167	-5.8 (52)	[-148, 118]	169	-10.1 (53)	[-159, 121]
MORNPP	Baseline	98	166 (54)	[69, 317]	94	166 (54)	[61, 356]	165	158 (51)	[65, 326]	168	172 (57)	[65, 330]
	Change	98	6.2 (66)	[-216, 187]	94	-14.2 (62)	[-226, 110]	165	-6.7 (59)	[-173, 146]	168	-15.2 (56)	[-213, 183]
MIDDYPRE	Baseline	99	147 (50)	[53, 281]	96	146 (51)	[64, 321]	167	138 (41)	[66, 328]	169	147 (44)	[74, 295]
	Change	99	-0.5 (60)	[-120, 152]	96	-3.1 (60)	[-193, 141]	167	0 (49)	[-156, 202]	169	-4.9 (48)	[-140, 123]
MIDDYPP	Baseline	99	164 (55)	[72, 313]	95	150 (49)	[74, 281]	165	164 (55)	[68, 397]	169	164 (54)	[61, 308]
	Change	99	-6.1 (62)	[-147, 184]	95	4.7 (59)	[-199, 148]	165	-10.8 (58)	[-188, 163]	169	-9.6 (55)	[-159, 138]
EVENPRE	Baseline	98	158 (59)	[52, 366]	95	156 (51)	[67, 282]	166	161 (59)	[70, 419]	169	160 (56)	[60, 385]
	Change	98	-2.2 (71)	[-275, 198]	95	-4.6 (56)	[-161, 146]	166	-4 (56)	[-270, 156]	169	-6.4 (65)	[-221, 169]
BEDTIME	Baseline	99	170 (63)	[59, 385]	95	162 (55)	[50, 359]	167	165 (58)	[69, 381]	169	173 (57)	[67, 427]

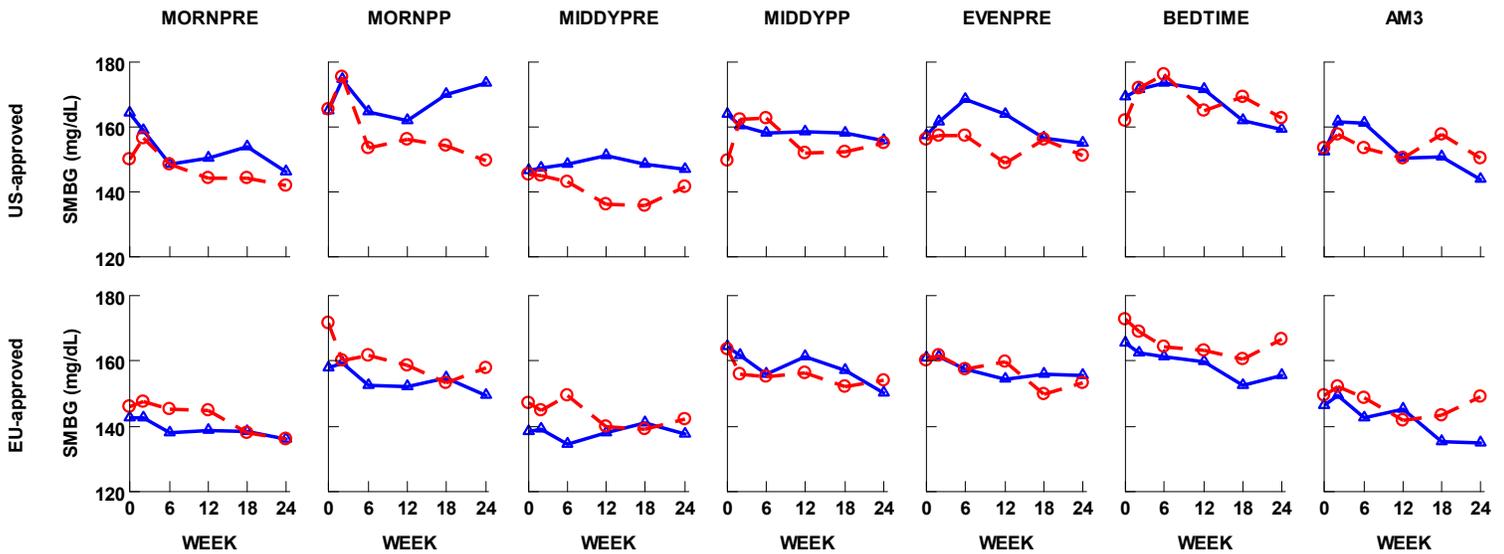
	US-approved						EU-approved					
	LY2963016			Lantus			LY2963016			Lantus		
	n	Mean SD	Min, Max	n	Mean SD	Min, Max	n	Mean SD	Min, Max	n	Mean SD	Min, Max
<b>Change</b>	99	-11.7 (68)	[-195, 124]	95	2.3 (63)	[-215, 124]	167	-9.1 (64)	[-214, 175]	169	-5.6 (58)	[-135, 166]
<b>AM3</b>	99	153 (56)	[51, 328]	93	154 (53)	[42, 294]	163	146 (52)	[31, 352]	164	149 (51)	[52, 351]
<b>Baseline</b>	99	-5.5 (67)	[-220, 139]	93	-1.5 (57)	[-199, 104]	163	-8.4 (53)	[-194, 122]	164	-0.9 (52)	[-174, 168]

Figure 7 displays the 7-point SMBG (mg/dL) over the 24-week treatment period.

**Figure 7 Seven-point SMBG (mg/dL) over time – T1DM Study ABEB**



US-, EU-approved Lantus subgroup:



For ANCOVA analysis, the between treatment group post prandial morning SMBG was nominal significant (not accounting for multiplicity) (p=0.02, overall study and p=0.03, US subgroup) (Tables 11, 12 and Fig. 8).

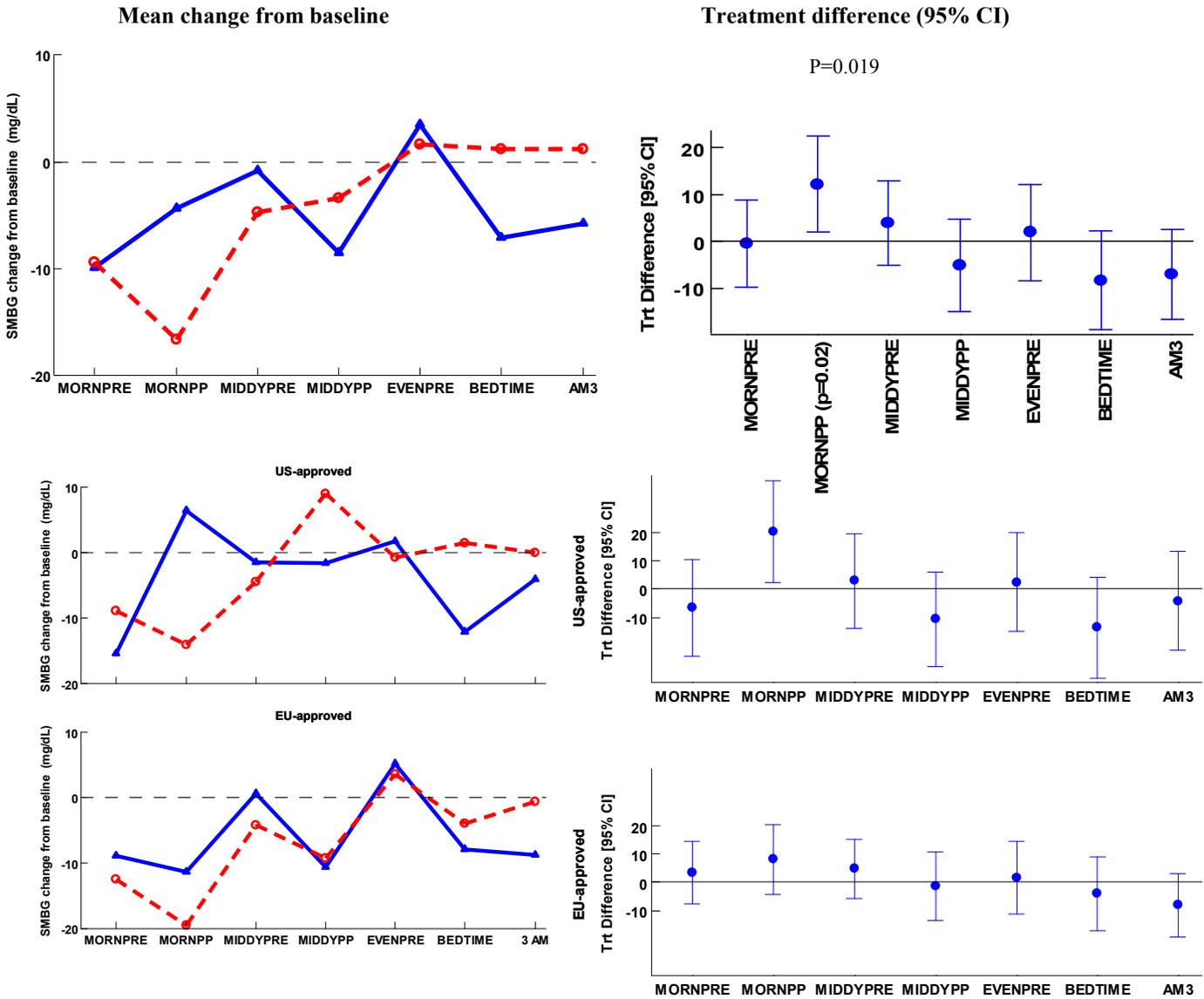
**Table 11 ANCOVA results of SMBG (mg/dL) change from baseline to week 24 (LOCF) (mg/dL) – T1DM**

SMBG	LY2963016 LSM (SE)	Lantus LSM (SE)	Trtdiff [95% CI] p value
MORNPRE	-9.9 (4.5)	-9.4 (4.6)	-0.5 [-9.9, 8.8] p=0.91
MORNPP	-4.4 (4.9)	-16.6 (5.0)	12.2 [2, 22.4] p=0.02*
MIDDYPRE	-0.9 (4.3)	-4.7 (4.4)	3.9 [-5.1, 12.9] p=0.4
MIDDYPP	-8.5 (4.8)	-3.4 (4.8)	-5.1 [-15.0, 4.8] p=0.31
EVENPRE	3.5 (5.0)	1.6 (5.0)	1.9 [-8.5, 12.2] p=0.72
BEDTIME	-7.1 (5.1)	1.2 (5.1)	-8.3 [-18.9, 2.2] p=0.12
AM3	-5.8 (4.6)	1.2 (4.7)	-7.0 [-16.7, 2.6] p=0.15

**Table 12 ANCOVA results of SMBG (mg/dL) change from baseline to week 24 (LOCF) (mg/dL) by Lantus subgroup – T1DM**

SMBG	US-approved			EU-approved		
	LY LSM (SE)	Lantus LSM (SE)	Trt difference [95% CI] p value	LY LSM (SE)	Lantus LSM (SE)	Trt difference [95% CI] p value
MORNPRE	-15.4 (6.4)	-8.8 (6.5)	-6.5 [-23.6, 10.6] p=0.45	-8.9 (5.1)	-12.5 (5.1)	3.6 [-7.5, 14.7] p=0.52
MORNPP	6.5 (6.8)	-14 (6.9)	20.5 [2.5, 38.6] p=0.03	-11.4 (5.6)	-19.5 (5.7)	8.1 [-4.2, 20.5] p=0.2
MIDDYPRE	-1.4 (6.3)	-4.4 (6.3)	3 [-13.7, 19.6] p=0.73	0.6 (4.8)	-4.2 (4.8)	4.8 [-5.6, 15.3] p=0.36
MIDDYPP	-1.6 (6.3)	9 (6.4)	-10.7 [-27.5, 6.2] p=0.21	-10.6 (5.6)	-9.3 (5.6)	-1.3 [-13.5, 11] p=0.84
EVENPRE	1.8 (6.5)	-0.7 (6.6)	2.5 [-14.9, 19.9] p=0.77	5.2 (5.9)	3.5 (5.9)	1.6 [-11.2, 14.5] p=0.8
BEDTIME	-12 (6.7)	1.5 (6.8)	-13.5 [-31.4, 4.3] p=0.14	-8 (6)	-4 (6)	-4 [-17.1, 9.1] p=0.55
AM3	-4 (6.5)	0 (6.7)	-4.1 [-21.5, 13.3] p=0.64	-8.7 (5.2)	-0.6 (5.2)	-8.1 [-19.5, 3.3] p=0.16

**Figure 8 T1DM 7-point SMBG (mg/dL) change from baseline to Week 24 (LOCF)**



## 2. Insulin

### Baseline insulin:

At screening (Visit 1), patients had to be on a basal/bolus insulin regimen for at least 1 year and the basal insulin had to be QD injection of NPH, Lantus (glargine), or detemir for at least 3 months (90 days) prior to screening and combined with prestudy mealtime injections of human regular insulin, or insulin analog lispro, aspart, or glulisine.

Patients who were using insulin glargine BID within 6 months (180 days) prior to Visit 1 were excluded from the study, as the study design involved QD treatment with insulin glargine or LY2963016, and switching from BID to QD insulin glargine dosing may not have been beneficial to the patient.

### Insulin titration:

Because the study participants had been on insulin for at least 1 year, it was possible that their insulins had already been optimized to some extent. For patients whose glycemic control was within desired levels on prestudy insulins, once they were switched from their prestudy insulins to LY2963016 or LANTUS® and insulin lispro on a unit-to-unit conversion, the investigators and patients continued managing the patient's insulin therapy in the manner that effectively maintained glycemic goals (HbA1c <7%, FPG ≤6.0 mmol/L [≤108 mg/dL], other preprandial capillary BGs 70 to 130 mg/dL [3.9 to 7.2 mmol/L], without incurring hypoglycemia).

The treatment period was composed of a titration period (12 weeks) and a maintenance period (12 weeks). To ensure that the HbA1c by Week 24 reflected glycemic control on the patient's insulin regimen, it was expected that most of the basal and bolus insulin adjustments would occur during the initial titration period (Weeks 0 through 6). However, titration could have been extended up to Week 12 for patients who needed more intensification to achieve glycemic targets.

The pre-meal insulin used was insulin lispro. Patients were expected to continue adjusting their bolus insulin. In the process of adjusting the basal and pre-meal insulin, investigators were to be mindful of keeping close to the 50% basal: 50% mealtime insulin ratio.

### Insulin dose (U/d) analysis:

ANCOVA model included treatment and time of baseline basal insulin injection (Daytime or Evening/Bedtime) as fixed effects and baseline HbA1c as covariate. Treatment difference in insulin change (U/d) from baseline to week 24 was not statistically significant for basal insulin, lispro insulin or total insulin (Table 13-15).

**Table 13 ANCOVA results for basal insulin dose change (U/d) at Week 24 (LOCF)**

	US-approved		EU-approved		ABEB	
LSmeans	LY2963016 n=99	Lantus n=96	LY2963016 n=169	Lantus n=170	LY2963016 n=268	Lantus n=266
Baseline (SE)	30.7 (1.53)	27.7 (1.55)	24.9 (0.96)	23.9 (0.99)	25.7 (0.91)	24.0 (0.93)
Change (SE)	2.1 (0.79)	2.2 (0.80)	-1.03 (1.24)	-2.01 (1.27)	2.0 (0.51)	2.0 (0.52)
Trt diff [95% CI]	-0.07 [-2.18, +2.04]		+0.02 [-1.15, +1.19]		-0.01 [-1.07, +1.06]	
p-value	p=0.95		p=0.98		p=0.99	

**Table 14 ANCOVA results for Lispro insulin change (U/d) at Week 24 (LOCF)**

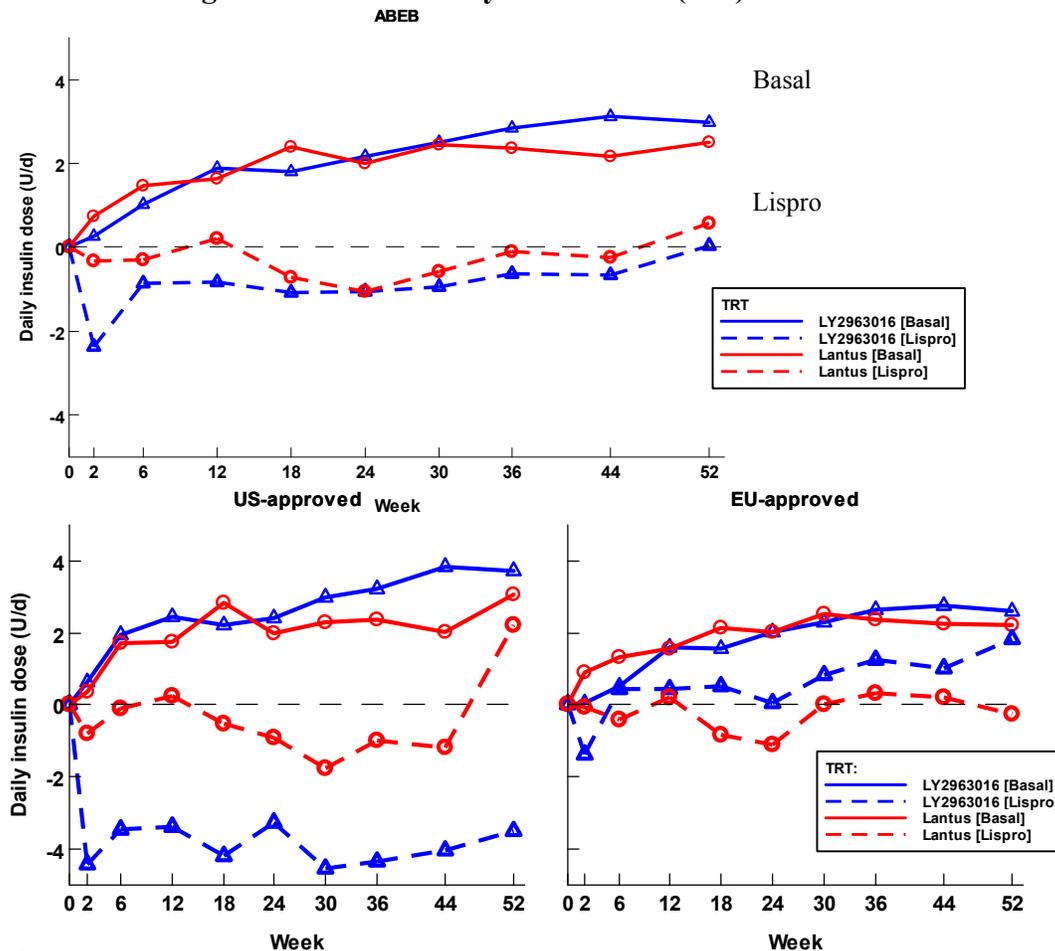
LSmeans	US-approved		EU-approved		ABEB	
	LY2963016 n=96	Lantus n=96	LY2963016 n=168	Lantus n=170	LY2963016 n=264	Lantus n=266
Baseline (SE)	29.3 (2.0)	25.0 (2.0)	27.6 (1.6)	28.4 (1.7)	27.6 (1.34)	26.5 (1.35)
Change (SE)	-2.38 (1.70)	-1.09 (1.70)	-1.03 (1.24)	-2.01 (1.27)	-1.28 (1.07)	-1.44 (1.09)
Trt diff [95% CI] p-value	-1.3 [-5.8, +3.2] p=0.573		+0.98 [-1.43, 3.39] p=0.43		+0.16 [-2.1, +2.4] p=0.888	

**Table 15 ANCOVA results for total insulin dose change (U/d) at Week 24 (LOCF)**

LSmeans	US-approved		EU-approved		ABEB	
	LY2963016 n=96	Lantus n=96	LY2963016 n=168	Lantus n=170	LY2963016 n=264	Lantus n=266
Baseline (SE)	59.7 (3.1)	52.7 (3.1)	52.7 (2.2)	52.4 (2.2)	53.4 (1.9)	50.5 (1.9)
Change (SE)	-0.13 (1.93)	+1.08 (1.93)	+1.31 (1.44)	+0.33 (1.47)	0.75 (1.23)	0.55(1.24)
Trt diff [95% CI] p-value	-1.21 [-6.29, +3.88] p=0.64		+0.98 [-1.82, +3.77] p=0.49		+0.20 [-2.36, +2.75] p=0.88	

Figure 9 displays mean daily basal and lispro insulin change over time.

**Figure 9 Mean change from baseline daily insulin dose (U/d) – T1DM**

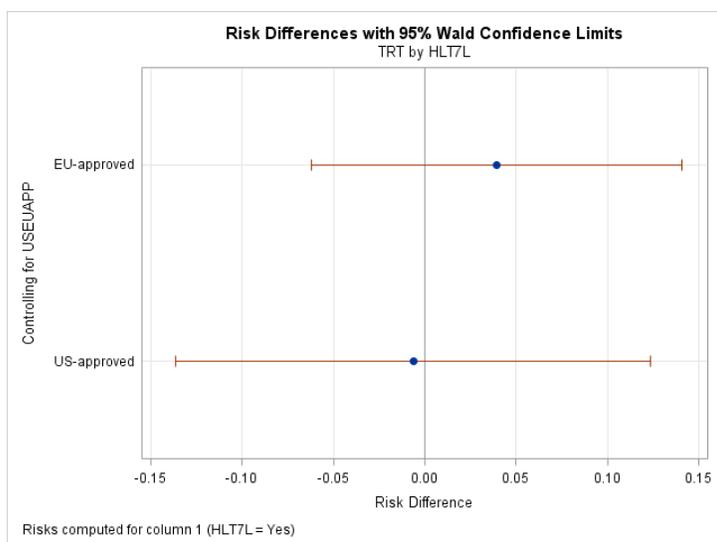


### 3. Proportion of patients with HbA1c <7% at Week 24 (LOCF)

The treatment difference in proportion of patients with HbA1c < 7% was not statistically significant (Table 16). The graph displays risk difference (95% CI) by subgroups. Treatment-by-subgroup interaction was not significant (p=0.28).

**Table 16 Proportion of patients achieving HbA1c < 7% at Week 24**

	<b>LY n=267</b>	<b>Lantus n=267</b>	<b>Treatment Difference</b>	<b>p-value</b>
<b>US-approved Lantus</b>	30/98 (31%)	30/96 (31%)	-0.6% [-14%, +12%]	0.92
<b>EU-approved Lantus</b>	62/169 (37%)	56/171 (33%)	+4% [-6%, +14%]	0.45
<b>Study ABEB</b>	92 (34%)	86 (32%)	+2% [-6%, +10%]	0.58

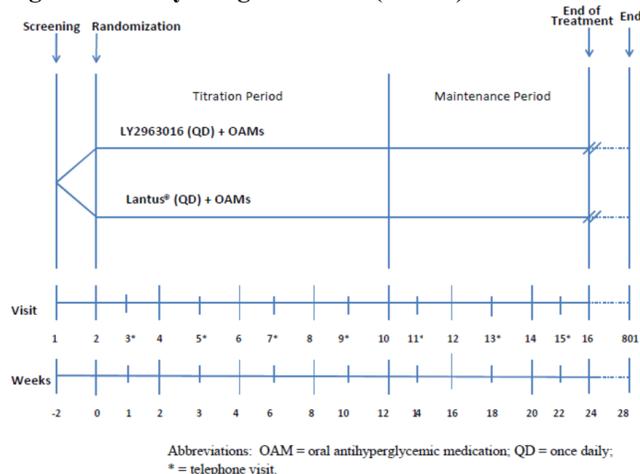


## 3.2 Evaluation of Efficacy – Study ABEC (T2DM)

### 3.2.1 Study Design and Endpoints

Study ABEC was a randomized, multinational, multicenter, active-controlled, double-blind, 24-week treatment study with a 4-week posttreatment follow-up in patients with type 2 diabetes mellitus (T2DM). The study was to show noninferiority of LY2963016 to Lantus in HbA1c change from baseline to Week 24 in T2DM patients who were either insulin naïve and had failed to achieve adequate glycemic control on at least 2 OAMs, or were already on Lantus along with at least 2 OAMs with adequate or inadequate glycemic control. Figure 10 displays the study design.

Figure 10 Study design – T2DM (ABEC)



Eligible patients were at least 18 years of age with a body mass index of  $\leq 45 \text{ kg/m}^2$ . Patients had been treated with 2 or more OAMs at stable doses for 12 weeks prior to visit 1, with or without Lantus, and had an HbA1c  $\geq 7\%$  and  $\leq 11\%$  if insulin naïve, or an HbA1c  $\leq 11\%$  if previously on Lantus.

### 3.2.2 Statistical Methods

The FAS was the primary analysis population which included all patients who were randomized and had taken at least 1 dose of study medication. All efficacy tests of treatment effects were conducted at a 2-sided alpha level of 0.05. No adjustments for multiplicity were performed. Sample size of 284 (568 total) completers per arm calculation assumed no treatment difference in HbA1c between LY2963016 and Lantus, common SD of 1.1% for HbA1c change from baseline, 0.05 2-sided significance level, and over 99% power (0.4% NIM). Assuming a 15% dropout rate at 24 weeks, the required number of randomized patients was 334 (668 total) per arm. The same sample size had 90% power to show noninferiority at 0.3% margin. Blinded sample size re-estimation was performed before the last patient had been enrolled in the study.

The primary analysis model for the HbA1c change from baseline to week 24 was an analysis of covariance model (ANCOVA) with treatment, country, sulfonylurea (SU) use (yes, no), time of basal insulin injection (daytime, evening/bedtime) as fixed effects and baseline HbA1c as a covariate. The primary treatment comparison was to compare LY2963016 versus Lantus at the 0.4% NIM using LOCF data. If the 0.4% NIM was met, then the upper limit of the 95% CI was

compared to the 0.3% noninferiority margin. This gate-keeping procedure controlled the family-wise type 1 error rate at a 1-sided 0.025 level.

Secondary efficacy variables included 7-point SMBG (pre-meal for each meal, post-meal for breakfast and lunch, bedtime and 3 AM), inpatient variability, as measured by the standard deviation (SD) of the FBG, HbA1c change from baseline to weeks 4, 8, 12, 16 and 20 or LOCF, percentage of patients achieved HbA1c target values (HbA1c < 7.0% and ≤ 6.5%), basal insulin dose (24-hour total measured in U/d and U/kg) at end of study and weight.

The analysis of the continuous secondary efficacy variables used the same ANCOVA model as the primary efficacy endpoint. For each efficacy variable, the analysis included all FAS patients with baseline and postbaseline observations.

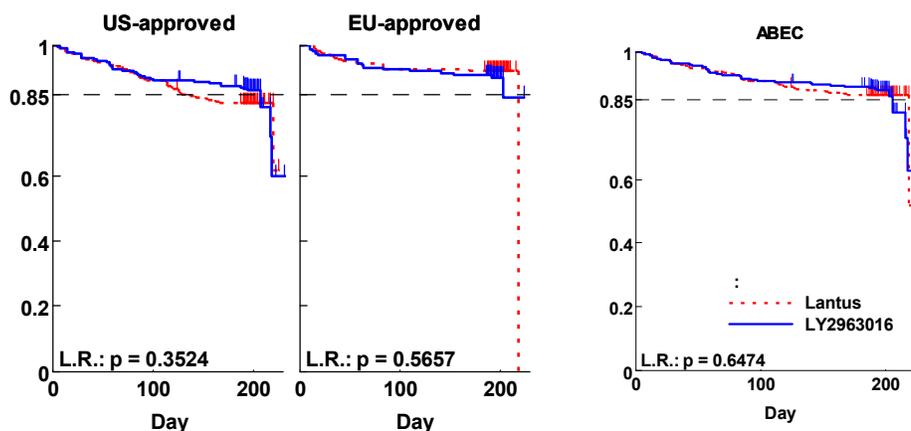
### 3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Of the 759 randomized patients 3 patients discontinued before receiving study drug. For the 756 FAS patients, 376 were in the LY2963016 group and 380 in the Lantus group. The completion rate at week 24 was 89% (334/376) in the LY2963016 group and 86% (328/380) in the Lantus group. Table 17 and Figure 11 display patient disposition for all randomized patients. The US subgroup has a higher discontinued rate (17%) than the EU subgroup (9%).

**Table 17 Patient disposition – T2DM**

	US-approved Lantus		EU-approved Lantus		ABEC	
	LY2963016	Lantus	LY2963016	Lantus	LY2963016	Lantus
n	213	215	166	165	379	380
Completed	180 (85%)	176 (82%)	149 (90%)	151 (92%)	329 (87%)	327 (86%)
Discontinued	33 (15%)	39 (18%)	17 (10%)	14 (8%)	50 (13%)	53 (14%)
Adverse Event	4 (1.9%)	9 (4.2%)	2 (1.2%)	1 (0.6%)	6 (1.6%)	10 (2.6%)
Death	0 (0%)	0 (0%)	1 (0.6%)	1 (0.6%)	1 (0.3%)	1 (0.3%)
Entry Criteria Not Met	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lack of Efficacy	1 (0.5%)	2 (0.9%)	0 (0%)	0 (0%)	1 (0.3%)	2 (0.5%)
Lost To Follow-Up	12 (5.6%)	7 (3.3%)	1 (0.6%)	3 (1.8%)	13 (3.4%)	10 (2.6%)
Physician Decision	6 (2.8%)	6 (2.8%)	3 (1.8%)	3 (1.8%)	9 (2.4%)	9 (2.4%)
Protocol Violation	5 (2.3%)	4 (1.9%)	3 (1.8%)	1 (0.6%)	8 (2.1%)	5 (1.3%)
Sponsor Decision	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Subject Decision	5 (2.3%)	11 (5.1%)	7 (4.2%)	5 (3%)	12 (3.2%)	16 (4.2%)

**Figure 11 Kaplan Meier curves for proportion of patients on study – All randomized patients**



## Demographics and baseline characteristics

The average age was approximately 59 years. The majority of patients were White (78%) and 50% of the patients were male. The mean BMI was approximately 32 kg/m<sup>2</sup>. Mean baseline HbA1c was 8.3%. More than 80% of patients were using SUs prior to randomization and approximately 40% of patients used Lantus at study entry (60% insulin naïve). Patients characteristics were similar between treatment groups (Tables 18, 19).

**Table 18 – Demographics – FAS**

	US approved		EU approved		ABEC	
	LY2963016 n=210	Lantus n=215	LY296301 6 n=166	Lantus n=165	LY2963016 n=376	Lantus n=380
Age (years)						
Mean (SD)	58 (10)	58 (10)	60 (11)	59 (10)	59 (10)	59 (10)
Median [min, max]	59 [31, 83]	58 [28, 81]	61 [34, 85]	60 [27, 82]	59 [23, 84]	59 [26, 82]
Age group n (%)						
< 65 years	148 (70%)	162 (75%)	116 (70%)	116 (70%)	264 (70%)	278 (73%)
≥ 65 years	62 (30%)	53 (25%)	50 (30%)	49 (30%)	112 (30%)	102 (27%)
Gender n (%)						
Male	110 (52%)	114 (53%)	69 (42%)	85 (52%)	179 (48%)	199 (52%)
Female	100 (48%)	101 (47%)	97 (58%)	80 (48%)	197 (52%)	181 (48%)
Race n (%)						
Caucasian	178 (85%)	173 (80%)	124 (75%)	118 (72%)	302 (80%)	291 (77%)
Black	26 (12%)	32 (15%)	0	0	26 (7%)	32 (8%)
Asian	3 (1.4%)	8 (4%)	26 (16%)	27 (16%)	29 (8%)	35 (9%)
American Indian or Alaskan native	1(0.5%)	1 (0.5%)	16 (10%)	20 (12%)	17 (5%)	21 (6%)
Multiple	2 (1%)	1 (0.5%)	0	0	2 (0.5%)	1 (0.3%)
Country n(%)						
Czech Republic			18 (11%)	18 (11%)	18 (5%)	18 (5%)
France			8 (5%)	8 (5%)	8 (2%)	8 (2%)
Germany			15 (9%)	13 (8%)	15 (4%)	13 (3%)
Greece			10 (6%)	12 (7%)	10 (3%)	12 (3%)
Hungary			32 (19%)	30 (18%)	32 (9%)	30 (8%)
Italy			6 (4%)	5 (3%)	6 (2%)	5 (1%)
Korea, Republic of			17 (10%)	15 (9%)	17 (5%)	15 (4%)
Mexico			29 (18%)	29 (18%)	29 (8%)	29 (8%)
Poland			12 (7%)	11 (7%)	12 (3%)	11 (3%)
Puerto Rico	39 (19%)	31 (14%)			39 (10%)	31 (8%)
Spain			10 (6%)	12 (7%)	10 (3%)	12 (3%)
Taiwan			9 (5%)	12 (7%)	9 (2%)	12 (3%)
United States	171 (81%)	184 (86%)			171 (46%)	184 (48%)
Duration of diabetes group in years; n(%)						
≤10	95 (45%)	109 (51%)	68 (41%)	77 (47%)	163 (43%)	186 (49%)
>10	115 (55%)	106 (49%)	98 (59%)	88 (53%)	213 (57%)	194 (51%)

**Table 19 – Baseline characteristics – FAS**

Baseline variables	US approved		EU approved		ABEC	
	LY2963016 n=210	Lantus n=215	LY2963016 n=166	Lantus n=165	LY2963016 n=376	Lantus n=380
<b>HbA1c (%)</b>						
<b>Mean (SD)</b>	8.4 (1.1)	8.2 (1.1)	8.3 (1.1)	8.4 (1.1)	8.3 (1.1)	8.3 (1.1)
<b>Median [min, max]</b>	8.3 [4.9, 11.3]	8.1 [5.9, 11.2]	8.2 [5.9, 10.9]	8.3 [6.0, 11.0]	8.3 [4.9, 11.3]	8.2 [5.9, 11.2]
<b>HbA1c (%) Group; n (%)</b>						
< 8.5%	118 (56%)	130 (60%)	92 (55%)	97 (59%)	210 (56%)	227 (60%)
≥ 8.5%	92 (44%)	85 (40%)	74 (45%)	68 (41%)	166 (44%)	153 (40%)
<b>Body Weight (kg)</b>						
<b>Mean (SD)</b>	98 (20)	95 (17)	81 (15)	84 (20)	90 (20)	90 (19)
<b>Median [min, max]</b>	97 [50, 165]	94 [55, 143]	79 [50, 120]	81 [44, 176]	88 [50, 165]	89 [44, 176]
<b>BMI (kg/m<sup>2</sup>)</b>						
<b>Mean (SD)</b>	34 (6)	33 (5)	30 (5)	31 (5)	32 (6)	32 (5)
<b>Median [min, max]</b>	34 [20, 46]	32 [21, 45]	30 [21, 44]	30 [20, 36]	32 [20, 46]	32 [20, 46]
<b>Sulfonylurea use; n(%)</b>						
Yes	172 (82%)	174 (81%)	143 (86%)	141 (85%)	315 (84%)	315 (83%)
No	38 (18%)	41 (19%)	23 (14%)	24 (15%)	61 (16%)	65 (17%)
<b>Time of basal insulin injection; n(%)</b>						
Daytime	120 (57%)	122 (57%)	67 (40%)	66 (40%)	187 (50%)	188 (49.5%)
Evening/Bedtime	90 (43%)	93 (43%)	99 (60%)	99 (60%)	189 (50%)	192 (50.5%)
<b>Stage of kidney disease at study entry; n(%)</b>						
Kidney damaged with normal or increased GFR (>90 mL/min/1.73 m <sup>2</sup> )	157 (75%)	157 (73%)	95 (57%)	101 (61%)	252 (67%)	258 (68%)
Mild reduction in GFR (60-89 mL/min/1.73 m <sup>2</sup> )	43 (20%)	46 (21%)	55 (33%)	56 (34%)	98 (26%)	102 (27%)
Moderate reduction in GFR (30=59 mL/min/1.73 m <sup>2</sup> )	10 (5%)	11 (5%)	16 (10%)	7 (4%)	26 (7%)	18 (5%)
Severe reduction in GFR (15-29 mL/min/1.73 m <sup>2</sup> )	0	1 (0.5%)	0	1 (0.6%)	0	2 (0.5%)
<b>Entry basal insulin; n(%)</b>						
Lantus	81 (39%)	76 (35%)	74 (45%)	68 (41%)	155 (41%)	144 (38%)
None	129 (61%)	139 (65%)	92 (55%)	97 (59%)	221 (59%)	236 (62%)

### 3.2.4 Results and Conclusions

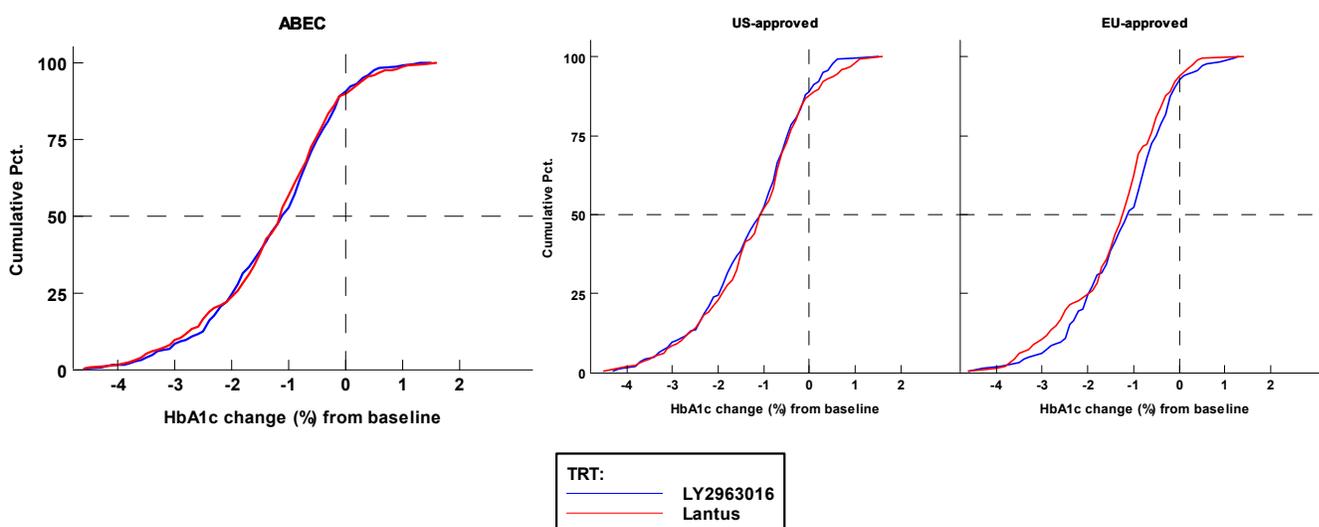
Primary efficacy endpoint: HbA1c (%) change from baseline to week 24 (LOCF)

From a HbA1c baseline of 8.3%, HbA1c median change from baseline to week 24 was -1.1% for both treatment groups (overall study) (Table 20, Figures 12 and 13).

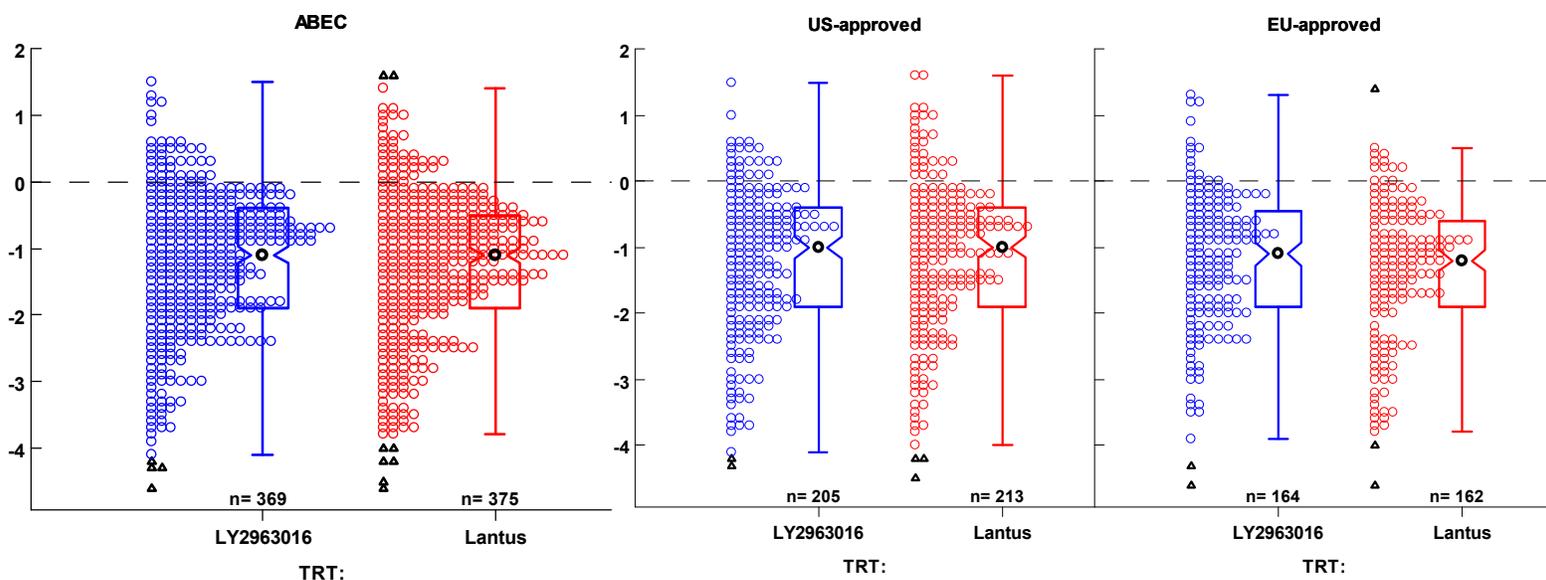
**Table 20 T2DM HbA1c (%) change from baseline to Week 24 (LOCF) descriptive statistics**

	Treatment	Variable	N	Mean	SD	Median	Min	Max
<b>US- approved</b>	LY2963016	BL	205	8.4	(1.1)	8.3	4.9	11.3
		Change		-1.2	(1.1)	-1	-4.3	1.5
	213	BL	213	8.2	(1.1)	8.1	5.9	11.2
		Change		-1.2	(1.2)	-1	-4.5	1.6
<b>EU- approved</b>	LY2963016	BL	164	8.3	(1.1)	8.2	5.9	10.9
		Change		-1.2	(1.1)	-1.1	-4.6	1.3
	Lantus	BL	162	8.4	(1.1)	8.2	6	11
		Change		-1.4	(1.1)	-1.2	-4.6	1.4
<b>ABEC</b>	LY2963016	BL	369	8.4	(1.1)	8.3	4.9	11.3
		Change		-1.2	(1.1)	-1.1	-4.6	1.5
	Lantus	BL	375	8.3	(1.1)	8.1	5.9	11.2
		Change		-1.3	(1.1)	-1.1	-4.6	1.6

**Figure 12 Cumulative distribution of HbA1c (%) change from baseline to week 24 (LOCF)**



**Figure 13 Boxplots of HbA1c (%) change from baseline to week 24 (LOCF)**



ANCOVA results showed that treatment difference (LY-Lantus) in HbA1c change from baseline to week 24 was +0.05% with an upper 95% CI of +0.17% (<0.4% (US margin) and <0.3% (EU margin)). The p-value was 0.40 for the study and 0.88 and 0.23 for the US subgroup and EU subgroup, respectively (Table 21). It is concluded that the LY2963016 was noninferior to Lantus in patients with T2DM.

**Table 21 ANCOVA\* results of HbA1c change (%) from baseline to Week 24 (LOCF) - ABEC**

Treatment n	ABEC		US subgroup		EU subgroup	
	LY n=369	Lantus n=375	LY n=205	US Lantus n=213	LY n=164	EU Lantus n=162
LSM Baseline (SE)	8.32 (0.08)	8.28 (0.08)	8.43 (0.10)	8.30 (0.10)	8.26 (0.10)	8.32 (0.10)
LSM Change (SE)	-1.29 (0.06)	-1.34 (0.06)	-1.29 (0.08)	-1.30 (0.08)	-1.25 (0.09)	-1.36 (0.09)
Treatment difference [95% CI], p-value	<b>+0.05 [-0.07, +0.17] p=0.40</b>		<b>+0.01 [-0.15, +0.18] p=0.88</b>		<b>+0.11 [-0.07, +0.29] p=0.23</b>	

\*Model includes treatment, country, sulfonylurea use and time of baseline basal insulin injection (daytime or evening/bedtime) as fixed effects and baseline HbA1c as covariate

**Secondary efficacy endpoint:**

**1. 7-point SMBG**

The 7-point SMBG were measured pre-meal for each meal, post-meal for breakfast and lunch, bedtime and 3 AM.

Table 22, 23 and Figure 14 display descriptive statistics and ANCOVA results for baseline and change from baseline for the 7-point SMBG. The treatment differences were not significant.

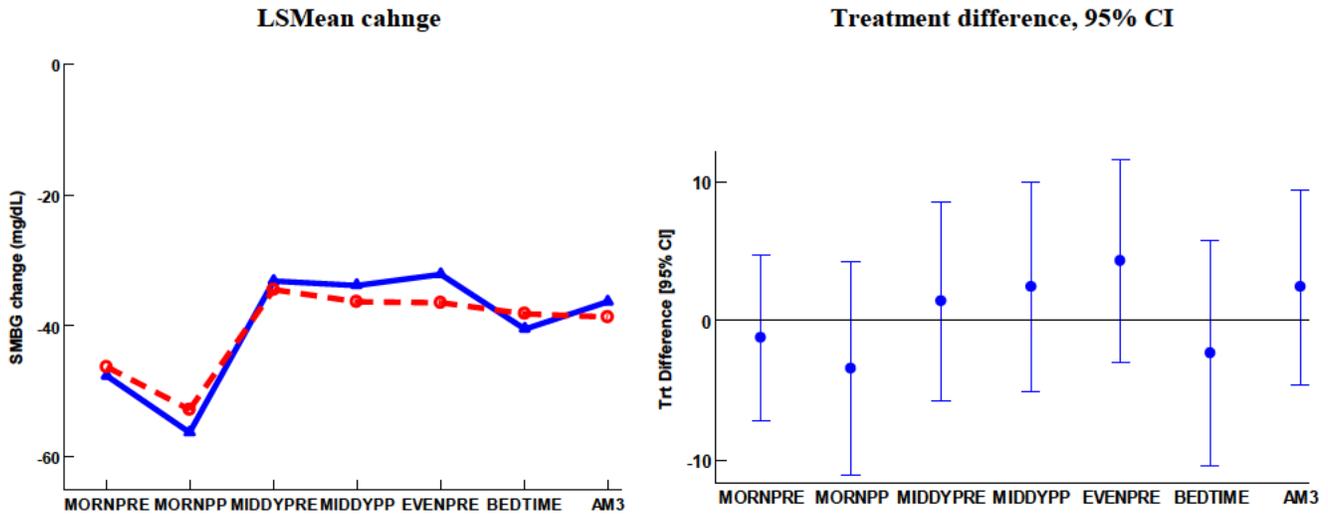
**Table 22 Baseline and change from baseline to week 24 (LOCF) of 7-point SMBG (mg/dL) – T2DM, ABEC**

7-point SMBG		LY2963016			Lantus		
		n	Mean (SD)	[Min, Max]	n	Mean (SD)	[Min, Max]
MORNPRE	Baseline	353	159 (45)	[54, 337]	359	160 (44)	[59, 327]
	Change		-49 (47)	[-234, 106]		-48 (44)	[-199, 78]
MORNPP	Baseline	356	211 (57)	[88, 399]	356	213 (53)	[97, 428]
	Change		-58 (59)	[-295, 156]		-54 (55)	[-316, 107]
MIDDYPRE	Baseline	357	164 (51)	[74, 348]	357	170 (53)	[44, 354]
	Change		-37 (55)	[-189, 129]		-38 (54)	[-253, 135]
MIDDYPP	Baseline	357	192 (52)	[84, 370]	353	196 (51)	[92, 380]
	Change		-35 (56)	[-242, 160]		-36 (56)	[-243, 127]
EVENPRE	Baseline	356	167 (52)	[69, 374]	354	173 (51)	[75, 323]
	Change		-30 (56)	[-235, 121]		-34 (52)	[-226, 109]
BEDTIME	Baseline	355	203 (55)	[66, 364]	354	201 (56)	[91, 447]
	Change		-43 (62)	[-245, 212]		-40 (58)	[-245, 168]
3 AM	Baseline	342	159 (52)	[67, 423]	341	161 (49)	[63, 331]
	Change		-37 (54)	[-323, 102]		-39 (50)	[-190, 82]

**Table 23 ANCOVA results of SMBG (mg/dL) change from baseline to week 24 (LOCF) – T2DM, ABEC**

	LY2963016 LSM (SE)	Lantus LSM (SE)	Trt difference [95% CI] p value
MORNPRE	-48 (3)	-46 (3)	-1.2 [-7.2, 4.7] p=0.68
MORNPP	-56 (3.9)	-53 (4)	-3.4 [-11.1, 4.3] p=0.38
MIDDYPRE	-33 (3.7)	-34 (3.7)	1.4 [-5.8, 8.6] p=0.7
MIDDYPP	-34 (3.8)	-36 (3.9)	2.4 [-5.1, 9.9] p=0.53
EVENPRE	-32 (3.7)	-36 (3.8)	4.3 [-3, 11.5] p=0.25
BEDTIME	-41 (4.1)	-38 (4.2)	-2.4 [-10.4, 5.7] p=0.57
AM3	-36 (3.8)	-39 (3.8)	2.4 [-4.6, 9.4] p=0.51

**Figure 14 T2DM 7-point SMBG (mg/dL) LSM change from baseline to Week 24 (LOCF)**



**Lantus (US, EU) subgroup:**

Tables 24 and 25 display the descriptive statistics and ANCOVA results, respectively for the 7-point SMBG. The 7-point SMBG changes from baseline to week 24 (LOCF) were not significant different between treatment groups (Fig 15).

**Table 24 Baseline and change from baseline to week 24 (LOCF) of 7-point SMBG (mg/dL) by Lantus subgroup – T2DM**

	US-approved						EU-approved					
	LY2963016			Lantus			LY2963016			Lantus		
	n	Mean SD	Min, Max	n	Mean SD	Min, Max	n	Mean SD	Min, Max	n	Mean SD	Min, Max
<b>MORNPRE</b>	194	165	[62,	201	163	[59,	159	152	[54,	158	155	[73,
Baseline		(46)	287]		(45)	327]		(43)	337]		(41)	289]
Change	194	-52	[-181,	201	-48	[-176,	159	-46	[-234,	158	-47	[-199,
		(50)	106]		(46)	78]		(42)	48]		(42)	50]
<b>MORNPP</b>	197	214	[88,	201	216	[97,	159	206	[112,	155	208	[106,
Baseline		(57)	397]		(51)	424]		(56)	399]		(56)	428]
Change	197	-61	[-218,	201	-55	[-277,	159	-54	[-295,	155	-54	[-316,
		(60)	156]		(57)	107]		(57)	77]		(53)	36]
<b>MIDDYPRE</b>	197	170	[77,	202	175	[44,	160	156	[74,	155	164	[83,
Baseline		(54)	348]		(55)	343]		(47)	332]		(50)	354]
Change	197	-42	[-189,	202	-38	[-210,	160	-30	[-185,	155	-37	[-253,
		(58)	129]		(57)	106]		(51)	115]		(50)	135]
<b>MIDDYPP</b>	197	195	[84,	199	199	[92,	160	187	[98,	154	193	[101,
Baseline		(52)	349]		(52)	380]		(51)	370]		(50)	348]
Change	197	-39	[-233,	199	-37	[-243,	160	-29	[-242,	154	-35	[-203,
		(58)	126]		(56)	127]		(54)	160]		(55)	122]
<b>EVENPRE</b>	197	171	[69,	200	174	[75,	159	163	[71,	154	172	[84,
Baseline		(55)	374]		(54)	323]		(48)	324]		(47)	312]
Change	197	-32	[-235,	200	-31	[-226,	159	-28	[-232,	154	-37	[-207,
		(60)	102]		(56)	93]		(52)	121]		(48)	109]
<b>BEDTIME</b>	196	210	[66,	199	205	[95,	159	194	[90,	155	197	[91,
Baseline		(55)	364]		(54)	447]		(54)	356]		(57)	430]
Change	196	-49	[-236,	199	-38	[-218,	159	-35	[-245,	155	-42	[-245,
		(61)	158]		(60)	168]		(63)	212]		(55)	95]

	US-approved						EU-approved					
	LY2963016			Lantus			LY2963016			Lantus		
	n	Mean SD	Min, Max	n	Mean SD	Min, Max	n	Mean SD	Min, Max	n	Mean SD	Min, Max
AM3 Baseline	192	165 (53)	[67, 423]	191	164 (49)	[63, 286]	150	152 (49)	[73, 361]	150	157 (49)	[65, 331]
AM3 Change	192	-40 (58)	[-323, 102]	191	-39 (51)	[-188, 76]	150	-33 (49)	[-194, 88]	150	-40 (48)	[-190, 82]

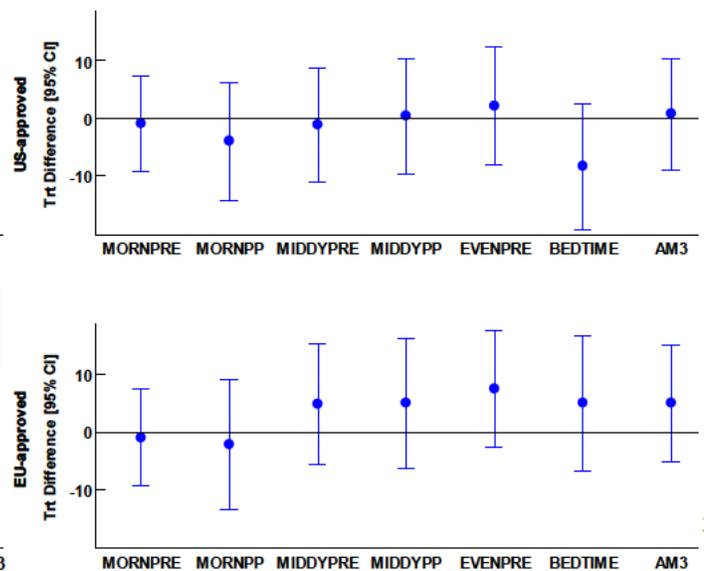
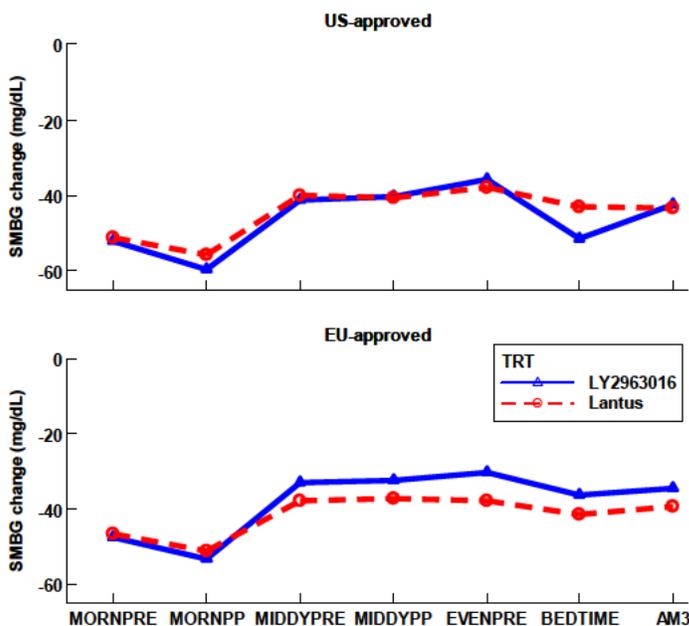
**Table 25 ANCOVA results of SMBG (mg/dL) change from baseline to week 24 (LOCF) (mg/dL) by Lantus subgroup – T2DM**

	US-approved			EU-approved		
	LY	Lantus	LY - Lantus	LY	Lantus	LY - Lantus
7-point SMBG	LSM (SE)	LSM (SE)	Trt difference [95% CI] p value	LSM (SE)	LSM (SE)	Trt difference [95% CI] p value
MORNPRE	-52 (3.5)	-51 (3.4)	-1 [-9.3, 7.3] p=0.82	-47 (3.7)	-46 (3.7)	-0.9 [-9.4, 7.5] p=0.83
MORNPP	-60 (4.3)	-56 (4.3)	-4 [-14.4, 6.3] p=0.44	-53 (5.0)	-51 (5.0)	-2.2 [-13.6, 9.2] p=0.71
MIDDYPRE	-41 (4.2)	-40 (4.1)	-1.2 [-11.1, 8.8] p=0.82	-33 (4.6)	-38 (4.6)	4.9 [-5.5, 15.2] p=0.36
MIDDYPP	-40 (4.2)	-41 (4.1)	0.3 [-9.6, 10.3] p=0.95	-32 (5.0)	-37 (5.0)	5 [-6.3, 16.3] p=0.39
EVENPRE	-36 (4.3)	-38 (4.2)	2.1 [-8.1, 12.4] p=0.68	-30 (4.5)	-38 (4.5)	7.5 [-2.7, 17.7] p=0.15
BEDTIME	-51 (4.5)	-43 (4.5)	-8.4 [-19.4, 2.5] p=0.13	-36 (5.2)	-41 (5.2)	5 [-6.8, 16.9] p=0.4
AM3	-43 (4.1)	-43 (4.1)	0.7 [-9, 10.4] p=0.89	-35 (4.4)	-40 (4.4)	5 [-5.1, 15] p=0.33

**Figure 15 T2DM 7-point SMBG (mg/dL) change from baseline to Week 24 (LOCF)**

LSm change from baseline

Treatment difference (95% CI)



## 2. Basal insulin dose

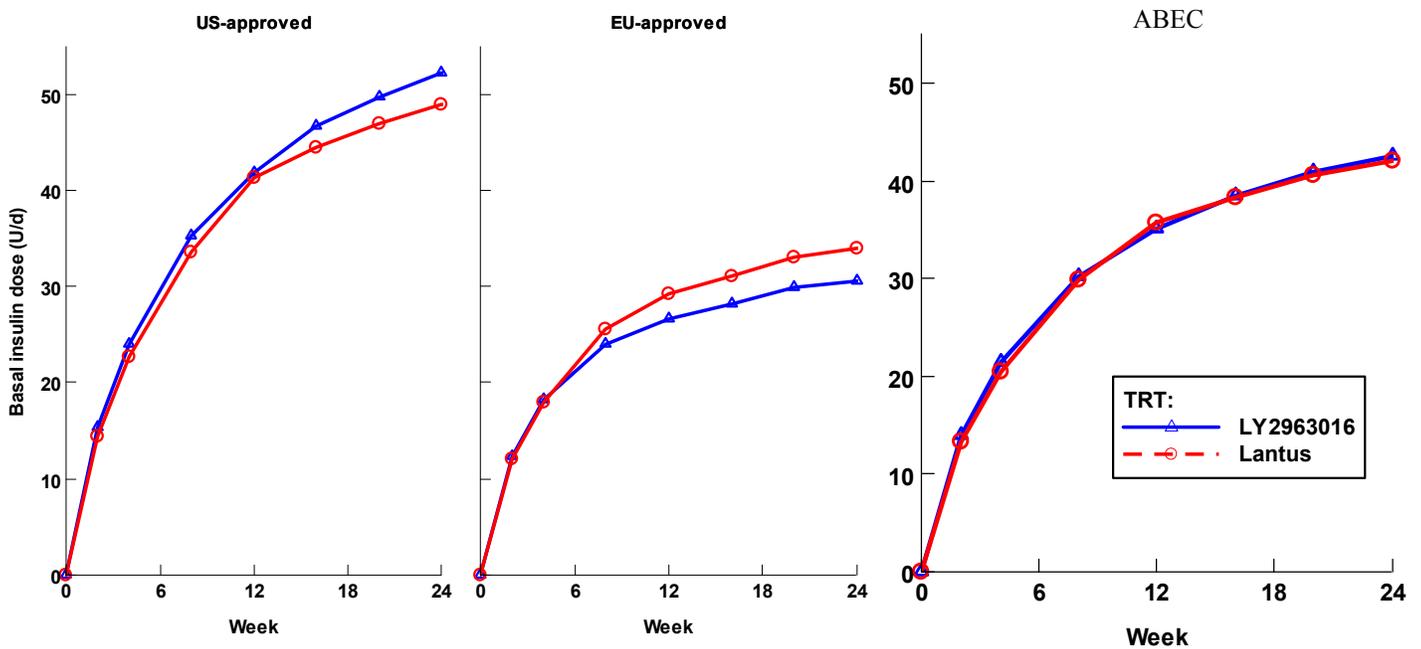
Treatment difference in basal insulin change (U/d) from baseline to week 24 was not statistically significant (Table 26). Figure 16 displays basal insulin over time.

**Table 26 ANCOVA\* results for daily basal insulin dose change from baseline (U/d) to Week 24 (LOCF)**

LSmeans (SE)	ABEC		US-approved Lantus		EU-approved Lantus	
	LY2963016 n=374	Lantus n=379	LY2963016 n=209	Lantus n=214	LY2963016 n=165	Lantus n=165
Baseline (SE)	15.4 (1.2)	12.0 (1.2)	19.2 (2.5)	13.3 (2.5)	11.0 (1.55)	9.6 (1.54)
Change (SE)	32.3 (2.5)	32.6 (2.5)	51.2 (3.57)	49.9 (3.62)	28.5 (2.45)	31.0 (2.44)
Trt difference [95% CI] p-value	-0.27 [-0.51, +4.60] p=0.913		+1.3 [-6.34, +9.00] p=0.736		-2.48 [-7.68, +2.71] p=0.347	

ANCOVA model included treatment, country and time of baseline basal insulin injection (Daytime or Evening/Bedtime) as fixed effects and baseline HbA1c as covariate

**Figure 16 Mean change from baseline of basal insulin dose – T2DM**

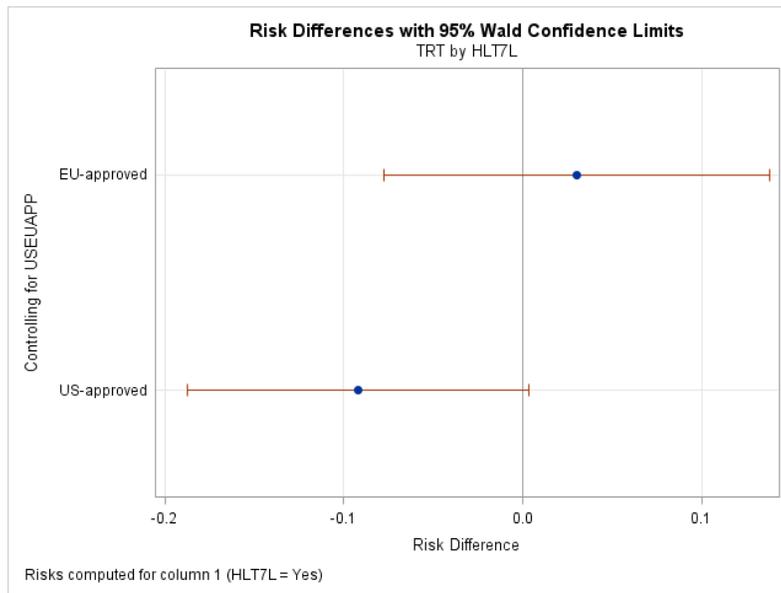


### 3. Proportion of patients with HbA1c <7% at Week 24 (LOCF)

Treatment difference in the proportion of patients with HbA1c<7% was not statistically significant (Table 27). The graph displays risk difference by subgroups. No treatment-by-subgroup interaction was detected (p=0.27)

**Table 27 Proportion of patients achieving HbA1c < 7% at Week 24**

	<b>LY2963016</b>	<b>Lantus</b>	<b>Treatment Difference</b>	<b>p-value</b>
<b>US-approved Lantus</b>	87/205 (41%)	110/213 (52%)	-9.2% [-19%, +0.3%]	0.06
<b>EU-approved Lantus</b>	93/164 (57%)	87/162 (54%)	+3% [-8%, +14%]	0.59
<b>Study ABEB</b>	180/369 (49%)	197/375 (53%)	-4% [-11%, +3%]	0.31



### 3.3 Evaluation of Safety

#### Severe hypoglycemia

Severe hypoglycemia was defined as a hypoglycemic event requiring assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions (if the patient indicated that he/she “was not capable of treating self and required assistance” (in response to a case report question “How was the treatment administered for the hypoglycemic event?”), and the investigator confirmed this (i.e., answered “Yes” to the question “Did the subject experience a severe hypoglycemic episode with neurological [cognitive] impairment requiring assistance from another person?”)).

The proportion of patients with at least one severe hypoglycemic event during the study was analyzed using Fisher’s Exact Test or the Pearson’s chi-square test for the FAS population (Statistical analysis plan of ABEB and ABEC).

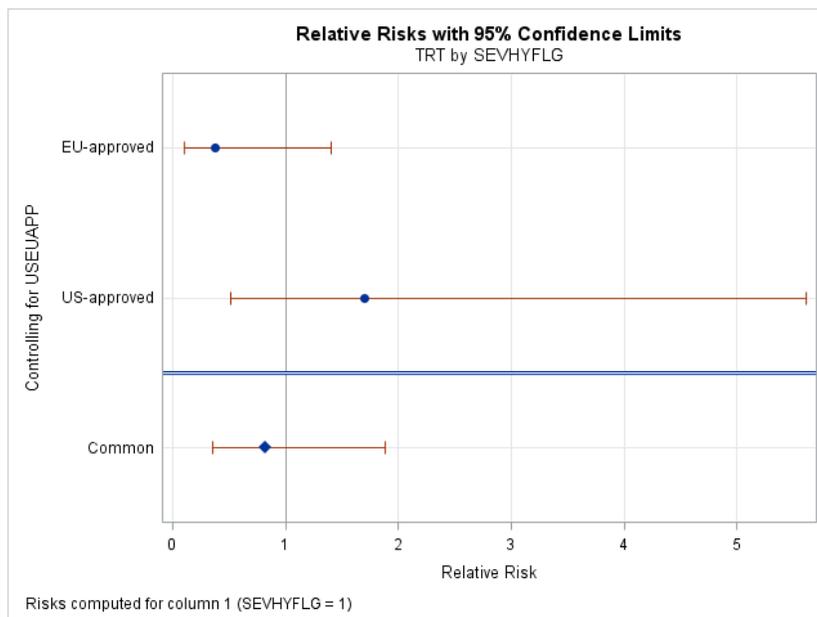
#### T1DM

During the 52-week study, a total of 11 patients had at least 1 event of severe hypoglycemia. During the 4-week follow-up one event of severe hypoglycemia (Lantus) was considered by the investigator to be related to study procedure.

Table 28 displays the percentage of patients with at least 1 severe hypoglycemia event for the 56-week duration. The p-value for the stratified analysis (US- and EU- approved Lantus subgroup) was not significant (0.65). Test for homogeneity of odds ratio was significant (p=0.09). The relative risk (LY/Lantus) of US-approved Lantus subgroup was 1.7>1 while the EU-approved Lantus subgroup was 0.4<1.

**Table 28 Relative risk of severe hypoglycemia - ABEB**

	ABEB		US		EU	
	LY	Lantus	LY	Lantus	LY	Lantus
n/N (%)	10/268 (3.7%)	12/267 (4.5%)	7/99 (7%)	4/96 (4%)	3/169 (1.8%)	8/171 (4.7%)
Relative risk [95% CI]	0.86 [0.35, 2.1]		1.7 [0.5, 5.6]		0.4 [0.1, 1.4]	



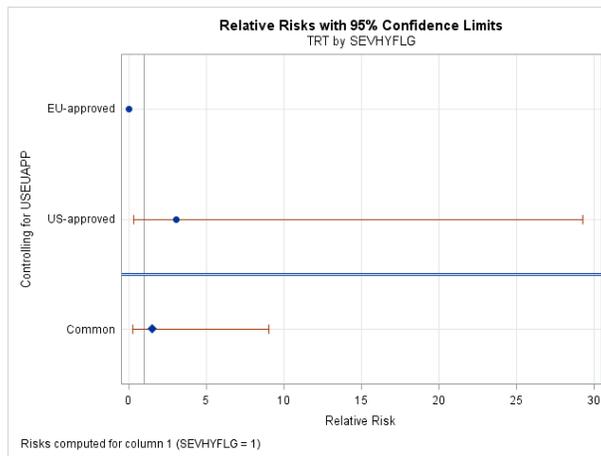
T2DM

A total of 4 patients reported 9 events of severe hypoglycemia (LY: 2 patients, 7 events; Lantus: 2 patients, 2 events) during the 24 weeks treatment period. One patient (603) reported severe hypoglycemia at Visit 801 (follow-up). All 5 patients were listed below. Table 29 displays the percentage of patients with at least 1 severe hypoglycemia event for the 28 weeks duration in the FAS population. The p-value for the stratified analysis (US- and EU- approved Lantus subgroup) was not significant (0.64). Test for homogeneity of odds ratio was not significant (p=0.16).

USEUAPP	TRT	USUBJID
US-approved	Lantus	ABEC-002-0000000200
US-approved	LY2963016	ABEC-006-0000000603
US-approved	LY2963016	ABEC-008-0000000812
US-approved	LY2963016	ABEC-015-0000001516
EU-approved	Lantus	ABEC-039-0000003900

**Table 29 Relative risk of severe hypoglycemia - ABEC**

	ABEC		US		EU	
	LY	Lantus	LY	Lantus	LY	Lantus
n/N (%)	3/376 (0.8%)	2/380 (0.53%)	3/210 (1.4%)	1/215 (0.47%)	0/166 (0%)	1/165 (0.6%)
Relative risk [95% CI]	1.52 [0.25, 9.02]		3.07 [0.32, 29.3]		-	



## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age, and Geographic Region

#### T1DM

More than half (58%) of the patients were males. The treatment-by-gender interaction was not significant ( $p=0.38$ ). Table 30 displays mean (SD) for baseline HbA1c and HbA1c change from baseline to week 24 (LOCF) by gender.

**Table 30 Means (SD) of baseline HbA1c and HbA1c change from baseline to week 24 (LOCF) by gender**

	Gender	n	LY		n	Lantus	
			Baseline	Change		Baseline	change
ABEB	F	112	7.9 (1.1)	-0.3 (0.7)	112	7.9 (1)	-0.4 (0.7)
	M	155	7.7 (1.2)	-0.3 (0.8)	155	7.7 (1)	-0.4 (0.7)
US	F	31	7.8 (1.2)	-0.2 (0.64)	39	7.9 (1)	-0.4 (0.69)
	M	67	7.7 (1.1)	-0.2 (0.73)	57	7.6 (1.1)	-0.5 (0.72)
EU	F	81	7.9 (1)	-0.3 (0.7)	73	7.9 (1)	-0.4 (0.75)
	M	88	7.6 (1.3)	-0.4 (0.82)	98	7.8 (1)	-0.4 (0.68)

#### Race:

The percentages of patients were 74%, 19%, 4%, 2% and 0.4% for White, Asian (Japanese), American Indian or American Native (Mexican), Black or African American, and Multiple, respectively. For ANCOVA, race was classified into white and nonwhite.

Treatment-by-gender interaction was significant ( $p=0.08$ ). The between treatment difference was +0.17% for White and -0.06% for the non-White. For US subgroup, the majority patients were Whites (94%). The number of patients in the non-white subgroup was too few to perform meaningful statistical testing. Table 31 presents mean and SD for baseline HbA1c and HbA1c change from baseline to week 24 (LOCF) by White and non-White.

**Table 31 Means (SD) of baseline HbA1c and HbA1c change from baseline to week 24 (LOCF) by race category**

	Race	n	LY		n	Lantus	
			Baseline(SD)	Change (SD)		Baseline(SD)	Change (SD)
ABEB	White	196	7.7 (1.15)	-0.29 (0.66)	201	7.8 (1.03)	-0.48 (0.66)
ABEB	Non-White	70	7.8 (1.09)	-0.41 (0.91)	66	7.8 (1.03)	-0.3 (0.82)
US-approved	White	88	7.6 (1.04)	-0.21 (0.6)	94	7.7 (1.05)	-0.43 (0.71)
US-approved	Non-White	9	9 (1.1)	-0.76 (1.24)	2	8.3 (1.2)	-0.05 (0.92)
EU-approved	White	108	7.8 (1.24)	-0.35 (0.71)	107	7.9 (1.02)	-0.51 (0.62)
EU-approved	Non-White	61	7.7 (0.99)	-0.36 (0.85)	64	7.7 (1.03)	-0.31 (0.82)

Age:

The percentage of patients less than 65 years in age was 95%. Treatment-by-age group-interaction in HbA1c (%) change from baseline was not significant (p=0.98). Table 32 displays means (SD) for baseline HbA1c and HbA1c change from baseline at week 24 (LOCF).

**Table 32 Means (SD) of baseline HbA1c and HbA1c change from baseline to week 24 (LOCF) by age group (<65, ≥65)**

	Age	LY			Lantus		
		n	Baseline(SD)	Change (SD)	n	Baseline(SD)	Change (SD)
ABEB	< 65	252	7.8 (1.16)	-0.33 (0.75)	256	7.8 (1.03)	-0.44 (0.72)
ABEB	≥ 65	14	7.4 (0.49)	-0.19 (0.44)	11	7.4 (0.96)	-0.28 (0.45)
US-approved	< 65	92	7.8 (1.12)	-0.26 (0.71)	91	7.7 (1.07)	-0.43 (0.72)
US-approved	≥ 65	5	7.3 (0.68)	-0.16 (0.05)	5	7.9 (0.56)	-0.42 (0.4)
EU-approved	< 65	160	7.8 (1.18)	-0.36 (0.77)	165	7.9 (1.01)	-0.45 (0.71)
EU-approved	≥ 65	9	7.4 (0.39)	-0.2 (0.55)	6	7 (1.07)	-0.17 (0.49)

## T2DM

### Gender

Males and females were evenly distributed (50%). Treatment-by-gender interaction in HbA1c (%) change from baseline was not significant (p=0.55). Table 33 displays mean and SD of baseline HbA1c and HbA1c change from baseline to week 24 (LOCF) by gender.

**Table 33 Means (SD) of baseline HbA1c (%) and HbA1c change from baseline to week 24 (LOCF) by gender**

	Gender	LY			Lantus		
		n	Baseline(SD)	Change (SD)	n	Baseline(SD)	Change (SD)
ABEC	F	194	8.3 (1.06)	-1.13 (1.09)	178	8.3 (1.09)	-1.17 (1.12)
ABEC	M	175	8.4 (1.12)	-1.33 (1.11)	197	8.3 (1.05)	-1.33 (1.15)
US-approved	F	98	8.3 (1.06)	-1.2 (1.14)	100	8.2 (1.08)	-1.1 (1.16)
US-approved	M	107	8.4 (1.16)	-1.27 (1.12)	113	8.3 (1.04)	-1.2 (1.19)
EU-approved	F	96	8.2 (1.06)	-1.06 (1.04)	78	8.3 (1.09)	-1.25 (1.08)
EU-approved	M	68	8.4 (1.06)	-1.42 (1.08)	84	8.5 (1.06)	-1.49 (1.09)

### Race

The percentages of patients were 79%, 8%, 7.5%, 5% and 0.4% for White, Asian, Black or African American, American Indian or Alaska Native and Multiple, respectively. Treatment-by-race (white, non-white) interaction was not significant (p=0.99). Table 34 displays the mean and SD of HbA1c baseline and HbA1c change from baseline to week 24 (LOCF) by race categories.

**Table 34 Means (SD) of baseline HbA1c and HbA1c change from baseline to week 24 (LOCF) by race**

	Race	LY			Lantus		
		n	Baseline(SD)	Change (SD)	n	Baseline(SD)	Change (SD)
ABEC	White	299	8.3 (1.08)	-1.23 (1.1)	290	8.2 (1.05)	-1.25 (1.13)
ABEC	non-	70	8.6 (1.11)	-1.22	85	8.5 (1.11)	-1.24

	Race	n	LY		n	Lantus	
			Baseline(SD)	Change (SD)		Baseline(SD)	Change (SD)
US-approved	White	176	8.3 (1.12)	(1.11)	172	8.2 (1.02)	(1.18)
	White			-1.28			(1.16)
US-approved	non-White	29	8.6 (1.09)	-1 (1.25)	41	8.5 (1.19)	-1.04
EU-approved	White	123	8.2 (1.02)	(1.09)	118	8.3 (1.07)	(1.23)
EU-approved	White			-1.16			(1.08)
EU-approved	non-White	41	8.6 (1.15)	-1.38	44	8.6 (1.05)	-1.43
				(0.99)			(1.12)

### Age

The percentage of patients <65 years of age was 72%. The treatment-by-age group interaction was not significant (p=0.46). Table 35 displays mean and SD for baseline HbA1c and HbA1c change from baseline to week 24 (LOCF) by age group.

**Table 35 Means (SD) of baseline HbA1c and HbA1c change from baseline to week 24 (LOCF) by age (<65, ≥65)**

	Age	n	LY		n	Lantus	
			Baseline(SD)	Change (SD)		Baseline(SD)	Change (SD)
ABEC	< 65	259	8.4 (1.11)	-1.29 (1.14)	273	8.4 (1.08)	-1.36 (1.18)
ABEC	≥ 65	110	8.1 (1.02)	-1.07 (1)	102	8 (0.96)	-0.97 (0.98)
US-approved	< 65	145	8.5 (1.13)	-1.28 (1.18)	160	8.3 (1.08)	-1.24 (1.21)
US-approved	≥ 65	60	8.1 (1.04)	-1.14 (1.01)	53	7.9 (0.95)	-0.91 (1.01)
EU-approved	< 65	114	8.4 (1.08)	-1.31 (1.09)	113	8.5 (1.08)	-1.52 (1.11)
EU-approved	≥ 65	50	8.1 (1)	-0.98 (1)	49	8.1 (0.98)	-1.04 (0.96)

### 4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

The EU-approved Lantus was not approved by the FDA. I presented all 3 analysis results, the overall study the US-approved Lantus subgroup and the EU-approved subgroup. From Tables 1 and 2, the upper CI of the treatment differences in HbA1c change from baseline to week 24 were less than the 0.4% noninferiority margin. It is concluded that LY2963016 is noninferiority to Lantus using the 0.4% NIM. For T1DM study, the treatment difference was significant for the US-approved Lantus subgroup (p=0.028) which also imply statistically LY2963016 was inferior to US-approved Lantus. The p-value of T1DM study ABEB was 0.055. In addition, the mixed model repeated measure (MMRM) analysis results (Table 36) are similar to the ANCOVA (LOCF) results (Tables 1 and 2).

**Table 36 MMRM results of HbA1c change (%)**

	All patients	US subgroup	EU subgroup
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<b>ABEB</b>	<b>LY</b>	<b>Lantus</b>	<b>LY</b>	<b>Lantus</b>	<b>LY</b>	<b>Lantus</b>
LSM Change (SE)	-0.38 (0.05)	-0.49 (0.05)	-0.24 (0.06)	-0.42 (0.06)	-0.45 (0.06)	-0.52 (0.06)
Treatment difference [95% CI], p-value	<b>+0.11 [-0.01, +0.22] p=0.066</b>		<b>+0.18 [+0.003, +0.35] p=0.046</b>		<b>+0.07 [-0.08, +0.21] p=0.35</b>	
<b>ABEC</b>						
LSM Change (SE)	-1.26 (0.06)	-1.31 (0.06)	-1.26 (0.08)	-1.23 (0.07)	-1.28 (0.08)	-1.42 (0.08)
Treatment difference [95% CI], p-value	<b>+0.05 [-0.09, +0.20] p=0.49</b>		<b>-0.03 [-0.23, +0.17] p=0.77</b>		<b>+0.15 [-0.06, +0.36] p=0.16</b>	

The observed power for US subgroup:

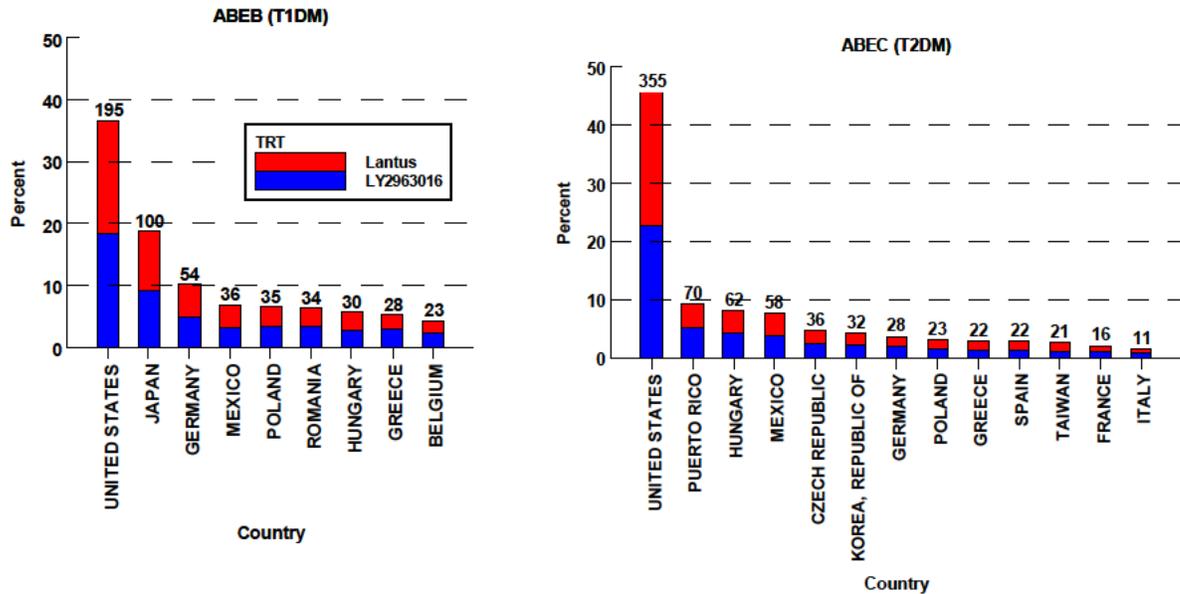
The T1DM study randomized 536 patients (one discontinued before receiving study drug). The T2DM study randomized 759 patients (three discontinued before receiving study drug). The percentage of patients in the US subgroup was 36% (195/535) for the T1DM study and 56% (425/756, US and Puerto Rico) for the T2DM study (Fig 17).

The sponsor calculated the observed power in the US subgroup using observed sample size and standard deviation of HbA1c change from baseline to week 24 (LOCF) with 0.4% NIM (Table 37). The calculation showed that the US subgroup has sufficient power to be a stand-alone study.

**Table 37 Observed power in US subgroup - 0.4% NIM**

	T1DM	T2DM
Observed # of patients/arm	97	212
Observed SD	0.70%	1.15%
Observed power (0.4% margin)	97%	94%

**Figure 17 Percentage and Number of patients by country**



**Sample size estimation and blinded sample-size re-estimation**

Table 38 displays the sample size estimation at week 24 for the studies using 2-sided significant level of 0.05.

**Table 38 Sample size calculation at week 24**

	T1DM	T2DM
# of patients/arm completers	184 (368 total)	284 (568 total)
#/arm with 15% dropout	216 (432 total)	334 (668 total)
Standard Deviation (SD)	0.88%	1.1%
0.4% NIM	>99%	>99%
0.3% NIM	90%	90%

**Blinded sample-size re-estimation**

The sponsor conducted sample-size re-estimation when approximately 75% of the pre-specified minimum patients,  $n_{min}$  were enrolled to ensure that the trial has an appropriate sample size to achieve the pre-specified power. The procedure does not use information on treatment assignments (blinded). The re-estimation used a Bayesian longitudinal model to impute final 24-week predicted values (multiple imputation) for each patient using all available HbA1c values. The estimate of the 24-week variability was then used to recalculate the sample size that was needed to have 90% power for the 0.3% NIM, assuming no between treatment difference. The study sample size was constrained between a prespecified minimum and a prespecified maximum. The blinded re-estimation provided an estimate (mean predicted sample) and uncertainty around the necessary sample size (Table 39).

**Table 39 Blinded sample size re-estimation**

	T1DM	T2DM
Power for 0.3% NIM	90%	90%
# of patients at week 12	n=295 with baseline HbA1c n=27 with week 12 HbA1c	n=474 with baseline HbA1c n=10 with week 12 HbA1c
Constrained sample size [ $n_{min}$ , $n_{max}$ ]	[400, 500]	[606, 792]
Mean predicted n and uncertainty	n=227 with 90% probability n<381	n=561 with 90% probability n<775
Final re-estimated n	500 (for safety database)	Enroll up to the maximum, 792
Randomized n	536	759

**Missing data issue:**

## T1DM

At week 24, 4% (20/534) of patients had missing HbA1c value (<W24 cohort) (7% of US-approved Lantus subgroup and 3% of EU-approved Lantus subgroup). Table 40 displays descriptive statistics by cohorts of <W24 and W24. The greatest mean HbA1c reduction (-0.75, n=6) was in the <W24 cohort for US-approved Lantus.

**Table 40 Descriptive statistics for patients cohorts (<Week 24, or Week 24)**

	Cohort	Treatment	N	Mean	SD	Median	Min	Max
US	<W24	LY2963016	7	+0.1	0.52	-0.1	-0.3	1.2
		Lantus	6	-0.75	0.86	-0.75	-2.1	0.4
	W24	LY2963016	91	-0.27	0.71	-0.2	-2.9	1.4
		Lantus	90	-0.4	0.69	-0.2	-3	0.7
EU	<W24	LY2963016	4	+0.3	0.89	0	-0.4	1.6
		Lantus	3	+0.3	1.3	0.3	-1	1.6
	W24	LY2963016	165	-0.37	0.75	-0.4	-4	1.2
		Lantus	168	-0.45	0.69	-0.4	-3.6	1.3
ABEB	<W24	LY2963016	11	+0.17	0.64	0	-0.4	1.6
		Lantus	9	-0.4	1.08	-0.5	-2.1	1.6
	W24	LY2963016	256	-0.34	0.74	-0.3	-4	1.4
		Lantus	258	-0.43	0.69	-0.4	-3.6	1.3

## US-approved Lantus T1DM:

Of the 195 patients in the FAS (randomized with one dose of study medication), one LY2963016 patient with only baseline HbA1c was excluded from the analysis. Of the 194 patients in the analysis, 181 (93%) of patients completed week 24 visit. Table 41 displays number of patients with last observed HbA1c by cohort of visit week. Patients with missing data (week 6 and week 12 cohorts) showed greater HbA1c reduction for Lantus-treated patients than LY2963016-treated patients (Table 42 and Fig 18).

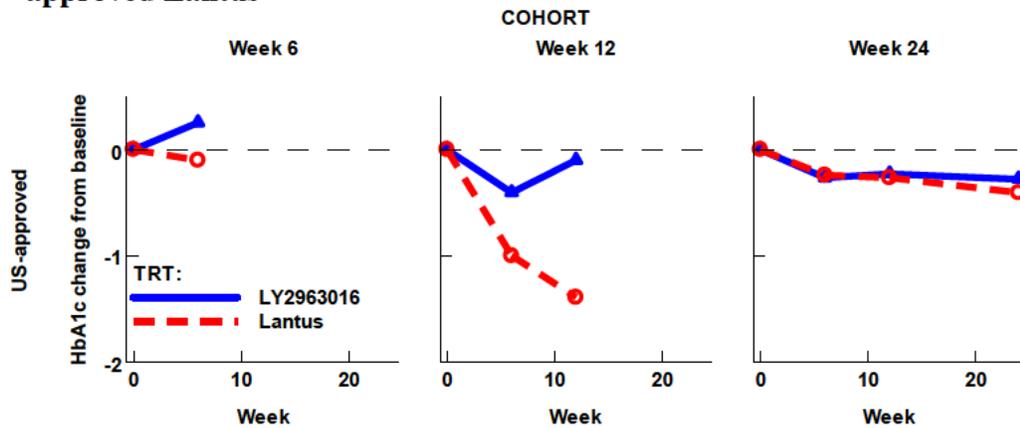
**Table 41 Number of patients with last observed HbA1c by visit week cohort – T1DM**

Cohort Week	US-approved Lantus		EU-approved Lantus		ABEB	
	LY2963016	Lantus	LY2963016	Lantus	LY2963016	Lantus
6	4 (4.1%)	3 (3.1%)	2 (1.2%)	2 (3.7%)	6 (2.3%)	5 (1.9%)
12	3 (3.1%)	3 (3.1%)	2 (1.2%)	1 (1.2%)	5 (1.9%)	4 (1.5%)
24	91 (92.9%)	90 (93.8%)	165 (97.6%)	168 (98.3%)	256 (96%)	258 (97%)
Total	98 (100%)	96 (100%)	169 (100%)	171 (100%)	267 (100%)	267 (100%)

**Table 42 Descriptive statistics – US-approved Lantus subgroup by cohort week**

Treatment	Cohort week	n	Mean	Std Dev	Min	Max
LY2963016	6	4	+0.25	(0.69)	-0.3	1.2
	12	3	-0.1	(0.10)	-0.2	0
	24	91	-0.27	(0.71)	-2.9	1.4
	LOCF	98	-0.25	(0.70)	-2.9	1.4
Lantus	6	3	-0.1	(0.46)	-0.5	0.4
	12	3	-1.4	(0.61)	-2.1	-1
	24	90	-0.4	(0.69)	-3	0.7
	LOCF	96	-0.43	(0.71)	-3	0.7

**Figure 18 HbA1c change from baseline over time by cohort of last visit week – US-approved Lantus**



## T2DM

Of the 744 patients in the efficacy analysis for HbA1c change from baseline, 90% (331/369) of LY2963016 and 88% (329/375) of the Lantus patients had no missing value (Table 43).

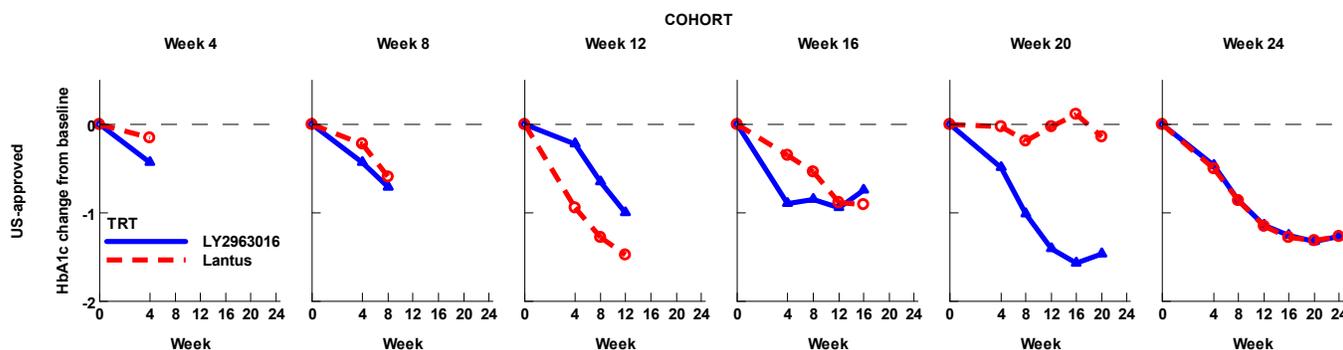
**Table 43 Number (%) of patients with last observed HbA1c by visit week cohort – T2DM**

Week	US-approved Lantus		EU-approved Lantus		ABEC	
	LY2963016 n=205	Lantus n=213	LY2963016 n=164	Lantus n=162	LY2963016 n=369	Lantus n=375
4	3 (1.5%)	10 (4.7%)	6 (3.7%)	6 (3.7%)	9 (2.4%)	16 (4.3%)
8	6 (2.9%)	4 (1.9%)	3 (1.8%)	1 (0.6%)	9 (2.4%)	5 (1.3%)
12	5 (2.4%)	6 (2.8%)	1 (0.6%)	2 (1.2%)	6 (1.6%)	8 (2.1%)
16	2 (1.0%)	9 (4.2%)	1 (0.6%)	0 (0.0%)	3 (0.8%)	9 (2.4%)
20	8 (3.9%)	7 (3.3%)	3 (1.8%)	1 (0.6%)	11 (3%)	8 (2.1%)
24	181 (88%)	177 (83%)	150 (92%)	152 (94%)	331 (90%)	329 (88%)

US-approved Lantus subgroup:

Of the 425 patients in the FAS population (at least 1 dose of study drug), 7 patients (5 LY2963016 and 2 Lantus) with only baseline HbA1c value were not in the analysis dataset. Of the 418 patients in the efficacy analysis, 358 (86%) completed week 24. Figure 19 displays HbA1c change from baseline over time by cohorts of patients

**Figure 19 Mean HbA1c change from baseline over time by cohort of last visit week – US-approved Lantus**



## 5.2 Conclusions and Recommendations

From studies ABEB and ABEC (T1DM and T2DM), it is concluded that LY is non-inferior to Lantus. For ABEB, treatment difference [95% CI] (LY – Lantus) was +0.11% [-0.002, +0.22]

(p=0.055). For ABEC, treatment difference [95% CI] (LY – Lantus) was +0.05% [-0.07, +0.17] (p=0.4). For US-approved Lantus subgroup, LY was both non-inferior (upper 95% CL +0.36% < 0.4% margin) and inferior (lower 95% CL +0.02% > 0) (p=0.028) to US-approved Lantus in T1DM. LY is non-inferior to EU-approved Lantus (95% CI, -0.08, +0.2 < 0.3% margin) (p=0.345). T2DM showed noninferiority of LY to Lantus in the overall study and the US- and EU-approved Lantus subgroups.

### 5.3 Labeling Recommendations

1. Table 15 (section 14) for Type 1 Diabetes Mellitus – Adult ( (b) (4) versus Another Insulin Glargine Product) (b) (4)  

2. (b) (4)  

3. There should be discussions on whether to present US-approved Lantus subgroup in the label.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LEE PING PIAN  
05/29/2014

MARK D ROTHMANN  
05/29/2014  
I concur

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 205-692**

**Applicant: Lilly**

**Stamp Date: 10/17/2013**

**Drug Name:** (b) (4) **NDA/BLA Type: 505 b (2)**  
**Insulin glargine injection in a disposable delivery device** **reference: Lantus**

**Indication: type 1 and 2 diabetes**

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
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.)	ISS			Studies are not integrated due to 2 different patient populations.
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

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

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

Please submit SAPs for studies ABEB and ABEC.

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

**STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA**

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

### Brief summary of controlled clinical trials

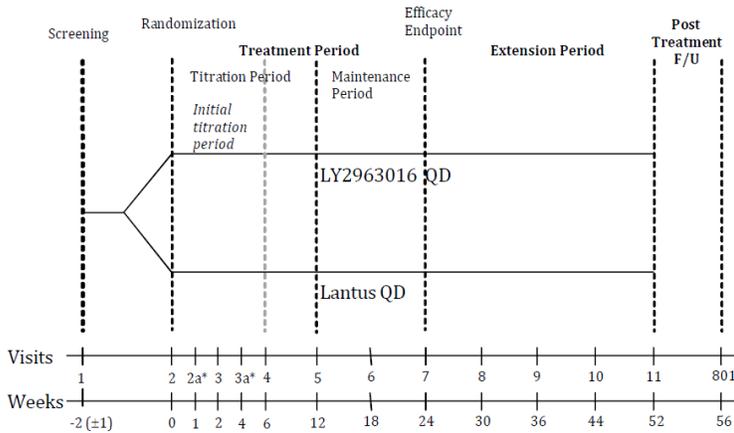
The following table contains information on the relevant trials contained in the submission.

Study number	Design	Treatment arms/Sample size	Primary endpoint/Analysis	Sponsor's findings															
<b>ABEB</b>	<b>Randomized, OL, MC (59, centers in 9 countries), 2-arm, AC, 24-wk treatment, 28-wk extension, 4-wk FU. in T1DM patients</b>	<table style="margin-left: auto; margin-right: auto;"> <tr> <td></td> <td><b>LY</b></td> <td><b>Lantus</b></td> </tr> <tr> <td><b>Rand</b></td> <td><b>269</b></td> <td><b>267</b></td> </tr> <tr> <td><b>FAS</b></td> <td><b>268</b></td> <td><b>267</b></td> </tr> <tr> <td><b>Comp</b></td> <td><b>253</b></td> <td><b>256</b></td> </tr> <tr> <td><b>% comp</b></td> <td><b>94%</b></td> <td><b>96%</b></td> </tr> </table> <p>(24-wk)</p>		<b>LY</b>	<b>Lantus</b>	<b>Rand</b>	<b>269</b>	<b>267</b>	<b>FAS</b>	<b>268</b>	<b>267</b>	<b>Comp</b>	<b>253</b>	<b>256</b>	<b>% comp</b>	<b>94%</b>	<b>96%</b>	<p><b>HbA1c change from baseline to Week 24 (LOCF)/ANCOVA (with country, time of basal insulin injection (daytime, evening/bedtime) and treatment as fixed effects, and baseline HbA1c as a covariate.</b></p> <p><b>If the NI margin of 0.4% is met, the upper limit of the 95% CI will be compared to the 0.3% NI margin.</b></p>	<p><b>HbA1c LSM change from baseline to wk 24 (FAS, LOCF):</b>  <b>LY, -0.35%</b>  <b>Lantus, -0.46%</b></p> <p><b>LSM difference (LY – Lantus) [95% CI]= +0.11% [-0.002%, +0.22%]</b></p> <p><b>1.LY NI to Lantus at both 0.4% and 0.3% NI margin (+0.22% &lt; 0.3%)</b></p> <p><b>2. Lantus NI to LY (-0.002% &gt; -0.4%)</b></p> <p><b>3.LY and Lantus were considered equivalent efficacy at 24-wk</b></p>
	<b>LY</b>	<b>Lantus</b>																	
<b>Rand</b>	<b>269</b>	<b>267</b>																	
<b>FAS</b>	<b>268</b>	<b>267</b>																	
<b>Comp</b>	<b>253</b>	<b>256</b>																	
<b>% comp</b>	<b>94%</b>	<b>96%</b>																	
<b>ABEC</b>	<b>Randomized, DB, MC (88 centers in 13 countries), 2-arm, AC, 24-week study, 4-wk FU in T2DM patients(insulin naïve and failed to achieve adequate glycemic control on <math>\geq 2</math> OAMs, or already administering Lantus along with <math>\geq 2</math> OAMs with adequate or inadequate</b>	<table style="margin-left: auto; margin-right: auto;"> <tr> <td></td> <td><b>LY</b></td> <td><b>Lantus</b></td> </tr> <tr> <td><b>Rand</b></td> <td><b>379</b></td> <td><b>380</b></td> </tr> <tr> <td><b>FAS</b></td> <td><b>376</b></td> <td><b>380</b></td> </tr> <tr> <td><b>Comp</b></td> <td><b>334</b></td> <td><b>328</b></td> </tr> <tr> <td><b>% comp</b></td> <td><b>89%</b></td> <td><b>86%</b></td> </tr> </table>		<b>LY</b>	<b>Lantus</b>	<b>Rand</b>	<b>379</b>	<b>380</b>	<b>FAS</b>	<b>376</b>	<b>380</b>	<b>Comp</b>	<b>334</b>	<b>328</b>	<b>% comp</b>	<b>89%</b>	<b>86%</b>	<p><b>HbA1c change from baseline to Week 24 (LOCF)/ANCOVA (with country, SU use, time of basal insulin injection (daytime, evening/bedtime) and treatment as fixed effects, and baseline HbA1c as a covariate.</b></p> <p><b>If the NI margin of 0.4% is met, the upper limit of the 95% CI will be compared to the 0.3% NI margin.</b></p>	<p><b>HbA1c LSM change from baseline to wk 24 (FAS, LOCF):</b>  <b>LY, -1.29%</b>  <b>Lantus, -1.34%</b></p> <p><b>LSM difference (LY – Lantus) [95% CI]= +0.05% [-0.07%, +0.18%]</b></p> <p><b>1. LY NI to Lantus at both 0.4% and 0.3% NI margin (+0.18%&lt;0.3%)</b></p> <p><b>2. Lantus NI to LY at lower CI, -0.07% &gt; -0.4%.</b></p> <p><b>3. LY considered equivalent efficacy to</b></p>
	<b>LY</b>	<b>Lantus</b>																	
<b>Rand</b>	<b>379</b>	<b>380</b>																	
<b>FAS</b>	<b>376</b>	<b>380</b>																	
<b>Comp</b>	<b>334</b>	<b>328</b>																	
<b>% comp</b>	<b>89%</b>	<b>86%</b>																	

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

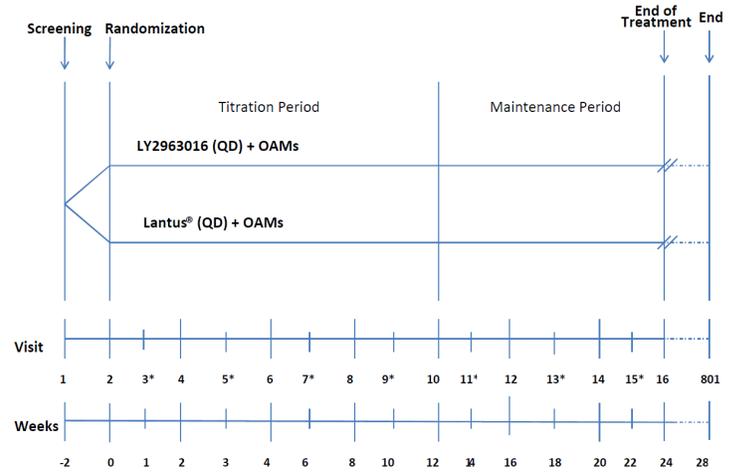
Study number	Design	Treatment arms/Sample size	Primary endpoint/Analysis	Sponsor's findings
	<b>glycemic control</b>			<b>Lantus.</b>

**Design: ABEB**



Abbreviations: F/U = follow-up; QD = once daily.  
\* Telephone visit.

**ABEC**



Abbreviations: OAM = oral antihyperglycemic medication; QD = once daily;  
\* = telephone visit.

## HbA1c change from baseline to week 24 descriptive statistics:

Site selection: Bhargava, Anuj

**ABEB:**

		Without site 8					Site 8				
Treatment	Variable	N	Mean	Std Dev	Min	Max	N	Mean	Std Dev	Min	Max
LY2963016	HBA1CBL	251	7.7	1.1	4.8	11.5	16	7.9	1	6.6	10.4
	chg		<b>-0.3</b>	0.7	-4	1.6		<b>-0.2</b>	0.8	-1.6	1.4
Lantus	HBA1CBL	253	7.8	1	5.3	10.3	14	7.7	1.3	5.2	10.1
	chg		<b>-0.4</b>	0.7	-3.6	1.6		<b>-0.7</b>	0.8	-2.1	0.7

**ABEC:**

		Without site 10					Site 10				
Treatment	Variable	N	Mean	Std Dev	Min	Max	N	Mean	Std Dev	Min	Max
LY2963016	HBA1CBL	355	8.4	1.1	4.9	11.3	14	7.9	1.1	6.3	10.4
	chg		<b>-1.2</b>	1.1	-4.6	1.5		<b>-0.9</b>	0.6	-1.9	-0.2

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

		Without site 10					Site 10				
Treatment	Variable	N	Mean	Std Dev	Min	Max	N	Mean	Std Dev	Min	Max
Lantus	HBA1CBL	367	8.3	1.1	6.0	11.1	8	7.8	1.3	5.9	9.6
	chg		<b>-1.3</b>	1.1	-4.6	1.6		<b>-0.8</b>	1.1	-2.8	0.6

ABEB: site 100 Reed, John

Treatment	Variable	N	Mean	Std Dev	Min	Max
LY2963016	HBA1CBL	2	6.8	0.3	6.6	7.0
	chg		<b>0.0</b>	0.7	-0.5	0.5
Lantus	HBA1CBL	15	7.8	1.0	6.0	9.6
	chg		<b>-0.5</b>	0.8	-3.0	0.52

ABEC: site 24 Ubani, Agnes

Treatment	Variable	N	Mean	Std Dev	Min	Max
LY2963016	HBA1CBL	10	8.4	1.4	7.0	11.3
	chg		<b>-1.2</b>	1.1	-3.4	-0.1
Lantus	HBA1CBL	4	7.3	0.2	7.0	7.6
	chg		<b>-1.2</b>	0.7	-1.5	-0.2

**STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA**

Lee ping pian	12/18/13
_____ Reviewing Statistician	_____ Date
Mark Rothmann	12/18/13
_____ Supervisor/Team Leader	_____ Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LEE PING PIAN  
12/18/2013

MARK D ROTHMANN  
12/19/2013  
concur